A new approach to computed tomography measurement of airway remodelling in paediatric asthma

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Shareable abstract (@ERSpublications)
Internal normalisation to reference structures on quantitative chest CT imaging (*e.g.* lung airway dimensions to adjacent vascular dimensions) provides a potential way to standardise image measurements to population characteristics https://bit.ly/3Rh9pnW

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The Global Initiative for Asthma (GINA) defines severe asthma as a subset of difficult-to-treat asthma that is refractory to oral or inhaled corticosteroid therapies despite appropriate delivery and adherence [1]. This definition is retrospectively based on treatment paradigms and response to treatment rather than on objectively measured criteria. Severe asthma represents approximately 5% of childhood asthma cases [2] and accounts for the greatest proportion of all asthma-related expenditures [3, 4]. Recent advances in our understanding of subtypes and progression of childhood severe asthma have been achieved through longitudinal cohort studies, including the Childhood Origins of Asthma (COAST) study [5], the Inner City Asthma Consortium [6] and the Severe Asthma Research Program (SARP) [7]. These studies found that phenotypes of asthma in children differ from those of adults and change more rapidly, and pulmonary function tests (PFTs) are often normal or near normal even in children with severe asthma [8]. However, more nuanced evaluations of using PFTs and imaging have revealed some shared patterns between paediatric and adult severe asthma, including comparable degrees of obstruction on imaging [9, 10] and patterns of non-reversible air trapping [11, 12]. Consequently, quantitative imaging measures of obstructive patterns may complement conventional PFTs and play an important role in phenotyping the paediatric asthma population.

Recent advances in imaging, specifically quantitative chest computed tomography (CT) and magnetic resonance imaging (MRI), provide a rich set of measures to improve understanding of obstructive disease in paediatric patients. The introduction of lower-dose CT scanners, including the first commercial photon-counting systems, which reduce CT noise and allow for much lower X-ray dose [13], make paediatric chest CT safer and clinically feasible. Moreover, advances in functional lung imaging with hyperpolarised xenon-129 MRI in children [10] have led to clinical approval from the United States Food and Drug Administration for use in children aged 12–18 years [14], allowing imaging without using ionising radiation. The arrival of these technologies, with the introduction of biologic therapies in particular, offers the potential for better management of therapy approaches in paediatric severe asthma. However, a better understanding of what is normal for obstructive physiology in the paediatric population is necessary to identify subtypes of childhood severe asthma and corresponding stages of remodelling and obstruction. The lack of standardisation of lung measures on CT and MRI for paediatric populations makes it difficult to assess what is normal and what is disease. One approach in the lungs is to establish an internal reference of normal that would scale with lung size and patient age.

In this issue of *ERJ Open Research*, VAN DEN BOSCH *et al.* [15] report use of a novel measure of airway remodelling on chest CT that normalises the bronchial outer diameter (B_{out}) to the companion artery lumen diameter (A) at equivalent segmental generation (giving the B_{out}/A ratio). Because the entire airway and vascular trees are automatically segmented on an inspiratory chest CT scan, this calculation can be

efficiently performed for all visible bronchus–artery (BA) pairs. Artery-normalised ratios for bronchial lumen (B_{lumen}/A) and wall thickness (B_{wt}/A) were similarly evaluated. This BA analysis method has the advantage of internally normalising airway remodelling measures to the individual patient. Using the ratio of the vascular lumen to the companion airway has a strong clinical rationale in that the classic radiological definition of bronchiectasis is an increased bronchoarterial ratio on axial chest CT scans. If the airway lumen is consistently dilated relative to its companion vascular lumen on axial CT, this pattern is considered suspicious for bronchiectasis. VAN DEN BOSCH *et al.* [15] used the BA analysis to evaluate airway remodelling in a retrospective study of paediatric patients with a diagnosis of severe asthma in 161 CT scans obtained in 131 patients over the years 2007–2019. Inclusion criteria were chest CT scan with severe asthma diagnosis between the ages of 4 and 18 years and a reconstructed slice thickness of $\leqslant$1.5 mm. Given the large age range of the participants, normalisation is essential to standardise the measurements of airway remodelling.

The findings of VAN DEN BOSCH *et al.* [15] showed much higher central airway remodelling than expected. The most surprising finding was the high prevalence and extent of bronchiectasis. Using the B_{out}/A ratio threshold of 1.5, nearly 82% of CT scans analysed showed bronchiectasis, with a median fraction of airways defined as bronchiectasis of 3.2% (interquartile range (IQR) 1.1–7.1%) per scan. Other imaging studies found a more modest prevalence for bronchiectasis of 20–30% in children with severe asthma [16], which was similar to the prevalence found by VAN DEN BOSCH *et al.* [15] using manual semi-quantitative scoring. Similarly high degrees of airway remodelling were found for the bronchial wall thickness to artery lumen ratio ($B_{wt}/A \geqslant 0.14$ as the cut-off). The percentage of BA pairs per CT scan showing bronchial wall thickening was substantial, with a median of 41.7% (IQR 24.0–79.8%) showing thickened airways. Lending further credibility to the approach, measures of air trapping and small airway disease, including increased low attenuation regions on CT and reduced forced expiratory flows between 25% and 75% of forced vital capacity ($FEF_{25–75}$) z-score, correlated with some measures of airway remodelling, including increased B_{wt}/A and decreased B_{lumen}/A.

These exciting findings speak to the potential sensitivity of CT to assess early airway remodelling in children with asthma. However, they are hindered by the lack of normative data, for both the airways and vasculature, in this study. Differences in pulmonary vascular anatomy between mild–moderate and severe asthma [17], as well as in response to asthma therapies [18, 19], have been demonstrated in adult asthma. Thus, pulmonary vascular structures are likely to be a poor reference for normal airway dimensions in asthmatic patients. Furthermore, a B_{out}/A ratio threshold of 1.5 is a best-guess estimate for adult asthma patients. While this threshold may also be appropriate for paediatric patients, further investigations are required. Full development and validation of the technique will require larger prospective studies using modern, low-dose protocols, probably with a therapy intervention to demonstrate expected response. This technique could also be applied beyond paediatric asthma to understand normal lung growth and development.

Can the clinical use of quantitative CT diagnose the onset and extent of airway remodelling in paediatric severe asthma? These data from VAN DEN BOSCH *et al.* [15] are among the first to purport a normalised airway measure of central airway remodelling, which is robust to data acquired using multiple scanners and protocols. Moreover, the findings in the current work are consistent with patterns of air trapping in children with severe asthma that suggest airway and parenchymal remodelling may be occurring much earlier in these patients than previously thought. A quantitative and early marker of the airway remodelling process could be extremely valuable in prospectively phenotyping childhood asthma to improve management and treatment approach [20].

Despite these limitations, these results are provocative and hypothesis generating, pointing to the possibility of much more pronounced airway remodelling in early stages of severe asthma. Importantly, the use of an automated method for normalisation of airway diameter to vascular lumen points to a potentially sensitive and standardised measure of airway remodelling, enabling evaluation of early asthma in paediatric patients.

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