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REVIEW

Computed tomographic imaging of the airways: relationship to structure and function

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ABSTRACT: Alterations in the structure of the airways, collectively termed airway remodelling, contribute to airflow obstruction in a variety of chronic lung diseases. While histology has provided valuable insights into the structure of airway wall remodelling, this technique is invasive and does not allow the longitudinal analysis of airway wall dimensions. Technical advances in computed tomography allow the assessment of airway wall dimensions, and are ideally suited for the noninvasive investigation of the pathogenesis of airway wall remodelling and the evaluation of new therapeutic interventions. The aim of this article is to review the use of computed tomography in the investigation of airway structure and function in health and disease.

KEYWORDS: Airways, asthma, chronic obstructive pulmonary disease, computed tomography, cystic fibrosis, lung structure and function

Alterations in the structure of the airways, collectively termed airway remodelling, contribute to airflow obstruction in a variety of lung diseases including: asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF). Airway remodelling is defined as changes in the composition, content and organisation of the cellular and molecular constituents of the airway wall; these changes can contribute directly to airway narrowing and/or exaggerate the effect of airway smooth muscle contraction. The detection and quantification of airway remodelling have been based on the use of histological examination. Such studies have provided valuable information on the processes and consequences of airway remodelling, but require access to surgical or autopsy samples of the airways and are necessarily cross-sectional in design. Noninvasive methods are required to further investigate the pathogenesis of airway wall remodelling, to assess changes over time, and to allow the assessment of new therapeutic interventions designed to attenuate or reverse these structural changes. Technical advances in computed tomography (CT) allow an assessment of airway wall thickness and cross-sectional area *in vivo* that is comparable to histological examination (fig. 1). However, the information that can be obtained from CT is essentially less detailed than that obtained on histological examination. For example, CT cannot distinguish which components of the airway wall are thickened. Despite this limitation, the ability to measure multiple airways relatively, noninvasively and repeatedly offers major potential advantages. The aim of the current article is to review the use of CT in the investigation of airway structure and function in health and disease. Although both qualitative and quantitative studies are reviewed, the quantitative studies are emphasised because of their inherent advantages and because they directly reflect the digital data on which this imaging modality is based.

GENERAL METHODS

The original CT scans designed to assess airway structure involved thin-slice images (typically 1–2 mm axial), which were acquired using a ''stop and shoot'' protocol and were reconstructed using an edge-enhancing algorithm, known as the high-resolution CT (HRCT) protocol. Usually, there was a gap of $\geqslant$10 mm between the images because of radiation concerns and the limitations in obtaining truly sequential images using the axial technique. Most of the published analysis techniques have been developed and validated using these acquisition paradigms, unless breath-hold time and radiation exposure were not a concern, such as in the study of phantoms or animals. Even the advent of spiral CT scanners,

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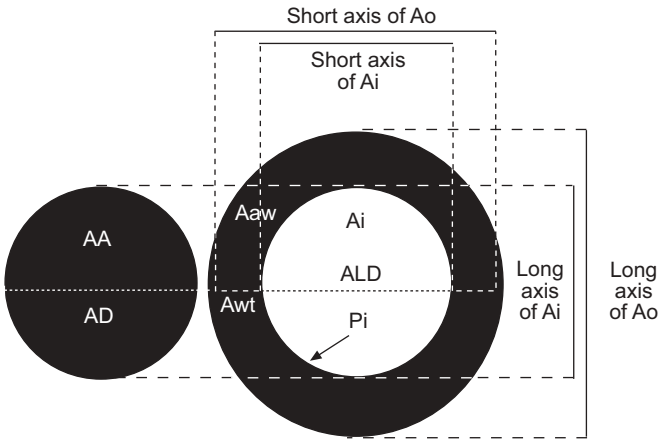

FIGURE 1. Computed tomography (CT)-estimated dimensions of the airway lumen and wall, and accompanying pulmonary artery. This schematic shows the various measurements that can be made on CT images of airways and the vessels, which frequently accompany them. Linear measurements include: the airway perimeter (Pi); the long and short axes of the outer airway area (Ao) and the lumen area (Ai); wall thickness (Awt); airway lumen diameter (ALD); airway outer diameter (AoD=ALD+Awt); and arterial diameter (AD). Ratios of various linear dimensions include: ALD/AD; Awt/AD; Awt/ALD; as well as long to short axis ratios, which are a measure of the obliquity of the section. The area dimensions include: Ai; airway wall area (Aaw); outer airway area (Ao=Aaw+Ai); and arterial area (AA). Ratios of various areas include: Ai/AA; Aaw/AA; and percentage wall area (WA%=Aaw/Ao × 100%). The square root of Aaw is often derived, since it is relatively linearly related to Pi. Finally, airway dimensions can be referenced to body surface area (*e.g.* Aaw/BSA and Awt/BSA).

where the images can be acquired while the table continuously moves, did not change this approach significantly. However, the introduction and proliferation of multidetector-row CT (MDCT) scanners have completely changed the approach to CT image acquisition. It is now possible to acquire thin-slice images of the whole chest, often referred to as volumetric imaging, with 0.5–1-mm thick slices during a single breath-hold. Furthermore, these scanners produce true isotropic voxels, allowing image reconstructions in which the Z dimension (slice thickness) is the same dimension as the X and Y (in plane) resolution. The isotropic voxels make it possible to measure airways in true cross-section at any location, using retrospective reconstruction of the images to achieve a cross-sectional image of the airway. A number of complex algorithms have been developed that allow this angle correction and measurement of the wall and lumen [1–4]. Therefore, studies can be tailored to the clinical or research question being asked in order to maximise image quality whilst minimising the radiation dose. Volumetric CT also allows the generation of maximal intensity projection and minimal intensity projection (MIN-IPS) images, and MIN-IPS images have been shown to be particularly helpful in the detection of subtle emphysema [5].

Images acquired for analysis of airways are usually obtained during suspended inspiration. Some investigators have proposed the use of spirometric gating, since airways dilate with increases in lung volume; the lumen area and the ratio of wall area to lumen area vary as a function of lung volume. Furthermore, the goal of imaging studies is often the comparison of airway dimensions (between individuals or within an individual over time), so it is important to compare images of the same airway at the same or closely comparable lung volume. Studies in experimental animals [6] have shown that airways are completely dilated at transpulmonary pressures >10 cmH_2O, and suggest that, if reasonable inspiratory efforts are made, it may be legitimate to compare airways over time without the need for spirometric gating. Conversely, the area–pressure curve of diseased airways is likely to be abnormal. If these airways are less compliant than normal, the lung volume and transpulmonary pressure at which the scan is performed could have a more important effect on airway dimensions.

CT scans of children and infants who cannot voluntarily hold their breath present a significant problem for airway analysis. Infants aged <4 yrs are usually sedated and scanned during quiet breathing; the resultant images have substantial motion artefact and are generally not suitable for the assessment of airway structure. To solve this problem, LONG and coworkers [7–9] developed, and employed, a CT technique called ''volume-controlled CT'', to scan sedated infants at a standardised volume during apnoea. Infants are hyperventilated, and the hypocarbia and Herring-Breuer reflex accompanying chest wall expansion causes an apnoea that is prolonged enough to acquire the images.

Since most of the CT studies of airways were carried out before the introduction of MDCT scanners, and because many institutions do not have the ability to control for lung volume during CT scans, the theoretical advantages of increased precision offered by these techniques have not yet been demonstrated and require further study. Investigators have had to resort to other methods to match airways, such as in a recent study by NIIMI *et al*. [10] where a large central airway that could easily be identified and measured on serial CT studies was compared before and after an intervention.

Quantitative assessment of larger airways

In the initial studies in which airway dimensions were measured using CT, the investigators relied on manual tracing of the airway images [11–15]. These techniques are extremely time consuming and prone to error. Therefore, computer-aided and automated techniques have since been developed to measure airway lumen and wall dimensions. The first such method for measuring airway lumen used a Hounsfield unit (HU) threshold cut-off value. This technique involves identifying the airway, and measuring the x-ray attenuation values within the lumen. MCNITT-GRAY *et al*. [16] reported that the airway lumen area could be accurately measured by including all pixels beyond a threshold cut-off of -500 HU, and KING *et al*. [17] reported that a threshold of -577 HU produced the least error. However, the most commonly reported method for measuring the airway lumen and wall areas relies on the ''full-width-at-half-maximum'' (or ''half-max'') technique. This method requires that a seed point be placed in the lumen and the x-ray attenuation values measured along rays cast from this point outward toward the airway wall in all directions. As a ray enters the wall, the attenuation will increase and then decrease as it passes into the lung parenchyma. The distance between the point at which the attenuation is halfway to the maximum on the lumen side and halfway to the local

minimum on the parenchymal side is considered to be the wall thickness (fig. 2) [18, 19]. Although this method provides a standardised and unbiased measurement, it has limitations. When CT scan measurements using this method are compared with phantoms and anatomical specimens [19], the CT scans consistently overestimate airway wall area and underestimate lumen area. These systematic errors are due to a combination of factors including: the limited spatial resolution of the CT scanner; the angle of orientation of the airway within the CT slice; the ability of the scanner to detect edges (the point-spread function); the reconstruction algorithm used; the analysis technique used; and inability to visualise the folding of the epithelium. NAKANO *et al*. [19] have shown that the half-max method results in very large fractional errors in the measurements of small bronchi. For this reason, techniques such as the maximum likelihood method [20] and score-guided erosion [17] have been developed.

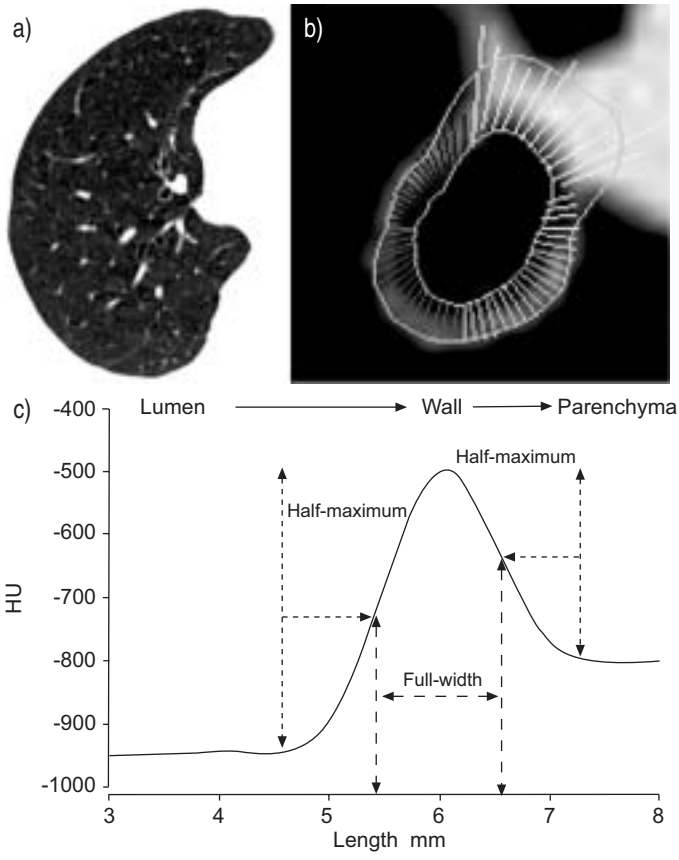

FIGURE 2. c) Airway wall measurement using the full-width at half-maximum algorithm. A representative x-ray attenuation curve for a ray that passes from the lumen through the airway wall and into the parenchyma is shown. The thickness of the wall is determined using the half-maximum point of the change in x-ray attenuation as the ray enters and exits the wall. A representative computed tomography image (a) and a magnified view of an airway (b) are shown. The rays can be seen to start at the lumen boundary of the wall and extend to the outer edge. Of note, some rays extend into the pulmonary artery because the artery has similar x-ray attenuation values as the airway wall. Those rays are manually deleted and the outer airway border is estimated from the remaining rays using a mathematical spline function. HU: Hounsfield unit.

The errors due to volume averaging are particularly important when airways are sectioned tangentially, as is the case with the majority of airways. KING *et al*. [17] attempted to compensate for the obliquity of the section, by defining the angle of deviation of each airway from the perpendicular using the centroid of the same airway on the two sections on each side of the section on which the measurements are made. SABA *et al*. [21] have developed an alternate technique for measuring airways that are not cut in cross-section. This method involves fitting an ellipse to the airway lumen and wall, and shows great promise in correcting the errors in measurement of obliquely cut airways. These techniques claim to be more accurate than the more commonly used techniques, but have not been generally applied, presumably because of the limited availability of the complex algorithms involved.

Quantitative assessment of smaller airways

In many airway diseases, the important site of airflow obstruction is the small airways [22–24]. It has been reported that airway lumens as small as a 0.5-mm diameter can be measured using CT [25], but, as mentioned previously, there are large errors associated with the measurements of airways this small when the data are obtained using routine clinical scanning parameters [19]. However, NAKANO *et al*. [26] compared airway measurements from CT scans and histological examination of excised lungs from smokers who had various degrees of airway obstruction. They compared the wall area of small airways (1.27-mm diameter) measured histologically with the wall area percentage of larger airways with a mean internal diameter of ~3.2 mm, and showed that there was a significant association (R^2=0.57; p=0.001) between the dimensions of the small and larger airways. These data suggest that, at least for COPD, measuring airway dimensions in the larger bronchi, which are more accurately assessed by CT, can provide an estimate of small airway remodelling. It is likely that the same pathophysiological process that causes small airway obstruction also takes place in larger airways where it has less functional effect.

Even with the use of automated airway detection, it is only possible to make a limited number of measurements in any individual at any time, and, thus, the issue of heterogeneity in airway dimensions is important both for between- and within-subject comparisons. KING *et al*. [27] measured heterogeneity in airway narrowing by comparing the variation within a scan to that between scans. However, this study did not address the issue of heterogeneity in baseline airway dimensions, which is important to estimate before the quantitative assessment of airway dimensions is established as an outcome measure in clinical studies. MATSUOKA *et al*. [28] measured airway wall dimensions from central to peripheral airways, using contiguous 2-mm sections obtained with a MDCT scanner in normal subjects. They reported the variation in various measures of airway lumen and wall dimensions within an individual scan, and as a function of distance from the hilum to the periphery. These data will prove valuable for assessing whether an observed difference or change is real or simply within the variation of the measurement [28].

Another approach for studying airways that are too small to visualise using CT is to perform expiratory scans, and assess the extent and degree of gas trapping (fig. 3). Heterogeneity of

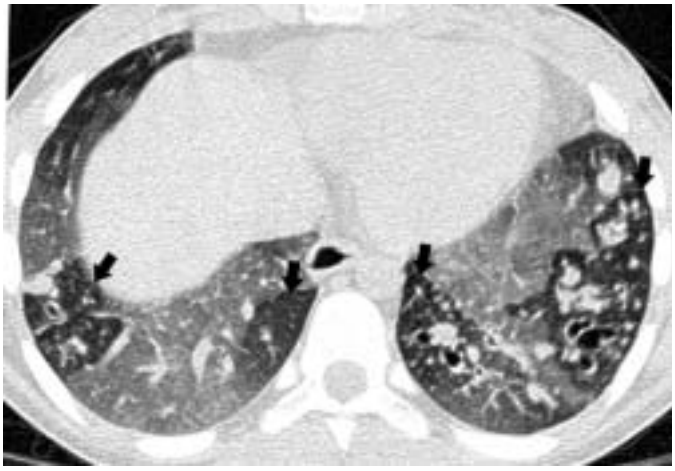

FIGURE 3. An expiratory high-resolution computed tomography scan of the lung base in a cystic fibrosis patient demonstrates bilateral areas of air trapping (arrows).

airway narrowing in disease causes variation in the regional lung volume at which airways close, and this, in turn, leads to heterogeneity in lung density on scans taken at end expiration [29–34]. A limitation of the use of expiratory CT scans is the difficulty in breath-holding at low lung volume. Consistency of expiratory scans may be aided by spirometric gating, but further research is needed to prove the value of these techniques in studying small airway disease.

Heterogeneity of lung attenuation is also present on inspiratory scans where it is attributed to mosaic perfusion. Decreased ventilation to areas of the lung with small airway obstruction results in decreased vascularity and CT attenuation. Blood-flow redistribution to normal lung results in areas of increased vascularity and CT attenuation. This combination of areas of decreased and increased attenuation and perfusion is known as mosaic perfusion. Regional variation in lung perfusion may be an indirect indicator of airway disease, since units with narrowed airways will receive less ventilation and, thus, will have low regional alveolar oxygen tension and hypoxic vasoconstriction.

Qualitative assessment of airways

A number of CT scoring systems have been developed that allow an assessment of the extent and distribution of airway abnormalities. These scoring systems have been applied in several diseases [35–45]. Scoring systems rely on the subjective detection and grading of direct and indirect signs of airway disease, such as airway wall thickening, bronchiectasis, mosaic perfusion and/or gas trapping [46–50]. However, qualitative studies are sensitive to the display settings (window width and level) of the images, are prone to inter- and intra-reader variability, and are time consuming and, therefore, expensive. While there is reasonably good inter-observer agreement for the diagnosis of bronchiectasis and gas trapping [50], subjective analysis is of very limited value in the assessment of airway wall thickening. It is possible that MDCT scanning can improve the between-observer agreement for bronchiectasis compared with traditional HRCT because of the contiguous slices, as suggested by a study using helical CT [51], but it is unlikely to improve the subjective analysis of airway wall thickness.

CT imaging protocols and safety

Radiation exposure is an important issue for any studies in which repeat CT scans are planned, as may be the case for CT imaging of airways. Estimates of risk for radiation-induced cancer show that infants and young children are much more susceptible than older children who are, in turn, more susceptible than adults [52–59]. Therefore, most airway research has been restricted to older adults (aged >55 yrs) where the risk is very low [52], or children with CF who have a decreased life expectancy [25, 36, 37, 60]. CT scanning of patients who have chronic lung disease and/or control subjects carries a small risk. In research studies, the potential benefit for patients with the disease and/or for the general population should outweigh this risk. In addition, patients and/or healthy control subjects must be informed of the radiation risks and potential benefits of participating in the study.

AIRWAY IMAGING IN ASTHMA

Airway dimensions

Asthma is characterised by chronic airway inflammation, airway remodelling and wall thickening, and reversible airflow obstruction due, in part, to airway smooth muscle contraction [61, 62]. CT scans of asthmatic patients have shown both decreased and increased bronchial lumen area, excessive airway narrowing in response to a variety of stimuli and airway wall thickening, in addition to mosaic perfusion and gas trapping on expiration [63–68]. LYNCH *et al*. [65] found that 77% of asthmatic patients and 153 (36%) of 429 bronchi assessed in asthmatic patients had an internal bronchial diameter to pulmonary artery diameter ratio >1. Of note, none of the patients had a bronchoarterial diameter ratio >1.5. As highlighted by LYNCH *et al*. [65], bronchial dilatation in asthmatic patients may partially reflect a reduction in pulmonary artery diameter, due to changes in blood volume or local hypoxia, or may be physiological; caution is advised in diagnosing mild bronchiectasis in this patient population. The detection of mild bronchiectasis can be a problem, especially when there are other reasons for a change in arterial or airway lumen, such as that which occurs at high altitude (*i.e.* hypoxic vasoconstriction) [69].

A number of investigators have compared airway lumen area in normal and asthmatic subjects. BEIGELMAN-AUBRY *et al*. [70] demonstrated a lower baseline airway lumen area in asthmatics compared with controls pre-bronchodilator, but the difference was abolished after salbutamol. In addition, the airway lumen diameter to arterial diameter ratio has been reported to be lower in asthmatic patients with a forced expiratory volume in one second (FEV_1) <60% (mean±SD 0.48±0.11) compared with control subjects (0.65±0.16) and asthmatics who had normal or slightly decreased FEV_1 values (0.60±0.16 and 0.60±0.18, respectively) [71]. Conversely, NIIMI *et al*. [72] found no decrease in lumen area in the right apical upper lobe bronchus in asthmatics, irrespective of disease severity, compared with a normal group.

OKAZAWA *et al*. [73] used CT scans to quantify the degree of airway narrowing produced by inhaled methacholine in normal and asthmatic subjects. They were able to clearly identify airway narrowing of intermediate-sized airways (fig. 4). There was no difference in the pattern of airway narrowing (*i.e.* large *versus* small airways) in the asthmatics as opposed to the normal

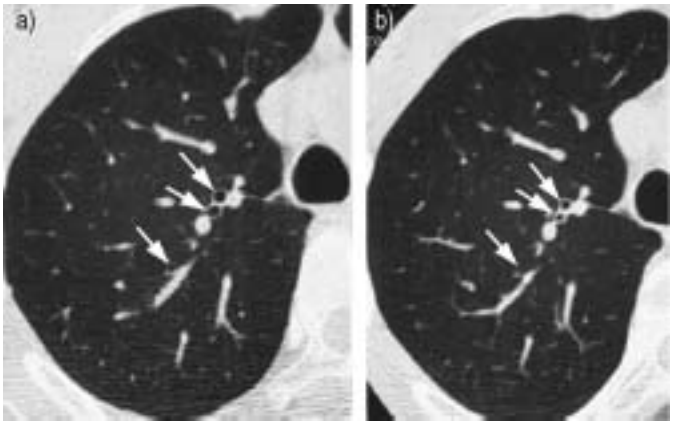

FIGURE 4. Views of the right upper lobe from a high-resolution computed tomography scan in an asthmatic patient before (a) and after (b) methacholine challenge. The decrease in bronchial diameter (arrows) after the inhalation of a dose of methacholine that caused a ~20% decrease in forced expiratory volume in one second can be clearly seen.

subjects, although, as expected, the same degree of narrowing was achieved using a much lower dose of methacholine in the asthmatics [73]. The frequency distribution of airway luminal area was shifted slightly towards smaller airway lumens in the asthmatics, and the airway walls were significantly thickened compared with normal subjects.

BROWN *et al*. [74] measured airway narrowing with increasing concentrations of inhaled methacholine in normal subjects who were prevented from taking a deep inspiration after the methacholine inhalation. They demonstrated airway luminal narrowing and no predilection for greater narrowing in any airway size that could be assessed. GOLDIN *et al*. [75] reported greater decreases in FEV1 and in airway lumen area in small airways after inhalation of methacholine in asthmatic as opposed to normal subjects. KING *et al*. [27] have recently shown that airway narrowing is heterogeneous in the large airways of asthmatics, and that this heterogeneity is larger than in control subjects.

BROWN *et al*. [76] measured airway dilation caused by a deep inspiration in asthmatics and normal subjects. It was found that deep inspiration dilated the airways to a comparable degree at baseline, but, after inhaling methacholine, deep inspiration caused further bronchial narrowing in asthmatics as opposed to substantial bronchodilatation in normal subjects. It was suggested that the inadequate bronchodilation in asthmatics following deep inspiration was due to an abnormality in the asthmatic subjects' smooth muscle response to stretch.

All relevant studies of adults and children [14, 34, 66, 72, 77–79] show that airway wall thickness is increased in asthmatic subjects, even when the asthma is mild. The degree of wall thickening is related to the duration and severity of asthma, and to the level of airway obstruction [66, 72, 77, 79]. NIIMI *et al*. [72] showed progressive thickening of the wall of the right apical segmental bronchus in asthmatics as a function of disease severity (baseline FEV1), but, surprisingly, there was no difference in the luminal area of this airway in the severe asthmatics compared with the control subjects or mild asthmatics. Interestingly, for a given degree of airflow obstruction, the airway wall of the right apical bronchus is substantially thicker in asthmatics compared with COPD patients [18, 72].

The relationship between airway wall thickness and airway responsiveness is interesting. Since airway hyperresponsiveness is thought to be a marker of asthma severity, it might be expected that hyperresponsiveness and wall thickness would be positively correlated. Computational modelling studies suggest that thickening of the adventitia, lamina propria and/or smooth muscle layers can all contribute towards an excessive response to contractile agonists. Indeed, BOULET *et al*. [80] found that individuals who had thicker airways were more responsive. In contrast, LITTLE *et al*. [66] did not find a relationship between airway wall thickness and airway hyperresponsiveness, which was confirmed in a recent study by NIIMI *et al*. [81] who found that the dose of methacholine required to increase respiratory resistance was not related to airway wall thickness in asthma. In fact, these authors reported that the slope of the methacholine dose–response curve was inversely related to airway wall thickness. A possible explanation of this finding could be that, at least in some subjects, the process that thickens the airways makes them stiffer and, therefore, less responsive to stimuli such as methacholine [82].

NIIMI *et al*. [10] have reported that the thickness of the right apical segmental bronchus, adjusted for body surface area, increases as a function of the duration of diagnosed asthma. They also found that 800 μg of inhaled beclomethasone *q.d.* for 12 weeks resulted in a significant decrease in the thickness of the right apical segmental bronchus, although the decrease did not return the airway dimensions to those of an age-matched asymptomatic control group [10].

Gas trapping

Decreased lung attenuation can be seen on inspiratory scans, but is more apparent on expiratory scans [83]. In asthmatics, low-attenuation areas (LAAs) on inspiratory CT have been reported [65, 84] and are most probably the result of pulmonary blood-flow redistribution secondary to local hypoxic pulmonary vasoconstriction caused by bronchiolar obstruction [63, 85].

On expiratory scans, regional differences in airway closure and/or emptying rate can markedly enhance the heterogeneity of lung attenuation. Although such ''gas trapping'' is apparent even in asymptomatic individuals who have normal lung function [86], it is markedly increased in patients with asthma and the degree of gas trapping is related to abnormalities of lung function [33, 34, 48, 70, 87].

MITSUNOBU *et al*. [32] showed that mean lung density on inspiratory scans decreased during exacerbations of asthma. GOLDIN *et al*. [75] showed that the distributions of attenuation values are shifted to the left (low density) during airway narrowing in CT scans acquired before and after methacholine challenge. In a double-blind, randomised, parallel-group pilot study, GOLDIN *et al*. [88] studied the relative efficacy of an extra-fine beclomethasone dipropionate inhaler (hydrofluoroalkane-beclomethasone dipropionate (HFA-BDP); median aerodynamic diameter of 0.8–1.2 μm) and a con-

ventional chlorofluorocarbon preparation (CFC-BDP; median aerodynamic diameter of 3.5–4.0 μm) in a group of 31 steroid-naive patients with mild-to-moderate asthma. CT was used to assess the relative efficacy of HFA-BDP and CFC-BDP on regional gas trapping. Pre-treatment CT was performed at residual volume before and after methacholine challenge. After 4 weeks of treatment, imaging was repeated before and after the same concentration of methacholine that was administered before the treatment. The quantitative analysis showed that the HFA-BDP group had a significant decrease in baseline gas trapping, and, after inhaled methacholine, they had less increase in gas trapping than subjects treated with CFC-BDP. No significant difference was demonstrated between the two treatment groups with respect to improvement in symptoms, spirometry or methacholine responsiveness. It was concluded that HFA-BDP showed greater efficacy to treat the peripheral airways in asthma, and that this effect is better assessed with functional imaging CT techniques than with conventional physiological tests.

An additional method of analysis, which reflects the heterogeneity of expansion of lung parenchyma, is accomplished by plotting the frequency *versus* the size of contiguous LAAs. The slope of this relationship has been shown to discriminate between severe and mild/moderate asthmatics, and between asthmatics who smoke *versus* nonsmokers [89].

Future directions

CT analysis of airway dimensions in asthma provides additional data to that derived from traditional measures of lung function. Although much work remains to be done in terms of standardising the approach to image acquisition and analysis, there is some evidence that CT may be a more sensitive end-point in clinical trials. As important questions remain to be answered for this common disease, the use of CT in research settings seems justified. The relationship between airway hyperresponsiveness and airway wall dimension (as assessed by CT) is confusing and is a topic that requires more study, as does the contribution of airway wall dimensions to the wide variation in airway responsiveness that can be demonstrated in normal individuals. More studies are needed that relate the degree of airway remodelling (as measured by histology) to the degree of airway wall thickening (as measured by CT) in subjects with asthma and COPD. VIGNOLA *et al*. [90] recently reported a significant relationship between sputum elastase and the ratio of matrix metalloproteinase-9 to the tissue inhibitor of metalloproteinase-1 and airway wall thickening in patients who have asthma and COPD. The relationships between CT airway dimensions and biomarkers of inflammation and repair in blood, bronchoalveolar lavage and exhaled breath condensate are important areas for further, future investigations.

AIRWAY IMAGING IN COPD

COPD occurs predominantly in smokers and is defined by abnormalities of expiratory flow [91]. Decreased expiratory flow in COPD is related to a combination of loss of lung elastic recoil and small airway obstruction. The pathological lesion that is best correlated with loss of lung recoil is emphysema, and CT scanning has been used extensively to detect and quantify emphysema [92–94]. Quantification of the airway lesions by CT has received less attention, but improvements in CT technology now make it possible to detect and quantify the airway abnormalities in these patients. The process that causes the small airway obstruction in COPD is inflammatory in nature and characterised by thickening of all the layers of the bronchiolar walls, as well as an accumulation of mucus in the airway lumen [23]. NAKANO *et al*. [18] measured lung attenuation and the dimensions of the right upper lobe apical segmental bronchus in 114 smokers, using the half-max method. Ninety-four of the smokers were obstructed (FEV_1 $37\pm15\%$ predicted), whereas 20 were unobstructed (mean FEV_1 $100\pm13\%$ pred), despite having a comparable smoking history. NAKANO *et al*. [18] chose the apical segmental bronchus to measure because it is usually cut in cross-section and can be reliably identified on CT, thereby allowing comparison between individuals. They found that the percentage of lung LAA and changes in airway dimensions (wall thickness and percentage of wall area) independently correlated with measures of airflow obstruction. The percentage of wall area was related to FEV_1 % pred, forced vital capacity (FVC) % pred and residual volume (RV)/total lung capacity (TLC), but not to lung diffusing capacity, while the percentage of LAA was related to FEV_1 % and FEV_1/FVC, as well as diffusing capacity. Interestingly, the increase in the percentage of wall area was related both to an increase in wall area and a decrease in lumen area, which contrasts with patients who have asthma, in whom the increased percentage of wall area in the same bronchus was related only to an increase in wall area with a preserved lumen area [72]. Some of the obstructed smokers had only an increase in percentage of wall area, whereas others had only an increased percentage of LAA, and some had both an increase in percentages of wall area and LAA. These data suggest that individual COPD patients may have emphysema or airway wall remodelling as their predominant phenotype, and that these phenotypes can be separated by use of CT scanning. COXSON *et al*. [95] measured all cross-sectioned airways and reported a similar result in a large group of obstructed index patients and their smoking siblings, and, in addition, observed that the airway and parenchymal phenotypes showed familial concordance, suggesting that the susceptibility to develop emphysema or airway disease is heritable. Recently, ORLANDI *et al*. [96] found that patients with COPD who have chronic bronchitis have increased airway wall thickening in comparison with more severely obstructed patients without chronic bronchitis. Conversely, COPD patients without chronic bronchitis had a more significant decrease in lung attenuation. It was suggested that COPD patients with chronic bronchitis have more severe airway remodelling, whereas those without chronic bronchitis have more severe emphysema.

The fact that the airway dimensions of a segmental bronchus relate to measures of airflow obstruction is surprising, since it has long been recognised that the major site of airway narrowing in COPD is membranous airways with an internal diameter <2 mm. The recent study by NAKANO *et al*. [26] may explain this result; it was found that the wall area per cent in larger airways, which are clearly identified and accurately measured by CT, was significantly related to the wall area in the bronchioles of the same patients measured histologically. This result supports the observation of TIDDENS *et al*. [97], who found

that cartilaginous airway wall thickening was related to airflow obstruction and to small airway inflammation, and suggests that a similar process affects both large and small airways in susceptible COPD patients. Thickening and narrowing of the larger airways, which are amenable to CT assessment, may serve as a surrogate measure to quantify the small airway inflammatory process. The ability to separate airway-predominant from parenchymal-predominant pathology in COPD may prove useful in applying specific therapies designed to prevent or ameliorate the airway remodelling or parenchymal destruction. In fact, it is conceivable that specific therapy directed at one of these processes could be contraindicated in individuals in whom the other process was predominant.

Future directions

Future studies in COPD will benefit from the use of spirometric gating and volumetric image acquisition. Three-dimensional reconstruction and correction for angled airways will enable investigators to make accurate comparisons of the same airways both within and between subjects. Intervention studies designed to measure changes in the airways and parenchyma, as assessed by CT, are now possible and may provide important insights in this increasingly prevalent disease. Although there are some data on the CT appearance of airway changes during exacerbations of bronchiectasis [98] and CF [99, 100], such knowledge is largely lacking in asthma and COPD, and this represents an important topic of future investigation in human and/or animal models. Another fruitful area for future studies is a determination of the minimal number of CT images that are required to adequately assess airway dimensions in COPD.

AIRWAY IMAGING IN CYSTIC FIBROSIS

Airway disease in CF is characterised by mucus plugging, chronic infection and an excessive inflammatory response, leading to peripheral airway changes in the first few months of life [101–119]. The characteristic airway abnormalities are bronchiectasis, thickening of the airway wall and mucus plugging [97, 103, 107, 120–126], as shown in figure 5.

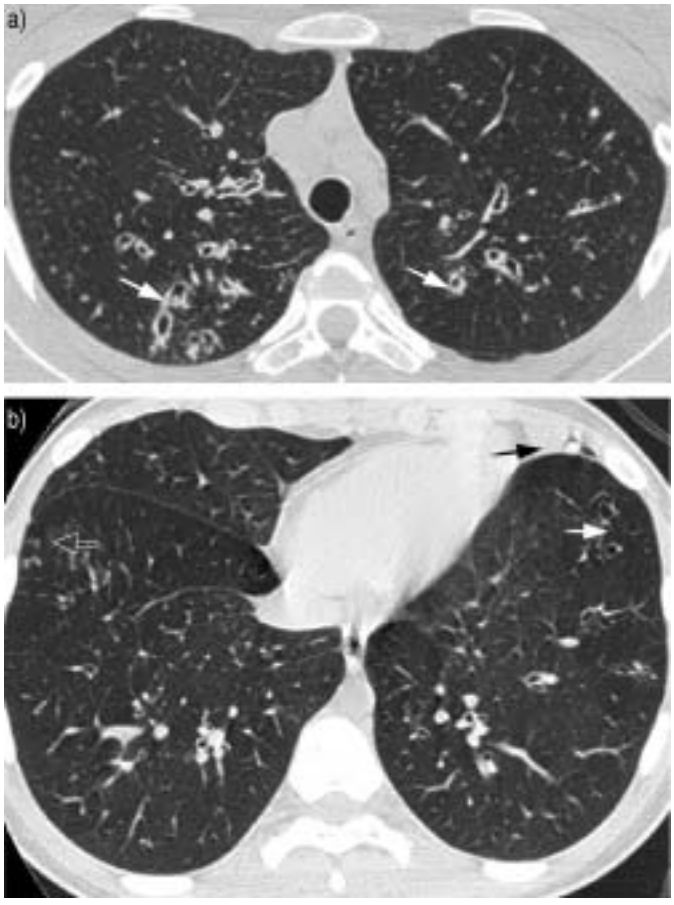

FIGURE 5. a, b) Extensive airway abnormalities evident on computed tomography (CT) in a child with cystic fibrosis (CF) with normal lung function. The CF patient was a 15-yr-old Caucasian female with forced expiratory volume in one second (FEV_1) 93% predicted, forced vital capacity (FVC) 110% pred, forced mid-expiratory flow 81% pred and FEV_1/FVC 76%. The CT images show bronchiectasis with either thick or thin walls (white arrow), atelectasis with an air bronchogram in the lingula (black arrow) and peripheral mucus plugging (open arrow). Mosaic perfusion is also present in both upper and lower lobes.

Qualitative studies

Qualitative CT studies have been performed since 1989, and HRCT airway scoring systems are the most frequently used methods to assess airway abnormalities in CF [35, 37, 59, 60, 99, 100, 102, 105, 127–153]. All of the systems consist of a composite score for subjective estimates of a number of features on CT scans, which include bronchiectasis, airway wall thickening, mucus plugging, *etc*. DE JONG *et al*. [37] compared the reproducibility of the Bhalla score and four modified scoring systems, and showed that all scoring systems were reproducible between and within observers with most interclass r-values >0.8. The between- and within-observer variability of scoring the individual components is less well documented. BRODY [128] has shown that the agreement between observers for bronchiectasis, mucus plugging and air trapping is 74%, 89% and 61%, respectively, and DE JONG *et al*. [37] reported κ-values ranging 0.40–0.61 for most features.

In several studies in which the relationship between lung structure and function has been measured, a strong correlation between measures of forced expiratory flow and HRCT scoring systems has been reported [37, 99, 138, 146, 147], except in studies of very young children [128, 134, 143]. The results of two longitudinal studies have suggested that HRCT scoring may be more sensitive than lung function in detecting disease progression in CF; in both studies, pulmonary function tests (PFTs) remained stable over 2 yrs, whereas the HRCT score detected worsening of disease [36, 130]. This is not an unexpected result, since HRCT can detect regional abnormalities such as small areas of atelectasis and bronchiectasis that may be functionally silent. A few, small clinical trials have been performed using HRCT score as an end-point, some of which failed to demonstrate a significant treatment effect; however, the time period between repeat scans was short [132, 137, 140, 153, 154].

Quantitative studies

To date, there have been no studies in which quantitative CT estimates of airway disease have been compared with pathological measures in CF patients. Quantitative assessments of airway dimensions have shown that there is an increase in airway wall thickness and lumen area (bronchiectasis) in CF

infants and children compared with controls. In CF infants, the dilatation of airway lumen (severity of bronchiectasis) increased significantly with age [25]. In a cross-sectional study, DE JONG *et al*. [37] did not find a correlation between quantitative measures of airway dimensions and PFTs. In a longitudinal study in which CT scans and PFTs were obtained at baseline and after an interval of 2 yrs, airway wall thickness increased without an increase in lumen area; there was a correlation between the increase in airway wall thickness and decrease in forced mid-expiratory flow ($FEF_{25–75}$) % pred [60]. Gas trapping is thought to be an early marker of airway disease in CF [150]. In two studies, the severity of gas trapping was evaluated by comparing distribution curves of the HU of individual pixels from inspiratory CT scans with curves from expiratory CT scans [30, 155]. This measure of air trapping discriminated between CF patients and control subjects, and correlated significantly with RV/TLC and $FEF_{25–75}$ % pred [30, 155].

Future directions

The majority of HRCT studies in CF have been carried out using semi-quantitative scoring systems. Aside from the inherent intra- and inter-observer variation, the major limitation of these scoring systems is the lack of consensus on which system to use and the failure to use definitions of CT abnormalities consistently. Quantitative studies of airway dimensions in children are challenging as a result of changes in airway size due to lung growth and the inability to identify airways on subsequent scans due to mucus plugging, or lack of a comparable CT section. In addition, there are real concerns about the risks associated with radiation. With the increasing life expectancy of CF patients, it is possible that these risks will outweigh the potential benefit afforded by early diagnosis.

Despite these concerns, there is accumulating evidence that CT can detect structural damage to the airways in infants and children who are too young to have conventional PFTs and/or when lung function is normal. It is also possible that these early changes are reversible and, therefore, should be treated before structural damage causes irreversible functional deficits. There is increasing evidence that early and aggressive therapy is improving quality of life and longevity in CF [102, 156–160], and, thus, a reasonable case can be made for regular routine CT scans to detect the earliest indication of airway disease. Ultimately, only a randomised clinical trial will answer the question of whether routine CT scanning is warranted in children with CF. To facilitate such studies, a robust quantitative technique to measure airway disease needs to be developed to use with, or in place of, the established CT scoring systems. In the search for early biomarkers of disease progression, it will be useful to compare CT with other noninvasive measures of pulmonary dysfunction, such as helium and sulphur hexafluoride washout ventilation curves [161, 162], or positron emission tomography measures of the intensity of lung inflammation [163]. Finally, more investigation is needed into the radiation hazard associated with different CT scan protocols to allow development of a protocol that produces the most beneficial information with the lowest risk to the subject.

OTHER IMAGING TECHNIQUES TO EVALUATE AIRWAYS

A number of novel techniques have been developed to image airways and/or the consequences of airway narrowing without the risk associated with ionising radiation. Endobronchial ultrasound is accomplished by introducing an ultrasonic probe into the airways *via* a fibreoptic bronchoscope, and this technique offers the advantage that the thickness of the different airway wall layers can be measured [164]. In one case study of an asthmatic subject, reversal of central airway oedema was demonstrated following anti-inflammatory therapy [165].

The advent of hyperpolarised gas magnetic resonance imaging (MRI) techniques has opened up whole new avenues of research into ventilation of the lung [166] and the measurement of airway dimensions. Using this technique, three-dimensional reconstruction of the airway lumen can be performed to the seventh generation of airways [167]. However, airway wall thickness cannot be quantified, and the limited availability of a hyperpolarised helium or xenon-129 source makes the widespread use of this method problematic [167]. It is likely that hyperpolarised gas MRI will remain a limited research tool for the immediate future.

CONCLUSION

Computed tomography scanning is poised to make a major contribution to the understanding of obstructive airway diseases. Improvements in computed tomography scanning techniques, together with faster quantitative algorithms to measure airway wall and lumen areas and to quantify and localise air trapping, are being applied with increased frequency in research efforts to understand the changes in airways that occur in chronic obstructive lung diseases. It is now possible to obtain computed tomography images with isotropic voxels and at standardised volumes, allowing longitudinal study of specific airways *in vivo*. Quantitative computed tomography has already led to an improved understanding of variations in airway dimensions in normal individuals, and to a better understanding of the airway changes that occur in asthma, chronic obstructive pulmonary disease and cystic fibrosis. With these refinements, quantitative computed tomography is ready for clinical application, initially in the setting of clinical trials, but ultimately in the clinical management of individual patients. Computed tomography imaging of the airways has inherent limitations: the subdivisions of the airway wall cannot be visualised, the pathological process causing changes in the airway wall cannot be appreciated, and airways <0.5 mm in lumen diameter cannot be visualised directly. Furthermore, the radiation dose of computed tomography limits its use in longitudinal studies, particularly in infants and children. Nevertheless, computed tomography is the only readily accessible, relatively noninvasive imaging modality that allows airway wall and lumen dimensions to be measured *in vivo*. With increased awareness of the role that airway remodelling plays in functional deterioration in these diseases, computed tomography will play an increasing role in research and clinical assessment.

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