Tomographic Imaging of Small Airways

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Key Words

Pulmonary imaging • Tomographic imaging • Ventilation imaging

Abstract

Three-dimensional lung imaging has become a routine investigation in clinical medicine. The clinical needs have driven the development of tomographic imaging, as much as the research into better imaging itself has driven some of the improvements in imaging. There has been a steady stream of publications in which tomographic imaging has been used to measure small airway structure and function in obstructive airway diseases. These data provide unique insights and information on pulmonary physiology because they provide direct measurements of the airways, rather than global information from lung function, and they provide topographical information, i.e. spatial distribution. Their utility is magnified when combined with other information such as lung function. In this article, the application of topographic imaging in relation to small airway function is discussed.

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Background

The small airways have long been considered an important if not critical location of common airway diseases of asthma, chronic obstructive airway disease (COPD), and

bronchiectasis. It is the predominant site of disease in obliterative bronchiolitis. Measurements of small airway function are improving with the refinement of noninvasive measures of function, such as multiple breath nitrogen washout (MBNW) and the forced oscillation technique (FOT) [1]. However, these measures are global in nature. Pulmonary imaging has the potential to provide direct measurements of small airway structure and function, which complements global measurements of airway function because of the spatial nature of the data. The unique and likely very important information that arises from imaging of small airways is the topography of disease. The potential importance of the topography of disease is inferred from the global studies in which results indicate that aberrations in ventilation distribution are not only universal but also an early manifestation of disease [2].

Small airway disease in asthma, COPD, and bronchiectasis causes ventilation to become increasingly uneven, and this is commonly referred to as ventilation heterogeneity. Thus, change in ventilation distribution is the basis of abnormal function measured by the FOT [3] and by inert gas washouts [4–6], both of which are considered to

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be functional measures of small airway disease. Both FOT and MBNW are theoretically capable of probing different small airway compartments. The FOT probes the lung periphery by use of lower oscillation frequencies, usually below the resonant frequency (6–8 Hz) [7]. The MBNW can be analyzed to provide an index of ventilation heterogeneity in the lung periphery at the diffusion front and an index in more proximal small airways where ventilation heterogeneity is due predominantly to convective flow-related heterogeneity [6]. Washouts of gases of differing density allow probing of distal versus more proximal lung compartments [5].

Although airway diseases may indeed involve all of the airways within a lung, the functional consequences are that ventilation becomes patchy and uneven (heterogeneous). Heterogeneous ventilation is visible by imaging, which suggests that uneven ventilation (and presumably abnormal airway structure and function) is present at relatively large length scales in comparison to the size of the small airways in question. The critical advance in the use of imaging to study small airways was the linking of small airway function to the observed patterns of ventilation. The large ventilation defects on imaging likely reflect small airway function as much large airway function. Support for this concept has arisen from multi-modality studies as discussed below. It is likely that imaging needs to be combined with other tools, i.e. lung function and modeling, to be useful [8].

The most prevalent data from imaging studies in airway disease is structural information from high-resolution computed tomography (HRCT). The resolution of HRCT is such that only large and medium sized airways can be measured, particularly when the x, y, and z voxel dimensions approximate $0.5 \times 0.5 \times 1$ mm. Given the thinness of airway walls, the z-axis thickness of 1 mm of current scanners means that, presently, the small airways are beyond the resolution of structural imaging. However, very high resolution structural imaging may be possible in the future if fine-beam technology such as synchrotron radiation can be sufficiently developed to allow in vivo imaging within the limits of radiation safety. Ventilation imaging is useful for examining the function of small airways given that disease causes ventilation abnormalities to occur in localized regions of sufficient size to be visible by functional imaging. Positron emission tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI) have been used in this way and their findings are relevant to small airway disease.

Positron Emission Tomography

Positron emission tomography is routinely used in clinical nuclear medicine for functional imaging. Its common application in respiratory medicine is for the detection of malignant metastases, particularly bronchogenic carcinoma, where 18 fluoro-deoxy glucose is commonly used as a marker. The annihilation of protons when they collide with electrons produces gamma radiation energy. The detectors register a gamma radiation source when detectors that are opposite each other simultaneously detect gamma rays.

Nitrogen 13 has been used for ventilation imaging by being dissolved in saline and then injected intravenously [9]. It enters the pulmonary circulation where it rapidly diffuses from the capillary blood to the alveolus. Therefore, the injection is done during a voluntary apnea, which allows time for the radioactive nitrogen to enter the lungs. Breathing then commences and the radioactive nitrogen is 'washed out' of the lungs and the topographical pattern of ventilation can then be measured. PET data therefore includes regional perfusion and regional ventilation with a time component. PET studies, therefore, are conducted entirely in the supine, decubitus, or prone position [10] and therefore represent ventilation and perfusion in those positions. Also, current technology only allows part of the lung to be visualized, although imaging of the entire lung will likely be used in the very near future.

The PET method is powerful in that it provides regional ventilation images, but it has been the interpretation of the results with computational modeling that has led to the most significant advances in the understanding of airway disease. In asthma, the occurrence of regional hypoventilation that can in some instances be very severe, suggesting complete closure of the airways, has long been known from ventilation imaging [11]. In fact, such severe regional heterogeneity is a common occurrence in routine ventilation/perfusion (V/Q) imaging in nuclear medicine for the diagnosis of suspected pulmonary embolism. This regional hypoventilation and closure has been interpreted using computational models of ventilation, making use of the time dimension that is also present in PET data, and also using lung mechanics information that was simultaneously measured [12–14]. In effect, this type of modeling of the data allows inferences of events occurring at a resolution below the level of the imaging itself.

The regions of hypoventilation and closure that are evident on PET images of asthmatics, particularly during bronchoconstriction, at first inspection suggest that se-

vere narrowing and closure of large airways are the predominant physiological abnormality. However, the results of the modeling studies suggest that narrowing and closure in fact starts at the level of the small airways and proceeds towards the airway opening in a cascading manner [12]. Such cascading behavior was predicted in fact prior to three-dimensional imaging studies [15], but from the point of view of airway opening rather than airway closure. Modeling airway narrowing and closure of small airways only, large airways only, and the combination of both small and large airways led to the conclusion that the mechanical changes in the lung with bronchoconstriction could only be caused by widespread narrowing in the small airways that is accompanied by severe narrowing or closure of a larger airway [13, 16].

PET data have also suggested that the bimodal distributions of V/Q ratios observed in asthma are due to V/Q inequality occurring within these regions of hypoventilation and closure [9]. In asthma ventilation heterogeneity occurring at a relatively large scale produces regions that are contiguous and obvious on three-dimensional ventilation and perfusion images, but within these regions there is heterogeneity at the 'sub-resolution level', which determines V/Q distributions and gas exchange.

Magnetic Resonance Imaging

MRI has gained increasing recognition in recent years as a modality for measuring regional ventilation and, by inference, small airway function. Imaging, however, requires enhancement using, for example, hyperpolarized helium 3 (He3), a by-product of nuclear weapon production or with hyperpolarized xenon [17]. Because of the limited availability of He3 [18], its use has been highly restricted and the majority of studies arise from North America.

Unlike PET, it is a measure of ventilation whereby He3 enters the lung by inhalation while the patient is lying in the MR scanner. It is also a measure from which function can be measured in the supine, decubitus, or prone position. Its entry into the lung is not dependent on perfusion but rather on the regional time constants. Because it is a true gas, it is able to diffuse and, therefore, the resultant distribution of He3 represents both convective flow and diffusive gas flow. He3 MR images have shown results qualitatively similar to those of PET studies, i.e. that there is patchy ventilation [19] and regions of severe hypoventilation or closure in asthma, particularly in uncontrolled asthma [20] and after bronchoconstriction [21].

One parameter that has potential for measuring small airway function is the apparent diffusion coefficient (ADC) [22]. The ADC is a measurement of the movement of He3 molecules by Brownian motion within the lung and is measured over short time scales and long time scales. The short time scale measurement indicates movement over very short distances that are around the dimensions of the alveolus. It, therefore, is increased in emphysema and strongly correlates with morphometric indices of emphysema in excised lung tissue [22]. The long time scale measures helium molecule movement over distances of the order of the size of the acinus [23].

He3 diffusion studies suggest that both short length scale diffusion and long length scale diffusion of He3 are increased in COPD [24], representing alveolar destruction and emphysema and well-developed collateral ventilation, respectively. The increased long ADC is interesting in terms of small airway function in that it likely represents increases in flow through collateral channels, which are known to be highly developed in COPD and can account for a significant proportion of total pulmonary airflow [25]. Three-dimensional maps of the long ADC have been generated showing the topographical distribution of what is likely to be collateral ventilation [24]. Movement of He3 from a well-ventilated region into a nonventilated region during a breath hold was described in a recent MRI study of a group of moderate and severe COPD patients [23]. Although this observation is circumstantial, it is consistent with gas movement via collateral channels even though some movement may have been via pendelluft, i.e. reverse directional flow out of one unit via its subtending airway and into a close-by unit.

Thus ADC data may reflect similar abnormalities in small airway function as represented by MBNW, particularly the index representing heterogeneities related to diffusion-convection interactions. Helium is less dense than air and, consequently, diffusion occurs more proximally. However, to date there are no published studies in which He3 MRI and MBNW have been combined to study small airway disease. The ADC will be unlikely to be used routinely as a sensitive index of early smoking-related emphysema and small airway disease, particularly given the cost, complexity, lack of availability of He3, and simplicity of MBNW. However, it may have specific research applications based on the topographical information, such as in studying disease mechanisms and drug responses.

Interestingly, the short and long ADC are also increased in asthma compared with control subjects, although not as much as in COPD [24]. The mechanisms which explain the increase in long ADC are unknown.

Fig. 1. HRCT scan of a patient who has obliterative bronchiolitis complicating allogeneic hematopoietic stem cell transplantation. Some small airways are visible, although they are slightly dilated compared with the accompanying blood vessel.

However, there is evidence that the resistance of collateral channels and respiratory airways is increased in asthmatics, which accounts for the increase in peripheral lung resistance [26]. Therefore, the observed increase in long ADC most likely represents different pathways of gas movement in the lung periphery in asthma, compared with COPD, and hence represents different abnormalities of function.

High-Resolution Computed Tomography

HRCT has been used to measure ventilation and airway wall structure in asthma and COPD (fig. 1). There is a very large body of HRCT studies aimed at examining airway structure and a smaller body of published data looking at function, including regional ventilation, gas trapping, and airway responses in relation to lung inflation. Structural imaging, like any measurement technique, has potential errors associated with it and there is some published data on calibrating or validating the accuracy of these airway measurements [27–33] (table 1).

The resolution of HRCT scanners in routine clinical use is too low to be able to resolve the small airways with any level of reliability [32, 34–36, 88]. However, findings from an important study in which excised lung lobes were scanned when quick frozen in inflation and subsequently examined morphometrically after inflation fixation suggest that there is a moderate-to-strong corre-

lation between the dimensions of the large and small airways [37]. The important implication of this observation is obvious: it infers that the increase in airway wall thickness in asthma that has been obvious in HRCT studies could similarly represent thickening of the small airways. Although this may be true in healthy airways and smokers, this remains an assumption in asthma since no equivalent correlative studies have been done on this disease, likely due to the scarcity of asthmatic lungs for scientific study.

Asthmatic airway walls are clearly thicker than non-asthmatic and COPD airway walls [38–40]. In asthma, the wall thickness correlates with increased reticular basement membrane thickness measured from bronchoscopic bronchial biopsies of large airways [41, 42]. Given the fact that reticular basement membrane thickness in large airways correlates with that in small cartilaginous airways, although not in membranous airways [43], there is a reasonable probability that large airway dimensions correlate with at least small cartilaginous airways in asthma. Interestingly, the increased airway wall thickness measured by HRCT correlates *inversely* with airway hyperresponsiveness (AHR), suggesting that airway wall thickening may protect against excessive airway narrowing [44]. This interesting observation requires independent confirmation but it is interesting that this is one of the few or only publications describing a relationship between airway wall thickness on HRCT and AHR in asthma, while the absence of a relationship has been reported in other studies [45, 46]. The strong relationship between small airway dysfunction, measured by nitrogen washout, and AHR [47] remains unexplained and, to date, HRCT studies have not contributed to understanding the underlying mechanisms. If small airway disease in asthma is due to airway wall remodeling and thickening, then one would expect a positive relationship between airway wall thickness on HRCT and the severity of AHR.

Apart from observations of differences in airway wall thickness between asthmatics and normal subjects, there have been surprisingly few insights gained from the many HRCT studies of airways in asthma. The nature of airway-narrowing asthma differs from normal by being more heterogeneous, i.e. some airways may narrow severely and close while other airways may even dilate [33, 48, 49]. Although small airways were not measured sufficiently reliably in these studies, it is likely or possible that the small airways narrowed in a similar pattern. Another important observation is the reduction in airway wall thickness with inhaled corticosteroid treatment [50,

Table 1. Comparisons of the strengths and weaknesses of the imaging modalities discussed in this paper

Modality	Strengths	Weaknesses
PET	Hardware availability in most institutions. Short $t_{1/2}$ allows multiple studies in a single session. Fusion imaging with CT combines ventilation with structure.	PET radiopharmaceutical generation and cost. Radiation exposure. Does not image the entire lung. Unable to image the small airways directly.
MRI	Hardware availability in most institutions. No radiation exposure. Multiple studies can be done in a single session.	Often high clinical demands reducing research access. High cost. Highly restricted access to He3. Potential claustrophobia within a narrow coil. Unable to image the small airways directly.
HRCT	Hardware availability in most institutions and usually high availability for research. Direct visualization of airways including some small airways, as well as indirect small airway measurement (gas trapping)	Radiation exposure. Difficult and complex image analysis algorithms to measure airway dimensions.
SPECT	Hardware availability in most institutions and usually high availability for research. Fusion imaging with CT combines ventilation with structure.	Radiation exposure. Potential upright inhalation of ventilation agent. Limited availability of Technegas ventilation agent.
Cone beam CT	High resolution sufficient to resolve small airway walls for in vivo imaging.	Radiation exposure. Not yet developed for lung imaging.
Micro-CT	Availability in most large research institutions. Ultra-high resolution which allows direct measurement of small airways.	Only for explanted tissues and whole, dead animals.
Synchrotron beam	Ultra-high spatial resolution which allows direct measurement of small airways. Live animal imaging. Relatively high imaging field of view. High temporal resolution allows imaging of ventilation.	Very limited number of machines. High cost. Ultra-high resolution which allows direct measurements of small airways. Not available for human imaging.

51], which may have been due to successful treatment of inflammation. Whether there were similar changes in small airway wall structure remains unknown.

Airway closure is a clinically important pathophysiological abnormality of asthma. Closure occurs in healthy individuals but is increased in asthmatics where it is associated with more severe disease as indicated by an increased risk of exacerbations [52, 53]. The site of closure is the terminal bronchiole in health [54]; however, in airway disease the site of closure will almost certainly be more variable and have a more variable distribution, and may affect a greater volume of the lung, as suggested by observations from a variety of imaging methods [9, 20, 55, 56].

Airway closure can be measured by HRCT by measuring gas trapping where on exhalation a region of the lung may not deflate normally because of a combination

of severe narrowing and closure [55, 57]. The lung parenchyma is much easier to measure than airway dimensions and, theoretically, in asthma, gas trapping should be a good measurement of small airway disease (probably better than direct HRCT measurement of the airways themselves). There is the assumption, nevertheless, that the elastic properties of the lung are close to normal such that any lack of deflation during exhalation is due to airway disease rather than parenchymal disease. Although there is very clear evidence that lung elastic recoil is reduced globally in asthmatics [58–61], it is probably a reasonable assumption that regional air trapping observed in expiratory HRCT is due predominantly to airway disease rather than to a localized increase in parenchymal compliance. In COPD, however, the presence of emphysema makes interpretation of expiratory CT studies difficult, where localized gas trap-

ping could be due to emphysema, airway disease, or a combination of both.

Improvements in air trapping induced by bronchial challenge have been observed after treatment with fine-particle beclomethasone [57, 62] and after treatment with montelukast [55]. Given that the site of airway closure is probably around the small airways at the acinar entrance [63] or perhaps more proximally in asthma, gas trapping on HRCT should be a good measure of small airway disease. Although HRCT has currently been unable to provide data on structural changes of small airways with treatment (though there is evidence of change in large airways), the HRCT data of gas trapping confirm that the distribution of abnormalities is regional in nature, i.e. there is increased topographical heterogeneity of abnormal function. The regional nature of small airway abnormalities is in keeping with that seen on ventilation studies [9, 20, 56].

Regional gas trapping on expiratory CT is associated with certain phenotypic characteristics of asthma [64]. More gas trapping seen on scans done at FRC in an asthma cohort was associated with more severe asthma, neutrophilic inflammation, longer duration of asthma, and airflow obstruction by multivariate logistic regression. These findings suggest that severe asthma is associated with greater small airway disease and this again is consistent with noninvasive lung function studies of small airways [52, 53, 65].

Another HRCT method that is potentially a measure of small airway function is ventilation imaging using xenon gas enhancement. Xenon is radio-opaque and has minimal but significant absorption from the lung. A dynamic CT image series can be taken while breathing from a one-way circuit containing a known concentration of xenon (wash-in), from which the structural soft tissue elements are subtracted resulting in image data of the xenon concentration. Regional ventilation has been measured from the dynamic time-based series of images [66, 67]. Regional ventilation distribution has also been measured after a wash-in period where asthmatic subjects breathed a 30% mixture of xenon, after which a single volumetric image was obtained during a breath-hold using dual-energy CT [68]. How much these image data reflect small airway function is speculative since, as for all imaging-derived regional ventilation data, it is uncertain how the topographical variations in ventilation are due to small airway disease or to large airway narrowing. Hence the importance of computational modeling that suggested that regional clusters of nonventilation, due to closure and near closure, were dependent on the hetero-

geneous caliber of small airways [12, 13, 16]. Radiation exposure, the practical difficulties of xenon administration, and the complex image processing are significant considerations for more widespread use of this technique in research.

Single Photon Emission Computed Tomography

SPECT is a three-dimensional imaging method used routinely in clinical nuclear medicine. Ventilation-perfusion SPECT for diagnosis of suspected pulmonary embolism is increasingly used because of its high sensitivity and specificity [69]. However, its application for measuring ventilation distribution has been relatively sparse [56, 70–78] (table 1). As a functional imaging technique, SPECT provides data on the topographical distribution of ventilation. Again, the interpretation of the distribution of ventilation in relation to small airway disease is theoretical, with no corroborative experimental studies to confirm the theoretical constructs.

Common radioactive ventilation markers used for SPECT imaging are Technegas, diethylene triamine penta-acetic acid (DTPA) aqueous aerosol, and xenon-133 gas. The physical properties of these agents are pertinent to how the data are interpreted in relation to the diseases being studied with these techniques. DTPA is a poor agent for imaging ventilation because of its large particle size. Once inhaled, the particles agglomerate and, along with their charge, alter their distribution [79], while alveolar deposition is also poor. Technegas, being an ultra-fine carbon particle aerosol of median particle diameter of around 150 nm [80], may impact airways where there is critical narrowing, where it has been suggested choke points exist in asthmatics [81]; this is clearly a large airway phenomenon. Technegas has a high peripheral deposition pattern which is stable and allows upright inhalation [78], which cannot be achieved with inert gas methods. Being a carbon particle, it is unlikely to reflect diffusive gas mixing in the lung and therefore is unlikely to be influenced by collateral ventilation. Because xenon is an inert gas it is likely distributed by both convective gas transport along small airways and diffusive movement via collateral channels. Krypton-81m has also been used but has a much shorter half-life of a few seconds [82] compared with the half-life of xenon-133 of several days. Therefore, these physical differences in tracer properties in relation to differences in study methodologies that are necessary, plus the physiologic differences in ventilation in disease, e.g. asthma versus COPD, make the interpre-

Fig. 2. a SPECT/CT fusion Technegas imaging of an asthmatic patient at baseline. Ventilation is mildly heterogeneous. The lack of apparent ventilation to the lung periphery is likely due to insufficient resolution to detect low ventilation. **b** Ventilation imaging post-methacholine challenge when FEV₁ was reduced by approximately 20%. Note the reduction in ventilated volume and more heterogeneous distribution, which is based on small airway function.

tation of ventilation studies in relation to small airway disease complex.

SPECT studies of regional ventilation in obstructive airway diseases show heterogeneous ventilation due to localized airway and/or parenchymal disease, and hypoventilation or nonventilation (fig. 2a, b), presumably due to either severe narrowing or airway closure, which suggest that there are lung regions that are more severely affected by disease than others [56, 77, 82, 83] and reflect similar observations from other imaging modalities [9, 20, 55]. Ventilation distribution using a fractal-like analysis and a simple coefficient of variation in emphysema [70, 77] shows, not surprisingly, that there is increased heterogeneity of ventilation. The basis of altered ventilation in COPD could be due to differing contributions of emphysema and small airway disease [84, 85], although measurement of the separate contributions in individuals remains unproven. Therefore, measurement of small airway function in COPD from ventilation imaging is complicated by the presence of emphysema. There are currently no published analyses of ventilation distribution in asthma from SPECT ventilation imaging.

Ultra-High Resolution Imaging

Ultra-high resolution imaging techniques that have sufficient resolution to image small airways directly, or ventilation contrast agents at the small airway level, are presently unavailable for human lung imaging applica-

tions. These applications have provided extraordinary detail in animal models and include synchrotron radiation imaging which provides detailed imaging of acini [86] and micro-CT which has a similar spatial resolution [33].

Cone beam CT imaging with flat panel detectors, however, has potential for lung imaging. Cone beam scanning technology, which provides image data with isotropic voxels down to 150 μm in size [87], would easily resolve small airway and acinar structures if the contrast is sufficient (table 1). They are used clinically in soft tissue applications such as maxillofacial and orthopedic surgery and their radiation dose is sufficiently low to allow lung imaging if the appropriate technical adjustments were possible. However, there would probably have to be physical modifications to the scanner to accommodate human in vivo imaging. However, the principle is encouraging for future X-ray imaging of small airways.

Conclusions

The imaging studies in small airway diseases on several different imaging modalities have provided highly informative and significant insights into asthma and COPD. These insights have mostly been inferred since the spatial resolution of the imaging techniques is higher than the resolution of the structure or function of interest. Nevertheless, evidence from the different techniques is consistent and shows that in asthma ventilation is het-

erogeneous with a wide range of function, that the topographical distribution is also heterogeneous, and that there are some clustered regions where airways are hyperresponsive, i.e. airways close when bronchoconstricted. COPD studies are more complex to interpret in the context of small airway disease since there is a complex interaction between the presence of parenchymal disease (emphysema) and small airway disease, but it may be possible to separate different contributions of emphysema versus small airway disease with combined use of CT and ventilation imaging in future studies.

Correlative studies combining ventilation distribution measured by imaging, and computational modeling and global measures of small airway function such as FOT and MBNW, are still needed. Since functional imaging of

ventilation is of low resolution, the interpretation of such imaging information in relation to small airway function necessitates a combined approach [8]. There are very few published studies of this nature. There is great potential for future advances in understanding small airway function in airway diseases and also for application to clinical medicine, particularly when ultra-high resolution structural imaging is developed sufficiently to allow human imaging in vivo.

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