Lung SPECT/CT

12

Paul J. Roach

12.1 Introduction

The accurate diagnosis of pulmonary embolism (PE) is challenging for both clinicians and imaging specialists. Misdiagnosis must be avoided because untreated PE has a mortality rate reported to be up to 30%, and unnecessary treatment with anticoagulation places patients at risk of bleeding [1–3].

For many years, the ventilation/perfusion (*V*/*Q*) lung scan was the primary imaging test to assess patients with suspected PE [4]. More recently, radiographic computed tomography pulmonary angiography (CTPA) is used preferentially in most patients [4–6]. These two imaging studies have largely replaced invasive pulmonary angiography and digital subtraction angiography in the assessment of patients with PE, and both are utilised widely in hospitals and imaging centres worldwide.

Experience with *V*/*Q* scintigraphy spans over 50 years, with its use first described by Wagner et al. in 1964 [7]. The principle of the test is that in patients with PE, lung perfusion is compromised secondary to occlusive thrombi in the pulmonary arterial tree, whereas ventilation to these areas is generally unaffected [8]. This results in the so-called ventilation/perfusion (*V*/*Q*) mismatch, i.e. where ventilation is normal but perfusion is reduced or absent [8, 9].

12.2 Limitations of Planar Lung Scintigraphy

Although widely used over many decades, the planar lung scan is a test that is widely recognised as having limitations [5, 10–13].

When the lungs are imaged in only two dimensions (2D), as occurs with planar imaging, there is significant overlap of anatomical segments, and as a result, it is frequently difficult to assign defects to specific lung segments. Accurately determining the extent of embolic involvement in each individual segment can also be problematic as the size and shape of each lung segment varies [12]. In addition, embolic defects may not be detected if there is 'shine through' occurring from underlying lung segments with normal perfusion. This can result in an underestimation of the extent of perfusion loss in patients with PE [14]. Furthermore, not all segments of the lungs are visualised on conventional planar lung scintigraphy. Specifically, the medial basal segment of the right lower lobe is not routinely seen on planar scintigraphy [12, 15].

In addition to these inherent technical limitations of planar (2D) lung scintigraphy, there are the problems posed by the widely used probabilistic criteria generally used to report these studies [16–20]. The use of probabilities for lung scan

P. J. Roach (✉)
Department of Nuclear Medicine, Royal North Shore Hospital, Sydney, NSW, Australia
e-mail: paul.roach@sydney.edu.au

H. Ahmadzadehfar et al. (eds.), *Clinical Applications of SPECT-CT*,
https://doi.org/10.1007/978-3-030-65850-2_12

reporting became widespread following the publication of the large multicentre PIOPED study in 1990 [21]. This landmark study highlighted some of the limitations of planar lung scanning, particularly in relation to specificity. Given the management implementations, if a patient is diagnosed with PE, this is a condition in which clinicians prefer binary (i.e. positive or negative) reports whenever possible, rather than inconclusive, 'indeterminate' or even probabilistic reports [22].

12.3 Advantages of SPECT Imaging

SPECT (single-photon emission computed tomography) is widely used in many areas of radionuclide imaging today because of its ability to image in three dimensions (3D). It has been shown to be superior to planar imaging in the evaluation of many conditions, such as assessing myocardial perfusion as well as brain and liver imaging [23, 24]. In contrast to planar imaging, SPECT avoids the problems introduced by segmental overlap and 'shine through' of the adjacent lung, making it better able to image all segments of the lungs and more accurately define the size and location of perfusion defects [12]. Hence, it would be expected that SPECT *V*/*Q* scintigraphy would be superior to planar imaging. Furthermore, with the widespread availability today of multi-detector gamma cameras (and increasingly SPECT/CT scanners) as well as improved computing power allowing faster processing, lung scintigraphy is ideally suited to SPECT acquisition.

The advantages of SPECT over planar lung imaging have been demonstrated in numerous published manuscripts over many years, both in animals and in humans. In a study performed in which subsegmental and segmental clots were induced in dogs, SPECT was shown to be more sensitive than planar imaging [25]. Similar results were described by Bajc and co-workers in a study that compared SPECT with planar imaging using ^{99m}Tc-DTPA aerosols and ^{99m}Tc-MAA in pigs [26]. Artificial emboli labelled with ^{201}Tl were induced and SPECT was found to have an increased sensitivity (91% versus 64%) and specificity (87% versus 79%) compared with planar imaging. In a study using Monte Carlo simulation of lungs containing defects to mimic PE, Magnussen and co-workers also demonstrated that SPECT was more sensitive than planar imaging (97% versus 77%) [15].

The advantage of SPECT imaging over planar lung scintigraphy has also been consistently demonstrated in human studies. In a series of 53 patients with suspected PE, Bajc and co-workers found SPECT to be more sensitive than planar imaging (100% versus 85%) in the detection of PE [27]. In addition, the authors concluded that SPECT demonstrated less interobserver variation and better delineation of mismatched defects compared with planar imaging. Collart and co-workers, in a study of 114 patients, also demonstrated that SPECT was more specific than planar imaging (96% versus 78%) and had better intra-observer reproducibility (94% versus 91%) and interobserver reproducibility (88% versus 79%) [28]. In a pivotal study of 83 patients with suspected PE, Reinartz et al. demonstrated that SPECT was superior to planar imaging in terms of sensitivity (97% versus 76%), specificity (91% versus 85%) and accuracy (94% versus 81%) [29]. In this paper, SPECT increased the number of detectable defects at the segmental level by 12.8% and at the subsegmental level by 82.6%.

Another advantage of *V*/*Q* SPECT imaging is that it has been consistently shown to have a much lower indeterminate rate than planar imaging, typically less than 5% [8, 30, 31]. In one large series from Canada, *V*/*Q* SPECT was shown to have a very high negative predictive value (98.5%) for PE with only 3% of studies being reported as indeterminate for PE [32].

The published data to date is consistent and taken together indicates that SPECT has a greater sensitivity and specificity and improved reproducibility compared with planar lung imaging.

12.4 Need for Correlation with Anatomical Imaging

From the viewpoint of the lung scan, ventilation/perfusion mismatch would ideally only be caused by PE, with all other pathological processes producing other scintigraphic appearances. Unfortunately, that is not the case and the reality is that many different pathological processes can affect pulmonary ventilation and perfusion. Ventilation/perfusion mismatch can be seen in other conditions, including congenital pulmonary vascular abnormalities, veno-occlusive disease, vasculitis, emphysema, radiation therapy-induced changes and extrinsic vascular compression from conditions such as neoplasm and mediastinal adenopathy [8, 33] (Fig. 12.1). To further complicate the issue, the classic *V/Q* 'mismatch' pattern is sometimes not seen in patients with PE. Subsequent to the acute embolic event, clots often become partly resolved or the process of recanalisation occurs, resulting in mismatch becoming less distinct. Furthermore, in some patients, pulmonary infarction occurs subsequent to PE resulting in a matched reduction (or loss) of both ventilation and perfusion on *V/Q* scintigraphy, an appearance typically seen with non-embolic pathologies [8]. Hence, it should be remembered that not all patients with PE will have *V/Q* mismatch, and not all patients with *V/Q* mismatch on lung scanning will have PE. For this reason, the chest X-ray appearances have been considered pivotal by many to aid in the interpretation of the *V/Q* scan, and the findings are often used to improve the accuracy and specificity of *V/Q* reporting [8, 21, 34]. At some centres, including my own at Royal North Shore Hospital, Sydney, the chest X-ray has often been used to triage individual patients prior to deciding which imaging test would be the most appropriate to perform. Patients with normal, or near-normal, radiographic appearances may be referred for *V/Q* scintigraphy, whereas those patients with abnormal radiographic appearances may preferentially be referred for CTPA [35]. The ability of CTPA to image the lung parenchyma gives it a definite advantage over lung scintigraphy as it can more readily identify conditions which may mimic PE clinically, such as pneumonia, abscess, pleural or pericardial effusions, aortic dissection, oesophageal rupture and malignancy [5, 6, 36, 37]. While the benefits of adding anatomical information to *V/Q* scans are well recognised, until recently, the only option

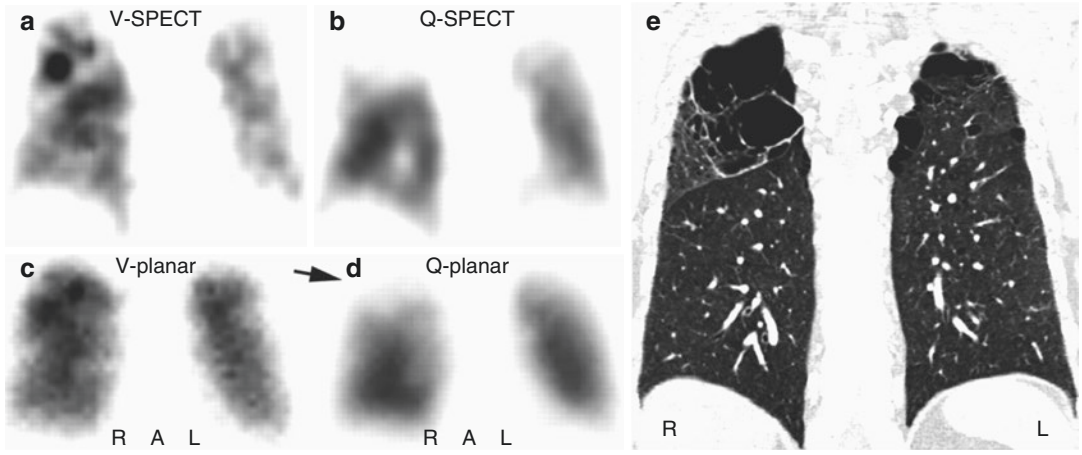

Fig. 12.1 Ventilation (*V*) and perfusion (*Q*) SPECT images in a patient with severe chronic obstructive pulmonary disease (COPD) and pulmonary emphysema. A large emphysematic bullae in the right upper lobe (**e**) seen on CT led to a false-positive diagnosis on *V/Q* scintigraphy (**b**, **d**, mismatch perfusion defects marked by *arrows*). The patient did not have PE. Technegas can ventilate into emphysematous bullae (**a**, **c**). In this case, the CT would have demonstrated the cause of the perfusion reduction evident on SPECT imaging and would have avoided the false-positive *V/Q* scan (*R* right, *A* anterior, *L* left). (Reprinted with permission from Reinartz et al. [29])

for reporting specialists has been to view a chest X-ray or a diagnostic CT scan performed non-contemporaneously [38].

12.5 Combining Functional and Anatomical Images

12.5.1 Visual and Software Fusion

Recent years have witnessed an increasing emphasis on combining the structural information provided by anatomical techniques, such as CT scanning, with the functional information provided by nuclear medicine imaging [39]. While reporting specialists have been able to visually compare different images placed side by side (the so-called visual fusion) for many years, the accuracy of such an approach is frequently limited [39, 40]. A more robust approach is to fuse SPECT or PET images with CT or MRI using sophisticated data-matching algorithms. This so-called software fusion has been used since the early 1990s with great success in many applications, such as brain imaging [39]. However, the 'deformable' and flexible nature of much of the body, as well as differences in the scanning bed shapes, arm positioning and breathing protocols can make accurate registration of a SPECT study and a diagnostic CT scan acquired on a separate scanner problematic [38]. Despite these limitations, our group has demonstrated the feasibility of the software fusion approach with lung scintigraphy. In a pilot study of 30 patients with suspected PE, SPECT perfusion data were fused with CTPA using commercial software which was based on an iterative approach employing an automated mutual information algorithm [38]. We demonstrated that all nine patients with positive CTPA studies performed as the initial investigation for PE had co-localised perfusion defects on the subsequent fused CTPA/SPECT images (Fig. 12.2). Of the 11 *V*/*Q* scans initially reported as intermediate probability, 27% were able to be reinterpreted as low probability due to co-localisation of defects with parenchymal or pleural pathology. While we have demonstrated that the approach of using software fusion is technically feasible and can improve the diagnostic accuracy of the lung SPECT, it may not be practical in all centres, particularly if the required software programs or operator experience is lacking.

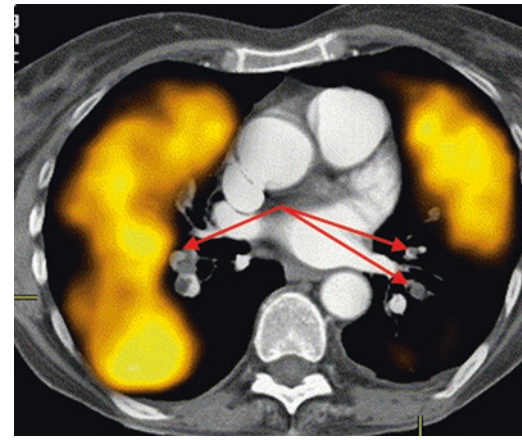

Fig. 12.2 Co-registered CTPA/perfusion SPECT (transverse slice) demonstrating extensive perfusion defects on SPECT corresponding with proximal bilateral PE shown on CTPA (*arrowed*). (Reprinted with permission from Roach et al. [41])

12.5.2 Hardware Fusion

With the increasing availability of integrated SPECT/CT and PET/CT scanners, 'hardware fusion' is now routinely employed in many areas of nuclear medicine practice [39]. As the two datasets are acquired on the same scanning bed in the same imaging session, much greater registration accuracy is seen with hybrid SPECT/CT scanners compared with software fusion techniques [39, 42–44]. At my own hospital campus in Sydney, where we have three SPECT/CT scanners, we routinely perform SPECT/CT scanning in most areas of nuclear medicine, including bone scans, gallium (infection) scans, myocardial perfusion studies as well as scans of the liver, parathyroid and adrenal glands. As well, irtually all lung scans are now done using SPECT/CT scanning. This is in addition to all of our PET scans which are performed on a hybrid PET/CT scanner.

12.6 *V/Q* Lung SPECT/CT

In the case of lung scanning, the emergence of hybrid SPECT/CT scanners gives reporting specialists two options to combine structural and functional data and potentially to improve overall diagnostic accuracy of the modality.

Firstly, SPECT perfusion can be co-registered with diagnostic CTPA studies. By combining the 3D scintigraphic perfusion data with a CTPA demonstrating the actual clot location, the advantages of each imaging test are realised. This may be of particular benefit if either study is inconclusive. However, as either study will be diagnostic in most patients, the value of this approach may be limited and, given the software and operator skill required, may not be feasible in many imaging centres.

Secondly, a *V/Q* SPECT can be performed concurrently with a 'low dose' CT done concurrently, or more typically sequentially, on the same scanning device. This technique is feasible in any imaging facility equipped with a SPECT/CT scanner. Several studies have shown a significant improvement in the diagnostic accuracy of the lung scan using this approach.

These two approaches are discussed in more detail below.

12.6.1 SPECT and CTPA Fusion

Co-registering the perfusion SPECT data with a diagnostic CTPA study is an approach which may be of particular value in cases of an inconclusive CTPA study. The concept of this approach is that the combined images may help to characterise the perfusion pattern seen scintigraphically in any area distal to a potential clot on the angiographic study [38] (Fig. 12.2). By combining the demonstrated very high sensitivity of perfusion SPECT with the high specificity of CTPA, an overall improved diagnostic accuracy of the combined investigation would be expected compared with either study alone. New generation hybrid devices are equipped with diagnostic multi-slice CT scanners, and hence it is possible to perform both *V/Q* SPECT and CTPA if required in a single imaging session. While this may not be feasible in all institutions or in all patients, it is an option with current generation scanner technology. An alternative way of fusing perfusion SPECT data with CTPA is to use commercial software programs to co-register the data which may have been acquired on different scanning devices. Such software programs can generate displays of ventilation, perfusion, lung CT, fusion images and CTPA. This approach may be of value in difficult or complex cases where a conclusive result cannot be made based on either study alone. In the case of CTPA, which is being used more frequently in many centres as the initial imaging study to evaluate suspected PE, one of the challenges faced by reporting radiologists is the increasing amount of data to review with each patient study [45]. In a study at my institution, we assessed whether the fusion of SPECT perfusion data could improve the accuracy of CTPA by guiding the attention of the reporting radiologist to the relevant pulmonary artery [46]. Of the 35 patients studied, there was an 8% increase in the sensitivity of CTPA when fused with SPECT perfusion data. This led to a change in final diagnosis (from PE negative to PE positive) in 6% of patients (Fig. 12.3). Provided adequate software is available to perform the fusion of perfusion SPECT and CTPA, this approach could be readily utilised in imaging departments and might potentially allow clots to be detected more accurately in difficult or inconclusive CTPA studies, thus improving the overall utility of the test. One approach might be to refer discordant SPECT *V/Q* and CTPA results for co-registration and consensus review with all data available. While either a CTPA or *V/Q* SPECT will be able to provide a diagnosis in most patients, there may be some instances where performing both studies on the same patient may be required to more confidently diagnose (or exclude) PE. This approach could be considered in patients where an accurate diagnosis is critical if either study yields an inconclusive result or is technically suboptimal.

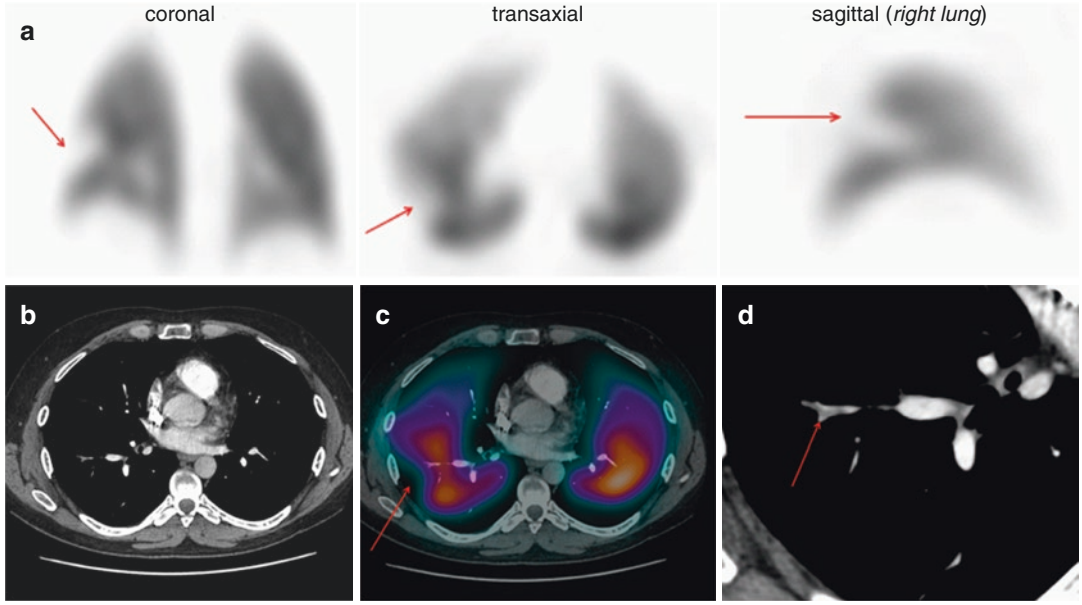

Fig. 12.3 Images of a 43-year-old male with suspected PE. Representative perfusion images of the *V*/*Q* SPECT (**a**) show a (mismatched) perfusion defect in the superior segment of the right lower lobe (*arrowed*). A CTPA (**b**) was reported as normal. A fused image of the CTPA and perfusion SPECT (**c**) was generated, and following a more targeted review by the radiologist of the vascular tree on the CTPA (**d**), an embolus was evident (*arrowed*). Fusion of SPECT and CTPA may help guide radiologists to the relevant part of the pulmonary vascular tree to review more carefully, thereby increasing the sensitivity of CTPA

12.6.2 Combined *V*/*Q* SPECT with Low-Dose CT

12.6.2.1 Overview

The second option is to perform a 'low dose' CT in conjunction with the *V*/*Q* SPECT study. In this case, the study is generally done without intravenous contrast and using a much lower beam current than diagnostic CT scanning. Typically, this is in the order of 20–80 mA s. This approach has the advantage of providing anatomical information, such as vascular, parenchymal and pleural abnormalities, which may explain the cause of perfusion defects seen on the *V*/*Q* SPECT scan. While *V*/*Q* SPECT has been shown to be highly sensitive, this approach may better characterise the case of any perfusion reductions, thus altering the final SPECT interpretation and improving overall specificity [47–49]. With the increasingly availability of hybrid SPECT/CT scanners, this approach can be easily performed in most nuclear medicine departments. The CT scan is typically done on the same scanning device, without the need to move the patient, usually immediately after the SPECT acquisitions have been done.

12.6.2.2 Protocols

In general, patients undergoing *V*/*Q* SPECT/CT studies have the ventilation SPECT study acquired first, followed in most cases by the perfusion SPECT and then the low-dose CT. Each of the acquisitions is detailed below.

Ventilation

For imaging ventilation, several alternatives exist. These include inert radioactive gases such as ^{81m}Kr and ^{133}Xe, radiolabelled aerosols such as ^{99m}Tc-diethylene triamine penta-acetic acid (^{99m}Tc-DTPA) and the ultrafine carbon suspension $^{99mTc\text{-}Technegas}$ [50]. Although the gases are considered to most accurately represent regional ventilation, these are typically not used due to the requirement for continuous administration during the acquisition and the high cost of the ^{81m}Kr generator [51]. Although ^{133}Xe gas has the advan-

tage of a longer half-life, its use is complicated by errors resulting from its recirculation due to clearance into the pulmonary circulation [52, 53]. Combined with its poor spatial resolution, it is a less than ideal agent to image ventilation [51].

Given these limitations, ^{99m}Tc-labelled particulate aerosols such as ^{99m}Tc-DTPA or the carbon-labelled nanoparticle ^{99m}Tc-Technegas are much more widely used due to their greater availability, low cost and good image quality [51]. Although the choice of agent depends on factors such as local availability and cost, both have been reported to produce SPECT ventilation scans of good diagnostic quality. The most widely available is ^{99m}Tc-DTPA, which can be used with doses of just 0.8 mCi (30 MBq) [27]. However, because of the relatively larger mean particle mass, problems may arise from central airway deposition, particularly in patients with chronic obstructive pulmonary disease (COPD) [54]. Technegas, with a smaller particle size, generally has greater alveolar penetration than ^{99m}Tc-DTPA. This results in less impaction in the central airways, with Technegas being demonstrated to have a similar distribution to that of an inert gas [55–59]. Together with its lack of lung clearance during image acquisition, Technegas is an ideal agent for ventilation SPECT. Typically, the doses of ^{99m}Tc-based imaging agents administered are identical to those used in conventional planar imaging. The EANM procedure guidelines for *V*/*Q* SPECT recommend an inhaled dose of 30 MBq Technegas [8]; however, some authors have proposed a slight increase in the administered dose in an attempt to improve image quality [29, 32]. At our institution, 13.5 mCi (500 MBq) of ^{99m}Tc is added to a Technegas generator, with the aim of delivering a dose of approximately 1.35 mCi (50 MBq) to the patient. This equates to a posterior count rate of approximately 2.0–2.5 kcps. The ventilation agent is usually administered with the patient lying supine so as to facilitate uniform distribution of activity throughout the lung fields [60]. Acquisition parameters for the ventilation study are described below in the section on "SPECT: gamma camera hardware, image acquisition and processing".

Perfusion

As with planar imaging, ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA) is generally used to assess perfusion [8]. The distribution of MAA, which is proportional to regional blood flow, will be reduced distal to vascular occlusions in the pulmonary arteries. Thus, it can be considered that perfusion imaging performed in this fashion has an inherent 'amplification' as even a small embolus can cause a large section of lung to be hypo-perfused. The dose of ^{99m}Tc-MAA used is dependent on the ventilation agent and dose used. If a radioactive gas is used, the dose of perfusion agent is typically lower than if a technetium-based ventilation agent is used. This is because the signal from the radioactive gas can be separated from that of the perfusion agent based on the energy level of the emitted photons. Additionally, in the case of ^{81m}Kr, the short half-life results in negligible gas remaining in the lungs during perfusion imaging. If a technetium-based agent is used for both ventilation and perfusion imaging, the typical approach is to 'drown out' the underlying ventilation signal by administering a substantially greater dose of perfusion agent. A perfusion-ventilation dose ratio of at least 3:1 is generally required [8, 60]. At my institution, the standard administered activity of ^{99m}Tc-MAA is 6 mCi (220 MBq). This results in an effective radiation dose for the combined ventilation and perfusion scan of approximately 2.5 mSv. Other authors have proposed the use of lower administered activities, including the EANM procedure guidelines for *V*/*Q* SPECT which recommend an inhaled dose of 30 MBq Technegas and 120 MBq of ^{99m}Tc-MAA [8]. It is advised that each site should review the image quality being acquired on their own local scanners and ensure that studies are optimised. The dose used by each department should be based on factors such as the collimator used, gamma camera sensitivity, processing parameters and the local radiation protection guidelines [60]. Some adjustment to acquisition times and/or administered doses may be required depending on the quality of images being generated.

In the case of pregnant patients, a dose reduction is usually implemented. This can be achieved

by omitting the ventilation scan or by reducing the administered dose of both the ventilation and perfusion agents, usually by half [60]. This will necessitate a longer acquisition time so as to maintain adequate count density thereby generating images of good quality. The CT scan may also be omitted in pregnant patients to reduce breast radiation exposure.

SPECT: Gamma Camera Hardware, Image Acquisition and Processing

To perform SPECT and SPECT/CT imaging, multiheaded hybrid gamma cameras are required [50]. A typical protocol that uses a modern SPECT/CT camera requires 25–30 min of total acquisition time for a ventilation and perfusion dataset and a CT scan of the thorax. At Royal North Shore Hospital, Sydney, our acquisition protocol uses 3° radial steps over 360° with the ventilation study acquired for 12 s per projection and the perfusion study acquired for 8 s per projection [60]. Other centres have reported adequate SPECT quality in as little as 6 min [32]. Although it is possible to perform SPECT with a single-head camera, the acquisition time becomes prohibitive for standard clinical practice, and if SPECT/CT imaging is to be performed, only multi-detector SPECT/CT scanners are commercially available. When using ^{99m}Tc radionuclides, low-energy, high-resolution collimators should ideally be used. These optimise image quality, although at the expense of reduced counts compared with low-energy all-purpose collimator [60]. If a higher-energy radionuclide such as ^{81m}Kr is used for ventilation, a medium energy collimator may be required. A matrix size of 128 × 128 (or greater) is appropriate for today's gamma cameras, although some reports have described using a 64 × 64 matrix with acceptable image quality [29, 50]. With image reconstruction, iterative techniques, such as the ordered-subset expectation-maximisation algorithm (OSEM), are increasingly replacing filtered back projection in many areas of image reconstruction in nuclear medicine [61]. These algorithms permit the inclusion of many physical aspects of the imaging process in the system model, such as attenuation, Compton scattering and resolution degradation. Consequently, they offer better control of signal-to-noise in the event that a study is low in counts [62].

For *V*/*Q* SPECT reconstruction, we use an ordered-subset expectation-maximisation algorithm (eight iterations, four subsets) smoothed with a post-reconstruction 3D Butterworth filter using a cut-off of 0.8 cycles/cm with an order of 9 [60]. Traditionally, corrections for photon attenuation and scatter are not routinely applied to *V*/*Q* SPECT, although they would be required for any quantitative analysis (e.g. individual lobar function, as discussed below).

CT Protocols for Use with SPECT *V*/*Q* Scans

Clinical SPECT/CT systems currently available from manufacturers typically have dual-head scintillation cameras positioned in front of the CT scanner and sharing a common imaging table. The CT scanner quality varies, and the commercial vendors have used two different approaches in recent years with their production of clinical SPECT/CT scanners. The original SPECT/CT imaging approach was to use a low-output, slow-acquisition CT scanner. The Infinia Hawkeye (General Electric Healthcare Systems, Milwaukee, WI) was the first SPECT/CT scanner marketed commercially. Its current iteration comprises a CT scanner consisting of a low-output X-ray tube (2.5 mA) and four linear arrays of detectors which can simultaneously acquire four 5-mm anatomic slices in 13.6 s with a spatial resolution of greater than 3 LP/cm. The slow scan speed (up to 4 min) can be an advantage in regions where there is physiologic motion because the CT image blurring from the motion is comparable to that of the emission scans, resulting in a good match in fused images. This is particularly relevant in lung SPECT/CT where ventilation and perfusion SPECT is acquired during normal tidal breathing [63].

The second approach, which has evolved more recently, has been the development of newer generation hybrid SPECT/CT systems which incorporate diagnostic helical (multi-slice) CT scanners combined with dual-head scintillation cameras. Each of the major commercial equipment vendors now market these devices. Various

configurations are available, with the number of slices ranging from 1 to, the ability to utilise variable tube currents (20–500 mA s), slice thicknesses (0.6–12 mm) and rotation speeds of 0.5–1.5 s [63]. These systems exhibit high contrast spatial resolution with approximately four to five times the patient radiation dose of that from the Infinia Hawkeye system. However, these systems can be used for diagnostic quality CT as well as for attenuation correction and anatomical localisation using low-dose parameters [64]. Given these advantages, these systems now account for most of the SPECT/CT scanners sold commercially today.

While breath holding is typically employed for diagnostic CT studies, this is not feasible during *V*/*Q* SPECT acquisitions, which typically take up to 15 min for each of the ventilation and perfusion scans. Hence, respiratory motion misregistration is a potential problem, and the ideal breathing protocol used for CT in *V*/*Q* SPECT/CT should ensure that the position of the diaphragm on the SPECT scans matches as closely as possible that of the CT images. To reduce misregistration between the SPECT and CT data as much as possible, it has been recommended that CT scans should be acquired during breath holding at mid-inspiration volume, or with the patient continuing shallow breathing during the CT acquisition [65].

The CT scan is typically acquired either between, or after, the two SPECT study acquisitions. The same principles of maintaining identical patient positioning throughout the study applies. It is preferable that the CT scan is not acquired prior to ventilation SPECT as the patient may move significantly during the ventilation procedure thus introducing misregistration artefact when co-registering the SPECT and CT data [63]. Acquisition parameters will vary between manufacturers and CT design.

Image Display and Reviewing

After co-registration of the ventilation, perfusion and CT datasets, the data are best viewed simultaneously in transverse, coronal and sagittal planes on a workstation. Each of the commercial vendors marketing SPECT/CT scanners provide software which can display SPECT/CT images across the range of typical clinical studies performed. There are also third-party solutions available, independent of the commercial SPECT/CT manufacturers. The software programs vary with some allowing for one dataset to be manually aligned with the others, whereas others allow for automatic registration of the studies to each other [66]. As noted above, image registration is best facilitated by reducing, or preferably eliminating, any patient motion between the ventilation SPECT, perfusion SPECT and low-dose CT studies. However, if significant patient motion has occurred between any of the three datasets, some image manipulation and adjustment will be required.

Although images can be printed to film, given the amount of data to be considered, SPECT/CT data are generally best reviewed directly on a workstation. This allows the reporter to interactively examine the linked ventilation and perfusion SPECT studies as well as the CT in each of the three orthogonal imaging planes and to adjust the relative image intensities, especially of fused images. The ability to triangulate defects should be an essential component of any software used to review and report *V*/*Q* SPECT/CT studies. Review of images on a workstation also facilitates the viewing of CT data in different windows so that the lungs, soft tissue and bones can all be reviewed as appropriate. An example of a typical *V*/*Q* SPECT/CT displays in a patient with PE is shown in Fig. 12.4.

In addition to tomographic display of *V*/*Q* SPECT images, further data processing can also be performed. In the case in which ^{99m}Tc is used for both ventilation and perfusion imaging, perfusion data can be corrected for the background activity of the preceding ventilation scan using image subtraction of co-registered datasets [27, 67]. Although this ventilation subtraction enhances perfusion defect contrast, it is not currently in widespread use. The use of SPECT also facilitates novel ways of displaying *V*:*Q* quotient data to assist image reporting. Palmer and coworkers have described a technique where these images can be presented as either 3D surface-shaded images or as tomographic sections in

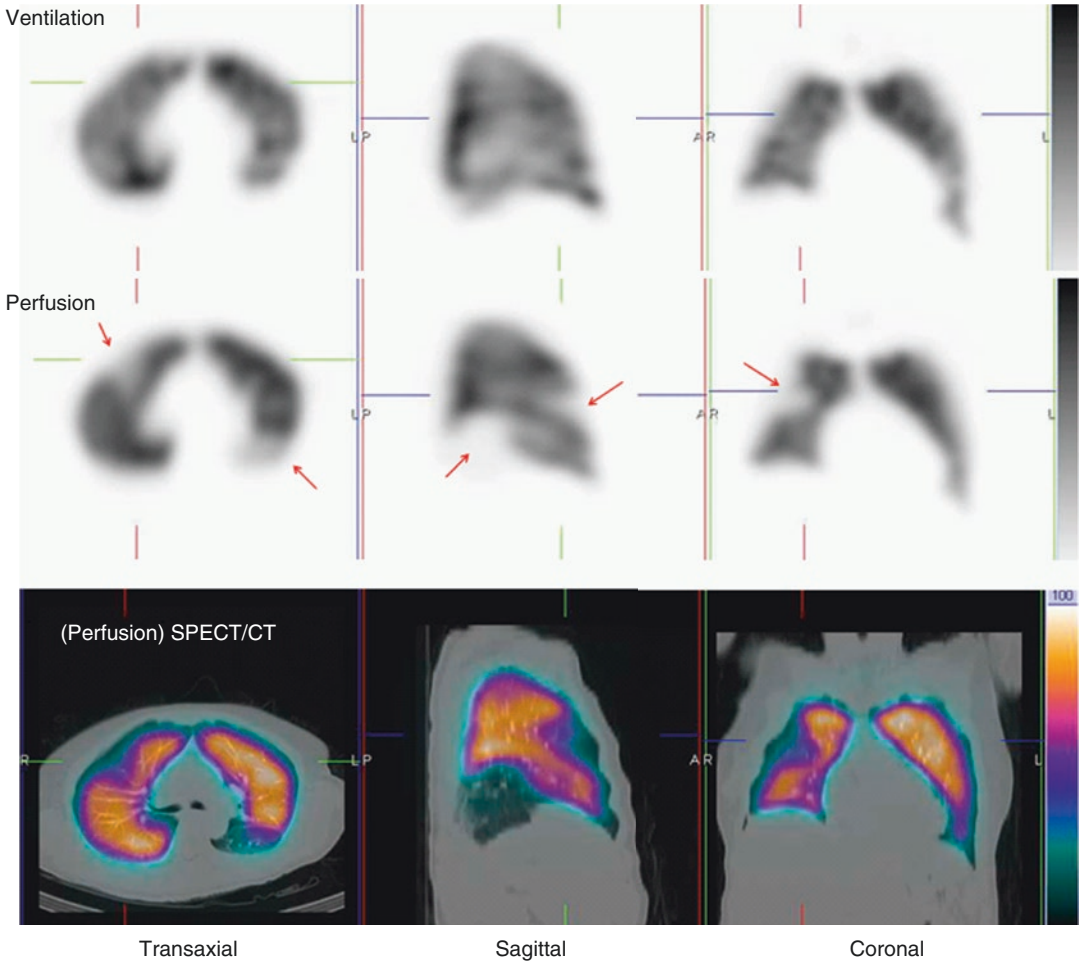

Fig. 12.4 Representative ventilation, perfusion and fused SPECT/CT images in a patient with multiple PE. Several mismatched defects are evident (*arrowed*). There are no underlying structural abnormalities on the CT to account for the perfusion reductions

each of the orthogonal planes [67]. These so-called quotient images can be helpful in facilitating image reporting and are a useful way of demonstrating the location and extent of mismatched defects. Figure 12.5 shows an example of an abnormal SPECT study and corresponding selected *V*:*Q* quotient images in a patient with multiple PE. SPECT imaging facilitates other novel ways of interpreting image data, such as objective analysis by examining the pixel-based *V*:*Q* ratio. Our group has described such an approach, and while not routinely available in commercial processing and display programs, such techniques have the potential to decrease the number of non-diagnostic or indeterminate scans [68, 69].

While there are several ways that *V*/*Q* SPECT studies can be reported, most reporting specialists would use the EANM reporting guidelines for *V*/*Q* SPECT. Originally published in 2009, these guidelines recommend that studies are reported as positive for PE if there is *V*/*Q* mismatch of at least one segment or two subsegments that conforms to the pulmonary vascular

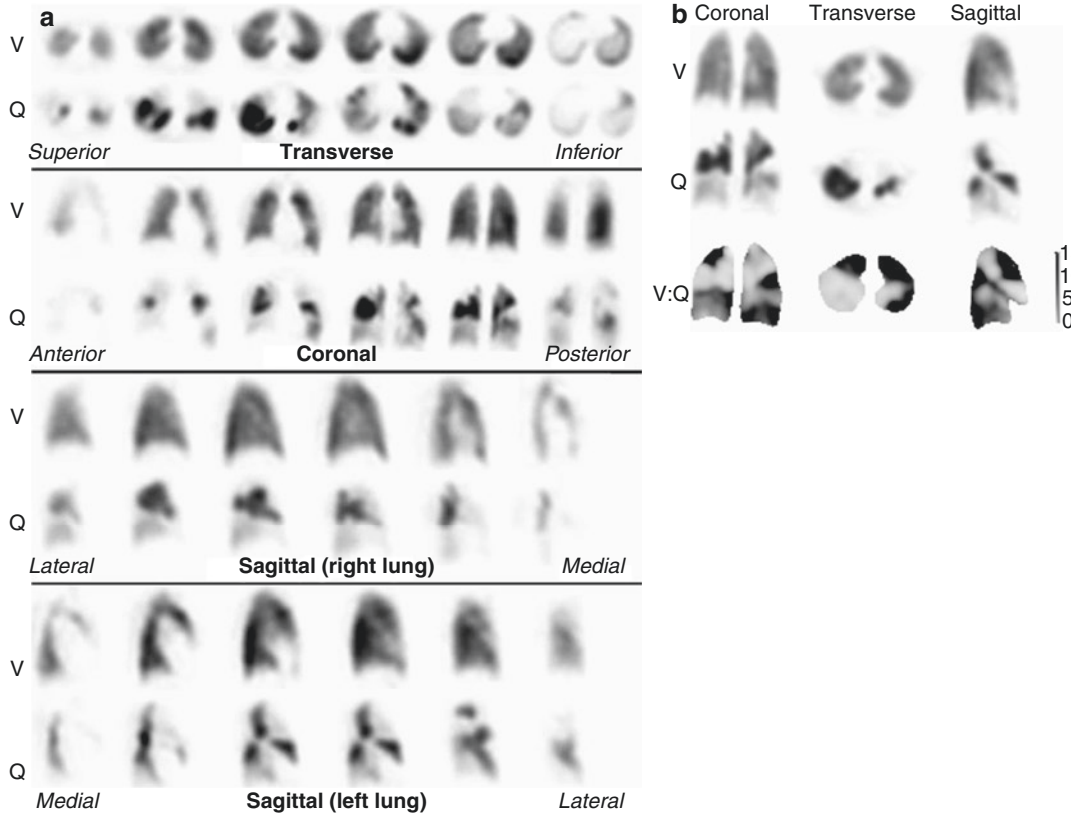

Fig. 12.5 (**a**) Example of a patient with multiple bilateral PE. Ventilation (*V*) and perfusion (*Q*) images are aligned and displayed in transverse, coronal and sagittal planes. Multiple perfusion defects in areas with normal ventilation can be seen. (**b**) Representative coronal, transverse and sagittal ventilation (*V*), perfusion (*Q*) and *V*:*Q* quotient images from the patient shown in (a). Areas of pulmonary embolism correspond to dark areas on the *V*:*Q* quotient images, indicating a high *V*:*Q* ratio value. (Reprinted with permission from Roach et al. [50])

anatomy [8]. These guidelines recommend that the study is considered negative for PE if there is either a normal perfusion pattern conforming to the anatomic boundaries of the lungs; matched or reversed mismatch *V*/*Q* defects of any size, shape or number in the absence of mismatch; or mismatch that does not have a lobar, segmental or subsegmental pattern. Studies are considered to be non-diagnostic for PE if there are multiple *V*/*Q* abnormalities not typical of specific diseases. While these guidelines do not specifically address *V*/*Q* SPECT/CT, the addition of the CT component is likely to help classify the *V*/*Q* SPECT pattern more appropriately, particularly given the information that the CT provides on the anatomy of each individual patient, particularly in relation to the borders of the lungs and segments, the location of the fissures and major vessels and the presence of any associated parenchymal disease. At my institution, we pay particular note of the location of the fissures, as a reduction in perfusion (and to a lesser degree ventilation) corresponding with the fissures is often noted on SPECT imaging. This seems most evident in the posterior aspects of the oblique fissures and is more noticeable on perfusion than ventilation SPECT images. We hypothesise that this is due to fact that alveoli predominate at the pleural surface and there is a relative paucity of pulmonary vessels, with the

pleura supplied by the bronchial circulation. Therefore, when SPECT imaging is performed, there is good distribution of Technegas (which has good peripheral penetration), whereas relatively little ^{99m}Tc MAA accumulates. We consider any linear perfusion reduction seen on SPECT corresponding to the fissures to be artefactual (Fig. 12.6).

While other reporting schema have been proposed for *V*/*Q* SPECT, it is certainly recommended

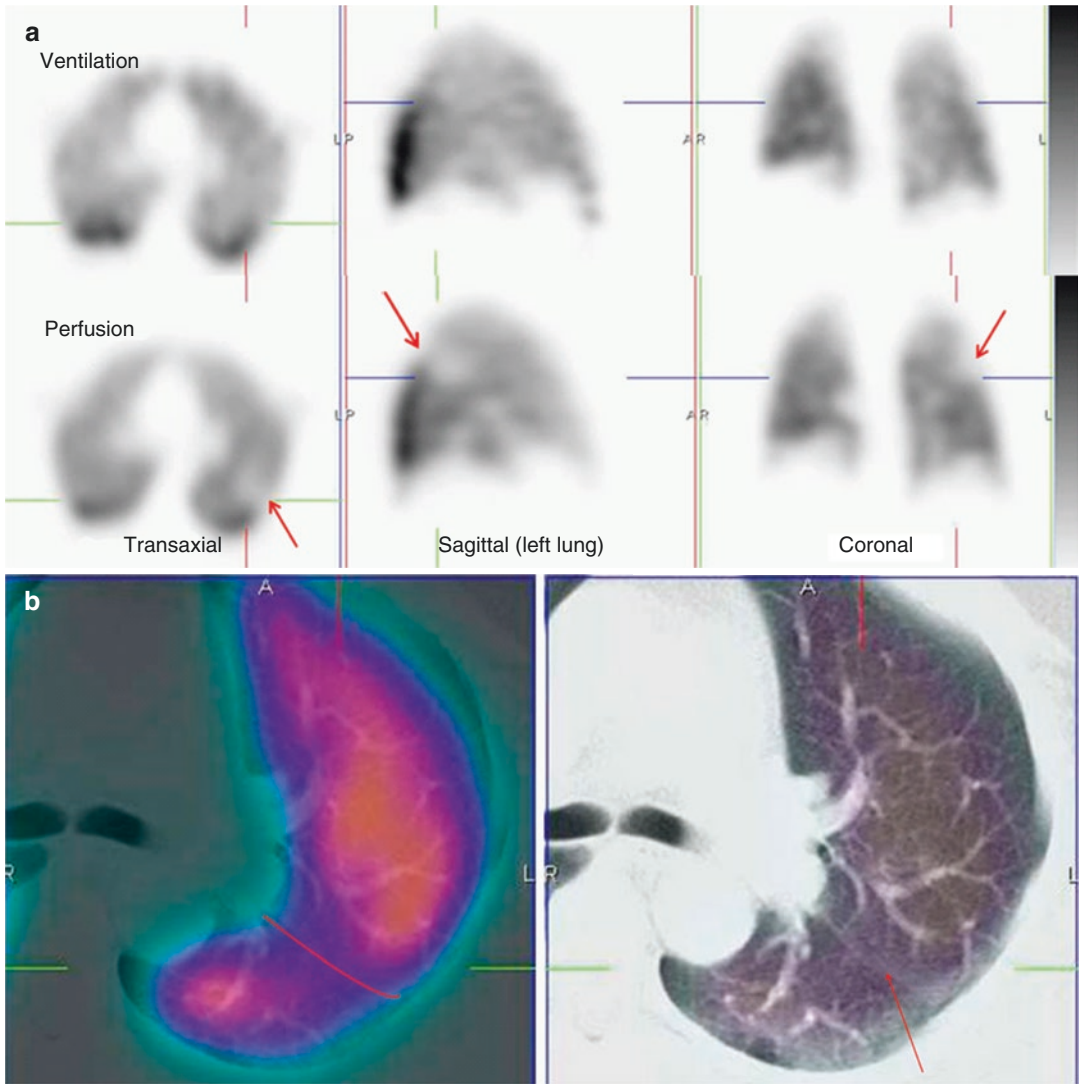

Fig. 12.6 (**a**) Representative ventilation and perfusion SPECT images in a patient with suspected PE show a linear mismatch in the left upper/mid-zone (*arrowed*). This is non-segmental in appearance. (**b**) Fused perfusion SPECT/CT (*left*) and the (unfused) CT (*right*) of the left lung show the perfusion reduction to correspond with the oblique fissure (marked and *arrowed* in *red*). SPECT/CT helps to characterise the cause of SPECT perfusion defects, thereby increasing the specificity of *V*/*Q* scintigraphy. EANM reporting guidelines for *V*/*Q* SPECT recommend that studies are reported as positive for PE if there is *V*/*Q* mismatch of at least one segment or two subsegments provided that it conforms to the pulmonary vascular anatomy. In this case, the defect does not conform to pulmonary vascular anatomy

that the probabilistic reporting used for many years with planar scintigraphy should not be used for *V*/*Q* SPECT/CT [29, 70]. Given the typical binary reporting approach to CTPA reporting, it is important that definitive reports be given for *V*/*Q* SPECT (and *V*/*Q* SPECT/CT) whenever possible so as to keep the test relevant as a primary screening test for patients with suspected PE.

12.7 Clinical Value of *V*/*Q* SPECT/ CT

Several studies have shown that combined SPECT/CT lung scanning improves specificity and overall diagnostic accuracy of lung scintigraphy.

In a preliminary study from my own institution, we performed ventilation (using Technegas) and perfusion SPECT studies as well as a low-dose (30–50 mA s) CT scan in 48 patients with suspected PE [71]. In this series, 16 patients were considered to have had PE based on clinical and imaging findings and follow-up, and of these, 15 patients (94%) had a positive *V*/*Q* SPECT scan. Of the remaining 32 patients without PE, six (19%) had false-positive *V*/*Q* SPECT scans; however, three of these patients (50%) were correctly reclassified as PE negative when the SPECT/CT scan was viewed. Hence the addition of a low-dose CT to *V*/*Q* SPECT improved the diagnostic accuracy of lung scintigraphy by reducing false-positive scan results by 50% in this pilot study. In particular, it was noted that low-dose CT could characterise physiological features such as pulmonary vessels and fissures, as well as pathological features such as consolidation and emphysema that can result in defects on perfusion scintigraphy.

More recently, the improvement in diagnostic accuracy by combining *V*/*Q* SPECT with low-dose CT has been confirmed in a prospective study by a group from Copenhagen, Denmark [31]. In this series of 81 consecutive patients, ^{81m}Kr gas was used as the ventilation agent, and the final diagnosis was based on a composite reference standard comprising ECG, lower limb ultrasound, D-dimer result and 6 months of clinical follow-up. They found that the sensitivities of *V*/*Q* SPECT alone and *V*/*Q* SPECT combined with low-dose CT were identical at 97%. However, the addition of low-dose CT imaging increased the specificity of SPECT scintigraphy from 88% to 100%. The addition of anatomical data demonstrated that mismatched perfusion defects could be attributed to structures such as fissures as well as pathological conditions such as emphysema, pneumonia, atelectasis and pleural fluid. The inconclusive rate for *V*/*Q* SPECT alone was only 5% (four patients); however, this fell to zero when SPECT was combined with low-dose CT imaging. These data do indicate that the combination of *V*/*Q* SPECT can yield very high sensitivity, specificity and overall accuracy in the diagnosis of PE.

These studies have also shown that concurrent low-dose CT is feasible to do in most Nuclear Medicine departments today, is well tolerated by patients (even those that were critically ill) and adds little overall imaging time to the acquisition (typically less than 1–2 min).

Some case examples from my institution showing the value of hybrid SPECT/CT imaging are shown in Figs. 12.7 and 12.8.

12.8 Is the Ventilation Scan Necessary?

Given that fused CT and perfusion SPECT can be readily performed, the need for a ventilation study may be questioned as the information from the CT may be adequate on its own to provide information on structural or airways abnormalities (CTPA + Q study). Several studies have assessed whether a CT scan can replace the need for a scintigraphic ventilation scan in patients with suspected PE. In a study of 30 patients from my own department, we found that 87% of the 96 mismatched perfusion defects seen on *V*/*Q* SPECT occurred in areas where there was no underlying parenchymal abnormality detected on CTPA to account for the perfusion reduction [72]. In the remaining 13% of mismatched *V*/*Q* defects, CTPA revealed corresponding parenchymal abnormalities, mostly subsegmental atelecta-

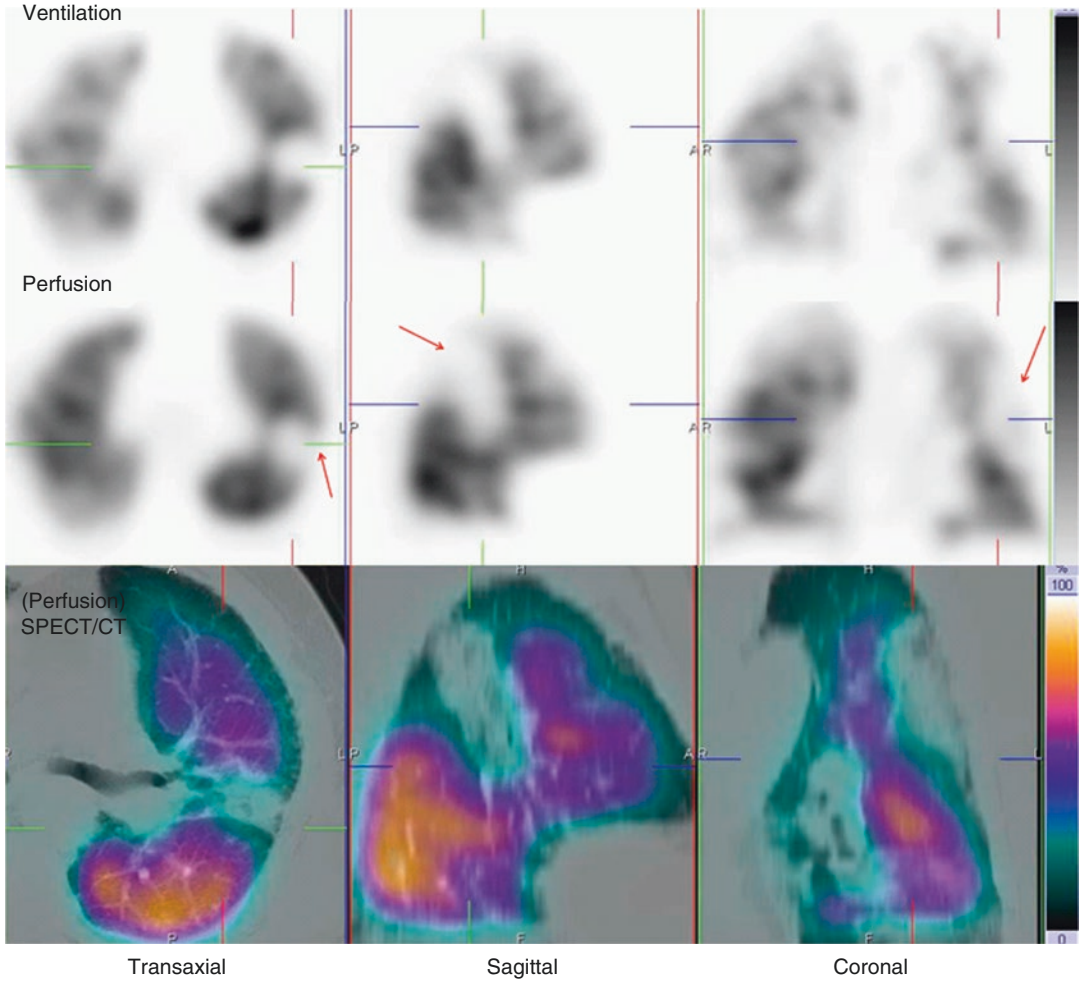

Fig. 12.7 Representative ventilation, perfusion and SPECT/CT images in an 84-year-old male with dyspnea. A large matched defect is evident on SPECT in the left upper and mid-zone (*arrowed*). This corresponds with extensive consolidation demonstrated on the SPECT/CT images. This is seen to lie anterior to the oblique fissure

sis, which correlated with the areas of perfusion reduction on the SPECT study. Of note, the extent of the parenchymal abnormality on CT in these mismatched *V*/*Q* defects was significantly smaller than the extent of perfusion reduction. Twelve mismatched perfusion defects on CTPA/Q were identified as false positives with matched defects evident on the *V*/*Q* images. These defects were seen in two asthmatic patients, presumably related to air trapping which has a similar CT appearance to hypo-attenuation from hypo-perfused lung distal to PE.

In the Danish study described above, results were also reported for the use of perfusion SPECT alone (i.e. ventilation omitted) combined with low-dose CT [31]. In this series, the sensitivity of this approach was high (93%), but the specificity fell to only 51% with the accuracy reported at 68%. In addition to the high false-positive rate, there was also a high non-diagnostic rate using this approach (17%).

Thus, while the literature remains limited, it does appear that omitting the ventilation component of the SPECT study will compromise accuracy, and, in particular, the specificity of *V*/*Q* SPECT scintigraphy, by producing a higher false-positive rate. The question of whether ventilation scans can be omitted in the evaluation of

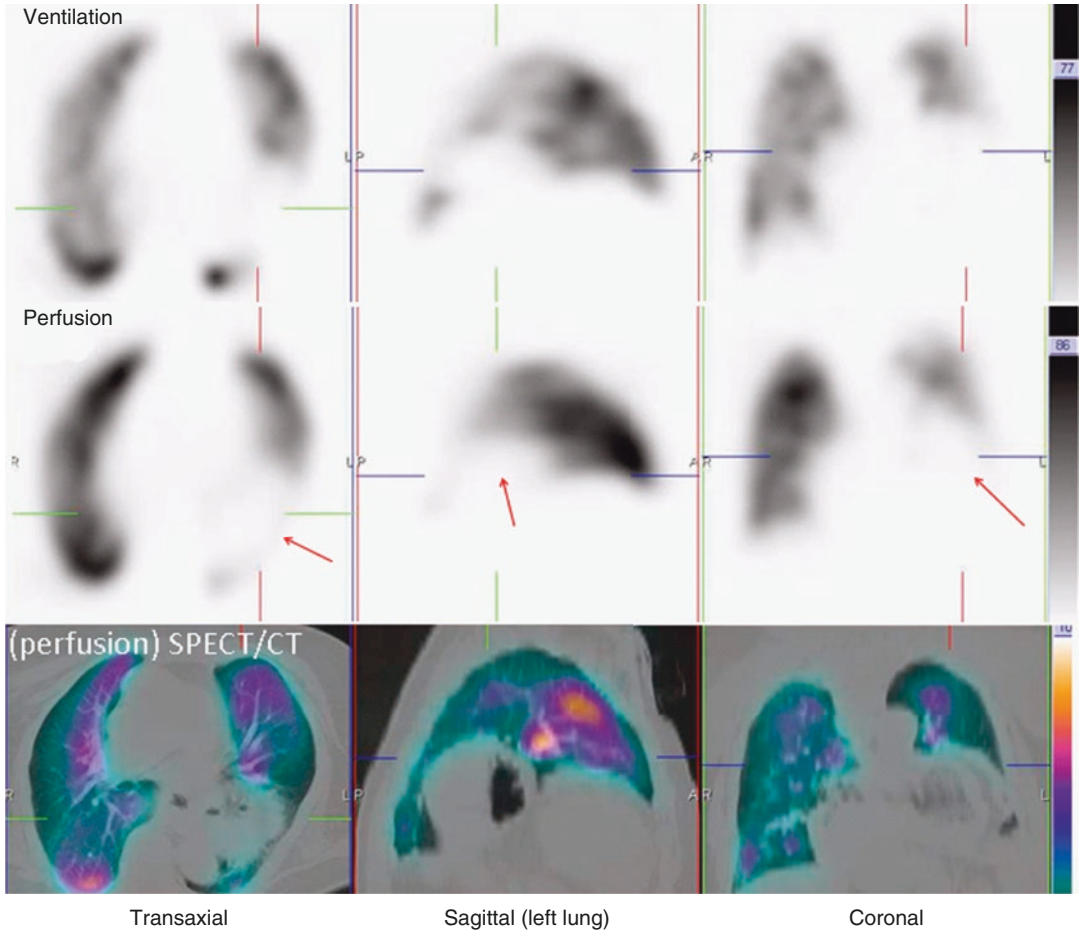

Fig. 12.8 Representative ventilation, perfusion and SPECT/CT images in a 63-year-old male with chest pain. A large matched defect is evident on SPECT in the left lower zone (*arrowed*). This corresponds with a large hiatus hernia on the SPECT/CT images

patients with suspected PE, has come under particular focus during the COVID-19 pandemic. Many centers, and professional associations, advised against the use of ventilation studies in patients with known, or suspected, COVID 19 due to the potential staff infection risks from the aerosol generating procedure [73–75]. While some centers ceased performing ventilation scans altogether, others (including our own) opted for a more selective approach. In patients in whom COVID-19 was not confidently excluded, we and others would perform a perfusion SPECT scan. If normal, PE is confidently ruled out. If there were perfusion abnormalities seen, a low dose CT would be done. If this showed physiological or pathological findings that could account for the areas of perfusion reduction, then PE could be confidently excluded. If not, a ventilation scan would generally then be required, with the operators taking appropriate safety precautions, including full PPE. Due to the requirement for decay of the perfusion scan, a delay of several hours at least would generally be required before the ventilation scan could be attempted. Some groups advocated a reversal of the usual order of scanning, i.e. a low dose perfusion followed by a higher dose ventilation scan to obviate the need for any delay [76]. However in our center, we found that image quality was adversely impacted by this approach, hence would recall the patients

several hours later, or the next day, for the ventilation component when it was required. The downside of this approach overall however is a delay in diagnosis in some patients. Nevertheless, we found that the combination of perfusion SPECT +/- low dose CT could rule out PE in the majority of patients referred to our department with suspected PE.

12.9 How Does *V/Q* SPECT/CT Compare with CTPA?

Multi-detector CTPA has evolved to the point where it is now widely used as the primary imaging investigation in patients with potential PE [4, 22]. While highly specific, its sensitivity is not perfect [77]. With the multi-detector CT scanners used in the large PIOPED II study, CTPA had a reported sensitivity of 83%, indicating that emboli were missed in one of every six patients [77]. Although the accuracy of CTPA appears to be high in cases in which the scan result is in keeping with the pretest clinical suspicion, this is not true of cases in which there is discordance between scan results and clinical likelihood.

CTPA, because of its anatomical nature, has an advantage of potentially diagnosing other pathologies, such as pneumonia or aortic dissection. However, this is at the expense of exposing the patient to increased radiation (something that is particularly concerning in the case of young women) and to the potential risks of contrast administration, such as allergy or nephrotoxicity [78, 79]. *V/Q* SPECT has been shown to be better able to quantify the extent of perfusion abnormalities (which may be valuable in guiding treatment decisions) and can assess reperfusion after PE, something not easily done with CTPA [70].

Overall, there is relatively little literature directly comparing SPECT *V/Q* and CTPA. In 2004, Reinartz and co-workers compared the performance of *V/Q* SPECT (using Technegas) with multi-detector (4-slice) CTPA [29]. In their series of 83 patients, they determined that SPECT was more sensitive (97% versus 86%) but less specific (91% versus 98%) than CTPA. Both modalities had comparable overall accuracy (94% versus 93%). In another series from Australia, Miles and co-workers prospectively compared *V/Q* SPECT with CTPA performed using a 16-slice scanner in 100 patients with suspected PE [80]. They also concluded that the overall accuracy of both examinations was comparable, suggesting that SPECT *V/Q* and CTPA could be used interchangeably. They concluded that SPECT *V/Q* has potential advantages over CTPA in that it was feasible to perform in more patients and had fewer contraindications, a lower patient radiation dose and fewer non-diagnostic findings. This study supports the notion that each of these studies has its advantages over the other. In the case of *V/Q* SPECT, its advantage is a high sensitivity, whereas CTPA has the advantage of a high specificity. Given that the literature directly comparing *V/Q* SPECT (and *V/Q* SPECT/CT) is limited, it would be desirable to perform a prospective multicentre trial to answer the question. However, this would be difficult for several reasons [70]. Firstly, evaluating the clinical effectiveness of rapidly evolving health technologies is problematic. In this case, both CT and *V/Q* SPECT technology continue to develop, and therefore, any published direct comparison inevitably reports on previous-generation technology. Secondly, a robust 'gold standard' is lacking for the diagnosis of PE resulting in the *V/Q* scan and/or CTPA being pivotal in determining the presence or absence of disease [27, 36]. Thirdly, ethics committees may, quite correctly, question the need to subject individuals to the radiation exposure from both *V/Q* SPECT and CTPA, especially in individuals without PE. Lastly, the time interval between the two studies being performed could result in embolus fragmentation, movement or lysis, thus affecting the perceived accuracy of each modality.

As stated above, the challenge for the *V/Q* scan is that ventilation/perfusion mismatch is not specific for PE, and in some cases of PE (e.g. in the case of pulmonary infarction), matched patterns can occur. For this reason, the anatomical information provided by a chest X-ray has been considered essential in the interpretation of *V/Q* scans. With the advent of SPECT/CT scanners, the integration of anatomical information from the CT with the functional information from SPECT is now feasible and

should increase the specificity of *V/Q* scanning. Other than PE, *V/Q* mismatch can be seen with conditions such as radiation therapy-induced changes and extrinsic vascular compression from conditions such as neoplasm and mediastinal adenopathy [8, 33]. Each of these can be detected with low-dose CT. Furthermore, matched changes can be seen with non-embolic aetiologies such as pneumonia, abscess, pleural or pericardial effusions, malignancy and pulmonary infarction [5, 6, 36, 37]. Once again, each of these should be evident if a CT, even if done at a 'low' diagnostic dose, is performed.

In the Danish study of *V/Q* SPECT/CT mentioned earlier, the authors directly compared the accuracy of current generation CTPA with *V/Q* SPECT/CT [31]. They found that SPECT and SPECT/CT both had higher sensitivity for the detection of PE than CTPA (done on the same hybrid machine equipped with a 16 slice CT scanner). Although CTPA had a specificity of 100%, its sensitivity was only 68%. The superior sensitivity of *V/Q* SPECT compared with CTPA has been demonstrated in other studies and raised questions about the use of CTPA as the primary imaging study for the detection of PE in clinical practice. The sensitivity of CTPA in this study is lower than the 83% noted in the large multicentre PIOPED II study, a figure that led the investigators of that study to conclude that additional information would be required to exclude PE due to the significant false-negative rate of CTPA [77].

Other concerns with the use of CTPA noted by the Danish authors include the risk of complications related to intravenous contrast (a factor which accounted for 50% of the 96 patients excluded from the study) and its high thoracic radiation dose. The use of iodinated contrast administration is a significant disadvantage of CTPA with reports of about 3% of patients experiencing some type of immediate contrast reaction and 0.06% requiring treatment [81]. Contrast-induced nephropathy is reported in 1–3% of patients with CTPA [82]. This compares with scintigraphy where side effects are all but non-existent [83].

High radiation exposure is another limitation of CTPA. Breast radiation dose from CTPA, which has been estimated between 10 and 70 mSv, is a particular concern in younger women [84–86]. By comparison, the breast radiation dose from the *V/Q* scan is in the order of 0.28–1 mSv [87]. While CTPA has overall radiation doses reported in the order of 8–20 mSv, the levels received from a low-dose CT study performed in conjunction with a lung SPECT study is much lower [35, 83–85]. Gutte and co-workers estimated that the radiation dose from their 20 mAs CT studies was approximately 1 mSv [31]. In my institution, using similar CT parameters (20–50 mA s), we have estimated radiation doses from the CT in the order of 1–2 mSv. This compares favourably with the 2–2.5 mSv from the *V/Q* scan itself and is well below the levels received from a diagnostic CTPA [83].

A further issue for CTPA is the rate of technical artefacts that can occur, primarily due to poor contrast opacification of the pulmonary arteries and motion artefacts, but also body habitus of some patients which can affect image noise [88]. Indeterminate study rates due to technical factors have been estimated at between 5% and 11% [30, 89, 90]. In pregnant patients, the rate is even higher, and it has been shown that as many as one-third of CTPA procedures performed during pregnancy are technically inadequate, even with 64-slice CT scanners [22, 91]. This is thought to be attributable to a greater pressure in the inferior vena cava during pregnancy. As a result, repeat studies are not infrequently performed to try to optimise the diagnostic accuracy of the study, resulting in doubling of the radiation dose. By comparison, technical artefacts should not impact *V/Q* SPECT/CT, and literature suggests that the test has a very high sensitivity and specificity; hence additional imaging should only rarely be required [31].

Both CTPA and *V/Q* SPECT have their strengths and weaknesses (listed in Table 12.1), and the test selected for any individual patient will vary according to patient factors (especially age and gender but also the presence of coexisting lung disease) as well as institution factors, including availability and local expertise. Given its excellent sensitivity and superior safety and radiation exposure profile, there is a strong argument that *V/Q* SPECT should be favoured as the initial screening test for PE [22]. The addition of a low-

Table 12.1 Summary of the advantages and limitations of CTPA and *V/Q* SPECT/CT

	CTPA	*V/Q* SPECT/CT
Sensitivity	Moderate	High
Specificity	Very high	Slightly lower
Accuracy with abnormal radiograph	Unaffected	Sometimes affected
Provides other diagnoses	Frequent	Frequent
Incidental findings require follow-up	Frequent	Less frequent
Radiation dose	High	Lower
Possible allergic reaction	Yes	No
Risk of contrast nephropathy	Yes	No
Technical failure rate	Higher	Rare
Availability (especially out of routine hours)	High	Usually lower
Accuracy in pregnancy	Lower	High
Accuracy in chronic PE	Lower	High
Performance in obstructive lung disease	Unaffected	May be affected
Role and accuracy in follow-up	Limited	Very good

dose CT further strengthens this argument as it addresses many of the advantages cited for CTPA (i.e. ruling out other conditions, such as pneumonia, abscess, pleural or pericardial effusions, malignancy). While diagnostic CT with intravenous contrast is needed to evaluate certain conditions, such as aortic dissection or coronary artery disease, the advent of *V/Q* SPECT/CT further enhances the overall diagnostic ability of *V/Q* scintigraphy, thus allowing centres to choose either CTPA or V/Q SPECT to assess suspected PE with either study being of generally high sensitivity and specificity. In the choice of which one to choose in specific patients, could be based on factors such as patient age, sex, contrast risk and local availability as well as operator and reporter expertise.

12.10 Clot Localisation

The addition of the CT data to SPECT *V/Q* also provides interesting insights into the accuracy of clot localisation on *V/Q* SPECT. As anatomical information is sparse when *V/Q* SPECT data is interpreted, assumptions must be made about the lung anatomy in each patient. Segmental lung maps (based on normal anatomical references) are typically utilised to assist reporting specialists in localisation of perfusion defects; however, individual anatomy varies, and in the case of PE, the lungs are frequently abnormal, with coexistent lung pathologies, such as atelectasis and pleural effusions, often seen [50, 92]. SPECT/CT imaging allows for segmental anatomy to be accurately determined in each individual patient, and this may facilitate more accurate localisation of clots into the correct lung segments. In a study from my centre of 30 patients with positive *V/Q* SPECT studies in which a normal lung tomographic segmental lung chart was used as a guide to localise segments, 20% of defects were assigned to the incorrect anatomical lung segment [93]. Inaccurate localisations were most commonly seen in the mid-zone segments and were most noticeable in patients with evidence of lower lobe volume loss on CT (Fig. 12.9). The fact that anatomical localisation of perfusion abnormalities on *V/Q* SPECT can be improved by adding CT data in a significant number of patients may be relevant in patients with non-diagnostic *V/Q* SPECT studies, many of whom would have a CTPA done subsequently to confirm the findings of the SPECT study. If the reporting radiologist is directed to specifically analyse the incorrect lung segment based on the assumptions of the patient's likely anatomy using the *V/Q* SPECT appearances, the sensitivity and accuracy of the study are reduced.

12.11 Consolidative Opacities

While *V/Q* mismatch is the well-described hallmark of PE, pulmonary infarction can result in matched changes of ventilation and perfusion, a

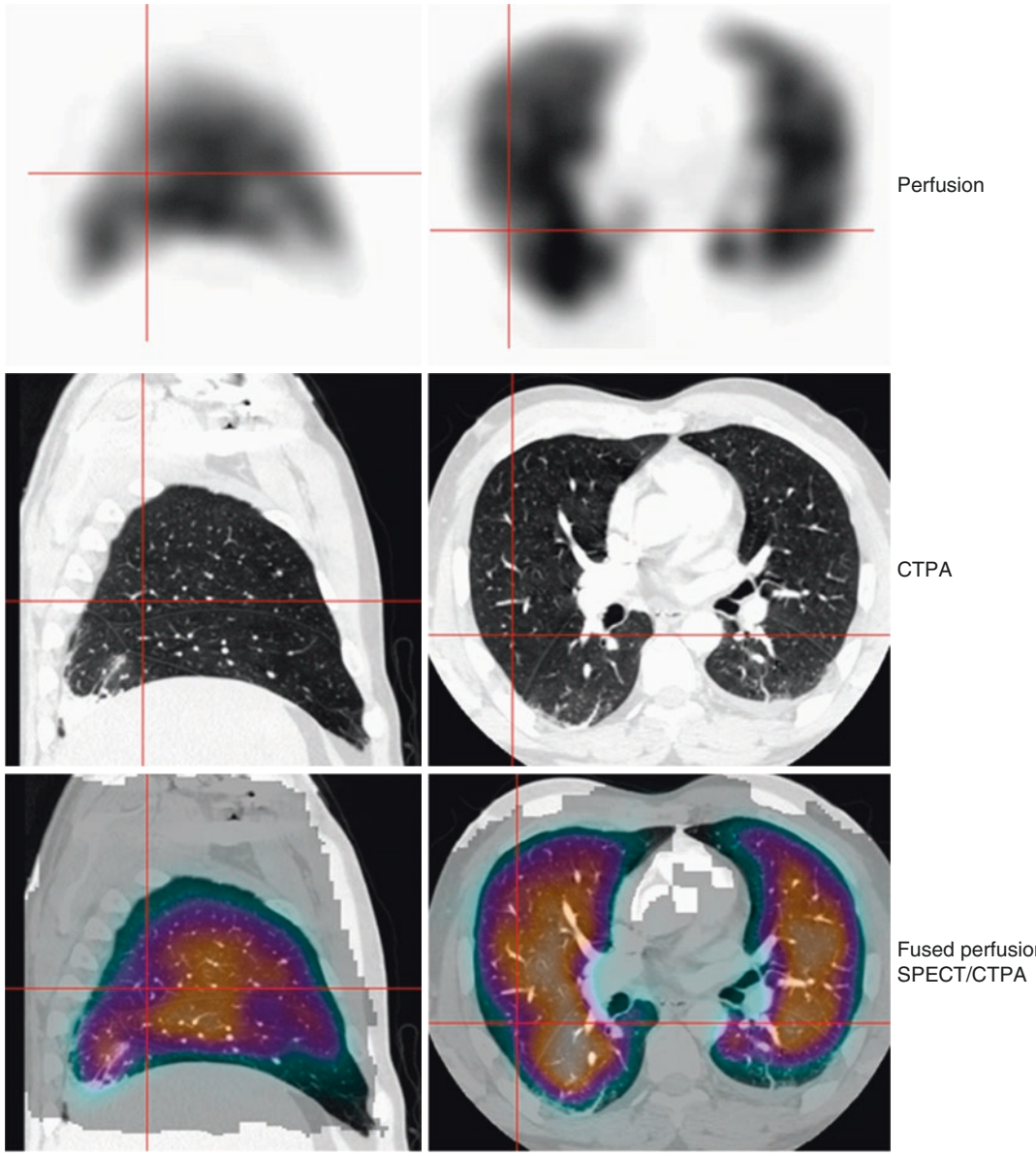

Fig. 12.9 Sagittal and transaxial perfusion, CTPA and fused perfusion SPECT/CTPA slices in a patient with PE. Based on normal lung charts, the defect shown (*red cross hair*) was localised to the superior segment of the right lower lobe. The CTPA demonstrates volume loss in the lower lobe due to atelectasis. The oblique fissure is displaced posteroinferiorly. When the two studies are fused, the perfusion defect localises to the posterior segment of the right upper lobe in this patient. Combining the SPECT study with the patient's CT can improve the accuracy of segmental localisation. (Reprinted with permission from Roach et al. [41])

pattern not usually associated with the diagnosis of PE. While determining the aetiology of pulmonary consolidation can be difficult, *V*/*Q* SPECT/CT may provide useful information which may help to characterise the underlying pathological process. In a study of 38 patients in which gated SPECT was performed, Zaki et al. found that consolidative opacities secondary to PE preferentially occur peripherally, whereas inflammatory disease-induced lesions tend to be seen preferentially at the

proximal portion of defects [94]. This study supports the premise that PE, and its sequelae including pulmonary infarction, typically affects the peripheral aspects of the lungs. When *V*/*Q* SPECT/CT demonstrates matched reductions more proximally, non-embolic causes may be more likely.

12.12 Barriers to Implementation of *V*/*Q* SPECT/CT

While the advantages of *V*/*Q* SPECT/CT studies compared with traditional planar imaging, SPECT-only scintigraphy and CTPA have been detailed above, the technique is still not routinely performed in many nuclear medicine departments. Surprisingly, in an era where SPECT (and now SPECT/CT) are routinely used in many areas of nuclear medicine, lung scintigraphy is still done using planar imaging in many part of the world, including in much of the United States [41]. There are several reasons why the transition to *V*/*Q* SPECT and hence *V*/*Q* SPECT/CT has not occurred.

Firstly, there is the lack of an ideal ventilation agent in some countries. As detailed above, Technegas is well suited to *V*/*Q* SPECT, and while it would ideally be used for *V*/*Q* SPECT/CT studies, it is not commercially available in some countries, including the United States. An alternative is to use ^{99m}Tc DTPA aerosols. In a direct comparison of Technegas and ^{99m}Tc DTPA aerosol in 63 patients, Jogi et al. showed that the SPECT images obtained using either ventilation agent were comparable, although in patients with obstructive lung disease, Technegas was clearly superior due to its better peripheral penetration [54]. While Technegas ideally would be used for ventilation SPECT imaging, this study does support the use of aerosols as an alternative should Technegas not be available locally.

Secondly, there is a wide body of literature describing the accuracy as well as the strengths and limitations of planar *V*/*Q* imaging [21, 34, 95]. Several large multicentre trials have been performed in numerous countries and the various reporting criteria used have been well established and periodically refined to help optimise the overall accuracy of the test [35, 96, 97]. A normal planar lung scan has a very high negative predictive value, and for reporting specialists with many years of experience, there may be the belief that there is little to be gained by making the transition to SPECT imaging. It should, however, be remembered that the published literature, as detailed above, consistently demonstrates improvements in sensitivity, specificity and reproducibility with SPECT imaging [8, 29, 70]. This is important in the era of CTPA which has increasingly supplanted the planar *V*/*Q* scan as the diagnostic imaging test of choice in many centres around the world, most noticeably in the United States [4, 6]. To restrict *V*/*Q* scintigraphy to a 2D methodology is, in many ways, analogous to a radiologist persisting with a chest X-ray for imaging the thorax and lungs, rather than transitioning to CT scanning. While reporting specialists, especially during the transition period, may prefer to acquire both planar and SPECT images on the same patient, this is problematic due to the amount of imaging time that would be required. As many patients would be unable to tolerate the time required (over 60 min), this is not feasible for many patients, especially those that are ill, dyspneic or elderly. Fortunately, planar images can be generated from SPECT data using several approaches. While we have described a technique using a reprojection method [98], many of the commercial vendors offer a simpler approach using an 'angular summing' method [29]. For those used to viewing planar images, this can be useful in the transition from planar imaging to SPECT-only imaging and may prove useful even beyond this point to give a general, familiar and rapid view of the lungs for quick evaluation.

Thirdly, For Nuclear Medicine specialists, particularly those not trained in cross-sectional anatomy, visualisation of the lungs in 3D is a challenge compared with the 2D approach of planar *V*/*Q* imaging. This requires knowledge of the cross-sectional anatomy of the lungs as well as the 3D appearances of lung segments, fissures, major vessels and airways as well as other intrathoracic structures. However, with the diffusion of PET/CT and SPECT/CT worldwide, nearly all specialists reporting Nuclear Medicine studies would increasingly be visualising the thorax in 3D, thus a shift to

V/*Q* SPECT, and *V*/*Q* SPECT/CT imaging should be less of a challenge to most specialists today than previously. In addition, cross-sectional imaging atlases and computerised programs are now commonly located in most Nuclear Medicine reporting rooms to further aid in this transition.

Finally, some reporters may be under the misconception that SPECT, and SPECT/CT, imaging takes significantly longer to perform than traditional planar imaging or is more difficult for technologists to perform. This is not the case. Many centres perform SPECT imaging faster than can be done with traditional six or eight view planar imaging [29, 32]. At my institution, where dual-headed SPECT/CT scanners are used, a typical acquisition protocol takes about 25–30 min [50]. Other centres report slightly faster image acquisition times with images produced of high diagnostic quality. For instance, the group from University Hospital in Lund, Sweden, acquired ventilation studies (using ^{99m}Tc-DTPA) in just under 11 min and perfusion images in just under 6 min [27]. The group from Centre Hospitalier Universitaire de Sherbrooke in Quebec, Canada, acquired their data in similar times having published studies using 12 min acquisition times for ventilation (using Technegas) and 6 min for perfusion utilising a dual-head scanner [32]. With current generation multi-slice CT scanners, the addition of a 'low dose' CT scan adds only 1–2 min to these times. Thus, image acquisition times in the range of 20–30 min are routine today with *V*/*Q* SPECT/CT. For technologists used to performing planar *V*/*Q* scans, the transition to SPECT is welcomed. The multiple repositioning of the detectors and patient arms required with planar imaging is no longer required, resulting in easier data acquisitions for the technologists. At Royal North Shore Hospital, the technologists now much prefer SPECT (and SPECT/CT) imaging for *V*/*Q* scintigraphy and would only choose to perform a planar study in unusual circumstances, such as for a patient who could not undergo SPECT imaging, e.g. if they were unable to lie supine on the scanning bed. With SPECT/CT scanning now standard in many areas of nuclear medicine, *V*/*Q* SPECT/CT acquisitions should be a quite routine procedure for nuclear medicine technologists.

12.13 Thrombus Imaging

Over the last few decades, there have been numerous attempts to develop radiolabelled thrombus imaging agents to assess deep venous thrombosis and PE. While none are yet in routine clinical practice, these agents allow differentiation of old clots from new and allow imaging of acute thrombus in any part of the body, most commonly in the legs and the lungs. While thoracic SPECT imaging has been performed using such agents in recent years, the lack of background activity complicates exact localisation of clot within the pulmonary vascular tree [99]. Hybrid SPECT/CT would be ideally suited for use with such agents, and this is another

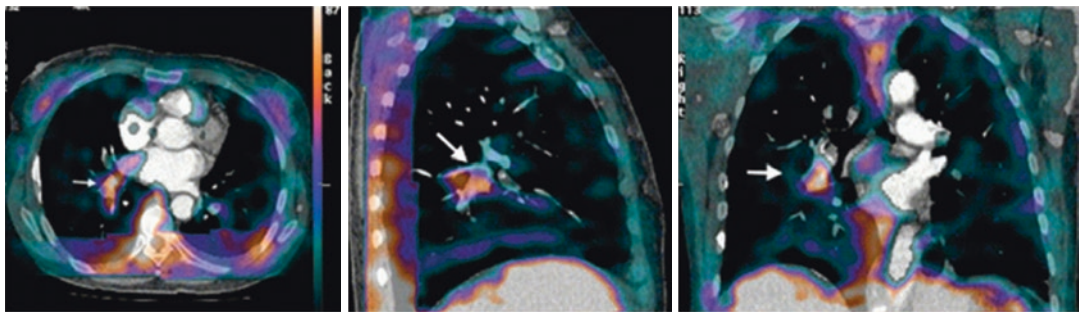

Fig. 12.10 Fused SPECT/CT images of acute PE after administration of ^{99m}Tc-labelled anti-d-dimer antibody fragments. The thrombus (*arrowed*) corresponds to an intravascular contrast-filling defect on the CTPA. (Reprinted with permission from Morris [99])

promising application in patients with suspected PE which may develop in the future (Fig. 12.10).

12.14 *V/Q* SPECT/CT: Role in Applications Other than PE

V/Q SPECT/CT is finding increased utility in a number of other conditions beyond its use in the diagnosis and management of PE. These include allowing optimal selection of radiotherapy fields for lung cancer therapy and the preoperative quantification of lung function prior to resection [63].

12.14.1 Radiotherapy Treatment Planning

In the treatment of patients with lung cancer, literature suggests that administering a higher dose of external beam radiotherapy is associated with improved survival [100, 101]. However, the dose is limited due to the sensitivity of normal lung and the development of radiation pneumonitis and fibrosis [102–105].

Patients with lung cancer requiring radiotherapy may have areas of healthy lung included in the radiotherapy fields. Considering that most of these patients will have a significant cigarette smoking history, they often begin treatment with marked impairment of their respiratory function and can ill afford further reductions in their lung function. Acute radiation toxicity occurs in up to 10% of patients receiving radiotherapy to the lungs. Long-term reductions also occur due to the development of radiation fibrosis. These two pathologies often overlap but both may progress independently of each other. Following radiotherapy, a decline in lung function has been demonstrated on respiratory function testing and on long-term sequential perfusion scanning. These changes peak in the period approximately 12–18 months after the radiotherapy and are dose dependent [106, 107]. Baseline perfusion scans can be used to identify which portions of the lungs have the most preserved function. It has been shown that perfusion scans can be used to modify radiotherapy fields in patients thereby affecting the total dose patient received by sparing perfused lung [108–111]. McGuire and coworkers report on an approach that reduced the $F_{(20)}$ and $F_{(30)}$ (the amount of lung receiving 20 Gy or 30 Gy, respectively) values by 16.5% and 6.1% compared to traditional therapy planning [112]. Ventilation SPECT can also be used to plan therapy (Fig. 12.11) [113]. Evidence that these manoeuvres alter long-term lung function remains sparse.

12.14.2 Lung Reduction Surgery Planning

In patients being considered for lung reduction surgery, perfusion imaging is often used to assess lobar function and to estimate the impact of lung surgery on the patient's pulmonary status. Using planar *V/Q* scintigraphy, an assessment of relative regional lung function can be made by dividing the lungs into various zones (typically upper, middle and lower thirds) and determining the relative contribution of each region to overall ventilation and perfusion. Due to overlap of pulmonary lobes and segments and differences in individual patient lung anatomy, such an approach is crude at best and lacks accuracy. The advent of hybrid SPECT/CT allows a similar approach being undertaken in 3D, and when combined with each individual patient's segmental anatomy (determined from their CT scan), a much more accurate assessment of lobar or segmental lung function can be derived (Fig. 12.12). In patients with non-small cell lung cancer, this approach has been shown to play a valuable role in predicting postoperative lung function following lung resection and is highly accurate as a predictor of postoperative FEV1 [114, 115].

One series reported a perfusion ratio of upper to lower lung and demonstrated that poor perfusion to the upper lobes was correlated with the decision to perform lung reduction surgery based on CT assessment [116]. In the US National Emphysema Treatment Trial, perfusion imaging was discontinued in 2001 as it did not add further prognostic

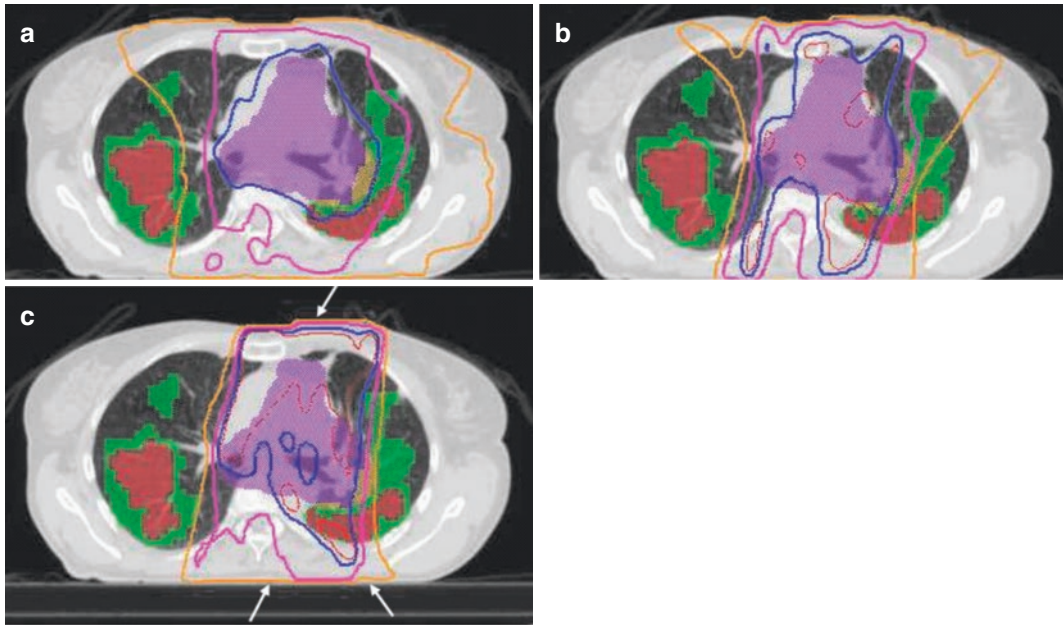

Fig. 12.11 These three transaxial images demonstrate ventilation as a percentage of maximum ventilation with green representing 50% (vv50) of maximum and red 70% or more (vv70). Isodoses of 66.5 Gy, 45 Gy and 20 Gy are shown as blue, pink and orange lines, respectively (white arrows). Image (**a**) has been calculated without reference to *V*/*Q* data, (**b**) using nine equally spaced beams to avoid vv50 and vv70 regions and (**c**) using a subset of three beam angles also avoiding vv50 and vv70. In this example, there is considerable reduction in the amount of well-ventilated lung being irradiated in both (**b**) and (**c**). The central *purple area* represents the planning target volume (PTV). (Reprinted with permission from Munawar et al. [113])

information to that obtained by other measures. There were a number of limitations to the original technique, specifically, overlap of the anatomic structures being analysed. SPECT scintigraphy, particularly with CT co-registration, allows for accurate segmentation of the lungs with lobar estimates of function made possible [42]. Whether this is of any additional benefit remains to be assessed.

12.15 Further Uses

V/*Q* SPECT/CT has further potential in assessing the physiologic basis of lung disease, both as a clinical and research tool. *V*/*Q* SPECT scintigraphy has been used to assess changes in ventilation after lung reduction surgery [117, 118], inhomogeneity of ventilation in emphysema patients [119], regional changes of ventilation and perfusion in asthma [120, 121] and the degree of lung perfusion impairment in patients with pulmonary arteriovenous fistulae [122] and in estimating regional lung function in patients with interstitial pulmonary disease [123]. Technegas SPECT has been analysed using three-dimensional fractal analysis to quantify heterogenous distribution of tracer [124]. The use of ventilation and perfusion imaging as an investigative tool for lung physiology is of increasing interest, particularly in evaluating the extent of airways closure in patients with airways disease [115] (Fig. 12.13). *V*/*Q* SPECT/CT would be well suited to identifying and quantifying the location and extent of non-ventilation in patients with airways disease. By comparing ventilation SPECT with a low-dose CT, it can be determined which areas of lung have non-ventilation (or malventilation) due to underlying emphysema as opposed to airways constriction [115].

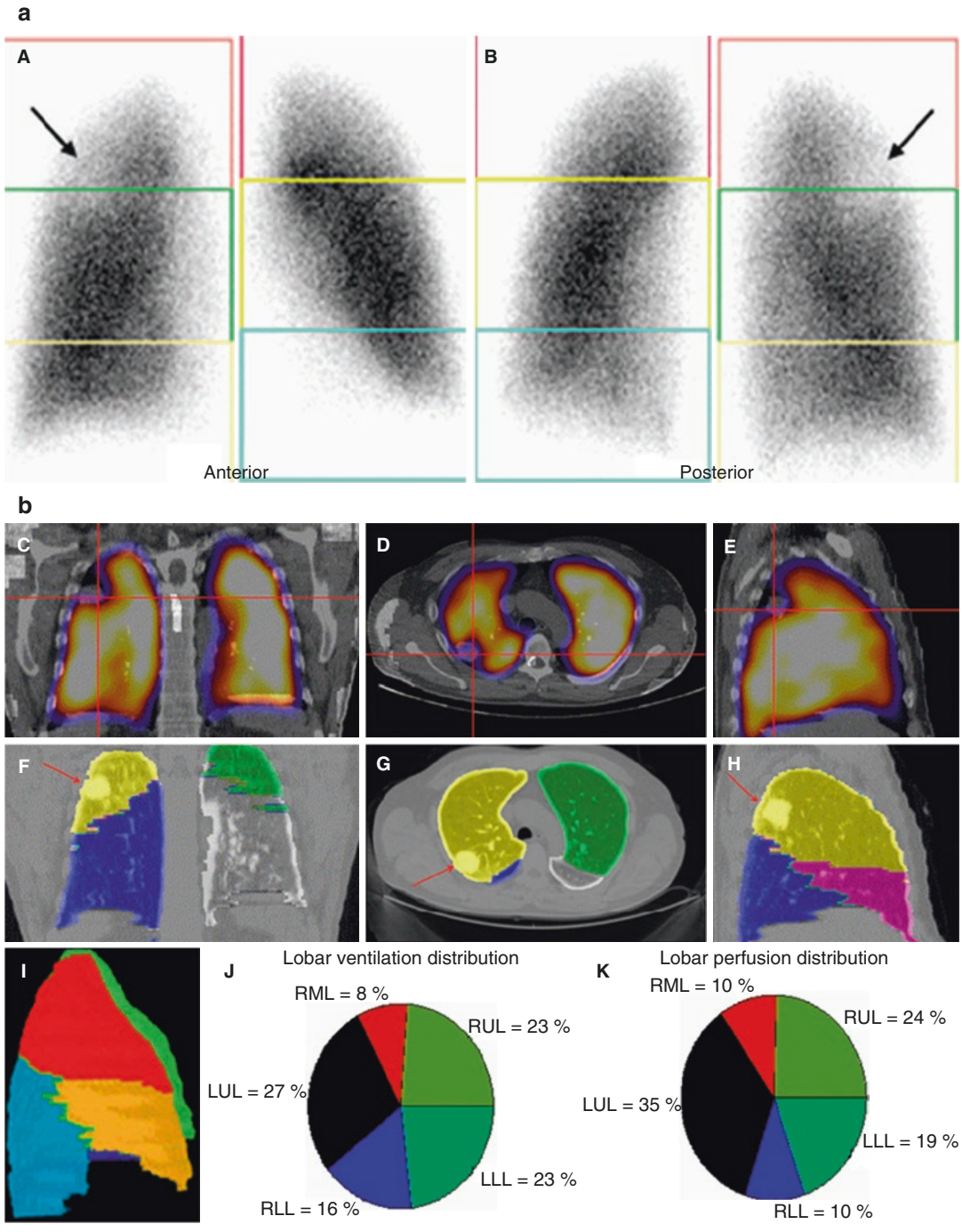

Fig. 12.12 (**a**) Anterior (*A*) and posterior (*B*) planar images in a patient with a right lung carcinoma (*arrowed*). The exact lobar location of the tumour cannot be determined on the planar imaging. (**b**) Fused SPECT/CT perfusion images in the coronal (*C*), transverse (*D*) and sagittal (*E*) planes show the tumour and corresponding perfusion defect (indicated by *cursors*). Corresponding CT scan slices in the coronal (*F*), transverse (*G*) and sagittal (*H*) planes (with patient-specific lobar region-of-interest derived from the CT) show the lesion to be located in the right upper lobe (*arrowed*). 3D patient-specific lobar region-of-interest images (*I*) can be generated and viewed as a rotating MIP image. The SPECT/CT allowed accurate determination of each lobe's relative contribution to overall ventilation (*J*) and perfusion (*K*)

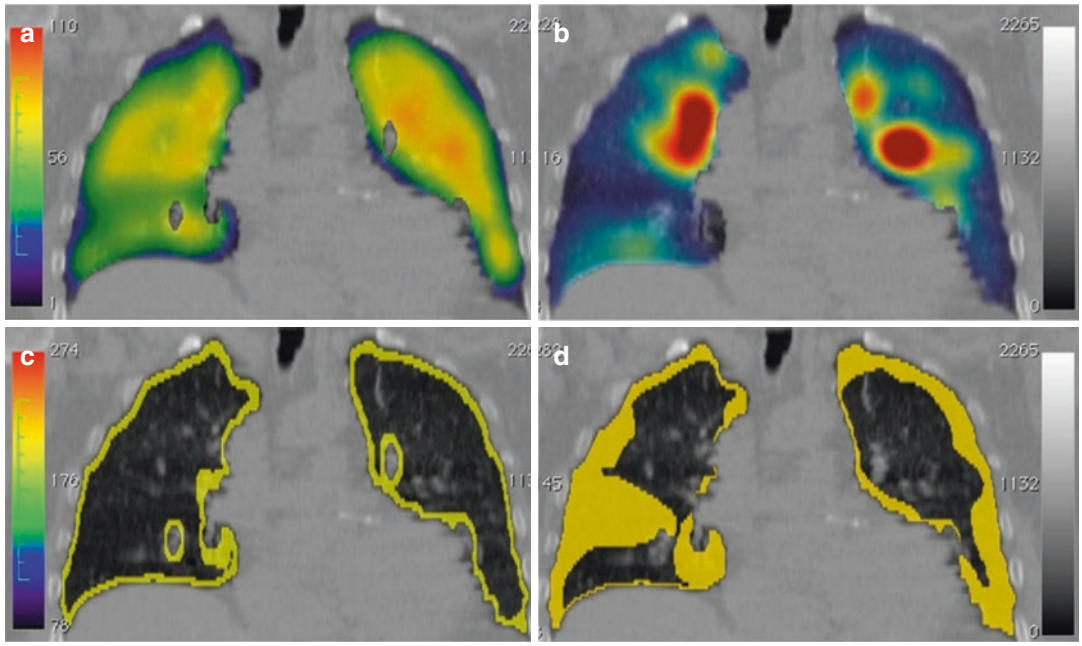

Fig. 12.13 (**a**) Ventilation SPECT/CT fusion image (coronal view) of an asthmatic subject who had severe airway hyperresponsiveness. (**b**) Ventilation SPECT/CT fusion after methacholine challenge when FEV1 had decreased by around 25%. (**c**) and (**d**) are processed images showing non-ventilation (in *yellow*) derived from fusion images. The development of large regions affected by airway closure is evident in the lower lung zones. (Reprinted with permission from King et al. [115])

12.16 Quantitative *V*/*Q* SPECT

As noted by Bailey and Willowson in our review article on *V*/*Q* SPECT/CT, many of the potential uses for SPECT *V*/*Q* in respiratory research mentioned above would benefit from quantitatively accurate *V*/*Q* scanning [63]. Quantitatively accurate image reconstruction is accepted as de facto in PET and PET/CT studies, but quantitatively accurate SPECT/CT is only a relatively recent development [125]. To examine the global quantitative accuracy in lung SPECT scanning, our institution examined the agreement between the calibrated ('true') dose of ^{99m}Tc-MAA administered to patients (assuming 100% trapping in the lungs) undergoing *V*/*Q* SPECT/CT studies with that estimated by CT-based attenuation corrected (AC) and scatter corrected (SC) reconstructed SPECT perfusion images after subtraction of the residual ventilation (Technegas) contribution [125]. In a series of 12 subjects, the average difference between the estimated and true activities was found to be −1%, with a range of −7 to +4%. A further validation study in the thorax using the same SPECT/CT AC and SC methodology was able to estimate the concentration of ^{99m}Tc-labelled red blood cells in an equilibrium blood pool SPECT image in the left ventricular chamber. It was found that the average difference between the measured and true concentrations was within −1% of the true value with a range of −6 to +5%, further attesting to the robustness of the methodology in a different imaging scenario [126]. To further define the regional accuracy achievable today, my institution has undertaken a study of the impact of CT-based attenuation and scatter correction to examine the effect on lobar quantification in the lungs. The impact of scatter correction in ventilation (*V*) and perfusion with ventilation subtracted (*Q* − *V*) SPECT studies on a global and regional basis was assessed by considering differences in the total lungs, differences in the left and right lungs separately and differences in each of the segments. Analysis of perfusion studies (*Q*) first

involved the subtraction of ventilation counts that remained in the lungs ($Q - V$) to ensure that counts relating to ^{99m}Tc-MAA perfusion only were included. Although scatter correction results in a decrease in overall counts, negative differences on a lobar level are still possible, as this represents the redistribution of counts to different segments. In the study, 21 consecutive subjects undergoing *V*/*Q* SPECT/CT scanning demonstrated that scatter correction, in conjunction with attenuation correction, was seen to have a significant impact on regional lung analysis, with an average difference of over 20% for both ventilation and perfusion studies, but this difference is consistently more substantial in the left lung than the right. For both the ventilation and perfusion analysis, the differences introduced by scatter correction, in order from largest to smallest, are in the left lower lobe, the left upper lobe, the right upper lobe, the right middle lobe and the right lower lobe, respectively. In ventilation studies, the average difference in reconstructed activity concentration as a result of scatter correction in the left lower lobe is as large as 30%. Such large variation over the different segments and dominance of scatter in the left lower lobe strongly suggests that a large contributing factor may be Compton scatter from the heart. This would explain the larger differences seen in the left lung as opposed to the right and again highlights the importance of performing patient-specific, nonuniform corrections particularly in regions of variable density, such as the chest. This highlights the importance of scatter correction being used in conjunction with attenuation correction to achieve accurate quantitative data when imaging the lungs with SPECT.

12.17 Conclusion

The addition of CT data to *V*/*Q* SPECT is an exciting and potentially invaluable development in the imaging of patients with suspected PE. In a single imaging procedure, patients can benefit from the high sensitivity of *V*/*Q* SPECT scintigraphy as well as the additional diagnostic information provided by three-dimensional morphological imaging of the lungs. This combination is of particular benefit in increasing the specificity of *V*/*Q* SPECT imaging. Clinically, a low-dose CT can help identify alternative causes of both matched and mismatched *V*/*Q* deficits, thus further improving the diagnostic utility of the study. Compared with CTPA, *V*/*Q* SPECT/CT has several advantages, including a higher sensitivity, a lower radiation dose, no risk of contrast-related allergy or nephrotoxicity and less technically inadequate studies. In some difficult cases, both a CTPA and a SPECT *V*/*Q* may be required to ultimately confirm, or exclude, the presence of PE. In these patients, co-registering the CTPA with the perfusion SPECT can help guide the radiologist to more closely examine an area of perfusion deficit and, in the case of discordant CTPA and *V*/*Q* SPECT results, may help to reach a consensus imaging diagnosis. In non-PE applications, it has been demonstrated that quantitatively accurate information from SPECT/CT can be obtained for uses such as measuring regional lung function, planning radiotherapy treatment and providing other functional measurements of respiratory physiology.

References

1. Dalen JE. Pulmonary embolism: what have we learned since Virchow?: treatment and prevention. Chest. 2002;122:1801–17.
2. Levine MN, Raskob G, Beyth RJ, Kearon C, Schulman S. Hemorrhagic complications of anticoagulant treatment: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:287S–310.
3. Nijkeuter M, Sohne M, Tick LW, Kamphuisen PW, Kramer MH, et al. The natural course of hemodynamically stable pulmonary embolism: clinical outcome and risk factors in a large prospective cohort study. Chest. 2007;131:517–23.
4. British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. Thorax. 2003;58:470–83.
5. Anderson DR, Kahn SR, Rodger MA, Kovacs MJ, Morris T, et al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. JAMA. 2007;298:2743–53.

6. Strashun AM. A reduced role of V/Q scintigraphy in the diagnosis of acute pulmonary embolism. J Nucl Med. 2007;48:1405–7.
7. Wagner HN Jr, Sabiston DC Jr, McAfee JG, Tow D, Stern HS. Diagnosis of massive pulmonary embolism in man by radioisotope scanning. N Engl J Med. 1964;271:377–84.
8. Bajc M, Neilly JB, Miniati M, Schuemichen C, Meignan 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. 2009;36:1356–70.
9. McNeil BJ, Holman BL, Adelstein SJ. The scintigraphic definition of pulmonary embolism. JAMA. 1974;227:753–6.
10. Glassroth J. Imaging of pulmonary embolism: too much of a good thing? JAMA. 2007;298:2788–9.
11. Dalen JE. New PIOPED recommendations for the diagnosis of pulmonary embolism. Am J Med. 2006;119:1001–2.
12. Meignan MA. Lung ventilation/perfusion SPECT: the right technique for hard times. J Nucl Med. 2002;43:648–51.
13. Schumichen C. V/Q-scanning/SPECT for the diagnosis of pulmonary embolism. Respiration. 2003;70:329–42.
14. Morrell NW, Nijran KS, Jones BE, Biggs T, Seed WA. The underestimation of segmental defect size in radionuclide lung scanning. J Nucl Med. 1993;34:370–4.
15. Magnussen JS, Chicco P, Palmer AW, Bush V, Mackey DW, et al. Single-photon emission tomography of a computerised model of pulmonary embolism. Eur J Nucl Med. 1999;26:1430–8.
16. Gray HW, McKillop JH, Bessent RG. Lung scan reporting language: what does it mean? Nucl Med Commun. 1993;14:1084–7.
17. Gray HW, McKillop JH, Bessent RG. Lung scan reports: interpretation by clinicians. Nucl Med Commun. 1993;14:989–94.
18. Goodman LR, Lipchik RJ. Diagnosis of acute pulmonary embolism: time for a new approach. Radiology. 1996;199:25–7.
19. Scott HR, Gillen GJ, Shand J, Bryden F, Milroy R. A structured approach to the interpretation and reporting of ventilation/perfusion scans. Nucl Med Commun. 1998;19:107–12.
20. Kember PG, Euinton HA, Morcos SK. Clinicians' interpretation of the indeterminate ventilation-perfusion scan report. Br J Radiol. 1997;70:1109–11.
21. PIOPED. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. JAMA. 1990;263:2753–9.
22. Leblanc M, Paul N. V/Q SPECT and computed tomographic pulmonary angiography. Semin Nucl Med. 2010;40:426–41.
23. Carrasquillo JA, Rogers JV, Williams DL, Shuman WP, Olson DO, et al. Single-photon emission computed tomography of the normal liver. AJR Am J Roentgenol. 1983;141:937–41.
24. Hacot JP, Bojovic M, Delonca J, Meier B, Righetti A. Comparison of planar imaging and single-photon emission computed tomography for the detection and localization of coronary artery disease. Int J Card Imaging. 1993;9:113–9.
25. Osborne DR, Jaszczak RJ, Greer K, Roggli V, Lischko M, et al. Detection of pulmonary emboli in dogs: comparison of single photon emission computed tomography, gamma camera imaging, and angiography. Radiology. 1983;146:493–7.
26. Bajc M, Bitzen U, Olsson B, Perez de Sa V, Palmer J, et al. Lung ventilation/perfusion SPECT in the artificially embolized pig. J Nucl Med. 2002;43:640–7.
27. Bajc M, Olsson CG, Olsson B, Palmer J, Jonson B. Diagnostic evaluation of planar and tomographic ventilation/perfusion lung images in patients with suspected pulmonary emboli. Clin Physiol Funct Imaging. 2004;24:249–56.
28. Collart JP, Roelants V, Vanpee D, Lacrosse M, Trigaux JP, et al. Is a lung perfusion scan obtained by using single photon emission computed tomography able to improve the radionuclide diagnosis of pulmonary embolism? Nucl Med Commun. 2002;23:1107–13.
29. Reinartz P, Wildberger JE, Schaefer W, Nowak B, Mahnken AH, et al. Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT. J Nucl Med. 2004;45:1501–8.
30. Laurence IJ, Redman SL, Corrigan AJ, Graham RN. V/Q SPECT imaging of acute pulmonary embolus – a practical perspective. Clin Radiol. 2012;67:941–8.
31. Gutte H, Mortensen J, Jensen CV, Johnbeck CB, von der Recke P, 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;50:1987–92.
32. Leblanc M, Leveillee F, Turcotte E. Prospective evaluation of the negative predictive value of V/Q SPECT using 99mTc-Technegas. Nucl Med Commun. 2007;28:667–72.
33. Li DK, Seltzer SE, McNeil BJ. V/Q mismatches unassociated with pulmonary embolism: case report and review of the literature. J Nucl Med. 1978;19:1331–3.
34. Miniati M, Pistolesi M, Marini C, Di Ricco G, Formichi B, et al. Value of perfusion lung scan in the diagnosis of pulmonary embolism: results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). Am J Respir Crit Care Med. 1996;154:1387–93.

35. Freeman LM. Don't bury the V/Q scan: it's as good as multidetector CT angiograms with a lot less radiation exposure. J Nucl Med. 2008;49:5–8.
36. Schoepf UJ, Costello P. CT angiography for diagnosis of pulmonary embolism: state of the art. Radiology. 2004;230:329–37.
37. Hall WB, Truitt SG, Scheunemann LP, Shah SA, Rivera MP, et al. The prevalence of clinically relevant incidental findings on chest computed tomographic angiograms ordered to diagnose pulmonary embolism. Arch Intern Med. 2009;169:1961–5.
38. Harris B, Bailey D, Roach P, Bailey E, King G. Fusion imaging of computed tomographic pulmonary angiography and SPECT ventilation/perfusion scintigraphy: initial experience and potential benefit. Eur J Nucl Med Mol Imaging. 2007;34:135–42.
39. Roach PJ, Bailey DL. Combining anatomy and function: the future of medical imaging. Intern Med J. 2005;35:577–9.
40. Vogel WV, Oyen WJ, Barentsz JO, Kaanders JH, Corstens FH. PET/CT: panacea, redundancy, or something in between? J Nucl Med. 2004;45(Suppl 1):15S–24.
41. Roach PJ, Bailey DL, Schembri GP, Thomas PA. Transition from planar to SPECT V/Q scintigraphy: rationale, practicalities, and challenges. Semin Nucl Med. 2010;40:397–407.
42. Bailey DL, Roach PJ, Bailey EA, Hewlett J, Keijzers R. Development of a cost-effective modular SPECT/CT scanner. Eur J Nucl Med Mol Imaging. 2007;34:1415–26.
43. Schillaci O. Hybrid SPECT/CT: a new era for SPECT imaging? Eur J Nucl Med Mol Imaging. 2005;32:521–4.
44. Lardinois D, Weder W, Hany TF, Kamel EM, Korom S, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. N Engl J Med. 2003;348:2500–7.
45. Schoepf UJ. Pulmonary artery CTA. Tech Vasc Interv Radiol. 2006;9:180–91.
46. Gradinscak DJ, Roach P, Schembri GP. Can perfusion SPECT improve the accuracy of CTPA? Eur J Nucl Med Mol Imaging. 2009;36:S463.
47. Gutte H, Mortensen J, Jensen C, von der Recke P, Kristoffersen US, et al. Added value of combined simultaneous lung ventilation-perfusion single-photon emission computed tomography/multi-slice-computed tomography angiography in two patients suspected of having acute pulmonary embolism. Clin Respir J. 2007;1:52–5.
48. Gutman F, Hangard G, Gardin I, Varmenot N, Pattyn J, et al. Evaluation of a rigid registration method of lung perfusion SPECT and thoracic CT. AJR Am J Roentgenol. 2005;185:1516–24.
49. Ketai L, Hartshorne M. Potential uses of computed tomography-SPECT and computed tomography-coincidence fusion images of the chest. Clin Nucl Med. 2001;26:433–41.
50. Roach PJ, Bailey DL, Harris BE. Enhancing lung scintigraphy with single-photon emission computed tomography. Semin Nucl Med. 2008;38:441–9.
51. Petersson J, Sanchez-Crespo A, Larsson SA, Mure M. Physiological imaging of the lung: single-photon-emission computed tomography (SPECT). J Appl Physiol. 2007;102:468–76.
52. van Beek EJ, Dahmen AM, Stavngaard T, Gast KK, Heussel CP, et al. Hyperpolarised 3He MRI versus HRCT in COPD and normal volunteers: PHIL trial. Eur Respir J. 2009;34:1311–21.
53. Suga K, Kawakami Y, Zaki M, Yamashita T, Shimizu K, et al. Clinical utility of co-registered respiratory-gated(99m)Tc-Technegas/MAA SPECT-CT images in the assessment of regional lung functional impairment in patients with lung cancer. Eur J Nucl Med Mol Imaging. 2004;31:1280–90.
54. 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;51:735–41.
55. Crawford AB, Davison A, Amis TC, Engel LA. Intrapulmonary distribution of 99mtechnetium labelled ultrafine carbon aerosol (Technegas) in severe airflow obstruction. Eur Respir J. 1990;3:686–92.
56. Amis TC, Crawford AB, Davison A, Engel LA. Distribution of inhaled 99mtechnetium labelled ultrafine carbon particle aerosol (Technegas) in human lungs. Eur Respir J. 1990;3:679–85.
57. Burch WM, Boyd MM, Crellin DE. Technegas: particle size and distribution. Eur J Nucl Med. 1994;21:365–7.
58. Lemb M, Oei TH, Eifert H, Gunther B. Technegas: a study of particle structure, size and distribution. Eur J Nucl Med. 1993;20:576–9.
59. Peltier P, De Faucal P, Chetanneau A, Chatal JF. Comparison of technetium-99m aerosol and krypton-81m in ventilation studies for the diagnosis of pulmonary embolism. Nucl Med Commun. 1990;11:631–8.
60. Bailey EA, Bailey DL, Roach PJ. V/Q imaging in 2010: a quick start guide. Semin Nucl Med. 2010;40:408–14.
61. Hudson HM, Larkin RS. Accelerated image reconstruction using ordered subsets of projection data. IEEE Trans Med Imaging. 1994;13:601–9.
62. Hutton BF, Hudson HM, Beekman FJ. A clinical perspective of accelerated statistical reconstruction. Eur J Nucl Med. 1997;24:797–808.
63. Roach PJ, Gradinscak DJ, Schembri GP, Bailey EA, Willowson KP, et al. SPECT/CT in V/Q scanning. Semin Nucl Med. 2010;40:455–66.
64. Patton JA, Turkington TG. SPECT/CT physical principles and attenuation correction. J Nucl Med Technol. 2008;36:1–10.
65. Delbeke D, Coleman RE, Guiberteau MJ, Brown ML, Royal HD, et al. Procedure guideline for SPECT/CT imaging 1.0. J Nucl Med. 2006;47:1227–34.

66. Studholme C, Hill DL, Hawkes DJ. Automated three-dimensional registration of magnetic resonance and positron emission tomography brain images by multiresolution optimization of voxel similarity measures. Med Phys. 1997;24:25–35.
67. Palmer J, Bitzen U, Jonson B, Bajc M. Comprehensive ventilation/perfusion SPECT. J Nucl Med. 2001;42:1288–94.
68. Harris B, Bailey D, Miles S, Bailey E, Rogers K, et al. Objective analysis of tomographic ventilation-perfusion scintigraphy in pulmonary embolism. Am J Respir Crit Care Med. 2007;175:1173–80.
69. Harris B, Bailey DL, Chicco P, Bailey EA, Roach PJ, et al. Objective analysis of whole lung and lobar ventilation/perfusion relationships in pulmonary embolism. Clin Physiol Funct Imaging. 2008;28:14–26.
70. Roach PJ, Bailey DL, Schembri GP. Reinventing ventilation/perfusion lung scanning with SPECT. Nucl Med Commun. 2008;29:1023–5.
71. Herald P, Roach P, Schembri GP. Does the addition of low dose CT improve diagnostic accuracy of V/Q SPECT scintigraphy? J Nucl Med. 2008;49:S91.
72. Gradinscak DJ, Roach P, Schembri GP. Lung SPECT perfusion scintigraphy: can CT substitute for ventilation imaging? Eur J Nucl Med Mol Imaging. 2009;36:S300.
73. Buscombe JR, Notghi A, Croasdale J, et al. COVID-19: guidance for infection prevention and control in nuclear medicine. Nucl Med Commun. 2020;41:499–504.
74. COVID-19 and ventilation/perfusion (V/Q) lung studies. J Nucl Med. 2020;61:23N–24N.
75. Zuckier LS, Moadel RM, Haramati LB, Freeman LM. Diagnostic evaluation of pulmonary embolism during the COVID-19 pandemic. J Nucl Med. 2020;61:630–631.
76. Schaefer WM, Knollmann D and Meyer PT. V/Q SPECT/CT in the Time of COVID-19: Changing the Order to Improve Safety Without Sacrificing Accuracy. Journal of Nuclear Medicine. 2021;62(7):1022–24. https://doi.org/10.2967/jnumed.120.261263.
77. Stein PD, Fowler SE, Goodman LR, Gottschalk A, Hales CA, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med. 2006;354:2317–27.
78. Roach PJ, Thomas P, Bajc M, Jonson B. Merits of V/Q SPECT scintigraphy compared with CTPA in imaging of pulmonary embolism. J Nucl Med. 2008;49:167–8; author reply 8.
79. Roach PJ, Bajc M. Acute pulmonary embolism. N Engl J Med. 2010;363:1972–3; author reply 4–5.
80. Miles S, Rogers KM, Thomas P, Soans B, Attia J, et al. A comparison of single-photon emission CT lung scintigraphy and CT pulmonary angiography for the diagnosis of pulmonary embolism. Chest. 2009;136:1546–53.
81. Toney LK, Lewis DH, Richardson ML. Ventilation/perfusion scanning for acute pulmonary embolism: effect of direct communication on patient treatment outcomes. Clin Nucl Med. 2013;38:183–7.
82. Barrett BJ, Parfrey PS. Clinical practice. Preventing nephropathy induced by contrast medium. N Engl J Med. 2006;354:379–86.
83. Schembri GP, Miller AE, Smart R. Radiation dosimetry and safety issues in the investigation of pulmonary embolism. Semin Nucl Med. 2010;40:442–54.
84. Hurwitz LM, Yoshizumi TT, Goodman PC, Nelson RC, Toncheva G, et al. Radiation dose savings for adult pulmonary embolus 64-MDCT using bismuth breast shields, lower peak kilovoltage, and automatic tube current modulation. AJR Am J Roentgenol. 2009;192:244–53.
85. Parker MS, Hui FK, Camacho MA, Chung JK, Broga DW, et al. Female breast radiation exposure during CT pulmonary angiography. AJR Am J Roentgenol. 2005;185:1228–33.
86. Hurwitz LM, Yoshizumi TT, Reiman RE, Paulson EK, Frush DP, et al. Radiation dose to the female breast from 16-MDCT body protocols. AJR Am J Roentgenol. 2006;186:1718–22.
87. ICRP. Radiation dose to patients from radiopharmaceuticals (addendum 2 to ICRP publication 53). Ann ICRP. 1998;28:1–126.
88. Jones SE, Wittram C. The indeterminate CT pulmonary angiogram: imaging characteristics and patient clinical outcome. Radiology. 2005;237:329–37.
89. Ryu JH, Swensen SJ, Olson EJ, Pellikka PA. Diagnosis of pulmonary embolism with use of computed tomographic angiography. Mayo Clin Proc. 2001;76:59–65.
90. U-King-Im JM, Freeman SJ, Boylan T, Cheow HK. Quality of CT pulmonary angiography for suspected pulmonary embolus in pregnancy. Eur Radiol. 2008;18:2709–15.
91. Ridge CA, McDermott S, Freyne BJ, Brennan DJ, Collins CD, et al. Pulmonary embolism in pregnancy: comparison of pulmonary CT angiography and lung scintigraphy. AJR Am J Roentgenol. 2009;193:1223–7.
92. Yap E, Anderson G, Donald J, Wong CA, Lee YC, et al. Pleural effusion in patients with pulmonary embolism. Respirology. 2008;13:832–6.
93. Gradinscak DJ, Roach P, Schembri GP. Can CT coregistration improve the accuracy of segmental localisation on V/Q SPECT? Eur J Nucl Med Mol Imaging. 2009;36:S463.
94. Zaki M, Suga K, Kawakami Y, Yamashita T, Shimizu K, et al. Preferential location of acute pulmonary thromboembolism induced consolidative opacities: assessment with respiratory gated perfusion SPECT-CT fusion images. Nucl Med Commun. 2005;26:465–74.
95. Worsley DF, Alavi A, Palevsky HI, Kundel HL. Comparison of diagnostic performance with ventilation-perfusion lung imaging in different patient populations. Radiology. 1996;199:481–3.
96. Sostman HD, Coleman RE, DeLong DM, Newman GE, Paine S. Evaluation of revised criteria for

ventilation-perfusion scintigraphy in patients with suspected pulmonary embolism. Radiology. 1994;193:103–7.
97. Gottschalk A, Sostman HD, Coleman RE, Juni JE, Thrall J, et al. Ventilation-perfusion scintigraphy in the PIOPED study. Part II. Evaluation of the scintigraphic criteria and interpretations. J Nucl Med. 1993;34:1119–26.
98. Bailey DL, Schembri GP, Harris BE, Bailey EA, Cooper RA, et al. Generation of planar images from lung ventilation/perfusion SPECT. Ann Nucl Med. 2008;22:437–45.
99. Morris TA. SPECT imaging of pulmonary emboli with radiolabeled thrombus-specific imaging agents. Semin Nucl Med. 2010;40:474–9.
100. Bradley J. A review of radiation dose escalation trials for non-small cell lung cancer within the Radiation Therapy Oncology Group. Semin Oncol. 2005;32:S111–3.
101. Belderbos JS, Heemsbergen WD, De Jaeger K, Baas P, Lebesque JV. Final results of a phase I/II dose escalation trial in non-small-cell lung cancer using three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys. 2006;66:126–34.
102. Hernando ML, Marks LB, Bentel GC, Zhou SM, Hollis D, et al. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys. 2001;51:650–9.
103. Kong FM, Hayman JA, Griffith KA, Kalemkerian GP, Arenberg D, et al. Final toxicity results of a radiation-dose escalation study in patients with non-small-cell lung cancer (NSCLC): predictors for radiation pneumonitis and fibrosis. Int J Radiat Oncol Biol Phys. 2006;65:1075–86.
104. Mazeron R, Etienne-Mastroianni B, Perol D, Arpin D, Vincent M, et al. Predictive factors of late radiation fibrosis: a prospective study in non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2010;77:38–43.
105. Roeder F, Friedrich J, Timke C, Kappes J, Huber P, et al. Correlation of patient-related factors and dose-volume histogram parameters with the onset of radiation pneumonitis in patients with small cell lung cancer. Strahlenther Onkol. 2010;186:149–56.
106. Zhang J, Ma J, Zhou S, Hubbs JL, Wong TZ, et al. Radiation-induced reductions in regional lung perfusion: 0.1-12 year data from a prospective clinical study. Int J Radiat Oncol Biol Phys. 2010;76:425–32.
107. Woel RT, Munley MT, Hollis D, Fan M, Bentel G, et al. The time course of radiation therapy-induced reductions in regional perfusion: a prospective study with >5 years of follow-up. Int J Radiat Oncol Biol Phys. 2002;52:58–67.
108. Christian JA, Partridge M, Nioutsikou E, Cook G, McNair HA, et al. The incorporation of SPECT functional lung imaging into inverse radiotherapy planning for non-small cell lung cancer. Radiother Oncol. 2005;77:271–7.
109. Lavrenkov K, Singh S, Christian JA, Partridge M, Nioutsikou E, et al. Effective avoidance of a functional spect-perfused lung using intensity modulated radiotherapy (IMRT) for non-small cell lung cancer (NSCLC): an update of a planning study. Radiother Oncol. 2009;91:349–52.
110. McGuire SM, Zhou S, Marks LB, Dewhirst M, Yin FF, et al. A methodology for using SPECT to reduce intensity-modulated radiation therapy (IMRT) dose to functioning lung. Int J Radiat Oncol Biol Phys. 2006;66:1543–52.
111. Yin Y, Chen JH, Li BS, Liu TH, Lu J, et al. Protection of lung function by introducing single photon emission computed tomography lung perfusion image into radiotherapy plan of lung cancer. Chin Med J. 2009;122:509–13.
112. McGuire SM, Marks LB, Yin FF, Das SK. A methodology for selecting the beam arrangement to reduce the intensity-modulated radiation therapy (IMRT) dose to the SPECT-defined functioning lung. Phys Med Biol. 2010;55:403–16.
113. Munawar I, Yaremko BP, Craig J, Oliver M, Gaede S, et al. Intensity modulated radiotherapy of non-small-cell lung cancer incorporating SPECT ventilation imaging. Med Phys. 2010;37:1863–72.
114. Ohno Y, Koyama H, Takenaka D, Nogami M, Kotani Y, et al. Coregistered ventilation and perfusion SPECT using krypton-81m and Tc-99m-labeled macroaggregated albumin with multislice CT: utility for prediction of postoperative lung function in non-small cell lung cancer patients. Acad Radiol. 2007;14:830–8.
115. King GG, Harris B, Mahadev S. V/Q SPECT: utility for investigation of pulmonary physiology. Semin Nucl Med. 2010;40:467–73.
116. Jamadar DA, Kazerooni EA, Martinez FJ, Wahl RL. Semi-quantitative ventilation/perfusion scintigraphy and single-photon emission tomography for evaluation of lung volume reduction surgery candidates: description and prediction of clinical outcome. Eur J Nucl Med. 1999;26:734–42.
117. Inmai T, Sasaki Y, Shinkai T, Ohishi H, Nezu K, et al. Clinical evaluation of 99mTc-Technegas SPECT in thoracoscopic lung volume reduction surgery in patients with pulmonary emphysema. Ann Nucl Med. 2000;14:263–9.
118. Komori K, Kamagata S, Hirobe S, Toma M, Okumura K, et al. Radionuclide imaging study of long-term pulmonary function after lobectomy in children with congenital cystic lung disease. J Pediatr Surg. 2009;44:2096–100.
119. Xu J, Moonen M, Johansson A, Gustafsson A, Bake B. Quantitative analysis of inhomogeneity in ventilation SPET. Eur J Nucl Med. 2001;28:1795–800.
120. Pellegrino R, Biggi A, Papaleo A, Camuzzini G, Rodarte JR, et al. Regional expiratory flow limitation studied with Technegas in asthma. J Appl Physiol. 2001;91:2190–8.
121. Fujita J, Takahashi K, Satoh K, Okada H, Momoi A, et al. Tc-99m Technegas scintigraphy to evaluate the

lung ventilation in patients with oral corticosteroid-dependent bronchial asthma. Ann Nucl Med. 1999;13:247–51.
122. Suga K, Kuramitsu T, Yoshimizu T, Nakanishi T, Yamada N, et al. Scintigraphic analysis of hemodynamics in a patient with a single large pulmonary arteriovenous fistula. Clin Nucl Med. 1992;17:110–3.
123. Sasaki Y, Imai T, Shinkai T, Ohishi H, Otsuji H, et al. Estimation of regional lung function in interstitial pulmonary disease using 99mTc-technegas and 99mTc-macroaggregated albumin single-photon emission tomography. Eur J Nucl Med. 1998;25:1623–9.
124. Nagao M, Murase K. Measurement of heterogeneous distribution on Technegas SPECT images by three-dimensional fractal analysis. Ann Nucl Med. 2002;16:369–76.
125. Willowson K, Bailey DL, Baldock C. Quantitative SPECT reconstruction using CT-derived corrections. Phys Med Biol. 2008;53:3099–112.
126. Willowson K, Bailey DL, Bailey EA, Baldock C, Roach PJ. In vivo validation of quantitative SPECT in the heart. Clin Physiol Funct Imaging. 2010;30:214–9.