Expert Opinion

informa
healthcare

Challenges in assessing regional distribution of inhaled drug in the human lungs

Stephen Newman[†] & John Fleming
[†]*Scientific Consultant, 6 Nelson Drive Hunstanton, Norfolk PE36 5DU, UK*

Introduction: Both the total amount of drug deposited in the lungs (whole lung deposition) and the amount deposited in different lung regions (regional lung deposition) are potentially important factors that determine the safety and efficacy of inhaled drugs. Radionuclide imaging is well established for quantifying the whole lung deposition of inhaled drugs, but the assessment of regional lung deposition is less straightforward, because of the complex nature of the lung anatomy.

Areas covered: This review describes the challenges and problems associated with quantifying regional lung deposition by the two-dimensional (2D) radionuclide imaging method of gamma scintigraphy, and by the three-dimensional (3D) radionuclide imaging methods of single-photon-emission computed tomography (SPECT) and positron-emission tomography (PET). The advantages and disadvantages of each method for assessing regional lung deposition are discussed.

Expert opinion: Owing to its 2D nature, gamma scintigraphy provides limited information about regional lung deposition. SPECT provides regional lung deposition data in three dimensions, but usually involves a ^{99m}Tc radiolabel. PET enables the regional lung deposition of radiolabeled drug molecules to be quantified in three dimensions, but poses the greatest logistical and technical difficulties. Despite their more challenging nature, 3D imaging methods should be considered as an alternative to gamma scintigraphy whenever the determination of regional lung deposition of pharmaceutical aerosols is a major study objective.

Keywords: gamma scintigraphy, positron-emission tomography, radionuclide imaging, respiratory drug delivery, single-photon-emission computed tomography

Expert Opin. Drug Deliv. (2011) ***8****(7):841-855*

1. Assessing deposition of inhaled drugs

The efficacy of inhaled drugs, whether given for treatment of lung disease or to achieve an effect in some other part of the body, depends on drug deposition in the lungs [1]. For example, when an inhaled bronchodilator dose is deposited entirely in the oropharynx of a patient with asthma, little or no clinical response is obtained, whereas a small fraction of that dose deposited in the lungs leads to significant bronchodilatation [2]. Perhaps surprisingly, the systemic side effects of inhaled asthma drugs may also be determined mainly by the amount of drug delivered to the lungs. A dose of 800 μg of the bronchodilator salbutamol, inhaled from a pressurized metered-dose inhaler (pMDI), caused a significant increase in pulse rate, which did not occur when the same dose was sprayed into the buccal cavity without inhalation [3]. Many glucocorticosteroids have low oral bioavailability, so that the fraction of the dose deposited in the upper airways and then swallowed may make little contribution to systemic drug levels [4].

10.1517/17425247.2011.577063 ISSN 1742-5247

Article highlights.

- Both whole lung deposition and regional lung deposition of inhaled drugs, quantified in radionuclide imaging studies, can assist our understanding of the factors that optimize lung deposition.
- The assessment of regional lung deposition is less straightforward than the assessment of whole lung deposition because of the complexity of the lung airway anatomy.
- Discussion is presented of the relative merits and difficulties of gamma scintigraphy, SPECT and PET imaging for assessing the regional deposition pattern in the lungs of inhaled drugs.
- Gamma scintigraphy is considered as the 'industry standard' for assessing deposition for new inhalers or formulations, but is a method limited by expressing regional lung deposition in only two dimensions.
- SPECT imaging is a three-dimensional imaging method, which allows regional lung deposition to be quantified with greater precision than by gamma scintigraphy, and which may allow differences in regional lung deposition between two regimens to be detected more readily.
- Both gamma scintigraphy and SPECT are limited by the use of ^{99m}Tc radiolabels, but PET imaging uses positron-emitting radionuclides such as ^{11}C, which can be incorporated into the molecular structure of many inhaled drugs. Regional distribution is presented in three dimensions. However, logistical and technical challenges have limited the use of PET for assessing regional lung deposition of inhaled drugs.
- Despite their more challenging nature, 3D imaging methods should be considered as an alternative to gamma scintigraphy whenever the determination of regional lung deposition of pharmaceutical aerosols is a major study objective.

This box summarizes key points contained in the article.

Lung deposition data have greatly enhanced our fundamental understanding of the factors that affect pulmonary drug delivery, and how to optimize this treatment modality. Lung deposition studies have proved to be very useful for assessing new inhaler devices or formulations, and for comparing them against established products [5,6].

The assessment of lung deposition consists of two elements, the total amount deposited in the lungs (whole lung deposition) and the amounts deposited in various lung regions (regional lung deposition). Whole lung and regional lung depositions can be quantified by radionuclide imaging methods [7,8]. The two-dimensional (2D) radionuclide imaging method of gamma scintigraphy has been used extensively to assess deposition of inhaled drugs, and in recent years increasing use has been made of the three-dimensional (3D) imaging methods of single-photon-emission computed tomography (SPECT) and positron-emission tomography (PET). The charcoal-block pharmacokinetic (PK) method [9] can be used for a range of drugs to quantify absolute pulmonary bioavailability, a parameter that is numerically similar to whole lung deposition [10]. Another PK method, the 30-min urinary excretion method [11], provides an index of relative pulmonary bioavailability for some drugs, by which two or more inhalers or formulations may be compared. Pharmacokinetic methods enable data about pulmonary drug delivery to be obtained without exposing subjects to ionizing radiation. However, a limitation of the PK methods is that the relationship between PK data and regional distribution of drugs in the lungs is not yet understood [12].

Our understanding of how to quantify whole lung deposition from inhaler devices using radionuclide imaging methods is now good [12]. Key elements in quantification include making appropriate corrections to data to allow for the attenuation and scatter of gamma rays that occurs in the human body [13,14]. The precision of both SPECT [15] and PET [16] for the determination of whole lung deposition is superior to that of gamma scintigraphy, but for many purposes gamma scintigraphy is a simpler and more practical option.

The regional distribution of many drugs in the lungs is potentially an important determinant of both efficacy and safety [17]. It is assumed that drugs need to be targeted towards their receptors for maximal effect. Receptor sites for inhaled drugs are not distributed uniformly within the bronchial tree; for example, the receptors for anti-muscarinic bronchodilators are concentrated most densely in the large conducting airways [18]. Drug aerosols may be targeted to different lung regions by varying the aerosol particle size, the mode of inhalation, or both these variables. It has been suggested that drug can be targeted to the large conducting airways using an aerosol with an aerodynamic diameter between 5 and 10 μm, introduced late in the breath, whereas drug can be targeted to the alveolated airways using an aerosol with an aerodynamic diameter between 1 and 5 μm, inhaled slowly and deeply [19]. Alveolar targeting strategies are sometimes used for delivery of specific drugs that are either needed to treat alveolar disease, or are to be absorbed into the systemic circulation through the alveolar epithelium [20]. The presence of asthma or chronic obstructive pulmonary disease leads to changes in regional lung deposition compared with that in healthy subjects. In asthma the airways are narrowed by a combination of bronchospasm, airway inflammation and mucus hypersecretion, so that deposition of aerosol particles and droplets by inertial impaction is more likely in the large central airways, and there is reduced likelihood that aerosol will penetrate into peripheral airways [21].

The assessment of regional lung deposition in a manner that gives useful data is more problematical than the assessment of whole lung deposition. The purpose of this paper is to discuss the challenges associated with the assessment of regional lung deposition, in both two and three dimensions.

2. The complexity of lung anatomy

When considering how to assess the regional distribution of inhaled drugs, it is important to recognize the complexity of the lung anatomy (**Figure 1**). The lungs may be described by

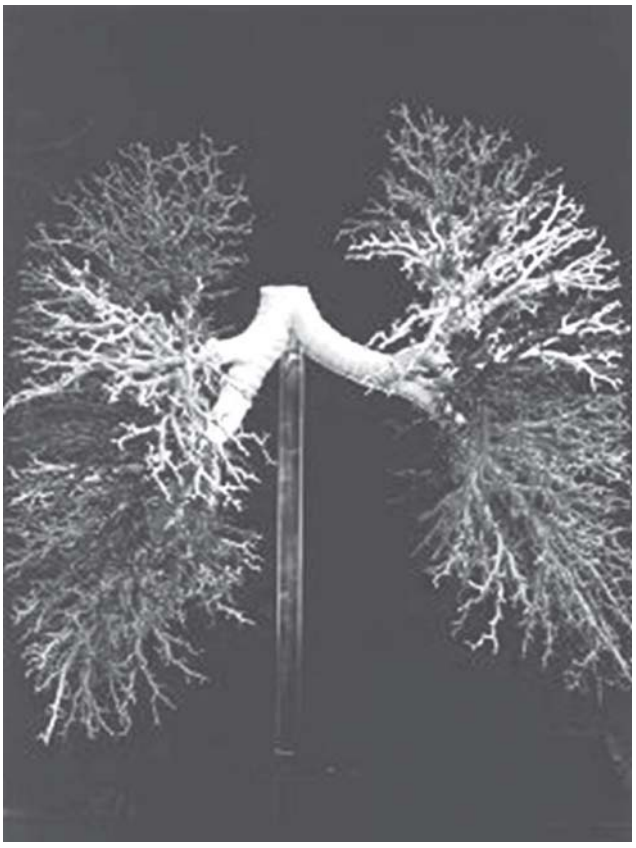

Figure 1. Photograph of lung cast illustrating the complexity of the airway tree. The airways branch approximately radially, demonstrating the reasoning behind the concepts of central-to-peripheral division of airways in two dimensions and shell analysis in three dimensions.
Reproduced with permission from [8].

a model such as that of Weibel [22], who considered the lungs (or 'bronchial tree') to consist of 23 branching airways, so that each airway of generation 'n' branches into two airways in generation 'n + 1'. Weibel defined the trachea as generation 0, reflecting the fact that it is in the thorax, but not in the lungs, and the main bronchi as generation 1. The conducting airways extend to generation 16 (terminal bronchioles) and the alveolated airways extend from generation 17 (respiratory bronchioles) to generation 23 (alveolar sacs). Of course, this model is simplistic, and there is much inter-subject variability in lung anatomy, in terms of both the number of airways and their orientation in space. It may be debated where exactly to place the boundary between conducting airways and alveolated airways [23]. Nevertheless, the Weibel model describes the lungs adequately to a first approximation.

The complexity of the lung anatomy lies at the root of the challenges associated with the assessment of regional lung deposition. With the possible exception of the major bronchi, it is obvious that any imaging method will not be able to visualize deposition at the level of individual airway generations. Not only is the lung structure complex, but also its complexity extends in three dimensions. Therefore, gamma scintigraphy starts with a major disadvantage because it reduces the distribution into only two dimensions; but even in three dimensions, the ability to provide detailed information about regional distribution will be limited by several factors, including the inherent resolution of the imaging method chosen.

3. Gamma scintigraphy

Most radionuclide imaging studies of pulmonary drug delivery have used the 2D method of gamma scintigraphy [6,24]. Imaging is carried out by a gamma camera, which usually has two detector heads, between which the subject either sits or stands, allowing simultaneous anterior and posterior lung images to be acquired. The geometric mean of anterior and posterior count rates is usually calculated. Each detector head includes a thin crystal of sodium iodide (diameter typically 40 cm), and there is a lead multi-hole collimator located between the subject and the crystal [25]. Passage of gamma rays to the crystal only through the collimator holes adjacent to their origin in the body allows an image of the distribution of radionuclide to be produced.

Radionuclides suitable for imaging by gamma camera emit photons with energies in the approximate range 100 – 300 keV. Gamma scintigraphic studies have generally utilized the radionuclide ^{99m}Tc (gamma ray energy 140 keV, physical half-life 6 h) to radiolabel drug-containing particles or droplets. Incorporating a radiolabel into the structure of a drug molecule is unusual in gamma scintigraphic studies because there is a lack of suitable radionuclides for this purpose. Most drug molecules are composed of hydrogen, carbon, nitrogen and oxygen, but these elements do not have isotopes that emit gamma rays with characteristics suitable for gamma camera imaging. The radionuclide ^{3}H emits only beta particles, which cannot be detected by gamma camera, whereas ^{11}C, ^{13}N and ^{15}O are all positron emitters, resulting in the production of a pair of 511 keV photons. Imaging of positron emitters can be performed on a gamma camera with suitable high energy collimators. However, the photon energy is too high for optimal gamma camera imaging because the photons can penetrate the lead septa in the collimator, and the image quality is likely to be significantly degraded.

Radiolabeling validation studies, which quantify drug and radiolabel particle size distributions by cascade impactor, may be used to show that the ^{99m}Tc radiolabel is an adequate marker for drug deposition [26,27]. However, as the radiolabel has only a physical association with drug particles and does not form part of the drug molecule, it is not normally possible to use a ^{99m}Tc radiolabel to monitor drug clearance. The clearance half-time of ^{99m}Tc in the form of pertechnetate is 10 – 15 min [28], owing to rapid absorption via the lung epithelium, and when this chemical form of radiolabel is used the imaging must be completed as quickly as possible to minimize

errors associated with radiotracer clearance [29]. For studies using nebulizers, the administration time usually extends over several minutes, and radiotracers that undergo slower absorption (e.g., ^{99m}Tc-DTPA (diethylene triamine pentaacetic acid)) or even zero absorption (e.g., ^{99m}Tc-labeled colloidal suspensions of albumin) are preferred [30]. The rate of loss of deposited particles by mucociliary clearance is greatest when the deposition is primarily in large central airways, and losses as high as 0.5%/min have been reported [31]. Methods to correct for losses of deposited particles from the lungs caused either by mucociliary clearance or pulmonary absorption have been proposed, based on the collection of sequential images [32].

Despite the availability of more sophisticated 3D methods, gamma scintigraphy is probably still the imaging method that in the first instance most investigators consider using to answer a question about pulmonary drug delivery. Perhaps because of this, gamma scintigraphy has been called the 'industry standard' [33], a term that reflects its proven utility and relative simplicity. The large number of gamma scintigraphy studies performed over a period of 30 years has allowed some useful meta-analyses to be carried out, for example showing the relationship between whole lung deposition and particle size parameters [34], and highlighting how the interaction of aerosol sprays with the upper airways affects both the magnitude of whole lung deposition and its variability [35].

The regional deposition data provided by gamma scintigraphy is limited by the fact that the 3D distribution of a radiolabel in the lungs is displayed as a 2D array of picture elements (pixels). Owing to the complexity of the bronchial tree described in Section 2, it difficult to relate 2D scintigraphic images to anatomical structures. Many different approaches have been used to divide the lung fields in scintigraphic studies into regions of interest (ROIs), and some examples are shown in **Figure 2**. The most common approach is to define a central (C) lung region and a peripheral (P) lung region to determine the counts in each of these regions, and then to express the regional deposition as a 'C/P' or 'P/C' ratio of counts [12,36-38]. Some algorithms also involve a third intermediate region, which may or may not be used in the calculation of C/P or P/C ratio. Sometimes these indices are normalized by dividing by a C/P or P/C ratio for a volume or ventilation scan using a radioactive inert gas (usually ^{133}Xe or ^{81m}Kr, respectively) [37,38]. It may also be possible to use data from a transmission scan to normalize the C/P or P/C ratio should a radioactive inert gas not be available. Some study centers use only data from posterior images in gamma scintigraphy studies, and this could result in a different value for a regional deposition index compared with that obtained from the geometric mean of anterior and posterior count rates.

Consideration of the accuracy and precision in defining these regions is important. Although small errors in definition of the overall lung ROI can be tolerated when estimating whole lung deposition, they are much more critical when estimating regional indices. Simulation studies have shown that errors in the P/C ratio of ~ 5%/mm occur for misalignment in the left/right direction [39]. Good alignment between the volume or ventilation images used to define the ROI and the image of aerosol deposition is therefore vital for good regional quantification. Normalization of the indices to a volume or ventilation image has been shown to reduce the variability in regional parameters due to differences in lung shape [39] or due to the protocol used to define the central and peripheral regions [40].

In practice, each individual study center has tended to use a consistent division of the lungs into regions, but the differences between study centers are such that comparisons between data obtained at different centers can seldom be made. For example, it is virtually impossible to compare regional deposition indices obtained with different divisions of the lung into regions as shown in **Figure 2**. Current efforts by a working group of the International Society for Aerosols in Medicine (ISAM) to standardize the methodology for scintigraphic studies may help to resolve this issue.

A major problem in the analysis of 2D lung images is that any ROI will contain a mixture of airways from many generations, possibly including large conducting airways, small conducting airways and alveoli. The nature of the problem is illustrated by **Table 1**, where the number of airways of different generations present in each of the central, intermediate and peripheral lung regions has been calculated for a 'typical' human lung [41]. This calculation showed that tracheobronchial airways are present in each of the central, intermediate and peripheral regions. In the central region, alveolated airways comprise ~ 99% of the airways by number, 95% of the airway surface area and 80% of airway volume. Methods have been described for recovering the missing third dimension in gamma scintigraphic studies [42], but these seem to have been little used so far.

Image resolution may be expressed as the full width half-maximum (FWHM), which represents the spread on an image of a point source of radioactivity. The inherent resolution of gamma scintigraphy is typically 10 – 14 mm FWHM [12], so that images are generally rather blurred. Resolution is determined mainly by the energy of the radionuclide used and by the design of the gamma camera collimator. The FWHM could be reduced and the resolution enhanced by using a collimator with fewer holes and hence broader lead septa. However, this would have a negative effect, because it would reduce the gamma camera efficiency and would require the use of a larger amount of radioactivity. Hence, in practice, gamma camera operation requires a compromise between the conflicting requirements of good resolution and high counting efficiency.

The gamma rays emitted by ^{99m}Tc undergo photoelectric absorption and Compton scattering by body tissues, and in order to quantify imaging data accurately, the recorded count rate must be corrected to allow for these processes. In practice, the count rate is reduced typically by ~ 50% for gamma rays

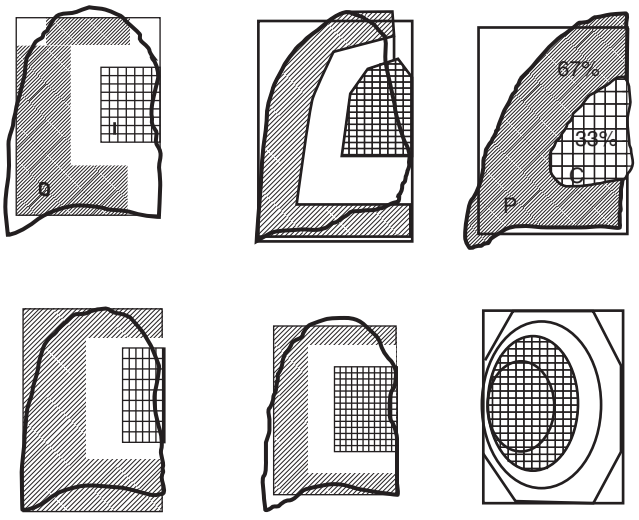

Figure 2. Examples of definitions of central and peripheral regions in gamma scintigraphy.
Reproduced with permission from [12].

Table 1. The number of airways in selected generations present in central, intermediate and peripheral lung regions from a gamma scintigraphy image in a 'typical' adult human.

Generation	Number of airways		
	Central	Intermediate	Peripheral
1	2	0	0
4	8	8	0
8	52	140	64
12	736	1608	1752
16	11,800	25,116	28,620
20	190,724	399,044	458,808
23	1,526,286	3,197,066	3,665,256

From [41].

emitted from the lungs and by 75% for gamma rays emitted from the stomach. However, as the distribution is compressed into two dimensions, it is impossible to know exactly the site from which any individual gamma ray has originated. Fortunately, deposition may be quantified by making simplifying assumptions, for example, by calculating an attenuation correction factor from a measurement of body thickness and knowledge of the linear attenuation coefficients for various body tissues [43]. Another widely used method for making tissue attenuation corrections involves imaging the transmission of gamma rays from a uniform 'flood field' source through the thorax of the subject [44]. This gives a 2D map of attenuation correction factors, which can be used to provide regional corrections. A 2D map of these factors may also be obtained from either 3D MRI or anatomical X-ray CT of the thorax [45]. Tissue attenuation correction can also be made from a comparison of the lung count rate with that from a known amount of injected ^{99m}Tc-labeled macro-aggregated albumin, which is assumed to be trapped entirely in lung capillaries [46].

Compton scattering affects the recorded count rate in two ways. When gamma rays traveling towards the gamma camera are scattered in a different direction, the observed count rate is reduced, but when gamma rays not traveling initially towards the gamma camera are scattered in the direction of the gamma camera, the observed count rate is increased. In practice, the presence of scatter means that the fall in count rate with increasing thickness of body tissue is rather less than that predicted by the theoretical linear attenuation coefficient. Correction for scattered photons may be made in two ways, either by explicitly subtracting the counts from the image [14] or by using a 'broad beam' linear attenuation coefficient [45]. Although the latter method is approximate, it has been shown to provide results that agree closely in quantifying whole lung deposition with explicit subtraction of scatter [45].

Despite the need to correct scintigraphic data for the effects of gamma ray attenuation and scatter, errors ~ 10% for whole lung deposition are achievable in gamma scintigraphic studies, even when the distribution is non-uniform. This is suggested by several pieces of evidence, including the observation of good agreement between whole lung deposition quantified by gamma scintigraphy and pulmonary bioavailability quantified by a pharmacokinetic technique [10], comparisons with simulated image data [47] and with SPECT data [45], and accurate quantification of dose accountability or 'mass balance' [48,49]. However, another study [14] reported wide variations in correction factors for attenuation and scatter depending on the methodology used, with the implication that these also lead to substantial differences in the value obtained for whole lung deposition. As the lung is not a homogeneous structure, it may be desirable to use separate attenuation correction factors for different lung regions. One study [50] suggested that attenuation correction factors are highly dependent on the regional distribution of aerosol, but another study disagreed with this finding [51].

A further problem when the lungs are viewed in two dimensions is that the stomach may overlap the corner of the lungs, especially for inhalation systems for which there is high upper airway deposition, and for which a significant amount of the dose is subsequently swallowed. When this occurs, some information about deposition in a peripheral lung region is lost. This primarily affects the left lung, and hence it is common to focus analysis of 2D images on the right lung.

As discussed above, there are several issues that create challenges when assessing the regional deposition pattern in the lungs by gamma scintigraphy. Nevertheless, a simple P/C ratio can be a useful index of regional lung deposition. Studies have shown that a P/C ratio responds appropriately to changes in aerodynamic particle size distribution (APSD), inhaled flow rate and airway patency [52]. In other words,

there was a statistically significant increase in P/C ratio with a decrease in mass median aerodynamic diameter from 6 to 2 μm, and with a decrease in inhaled flow rate from 80 to 30 l/min. Also, the P/C ratio was significantly higher in healthy subjects than in patients with mild-to-moderate asthma whose airways are narrowed by bronchospasm and other factors. The change in P/C ratio with particle size was also independently demonstrated by another study [53]. The P/C ratio has been shown to correlate significantly with the 24 h retention in the lungs of an insoluble or poorly soluble radiotracer [52,54], which is sometimes considered to be a functional measure of alveolar deposition [55]. However, this assumes that there is no long-term component of retention on the conducting airways of the lungs. Perhaps surprisingly, a meta-analysis of > 100 regimens from studies undertaken at a single center showed that there was little or no correlation between whole lung deposition and P/C ratio [54].

4. Single-photon-emission computed tomography

SPECT uses the same gamma camera heads as those used in gamma scintigraphy, but the imaging system is configured with two or three heads that rotate around the supine subject. Images are taken from multiple angles by moving the detector heads either in regular steps, or continuously [15,56]. The images taken from multiple angles are used to reconstruct the original distribution in three dimensions [57]. The distribution is then expressed as a 3D array of volumetric picture elements (voxels). Some study centers use SPECT imaging solely to assess regional lung distribution, and quantify whole lung deposition and upper airway deposition from concurrent 2D images [15]. Other study centers quantify whole lung deposition and upper airway deposition from SPECT imaging sequences of the head, thorax and abdomen [56,58].

In common with gamma scintigraphy, most SPECT lung studies have used the radionuclide ^{99m}Tc to radiolabel a component of the formulation, and hence the requirements for radiolabeling development and validation are similar to those in gamma scintigraphy. The resolution of SPECT imaging is similar to that of gamma scintigraphy (FWHM 10 – 14 mm) [12], but the major advantage that SPECT offers is to avoid compression of the pulmonary distribution into only two dimensions. This has two consequences: first the overlap of smaller and larger airways is largely eliminated, so that it is much easier to relate deposition patterns to lung anatomy; and second, the fundamental basis for quantification is better than in gamma scintigraphy [39]. Using either MRI or high-resolution X-ray CT, it is possible to build-up a 3D map of attenuation coefficients, which allows precise tissue attenuation corrections to be made [59]. Corrections can also be made for scattered radiation and for the partial volume effect, which can cause gamma ray counts to be assigned to a region of interest adjacent to the one from which they have truly originated [60,61]. SPECT can detect differences in regional lung deposition that are either missed, or are demonstrated only weakly, by gamma scintigraphy [53,56,62].

Anatomical co-registration can be achieved either from a second imaging modality (MRI or CT), or from a transmission scan using a source of radioactivity integral to the camera. Imaging devices are now available that allow both SPECT and CT to be obtained with the same hardware, and without the need to move the subject [63]. The use of these combined SPECT/CT devices has obvious advantages for image co-registration compared with obtaining SPECT and CT data in different imaging devices [51].

There are three major ways in which regional lung deposition data obtained in SPECT studies may be displayed: (i) in transverse, coronal and sagittal sections through the lungs [62]; (ii) by considering the lung to consist of a series of concentric shells radiating from the hilum [59]; and (iii) using a data inversion method to calculate from the shell distribution data the amount of deposition in individual airway generations [15,59,61]. **Figure 3** illustrates the assessment of regional lung deposition in transverse slices and in concentric shells. **Figure 4** shows SPECT data from a healthy subject and an asthmatic patient, where regional lung deposition has been assessed in transverse sections, and also in shells and as deposition per generation.

The derivation of deposition expressed as the amount in different airway generations potentially relates deposition to lung anatomy in a clear and clinically relevant way. Assessment of deposition per generation requires assumptions to be made about the anatomical structure, in terms of both the number of airways and their spatial orientation. Two types of spatial model of the airways have been described, the conceptual model [64], which relates lung volumes in different generations to the shell structure described above, and deterministic models, which describe the actual spatial locations of each airway [65,66]. Most such assessments have assumed that each lung consists of 23 branching airways according to the model of Weibel (Section 2). The data produced by these calculations are credible, for example showing how an aerosol with a mass median aerodynamic diameter (MMAD) 2 μm inhaled by a healthy subject has its major deposition peak around generation 20, whereas an aerosol with a MMAD 6 μm inhaled by an asthmatic has a second deposition peak in generations 4 and 5 (**Figure 4**). The assessment of deposition per generation is challenging to validate, but encouraging data have been obtained using a simulation technique. A distribution pattern across 23 airway generations was assumed, and this was used to produce a simulated image in three dimensions. This image was then analyzed, and the actual and estimated amounts of deposition in different airway generations showed good agreement [67].

Misalignment between the lung volume of interest defined from an anatomical image and the aerosol deposition image is a potential source of error in calculating regional deposition parameters. In this respect there is an advantage in acquiring the anatomical image at the same time as the aerosol image,

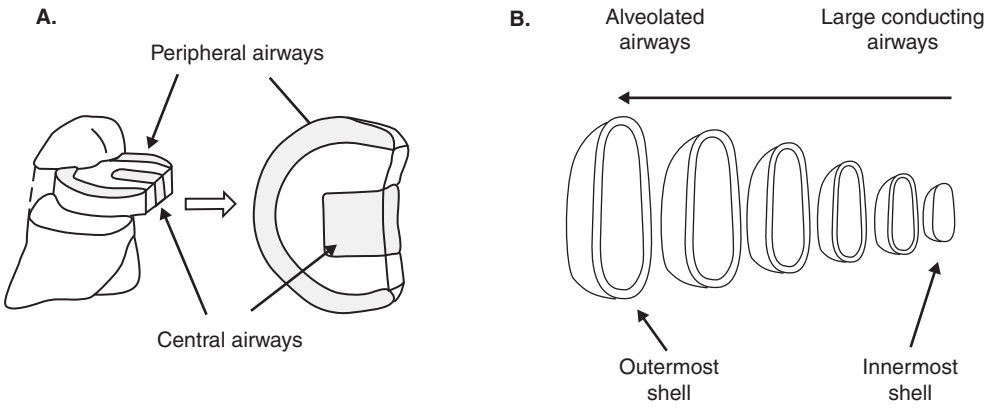

Figure 3. Methods of expressing regional lung deposition in single-photon-emission computed tomography and positron-emission tomography (A) using central and peripheral volumes of interest defined in transverse plane, and (B) six concentric shells created from a radial transform of the lung shape around the hilum of the lung where the main bronchus enters the lung envelope.

A. Adapted from [62].

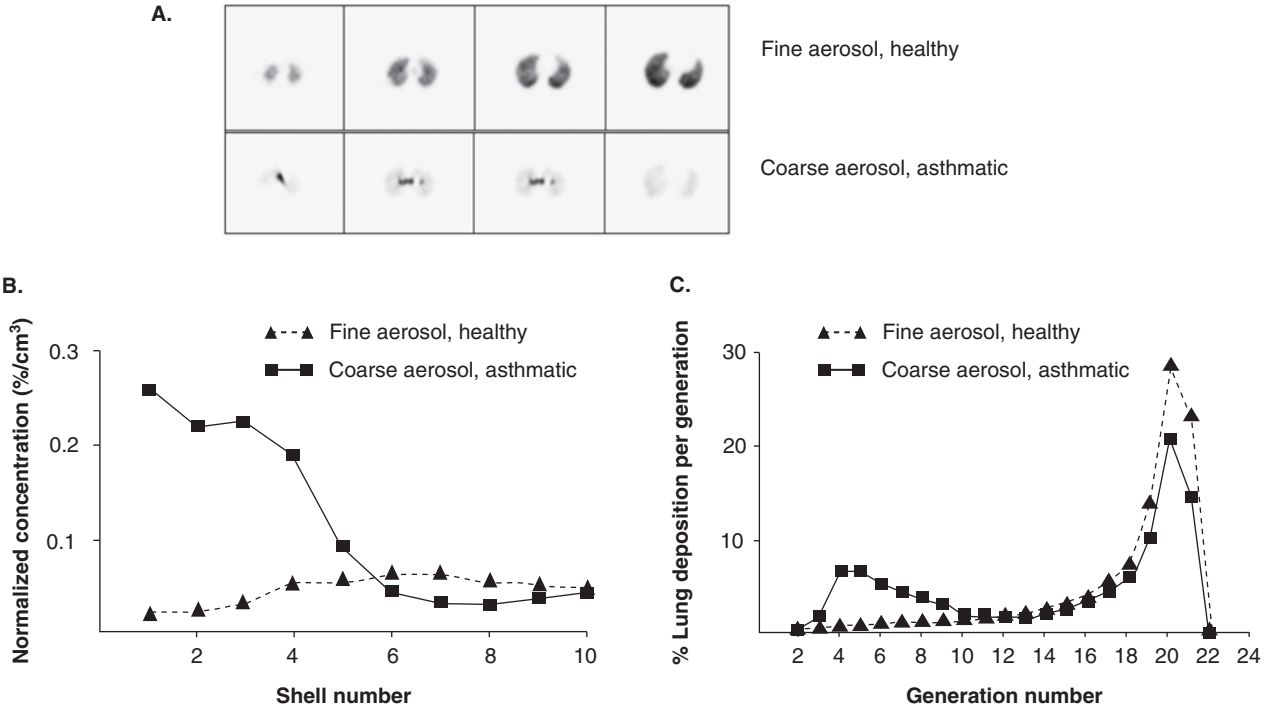

Figure 4. A. Example images from a single-photon-emission computed tomography study comparing the images obtained from a healthy subject breathing a fine (MMAD 2 μm) aerosol and an asthmatic patient breathing a coarse (MMAD 6 μm) aerosol. Transverse lung sections show a high concentration in central regions in the asthmatic subject, whereas the distribution in the healthy subject is much more uniform. This difference in distribution is reflected in the quantitative analysis (**B**) into 10 shells and (**C**) as deposition per generation.

Adapted from [61].

MMAD: Mass median aerodynamic diameter.

as in some transmission protocols [68], or immediately after it, as in SPECT/CT [51]. However, simulation studies have shown that the influence of misalignment in 3D imaging is much less critical than in gamma scintigraphy. Errors in P/C ratio of < 1%/mm of misalignment occur in three dimensions compared with 5%/mm in two dimensions [39]. Anatomical images acquired using a separate imaging device need to be aligned to the SPECT imaging position. This can be achieved using external markers placed at defined anatomical locations in each image [69], or using sophisticated multimodality image alignment tools [70]. Longer SPECT acquisitions may also incur error due to patient movement, and it is therefore important to keep the patient as still as possible during imaging. Methods have been described for both detecting and correcting for movement during tomographic acquisition [71].

The time required to complete lung imaging with SPECT is generally longer than the imaging time for gamma scintigraphy because the lungs must be imaged from multiple angles. For example, the time required for 32 pairs of 20-s images with a twin-headed gamma camera is ~ 10 min. During this time, radiotracer can be removed from the lungs by absorption or by mucociliary clearance depending on the nature of the radiolabel. One way of reducing imaging time would be to use a larger quantity of radiolabel, but of course this results in a higher radiation dose to the patient or volunteer as well as potentially increased exposure for laboratory and imaging staff. This problem can be addressed by using slowly absorbed or non-absorbed radiotracers, such as ^{99m}Tc-DTPA or ^{99m}Tc-colloid, respectively. These radiotracers can easily be added to liquid formulations delivered by nebulizers. However, they are removed from the central airways of the lungs by mucociliary clearance, and preferential loss of radiotracer from central airways could result in a significant error in the assessment of regional lung deposition. Correction may be made for losses of deposited particles that occur during the SPECT imaging sequence, from comparison of the whole lung radioactivity before and after SPECT imaging [51].

Slowly cleared radiotracers are generally preferred for SPECT studies, but DTPA cannot be used to label all formulations. A new radiolabeling method (Technecoat) for dry powder formulations has been developed, involving carbon nanoparticles (Technegas) labeled with ^{99m}Tc [72]. The Technegas particles coat the surface of drug particles, which can then be blended with lactose carrier. The clearance half-time of radiolabel was shown to be ~ 3 h, suggesting that the Technecoat method is suitable for use in SPECT studies with dry powder formulations [73]. Some formulations, such as those in many pMDIs, are most amenable to being radiolabeled with ^{99m}Tc as pertechnetate [6], which is rapidly removed from the lungs [28]. New radionuclide imaging methods suitable for SPECT studies of pMDIs need to be investigated [12].

The potential errors arising from rapid radiotracer clearance have also been addressed by 'fast' or 'rapid' SPECT, in which imaging time is markedly reduced [68,74]. Using a three-headed gamma camera, lung counts have been collected in 1-min clockwise and anticlockwise rotations of the detector heads, summed to make a 2-min image. Fast SPECT studies are also possible with twin-headed gamma cameras [75]. In common with many studies involving the administration of radioactive materials to man, a balance must be struck between the potentially conflicting requirements of using as little radioactivity as possible to minimize the radiation dose, completing the imaging as quickly as possible to prevent any change in distribution from occurring during imaging and obtaining as many counts as possible to achieve acceptable counting statistics. Fast SPECT aims to minimize any change in radiotracer distribution in the body, but requires care to be taken in selecting the amount of radiotracer used in order to find an acceptable balance between radiation dose and counting statistics. One group of investigators reported that it is necessary to deposit at least 10 MBq ^{99m}Tc in the lungs to get good image quality with a total imaging time of 2 min [56], and that the lungs may not be clearly delineated if the amount of radioactivity deposited there is < 5 MBq. However, the European Association of Nuclear Medicine guidelines for SPECT ventilation imaging suggest that a minimum of 25 MBq ^{99m}Tc should be deposited in the lungs, with a 10-min acquisition period [76]. The fast SPECT protocol described by Eberl *et al.* [56] includes several features to enable acceptable images to be obtained, all aimed at reducing noise in the reconstruction: a relatively high sensitivity collimator, an iterative reconstruction scheme with a small number of iterations and the omission of scatter correction. The last feature may limit the accuracy of quantification with this method. As in the case of gamma scintigraphy, there is a lack of standardization of methodology between different study centers, which makes the comparison of data obtained at different centers very challenging.

Radiation doses from different procedures are difficult to compare because they depend on many factors, including the radionuclide, its chemical form and its distribution in the body. Radiation doses from SPECT studies to assess pulmonary drug delivery are generally higher than those in gamma scintigraphy studies. Effective radiation doses estimated by investigators for gamma scintigraphy are in the range 0.02 – 0.7 mSv, associated with depositing from 2 to 20 MBq ^{99m}Tc in the lungs [77]. For some inhaler devices that are very inefficient, it could be necessary to deposit 100 MBq ^{99m}Tc in the body to achieve lung deposition of 10 MBq in a SPECT study. Despite these issues, the effective (whole body) radiation dose from a fast SPECT lung study was estimated not to exceed 1.3 mSv, which is relatively low compared with the dose from many nuclear medicine or radiological diagnostic procedures [56]. When estimating radiation dose from SPECT lung procedures, any extra dose from a CT scan used for co-registration purposes must be taken into account. Doses for CT of the lung may vary between 0.8 and 3.5 mSv depending on the protocol being adopted.

5. Positron-emission tomography

PET imaging involves dedicated scanners with a ring-shaped array of detector elements [78,79]. These detect coincidences between the pairs of 511 keV photons that are produced following positron decay. The emitted positron quickly meets an electron and annihilates, forming the two photons moving in opposite directions. The lines of response from many coincident events are stored on a data processing system and can be reconstructed to provide a 3D distribution of the positron-emitting radionuclide in the body. PET imaging presents distributions in a 3D array of voxels in a manner analogous to SPECT, but its resolution is superior, with FWHM in the region of 4 – 6 mm [12,80]. However, it has been questioned whether the resolution in the lungs is really this good because the emitted positrons may have longer ranges when they are stopped by low-density lung tissue [81]. Data presentation resembles that in SPECT, in other words the deposition pattern is quantified in sections through the lungs in transverse, coronal or sagittal planes, in a series of concentric shells, or as deposition per airway generation [82]. Autoradiographic images in dogs were shown to agree with the deposition pattern in the larger airway generations that had been quantified in a PET study [83], providing some degree of validation for data presentation as the amount deposited in different airway generations.

As ^{11}C, ^{13}N, ^{15}O and ^{18}F are all isotopes of elements that constitute drug molecules and are positron emitters, it is possible to incorporate a positron-emitting radiotracer in the structure of a drug molecule to produce a drug analogue that is chemically identical to the original product [80,84,85]. Direct labeling of a drug molecule eliminates the slight uncertainty in gamma scintigraphy and SPECT about what exactly is being imaged with a surrogate ^{99m}Tc label, that is, that ^{99m}Tc labeling only tells us about the deposition of radiolabeled particles. Direct labeling also allows drug clearance to be monitored in addition to drug deposition, so that PET provides information not only about drug deposition, but also its fate over time. Combined PET/CT devices, allowing accurate co-registration of PET images with anatomical data, are now available, analogous to SPECT/CT devices [81].

PET offers advantages in terms of using direct radiolabeling of drug molecules, achieving the best image resolution and being able to assess drug clearance as well as deposition (**Figure 5**). Hence, the reader may wonder why PET imaging is not the routine method for assessing regional lung distribution of inhaled drugs. Unfortunately, these important advantages are offset by a series of challenges that are mainly practical and logistical in nature.

An initial challenge is the development of a radiolabeled analogue of a drug molecule. Anecdotal evidence suggests that this can take months or even years to perfect, and can be very expensive. Budgets of US$1 million for radiolabeling development and validation have been suggested [80]. This issue alone could place PET imaging of pulmonary drug distribution outside the budget and, perhaps just as importantly, outside the timelines of most pharmaceutical company development programs.

PET hardware itself is also expensive, and investigators often need to find time on PET scanners that have busy clinical schedules. At present, there are still relatively few centers possessing PET scanners, whereas gamma cameras suitable for both gamma scintigraphy and SPECT are available in most hospitals large enough to possess a nuclear medicine department. Many PET scanners have fields of view that are too short ($\leq$ 20 cm) to include the entire lungs in a single image, and it may be necessary to take multiple images that can then be joined together [56]. This problem has been addressed by modern PET scanners with longer fields of view [12].

The radionuclides ^{11}C, ^{13}N and ^{15}O all have very short half-lifes (20, 9 and 2 min, respectively), which creates some issues. With the possible exception of ^{11}C, these radionuclides cannot realistically be generated off-site and transported to the imaging center, so an on-site cyclotron is needed. Once the radionuclide is available, the following sequence of events needs to occur: i) synthesis of the radiolabeled drug analogue; ii) possible incorporation of the radiolabeled drug into an inhaler device; iii) carrying out of quality control checks; iv) administration to the subject; and v) imaging. All this takes place with the radiolabel rapidly decaying, so that the amount of radionuclide required at the outset may be very high, and it may be difficult to ensure that the amount available at the time of administration is neither too high nor too low.

Bearing in mind these challenges, it is not surprising that PET has been used relatively little to assess the regional distribution of inhaled drugs, especially from multidose inhalers (pMDIs and dry powder inhalers). One study involved triamcinolone acetonide labeled with ^{11}C and delivered by pMDI [86], but only a few subjects were studied. Another possibility is to use the positron-emitting radionuclide ^{18}F, which has a half-life of 109 min, making it much more user-friendly. However, relatively few drug molecules contain an ^{18}F atom, fluticasone propionate being a notable exception [87]. If the drug molecule itself is not radiolabeled with the positron-emitting radionuclide, then one of the major potential advantages of PET is lost.

In nuclear medicine, PET imaging with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) has an important role because this radiopharmaceutical can reveal metabolically active areas such as tumors and areas of infection or inflammation [88]. ^{18}F-FDG has been used to label the contents of nebulizers, where it is mixed with the drug formulation [16], and also to label dry powder particles for delivery by dry powder inhaler [89]. Studies with nebulized ^{18}F-FDG have also been used investigate the change in aerosol distribution in asthmatic patients following treatment, and it has the potential to provide much fundamental information about the relationship between regional lung deposition of inhaled drugs and their effects [80,90]. The effective radiation dose from a PET study was estimated as 1.0 mSv for 37 MBq ^{18}F deposited in the lungs [16].

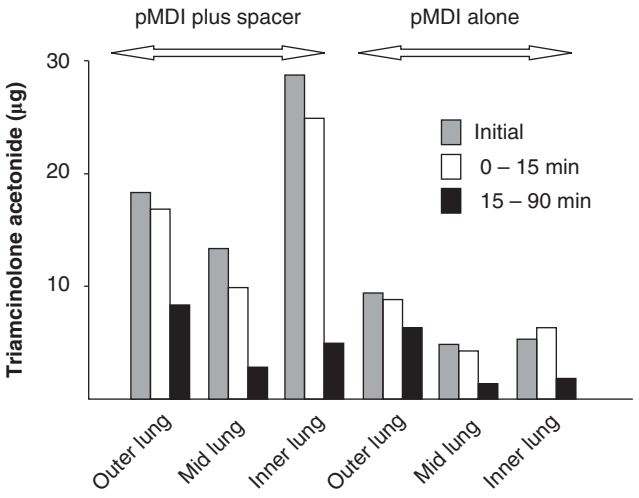

Figure 5. Deposition and clearance of ^{11}C-labeled TAA determined by positron-emission tomography imaging. The mean mass of TAA in 'outer', 'mid' and 'inner' lung zones is shown for studies using a pMDI with spacer, and pMDI alone, and for three time periods (initial, average of 0 – 15 min post-inhalation, and average of 15 – 90 min post-inhalation).

Adapted from [86].

pMDI: Pressurized-metered dose inhaler; TAA: Triamcinolone acetonide.

6. Conclusions

Both total and regional lung deposition of inhaled drugs are likely to be important for determining the efficacy and safety of inhaled drugs, and can be quantified by the radionuclide imaging methods of gamma scintigraphy, SPECT and PET. Gamma scintigraphy is considered the 'industry standard' for assessing deposition for new inhalers or formulations, but it is limited by expressing regional lung deposition only in two dimensions and by the use of ^{99m}Tc radiolabels. SPECT imaging is a 3D imaging method, which allows regional lung deposition to be quantified with greater precision than by gamma scintigraphy, and which may allow differences in regional lung deposition between two regimens to be detected more readily. However, like gamma scintigraphy, it uses ^{99m}Tc radiolabels rather than a radiolabel incorporated into the structure of a drug molecule. PET imaging uses positron-emitting radionuclides such as ^{11}C, which can be incorporated into the molecular structure of inhaled drugs. Regional distribution is presented in three dimensions and with the best resolution of the three radionuclide imaging methods. However, some significant practical issues have limited the use of PET for quantifying regional lung deposition of inhaled drugs, perhaps most notably the difficulties of producing a radiolabeled drug analogue and the very short half-lifes of the most suitable radionuclides. Despite their more challenging nature, 3D imaging methods should be considered as an alternative to gamma scintigraphy whenever the determination of regional lung deposition of pharmaceutical aerosols is a major study objective.

7. Expert opinion

Three radionuclide imaging methods are available for assessing pulmonary drug delivery, and each provides a range of challenges, as summarized in **Table 2**. How should investigators choose which method to use? Although gamma scintigraphy has attracted criticism and has even been described as semiquantitative, the general consensus is that this imaging modality is adequate for most purposes if the main study objective is to assess whole lung deposition [12]. This explains why gamma scintigraphy is still probably considered to be the 'industry standard'. However, when the assessment of regional lung deposition is equally or more important than the assessment of whole lung deposition, one of the 3D imaging methods (SPECT or PET) may be preferred, because these methods are much more capable of relating regional lung deposition to lung anatomy. Bearing in mind the logistical and technical challenges posed by PET studies to quantify regional lung deposition of inhaled drugs, SPECT may represent a more practical alternative.

Gamma scintigraphy provides some information about regional lung deposition, which has been shown to correlate with the relative amounts of deposition in ciliated and non-ciliated airways, based on the 24 h retention of an insoluble or poorly soluble radiolabel. The lack of correlation between whole lung deposition and regional lung deposition indices in gamma scintigraphy requires further investigation [54]. It might be anticipated that inhaler systems that achieve high whole lung deposition would also achieve a relatively peripheral distribution within the lungs. However, in practice the characteristics of pharmaceutical aerosols may prevent whole lung deposition and regional lung deposition from being closely related. Pharmaceutical aerosols are often heterodisperse in nature, in other words the aerosol spray or cloud contains particles and droplets with a wide spectrum of sizes. Deposition of the large particle component in the upper airways is likely to determine the fractionation of the dose between the upper airways and lungs, but if these larger particles do not enter the lungs then they cannot influence regional lung deposition. The lack of correlation between whole lung deposition and regional lung deposition confirms subjective impressions based on the appearance of scintigraphic images. In the authors' experience, a high whole lung deposition for some inhaler products may be combined with a very uniform distribution throughout the lung regions, and hence a high P/C ratio, but for other products may be combined with concentration of deposition in the central lung region and hence a low P/C ratio. Other studies [52,59] have shown that regional lung deposition patterns may be more sensitive to changes in particle size than changes in whole lung deposition and regional lung deposition. Poor correlation between regional lung

Table 2. Summary of major challenges in the assessment of regional deposition of inhaled drugs by gamma scintigraphy, SPECT and PET.

Gamma scintigraphy
Compression of lungs into two dimensions
Avoiding errors associated with rapid radiotracer clearance
Poor image resolution (FWHM 10 – 14 mm)
Regional differences in gamma ray attenuation
Stomach/lung overlap
Errors associated with inaccurate definition of lung regions
Drug molecule not radiolabeled
Lack of standardization of methodology limits inter-laboratory comparisons
SPECT
Avoiding errors associated with rapid radiotracer clearance
Poor image resolution (FWHM 10 – 14 mm)
Drug molecule not radiolabeled
New radiolabeling methods are required for some formulations
Validation of deposition per generation
Achieving correct balance between rapid imaging, low radiation dose and good counting statistics
Lack of standardization of methodology limits inter-laboratory comparisons
PET
Development of radiolabeled drug analogue may be difficult and time-consuming
Practical problems resulting from short radiotracer half-lifes
Expensive hardware
Nearby cyclotron and radiochemical expertise needed
Validation of deposition per generation
Short field of view may necessitate multiple lung images

FWHM: Full width half-maximum; PET: Positron-emission tomography; SPECT: Single-photon-emission computed tomography.

deposition and regional lung deposition may reflect the dependence of deposition on a wide variety of factors related to the characteristics of the aerosol being inhaled, the mode of inhalation and the airways of the subject [21].

SPECT imaging has enhanced our fundamental understanding of pulmonary drug delivery and has the capability to provide superior information about regional lung deposition compared with gamma scintigraphy, while using the same or similar gamma cameras and ^{99m}Tc radiolabeling methods. The ability to co-register SPECT images with 3D anatomical data obtained by MRI and SPECT is a powerful advantage. Imaging devices that allow combined SPECT and CT to be carried out without moving the subject are likely to provide the most accurate co-registration, although a potential drawback of using CT is the extra radiation dose. This could limit the number of replicate exposures that a subject can be allowed, and hence could limit the designs of study possible using combined SPECT and CT.

PET is the most complex imaging method used to assess pulmonary drug delivery, and several practical issues (radiolabeling issues, access to equipment and cost) are likely to limit its use. PET should not be used simply to compare two or more inhaler devices or formulations, but should be reserved for studies where it can provide unique information, including drug kinetics, interactions with receptors, and correlations between regional lung deposition, clearance and regional clinical effects. Although it may be easier to provide quantitative data with PET than with SPECT [91], the use of iterative algorithms ensures that quantitative imaging is also readily achievable with SPECT.

At present, there is no agreed methodological standardization between different study centers performing radionuclide imaging studies. This problem is particularly relevant to the assessment of regional lung deposition, for all three radionuclide imaging methods. For example, different study groups carrying out gamma scintigraphy studies divide the lungs into between 2 and 10 regions [12,42]. The regions have a variety of shapes, sometimes matching the lung borders and sometimes having right-angled corners. Comparison of regional lung deposition data between study centers is almost impossible at present, and some agreed common approach would be useful for future studies. It could also be applied retrospectively to past studies, although reanalyzing data from numerous old studies would be a huge workload. Standardization of methodology would have other benefits, for example helping to ensure the quality of radionuclide imaging data, and would ease some of the concerns expressed by regulators about data obtained with these techniques. The efforts of the ISAM working group, which is discussing these issues, are very much to be welcomed.

What other methodologies could be available to us in the future for assessing regional lung deposition of inhaled drugs in man? The use of iron oxide nanoparticles traced by MRI has been described in animal studies [92,93], but it is questionable whether such particles would be considered suitable as markers for drugs in human studies. Another possible future approach is mathematical modeling of deposition, which has become increasingly sophisticated in recent years. Simple modeling methods seem able to predict fairly accurately the partitioning of deposition between whole lung and upper airways [94-96]. More complex modeling methods can predict deposition in individual airway generations and at individual airway bifurcations [97,98], although of course such predictions are difficult to validate. We are probably many years away from being able to rely on modeling methods alone, although this is a possible long-term goal in the assessment of regional distribution of inhaled drugs.

Acknowledgment

J Fleming would like to acknowledge the support of the Southampton Respiratory Biomedical Research Unit funded by the UK National Institute of Health Research.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Selroos O, Pietinalho A, Riska H. Delivery devices for inhaled asthma medication: clinical implications of differences in effectiveness. Clin Immunother 1996;6:293-9
2. Ruffin RE, Montgomery JM, Newhouse MT. Site of beta-adrenergic receptors in the respiratory tract: use of fenoterol administered by two methods. Chest 1978;74:256-60
3. Collier JG, Dobbs RJ, Williams I. Salbutamol aerosol causes a tachycardia due to the inhaled rather than the swallowed fraction. Br J Clin Pharmacol 1980;9:273-4
4. Barnes PJ, Pedersen S, Busse W.W. Efficacy and safety of inhaled corticosteroids: new developments. Am J Respir Crit Care Med 1998;157:S1-53
5. Dolovich MB. Measuring total and regional lung deposition using inhaled radiotracers. J Aerosol Med 2001;14(Suppl 1):S35-44
6. Newman SP, Pitcairn GR, Hirst PH, Rankin L. Radionuclide imaging technologies and their use in evaluating asthma drug deposition in the lungs. Adv Drug Deliv Rev 2003;55:851-67
7. Berridge MS, Lee Z, Heald DL. Regional distribution and kinetics of inhaled pharmaceuticals. Curr Pharm Des 2000;6:1631-51
8. Newman S, Anderson P, Byron P, et al. Respiratory drug delivery: essential theory and practice. Richmond: RDD Online/ Virginia Commonwealth University, 2009
9. Borgstrom L, Nilsson M. A method for determination of the absolute pulmonary bioavailability of inhaled drugs: terbutaline. Pharm Res 1990;7:1068-70
10. Newman SP, Steed K, Hooper G, et al. Comparison of gamma scintigraphy and a pharmacokinetic technique for assessing pulmonary deposition of terbutaline sulphate delivered by pressurized metered dose inhaler. Pharm Res 1995;12:231-6
11. Hindle M, Chrystyn H. Determination of the relative bioavailability of salbutamol to the lung following inhalation. Br J Clin Pharmacol 1992;34:311-15
12. Scheuch G, Bennett W, Borgstrom L, et al. Deposition, imaging and clearance: what remains to be done? J Aerosol Med Pulm Drug Deliv 2010;23(Suppl 2):S39-57

•• **Describes current state-of-the-art in radionuclide imaging, with suggestions for future research.**

13. Everard ML, Dolovich MB. In vivo measurement of lung dose. In: Bisgaard H, O'Callaghan C, Smaldone GC, editors, Drug Delivery to the Lung. Marcel Dekker, New York; 2002. p. 173-209
14. Lee Z, Berridge MS, Nelson AD, Heald DL. The effect of scatter and attenuation on aerosol deposition as determined by gamma scintigraphy. J Aerosol Med 2001;14:167-83
15. Fleming JS, Conway JH. Three-dimensional imaging of aerosol deposition. J Aerosol Med 2001;14:147-53

• **Useful brief summary of 3D imaging methods.**

16. Dolovich M, Nahmias C, Coates G. Unleashing the PET: 3D imaging of the lung. In: Dalby RN, Byron PR, Farr SJ, et al. editors, Respiratory Drug Delivery VII. Serentec Press, Raleigh; 2000. p. 215-30
17. Pritchard JN. The influence of lung deposition on clinical response. J Aerosol Med 2001;14(Suppl 1):S19-26
18. Howarth PH. Why particle size should affect clinical response to inhaled therapy. J Aerosol Med 2001;14(Suppl 1):S27-34
19. Bennett WD, Brown JS, Zeman KL, et al. Targeting delivery of aerosols to different lung regions. J Aerosol Med 2002;15:179-88
20. Taylor G, Gumbleton M. Aerosols for macromolecule delivery: design challenges and solutions. Am J Drug Deliv 2004;2:143-55
21. Labiris NR, Dolovich MB. Pulmonary drug delivery. Part 1: physiological factors affecting therapeutic effectiveness of aerosolised medications. Br J Clin Pharmacol 2003;56:588-99
22. Weibel ER. Morphometry of the Human Lung. Academic Press, New York; 1963
23. Fleming JS, Quint M, Bolt L, et al. Comparison of SPECT aerosol deposition data with twenty-four-hour clearance measurements. J Aerosol Med 2006;19:261-7
24. Cherry SR, Sorenson JA, Phelps ME. Physics of nuclear medicine. Saunders, Philadelphia; 2003
25. Newman SP, Pitcairn GR. Gamma scintigraphy and SPECT. In: Lappin G, Temple S, editors, Radiotracers in Drug Development. Taylor and Francis, Boca Raton; 2006. p. 269-88
26. Walker PS, Petterson GL, Bondesson E, Conway JH. An advanced and detailed in vitro validation procedure for the radiolabelling of carrier-free terbutaline sulphate dry powder. J Aerosol Med 2001;14:227-36
27. Roller CM, Schaefer NC, Zhang G, Daviskas SG. In vitro validation of ^{99m}Tc-HFA-FP delivered via pMDI-spacer. J Aerosol Med 2006;19:254-60
28. Walker PS, Conway JH, Fleming JS, et al. Pulmonary clearance rate of two chemically different forms of inhaled pertechnetate. J Aerosol Med 2001;14:209-15
29. Hasani A, Agnew JE, Toms N, et al. Scintigraphic assessment of lung drug deposition distribution using a radiolabelled drug surrogate: significance of radiolabel transport post deposition as a source of error. In: Drug Delivery to the Lungs X. The Aerosol Society, Portishead; 1999. p. 96-9
30. Marthin JM, Mortensen J, Pressler T, et al. Pulmonary radioaerosol mucociliary clearance in diagnosis of pulmonary ciliary dyskinesia. Chest 2007;132:966-76
31. Mortensen J, Lange L, Nyboe J, et al. Lung mucociliary clearance. Eur J Nucl Med 1994;21:953-61
32. Coates AL, Green M, Leung K, et al. The challenges of quantitative measurement of lung deposition using ^{99m}Tc-DTPA from delivery systems with very different delivery times. J Aerosol Med 2007;20:320-30
33. Smaldone GC. Radionuclide scanning, respiratory physiology and pharmacokinetics. J Aerosol Med 2001;14:135-7
34. Newman SP, Chan H-K. In vitro - in vivo comparisons in pulmonary drug delivery. J Aerosol Med 2008;21:77-84

35. Borgstrom L, Olsson B, Thorsson L. Degree of throat deposition can explain the variability in lung deposition of inhaled drugs. J Aerosol Med 2006;19:473-83

36. Smaldone GC. Deposition patterns of nebulized drugs: is the pattern important? J Aerosol Med 1994;7(Suppl 1):S25-31

37. Agnew JE. Characterizing lung aerosol penetration. J Aerosol Med 1991;4:237-49

38. Dolovich MB. Practical aspects of imaging techniques employed to study aerosol deposition and clearance. In: Hickey AJ, editor, Pharmaceutical Inhalation Aerosol Technology. 2nd edition. Marcel Dekker, New York; 2003. p. 171-213

39. Fleming JS, Sauret V, Conway JH, et al. Evaluation of the accuracy and precision of lung aerosol deposition measurements from single-photon emission computed tomography using simulation. J Aerosol Med 2000;13:187-98

40. Biddiscombe M, Underwood R, Meah S, Usmani O. Gamma scintigraphy: how should we measure regional lung deposition? European Respiratory Society Annual Congress, Barcelona, 2010, e-poster

41. Schroeter JD, Pritchard JN, Hwang D, Martonen TB. Airway identification within planar gamma camera images using computer models of lung morphology. Pharm Res 2005;22:1692-9

42. Tossici-Bolt L, Fleming JS, Conway JH, Martonen TB. Analytical technique to recover the third dimension in planar imaging of inhaled aerosols: (1) impact on spatial quantification. J Aerosol Med 2006;19:565-79

43. Pitcairn GR, Newman SP. Tissue attenuation corrections in gamma scintigrpahy. J Aerosol Med 1997;3:187-98

44. Macey DJ, Marshall R. Absolute quantitation of radiotracer uptake in the lungs using a gamma camera. J Nucl Med 1982;23:731-5

45. Fleming JS, Conway JH, Bolt L, Holgate ST. A comparison of planar scintigraphy and SPECT measurement of total lung deposition of inhaled aerosol. J Aerosol Med 2003;16:9-19

• **Illustrates how SPECT imaging has more precision than γ scintigraphy for assessing regional lung deposition of inhaled drugs.**

46. Forge NI, Mountford PJ, O'Doherty MJ. Quantification of technetium-99m lung radioactivity from planar images. Eur J Nucl Med 1993;20:10-15

47. Fleming JS, Conway JH, Holgate ST, et al. Evaluation of the accuracy and precision of lung aerosol deposition measurements from planar imaging using simulation. Phys Med Biol 1998;43:2423-9

48. Coates AL, Dinh L, MacNeish CF, et al. Accounting for radioactivity before and after nebulization of tobramycin to ensure accuracy of quantification of lung deposition. J Aerosol Med 2000;13:169-78

49. Taylor G, Warren SJ. Methods for tissue attenuation correction in inhalation pharmaceutical scintigraphy studies. In: Dalby RN, Byron PR, Peart J, et al. editors, Respiratory Drug Delivery 2010. Davis Healthcare International, River Grove, Illinois; 2010. p. 929-33

50. Moller W, Felten K, Meyer G, et al. Corrections in dose assessment of Tc-99m radiolabeled aerosol particles targeted to central human airways using planar gamma camera imaging. J Aerosol Med Pulm Drug Deliv 2009;22:45-54

51. Fleming JS, Conway JH, Majoral C, et al. The use of SPECT-CT to assess the fate of inhaled aerosol. J Aerosol Med Pulm Drug Deliv 2011;24:49-60

•• **Describes the use of combined SPECT and CT with a single imaging device, for assessing regional lung deposition.**

52. Newman SP, Hirst PH, Pitcairn GR, Clark AR. Understanding regional lung deposition in gamma scintigraphy. In: Dalby RN, Byron PR, Farr SJ, editors, Respiratory Drug Delivery VI. Interpharm Press, Buffalo Grove; 1998. p. 9-15

53. Fleming JS, Halson P, Conway J, et al. Three-dimensional description of pulmonary deposition of inhaled aerosol using data from multimodality imaging. J Nucl Med 1996;37:873-7

54. Clark AR. Beyond the throat: preferred methods of assessing regional distribution in the lung. In: Dalby RN, Byron PR, Peart J, et al. editors, Respiratory Drug Delivery 2010. Davis Healthcare International, River Grove; 2010. p. 235-44

55. Camner P, Philipson K. Human alveolar deposition of 4 μm Teflon particles. Arch Environ Health 1978;36:171-5

56. Eberl S, Chan H-K, Daviskas E. SPECT imaging for radioaerosol deposition and clearance studies. J Aerosol Med 2006;19:8-20

•• **Useful review of SPECT imaging, including 'fast' SPECT.**

57. Lawson RS. SPECT reconstruction. In: Mathematical Techniques in Nuclear Medicine IPEM Report 100, Institute of Physics and Engineering in Medicine, New York, 2011. p. 172-244

58. Glover W, Chan H-K, Eberl S, et al. Lung deposition of mannitol powder aerosol in healthy subjects. J Aerosol Med 2006;19:522-33

59. Fleming JS, Hashish AH, Conway JH, et al. Assessment of deposition of inhaled aerosol in the respiratory tract of man using three-dimensional multimodality imaging and mathematical modeling. J Aerosol Med 1996;9:317-27

60. Rousset OG, Ma Y, Evans AC. Correction for partial volume effects in PET: principle and validation. J Nucl Med 1998;39:904-11

61. Fleming JS. Measuring drug deposition by airway generation in humans. In: Dalby RN, Byron PR, Peart J, et al. editors, Respiratory Drug Delivery IX. Davis Healthcare International, River Grove; 2004. p. 187-93

• **Review of SPECT imaging for assessing deposition in individual airway generations.**

62. Phipps PR, Gonda I, Bailey DL, et al. Comparisons of planar and tomographic gamma scintigraphy to measure the penetration index of inhaled aerosols. Am Rev Respir Dis 1989;139:1516-23

63. Bocher M, Balan A, Krausz Y, et al. Gamma camera-mounted anatomical X-ray tomography: technology, system characteristics and first images. Eur J Nucl Med 2000;27:619-27

64. Fleming JS, Sauret V, Conway JH, Martonen TB. Validation of the conceptual anatomical model of the lung airway. J Aerosol Med 2004;17:260-9

65. Tawhai MH, Pullan AJ, Hunter PJ. Generation of an anatomically based three-dimensional model of the

conducting airways. Ann Biomed Eng 2000;28:793-802

66. Martonen TB, Schroeter JD Fleming JS. 3D in-silico modelling of the human respiratory system for inhaled drug delivery and imaging analysis. J Pharm Sci 2007;96:603-17

67. Fleming JS, Conway JH, Holgate ST, et al. Comparison of methods for deriving aerosol deposition by aerosol generation from three-dimensional radionuclide imaging. J Aerosol Sci 2000;31:1251-9

68. Eberl S, Chan H-K, Daviskas E, et al. Aerosol deposition and clearance measurement: a novel technique using dynamic SPET. Eur J Nucl Med 2001;28:1365-72

69. Hill DLG, Hawkes DJ, Crossman JF, et al. Registration of MR and CT images for skull base surgery using point like anatomical features. Brit J Radiol 1991;64:1030-5

70. Hawkes DJ. Algorithms for radiological image registration and their clinical applications. J Anat 1998;193:347-61

71. Kyme AZ, Hutton BF, Hatton RL, et al. Practical aspects of a data-driven motion correction approach for brain SPECT. IEEE Trans Med Imaging 2003;22:722-9

72. Pitcairn G, James J, Joyson A, et al. TechneCoat: a novel method for radiolabelling dry powder formulations in radionuclide imaging studies. In: Dalby RN, Byron PR, Peart J, et al. editors, Respiratory Drug Delivery VIII. Davis Horwood, Raleigh; 2002. p. 553-6

73. Ito H, Pitcairn G, Hirst P, et al. An in vivo study to assess the suitability of Technegas as a SPECT imaging agent for pulmonary drug formulations. In: Dalby RN, Byron PR, Peart J, et al, editors, Respiratory Drug Delivery VIII. Davis Horwood, Raleigh; 2002. p. 439-42

74. Chan H-K, Eberl S, Daviskas E, et al. Changes in lung deposition of aerosols due to hygroscopic growth. A fast SPECT study. J Aerosol Med 2002;15:307-11

75. Conway JH, Walker P, Fleming JS, et al. Three-dimensional description of the deposition of inhaled terbutaline sulphate administered via Turbuhaler. In: Dalby RN, Byron PR, Farr SJ, et al, editors, Respiratory Drug Delivery VII. Serentec Press, Raleigh; 2000. p. 607-9

76. Bajc M, Neilly JB, Miniati M, et al. EANM guidelines for ventilation/perfusion scintigraphy: part 1 pulmonary imaging with ventilation/perfusion single photon emission tomography. Eur J Nucl Med 2009;36:1356-70

77. Bennett WD, Daviskas E, Hasani A, et al. Mucociliary and cough clearance as a biomarker for therapeutic development. J Aerosol Med Pulm Drug Deliv 2010;23:261-72

78. Rhodes CG, Hughes JMB. Pulmonary studies using positron emission tomography. Eur Respir J 1995;8:1001-17

79. Lee Z, Berridge MS. PET imaging-based evaluation of aerosol drugs and their delivery devices: nasal and pulmonary studies. IEEE Trans Med Imaging 2002;21:1324-31

80. Dolovich MB. 18F-fluorodeoxyglucose positron emission tomographic imaging of pulmonary functions, pathology, and drug delivery. Proc Am Thorac Soc 2009;6:477-85

•• **Review of use of PET imaging in the assessment of pulmonary drug delivery.**

81. Bailey DL. Imaging the airways in 2006. J Aerosol Med 2006;19:1-7

82. Lee Z, Berridge MS, Finlay WH, Heald DL. Mapping PET-measured triamcinolone acetonide aerosol distribution into deposition by airway generation. Int J Pharm 2000;199:7-16

83. Weinberg BD, Schomisch SA, Rahmatall M, et al. Mapping of PET-measured aerosol deposition: a comparison study. J Aerosol Sci 2005;36:1157-76

84. Pike VW. The status of PET radiochemistry for drug development and evaluation. Drug Inform J 1997;31:997-1013

85. Aboagye EO, Price PM, Jones T. In vivo pharmacokinetics and pharmacodynamics in drug development using positron-emitting tomography. Drug Discov Today 2001;6:293-302

86. Berridge MS, Lee Z, Heald DL. Pulmonary distribution and kinetics of inhaled ^{11}C triamcinolone acetonide. J Nucl Med 2000;41:1603-11

•• **Assessment of regional lung deposition and clearance for an inhaled drug labeled with 11C.**

87. Constantinou M, Waters SL, Steel CJ, et al. Flixotide pressurized metered dose inhalers loaded with ^{18}F-fluticasone dipropionate particles for drug deposition studies in humans with PET – formulation and analysis. J Label Comp Radiopharm 2004;47:55-70

88. Basu S, Alavi A. Unparalleled contribution of ^{18}F-FDG PET to medicine over 3 decades. J Nucl Med 2008;49:17N-21N and 37N

89. Yanai M, Hatazawa J, Ojima F, et al. Deposition and clearance of inhaled 18FDG powder in patients with chronic obstructive pulmonary disease. Eur Respir J 1998;11:1342-8

90. Dolovich M, Labiris R. Imaging drug delivery and drug responses in the lung. Proc Am Thorac Soc 2004;1:329-37

91. Berridge MS, Heald DL, Lee Z. Imaging studies of biodistribution and kinetics in drug development. Drug Dev Res 2003;59:208-26

92. Martin AR, Thompson RB, Finlay WH. MRI measurement of regional lung deposition in mice exposed nose-only to nebulized superparamagnetic iron oxide particles. J Aerosol Med Pulm Drug Deliv 2008;21:335-42

93. Martin AR, Redman GES, Waszak P, et al. Influence of an externally applied magnetic field on the regional deposition patterns of iron oxide loaded high aspect ratio particles in mechanically ventilated rabbits. In: Dalby RN, Byron PR, Peart J, et al. editors, Respiratory Drug Delivery 2010. Davis Healthcare International, River Grove; 2010. p. 785-9

94. Thiel CG. Can in vitro particle size measurements be used to predict pulmonary deposition of aerosol from inhalers? J Aerosol Med 1998;11(Suppl 1):S43-52

95. Finlay WH, Martin AR. Recent advances in predictive understanding of respiratory tract deposition. J Aerosol Med Pulm Drug Deliv 2008;21:189-206

96. Byron PR, Hindle M, Lange CF, et al. In vivo–in vitro correlations: predicting pulmonary drug deposition from pharmaceutical aerosols. J Aerosol Med Pulm Drug Deliv 2010;23(Suppl 2):S59-69

97. Martonen TB, Musante CJ, Segal RA, et al. Lung models: strengths and limitations. Respir Care 2000;45:712-36

98. Martonen TB, Smyth HD, Isaacs KK, Burton RT. Issues in drug delivery: concepts and practice. Respir Care 2005;50:1228-52

• **Review of state-of-the-art for mathematical modeling of deposition.**

Affiliation

Stephen Newman[†1] PhD & John Fleming[2] PhD
[†]Author for correspondence
[1]Scientific Consultant,
6 Nelson Drive, Hunstanton,
Norfolk PE36 5DU, UK
E-mail: steve.newman@physics.org
[2]Professor,
Respiratory Biomedical Research Unit,
Southampton University Hospitals NHS Trust,
Southampton SO16 6YD, UK