Computed tomography scans in severe asthma: utility and clinical implications

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Purpose of review
Asthma is a global burden, affecting 5% of the general adult population, of whom approximately 5–10% suffer from severe asthma. Severe asthma is a complex heterogeneous disease entity, with high morbidity and mortality. Increasingly novel techniques in computed tomography (CT) are being used to understand the pathophysiology of severe asthma. The utility and clinical implications of these CT techniques are the focus of this review.

Recent findings
Novel qualitative and quantitative CT imaging techniques have enabled us to study the large airway architecture in detail, assess the small airway structure, and perform functional analysis of regional ventilation.

Summary
Despite advances in CT imaging techniques, there is an urgent need for both proof-of-concept studies and large cross-sectional and longitudinal clinical trials in severe asthma to validate and clinically correlate imaging derived measures. This will extend our current understanding of the pathophysiology of severe asthma, and unravel the structure–function relationship, with the potential to discover novel severe asthma phenotypes and predict mortality, morbidity, and response to existing and novel pharmacological and nonpharmacological therapies.

Keywords
airway disease, computed tomography, severe asthma

INTRODUCTION

Over 300 million people worldwide have asthma, with the prevalence in the UK being among the highest in the developed world [1]. Asthma affects approximately 5% of the general adult population, of whom approximately 5–10% suffer from severe asthma. This group of patients are of particular importance, as they contribute to the vast majority of the economic burden of asthma in Europe due to frequent exacerbations, hospitalizations, and death.

Computed tomography (CT) scans in asthma are typically indicated to either identify associated conditions, such as bronchopulmonary aspergillosis, or detect conditions that mimic asthma, such as hypersensitivity pneumonitis. In severe asthma, the potential role for CT is considerably wider. CT provides detailed macroscopic anatomical examination of the lung parenchyma. Multidetector row CT (MDCT) scanners facilitate isotropic acquisition of the whole chest with sub-millimetre resolution within a single breath hold. Furthermore, rapid advances in postprocessing software for CT images now permit multiplanar reconstructions, three-dimensional surface and volume images of the airway tree and lung parenchyma, detailed quantitative analysis, and virtual bronchoscopy. Quantitative imaging techniques have given us the ability to obtain direct measurements by three-dimensional assessment of the large airways as well as indirect assessment of the small airways by densitometric measures of paired inspiratory and expiratory scans. In addition to the acquisition of detailed anatomical data of the lungs, CT can now also provide functional assessment of ventilation and

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KEY POINTS

- Asthma is a global burden, affecting 5% of the adult population, of whom 5–10% suffer from severe asthma, with high morbidity and mortality.
- Asthma is a complex, heterogeneous disease process with different clinical and pathophysiological characteristics.
- Novel qualitative and quantitative computed tomography (CT) imaging techniques have enabled us to study the large airway architecture in detail, assess the small airway structure, and perform functional physiological evaluations.
- True understanding of the structure–function relationship in severe asthma can only be achieved by integration of all data, as well as large cross-sectional and longitudinal clinical trials to validate and clinically correlate imaging-derived measures.

perfusion. Current guidelines for severe asthma [2,3] highlight CT as a tool for disease evaluation, and its applications are likely to increase. In particular, the identification of airway remodelling patterns in various phenotypes of severe asthma, and the ability to relate airway structure using CT to important clinical outcomes, airway physiology and inflammation may help to close the gap in our understanding of severe asthma phenotypes, and to target treatment more effectively.

QUALITATIVE ASSESSMENT OF COMPUTED TOMOGRAPHY SCANS IN ASTHMA

Qualitative assessments of CT findings in asthma patients have been performed in a number of studies [4–10]. Gupta *et al.* [4] found that in a cohort of 185 severe asthma patients, the prevalence of bronchiectasis was 40%, which was similar to the median of the reported studies of 31%. Bronchiectasis in asthma patients was associated with longer disease duration [4,5,7,9] and poorer lung function [4,10]; however, association with disease severity was found in some studies [5] but not in others [5,6,8]. Whether or not bronchiectasis in severe asthma is a comorbidity, resulting in 'difficult' to manage asthma, or represents structural change or remodelling with natural progression of the disease [8] is not known, and longitudinal studies are required to ascertain this differentiation.

Bronchial wall thickening is a common feature of severe asthma. Gupta *et al.* reported a prevalence of 62% [5] and others have found bronchial wall thickening to be more prevalent in asthma patients compared with healthy controls [6,9], and associated with asthma severity and longer disease duration [5–7,10].

QUANTITATIVE ASSESSMENT OF LARGE AIRWAYS IN ASTHMA

Advances in CT technology and postprocessing software have made quantitative assessments of the airway tree and lung parenchyma possible. However, the exact measurement of the airway wall, which involves the identification of lumen wall and wall parenchyma boundaries on CT images, is still an inexact science with a number of algorithms being proposed by researchers. One of the earliest and most widely used techniques is the 'full-width at half-maximum' principle (Fig. 1) [11]. This technique can cause systematic errors in airway wall and lumen estimation [12], due to the blurring of edges by the CT scanner's point spread function, oblique orientation of the airways, algorithm used for image reconstruction, and/or size of airway analysed. Methods that have been devised to overcome such problems include the 'Laplacian and Gaussian' algorithm [13], which utilizes smoothening and edge detection filters to segment airways, 'integral-based method', which minimizes the CT's blurring effect, and 'phase congruency method', which uses multiple reconstruction algorithms to localize airway wall, to name but a few. Most of these new software platforms, however, have been designed for volumetric CT scans and not for the standard high-resolution CT scans, which limits their application to retrospective analysis of archived scans.

More recently, software can be used on volumetric CT scans for three-dimensional analysis of the airway tree, which allows lumen extraction, generation of the airway centreline, segmentation of the airway tree up to the fifth and sixth generation, and measurement of airway dimensions on reformatted images orthogonal to the long axis to minimize errors due to oblique orientation.

Various studies have utilized CT for noninvasive quantitative assessment of proximal airway structural changes in asthmatic adults [14▪▪,15–21] and children [22,23]. de Blic *et al.* [22] demonstrated, in children with severe asthma, a correlation between bronchial wall thickening and reticular basement membrane thickness; Saglani *et al.* [23] did not. Other studies have shown that asthma patients have increased airway wall thickness regardless of disease severity [4,16,18,21], whereas others have demonstrated a correlation between CT-assessed airway remodelling and asthma severity [17,19,20]. However, there is some inconsistency between

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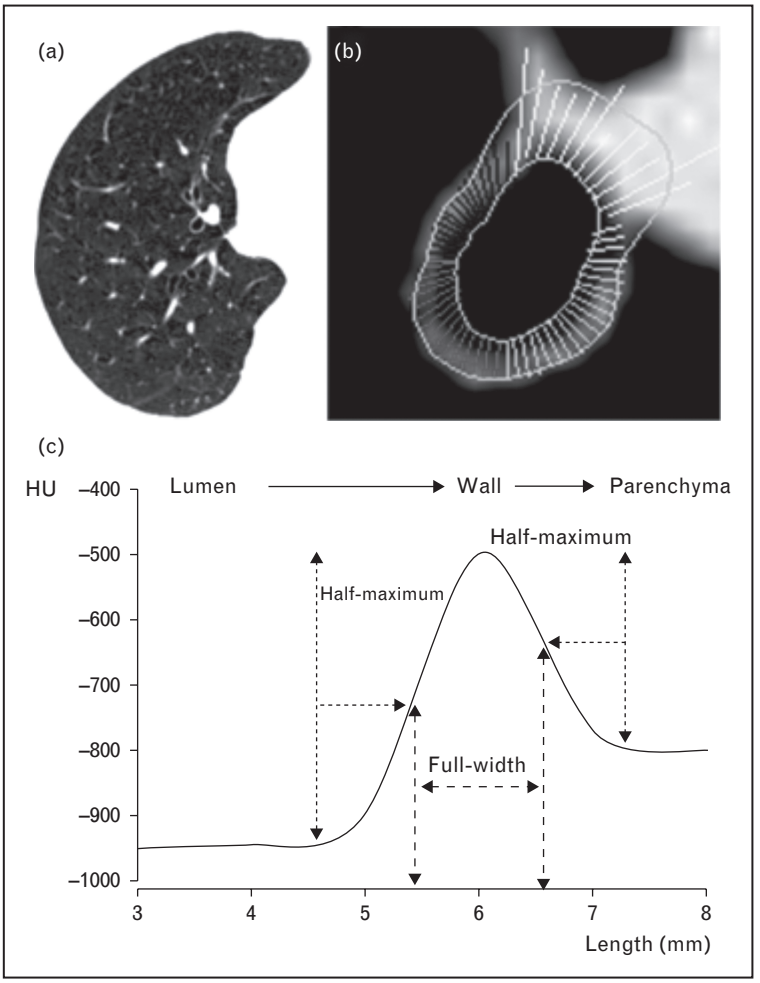

FIGURE 1. Airway dimension estimation using full-width at half-maximum principle. (a) A representative computed tomography image is shown. (b) A magnified view of an airway is shown. Rays can be seen between the inner and outer boundary of the airway wall. Some rays extend into the pulmonary artery because the artery has similar X-ray attenuation values as the airway wall. Those rays are manually eliminated and the airway dimension calculated using the remaining rays. (c) A representative X-ray attenuation profile for a ray that passes from the airway lumen to the lung parenchyma through the airway wall is shown. The inner and outer airway wall boundary is estimated based on points at which X-ray attenuation value is half way to the local maximum and half way to the local minimum respectively [11].

researchers on the airway lumen in asthma. Niimi *et al.* [20] reported no significant difference in lumen area of asthma patients of varying severity and healthy controls. Gupta *et al.* [14▪▪], on the other hand, demonstrated that the right upper lobe apical bronchus (RB1) lumen area corrected for BSA was significantly narrowed, in 99 severe asthma patients, compared with healthy individuals. In asthma, airway wall thickening has been correlated with airflow limitation [14▪▪,17,20], airway hyperresponsiveness [17,21,24], and air trapping on expiratory CT.

Only very few studies have explored the link between CT-assessed remodelling and airway inflammation in asthma. Little *et al.* [19] failed to find an association between airway wall geometry and sputum neutrophils. Niimi *et al.* [20,24] failed to find an association between sputum eosinophilia and airway wall geometry in two quantitative airway-imaging studies; in contrast, de Blic *et al.* [22] demonstrated an association between bronchoalveolar lavage eosinophil cationic protein levels and airway wall thickening in a childhood severe asthma cohort. Gupta *et al.* [4] have demonstrated an increase in RB1% wall area in individuals with and without eosinophilic inflammation, which was associated with the preceding burden of neutrophilic inflammation over time measured by repeated sputum analysis (Fig. 2). Furthermore, Siddiqui *et al.* [21] have demonstrated that although severe asthma and eosinophilic bronchitis have a similar degree of airway eosinophilic inflammation,

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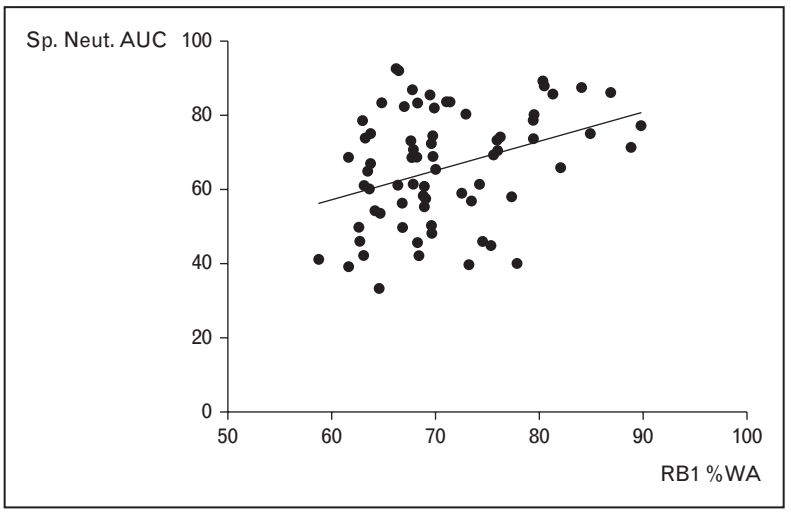

FIGURE 2. Correlation between right upper lobe apical segmental bronchus (RB1) percentage wall area (%WA) and sputum neutrophil area under the curve (Sp. Neut. AUC%) in patients with severe asthma ($r = 0.36$, $P < 0.005$) [14▪▪].

eosinophilic bronchitis patients lacked airway wall thickening with maintained patency of the RB1 lumen area as compared with severe asthma patients.

CT assessment of airway remodelling has proven to be a sensitive measure to detect and quantify change after the administration of treatments. Three different studies have demonstrated a significant decrease in airway wall thickness/area after the administration of inhaled corticosteroids [25–27]. Halder *et al.* [28] demonstrated a decrease in RB1 wall area after 1 year of treatment with anti-IL-5 compared with placebo, of approximately10%, in 52 severe refractory asthma patients with eosinophilic airway inflammation, which is similar to the approximately 11% wall area/BSA change demonstrated by Niimi *et al.* [27]. These findings support the view that changes in proximal airway geometry are clinically important. This altered geometry in severe asthma patients compared with healthy controls may be the key to understanding the physiological characteristics of asthma, such as airway hyperresponsiveness and airflow obstruction; however, at present, results are conflicting [14▪▪,17,20,21,24]. This discrepancy between CT studies may be due to methodological variation, difficulties in measuring proximal airways dimensions, inability of CT to identify all components of airway remodelling, and the mere complexity of structural and functional interactions in asthma, which only accentuates the need for further prospective interventional and longitudinal studies.

Importantly, to date, most studies have been undertaken in single centres, and there are a number of potential issues for multicentre trials. Standardization across centres should include not only the software but also the CT parameters of acquisition and reconstruction of images, and the parameters used for assessing the dimensions of the airways (wall area, wall thickness, wall area %, and wall area/BSA). This can in part be addressed with the appropriate use of phantoms to validate different scanners [29]. More importantly, the choice of airways to be measured should also be standardized: one or two bronchi (upper and lower lobes) or multiple segmental or sub-segmental bronchi. Current data suggest that RB1 correlates well with non-RB1 proximal airways in severe asthma, despite heterogeneity of remodelling [14▪▪,17,21]. But volumetric measurements of multiple airways would provide a more comprehensive assessment. The compromise between simplicity of outcome measure and detail has not been fully explored and will need to be addressed if this measure has a place in clinical trials. Similarly, to use such CT quantitative assessments of airway dimensions to measure outcomes after interventions, the reproducibility of these measurements between two successive acquisitions (interscan variability) needs to be fully established [30]. This is critical to define the threshold required to consider modifications in airway dimensions as significant.

QUANTITATIVE ASSESSMENT OF SMALL AIRWAYS IN ASTHMA

The small airways (peripheral membranous bronchioles less than 2 mm in diameter) are also significantly affected in asthma [31], with the presence of significant inflammation [32] and airway remodelling [33] being demonstrated in the small airways of asthma patients. CT scanners, however, cannot be

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used for the direct evaluation of the dimensions of the small airways as they are beyond the currently available resolution. Indirect changes caused by the small airways on the lung parenchyma can however be detected on CT, as small airways dysfunction results in reduced ventilation of part of the lung, which results in a reflex reduction in perfusion highlighted as areas of decreased attenuation on CT images [34]. Heterogeneity of lung attenuation in asthma can be noticeably accentuated in expiratory scans compared with inspiratory CT scans, due to regional differences in small airway closure or emptying rate. Low attenuation areas can then be quantified using the 'density mask' technique [35]. Although asymptomatic individuals with no lung function abnormalities also demonstrate low-attenuation regions on CT scans [36], asthma patients have significantly more air trapping which correlates well with lung function abnormalities [37–40]. Various indices to quantify air trapping in asthma on CT have been developed, including −850 HU attenuation threshold at functional residual capacity [38], percentage of pixels below −900 HU in expiratory scans [40], mean lung density expiratory-to-inspiratory ratio [39], difference between inspiratory and expiratory lung attenuation [41], and median lung attenuation or lowest 10th percentile lung attenuation frequency distribution [42].

Air trapping has been shown to correlate with asthma severity [43], yet the relationship is not fully understood. Busacker *et al.* [38] found that individuals with air trapping were significantly more likely to have a history of asthma-related hospitalization and intensive care visits compared with those without air trapping, which suggests that CT-assessed air trapping could potentially be used to identify the 'at-risk' asthma phenotype. CT-assessed air trapping has also been associated with airway hyperresponsiveness [40,43], disease duration [38], airflow limitation [38–40], and evaluation of response to inhaled corticosteroid therapy [41].

Similar to the proximal airways assessment, there is a wide variation in scanning protocols and indices of air trapping utilized by researchers. Yet, quantitative CT assessment of small airways in asthma will undoubtedly further our understanding of disease pathogenesis in asthma.

SYNCHROTRON RADIATION COMPUTED TOMOGRAPHY AND DUAL-ENERGY COMPUTED TOMOGRAPHY

To evaluate asthma, it is necessary to perform both a morphological assessment of the airways and a functional analysis of regional ventilation. This can be achieved by using synchrotron radiation CT/dual-energy CT. Ventilation imaging can be accomplished through nonradioactive xenon (Xe) enhanced CT. Xe is radiodense which makes it possible, using CT, to track the density changes occurring regionally at the bronchoalveolar levels after inhalation of Xe. Two Xe CT techniques have been developed to assess regional ventilation: single breath and multiple breaths. In the former, imaging is performed after the individual takes a single deep breath of high Xe concentration mixture [44]. As a result of its simplicity and lower radiation burden, there is more interest in the single-breath technique [44]. Synchrotron radiation CT and dual energy CT can both be used for the single-breath technique.

Chae *et al.* [45] showed that ventilation defects could be demonstrated in stable asthma patients by Xe ventilation dual energy CT. They also showed that the ventilation defect score correlated with FEV_1/FVC ratio, diffusion capacity (DLco), and residual lung volumes. The configuration and location of regional ventilation defects on dual-energy CT were similar to those on helium MRI [45]. Lung perfusion imaging can also be performed using dual-energy CT scanning, as it can provide an iodine map of the lung microcirculation [46]. Although true perfusion imaging is not performed using dual-energy CT, as it visualizes only blood volume and not blood flow, it may help in assessment of perfusion alterations due to vascular remodelling, an important feature of asthma. Apart from demonstrating morphology and regional perfusion or ventilation defects, dual-energy CT can potentially be helpful in understanding the pathogenesis of the disease, especially helping in phenotyping patients with severe asthma and evaluating response to treatment.

CONCLUSION

Severe asthma is a complex heterogeneous disease entity, with high morbidity and mortality. CT imaging technology, with its unprecedented diagnostic proficiency, has provided us with an opportunity to extend our understanding of this heterogeneous disease. Novel qualitative and quantitative imaging techniques have enabled us to study the large airway architecture in detail, assess the small airway structure, and perform functional physiological evaluations. Despite these spectacular advances in CT imaging techniques, there is an urgent need for both proof-of-concept studies and large cross-sectional and longitudinal clinical trials in severe asthma to validate and clinically correlate imaging-derived measures. This will extend our current understanding of severe asthma pathophysiology and unravel

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the structure–function relationship, which has the unprecedented potential to discover novel severe asthma phenotypes and predict mortality, morbidity, and response to existing and novel pharmacological and nonpharmacological therapies.

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Conflicts of interest

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- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 92).

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