

Can computed tomography help us identify asthmatic phenotypes?

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Subjects with uncontrolled asthma account for the majority of health care costs attributed to asthma.¹ New approaches are needed to properly characterize asthma phenotypes to capture the complexity of this disease. The term “endotype” was coined by Anderson² as a way to classify subtypes of asthma that differ functionally and pathologically on a molecular level. Cluster analyses have been performed in adults^{3,4} and children⁵ that have identified distinct clinical phenotypes of asthma that differ in patient characteristics, lung function, health care use, and medication use, but further work needs to be done to better define biomarkers that can easily classify these patients and guide therapy.

Quantitative computed tomographic (CT) imaging is emerging as a useful tool in the study of asthma that can assist in the phenotyping of the disease and offers a unique wealth of objectively determined structural and functional information not readily available through traditional measures.⁶ CT measures of airway wall remodeling correlate well with lung function, asthma severity, and histologic airway wall remodeling.⁷⁻⁹ Lung densitometry can identify severe asthma phenotypes associated with increased health care use,¹⁰ and a decrease in air trapping is associated with improvement in lung function.¹¹ Fractal analysis of the airway tree offers an assessment of structural complexity, which is often reduced in asthmatic patients.¹² These quantitative CT measures each contribute to the characterization of the asthmatic patient in unique ways that build on the information gained by traditional sputum and blood biomarkers. In this issue of the *Journal*, Gupta et al¹³ apply cluster analytic

techniques to these quantitative CT measures in asthmatic and healthy control subjects to identify novel asthma phenotypes.

Gupta et al¹³ identified 3 distinct CT-derived phenotypic clusters. Cluster 1 patients demonstrated the most impaired lung function, increased wall volume, and, paradoxically, a high lumen volume, possibly related to the fact that these subjects had the highest degree of air trapping measured by using both CT air trapping and spirometric methods. The increase in cluster 1 in both wall and lumen volume, although possibly related to increased air trapping in this group, could represent the presence of coexisting bronchiectasis, as alluded to by the authors. The question of bronchiectasis could be explored further through additional quantitative evaluations of luminal airway tapering measures. Subjects in cluster 2 had little impairment in lung function and the least air trapping but, surprisingly, had a higher wall volume than cluster 1, suggesting more airway thickening. Subjects in cluster 3 had severe impairment in lung function, and subjects in this cluster tended to be more obese. Subjects in cluster 3 had more airway remodeling (higher percentage wall volume) with a narrowed airway lumen and a high degree of air trapping, although not as pronounced as in cluster 1. Fractal dimension was surprisingly higher in cluster 1 than in cluster 2, and subjects in cluster 3 had the lowest fractal dimension. Although fractal dimension, as measured in this study, could be associated with reduced airway detail because of downstream remodeling and mucus-based pruning, it also could also be related to the increased air trapping observed in cluster 1 subjects. Both clusters 1 and 3 were predominantly comprised of subjects with severe asthma. This study identifies novel phenotypes of asthma with distinct variations of airway remodeling, as reflected by quantitative CT. As noted previously, airway remodeling is not a uniform process across airway segments, and therefore this might generate distinct endotypes with varying features of airflow obstruction, air trapping, and bronchiectasis.⁷

A few limitations are present in the current study. These newly defined clusters do not correspond to known clinical clusters. For example, Moore et al³ describe 5 distinct clusters of asthma as defined by demographic data, spirometry, and medication use. The clusters in the study by Moore et al³ encompass a wide range of severities and symptomatology that are more reflective of the heterogeneity of asthma in clinical practice. This complexity is not fully captured by the CT-derived clusters in the current study. If cluster 1 truly reflects a bronchiectasis phenotype, the percentage of subjects that fall into this cluster (18%) is similar to that in prior studies.¹⁴ This might in part be reflective of the severity of the study population because the definition used for severe asthma in this study is reflective of refractory therapy-resistant asthma and is more stringent than the criteria typically used in clinical practice. The cluster results of Gupta et al¹³ are based on quantitative CT analysis of only 1 segment (RB1) of 20. Given the complexity and heterogeneity of the

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airway tree that is augmented in patients with airway diseases, it is unfortunate that more segmental pathways were not included in the cluster analysis; perhaps additional CT phenotypes could have been identified. Phenotypes might not be defined simply by the remodeling of a particular airway segment but rather could be distinguished by the remodeling of a pattern of segmental changes. The current analysis did not allow for the possibility of heterogeneous remodeling. We recognize that the whole airway tree was included within the fractal assessment, but it is concerning that the only difference found among the 3 groups (healthy subjects were significantly different from those with mild-moderate asthma) seems to be more related to 4 outliers within the normal population rather than to any differences associated with the asthmatic population. Because the full 3-dimensional branching structure was available from these data sets, an opportunity might have been missed by the reduction of the data set to 2 dimensions in the assessment of the so-called "airway fractal dimension." Finally, it is unclear why the mean lung density ratio was used as a measure of air trapping when the absolute measures of air volume at total lung capacity and functional residual capacity were available, as well as why lobar-level metrics were not included.

One puzzling finding is that the asthma control, quality of life, and rate of severe exacerbations did not differ between the clusters. This might reflect the smaller sample sizes in each group or a dissociation between these important clinical end points and the CT airway remodeling findings. Further work must be done to better define quantitative CT phenotypes in larger studies that will help define whether these airway changes correlate with clinical end points.

Despite the limitations discussed above, the authors should be commended for their use of multiple robust quantitative CT techniques to begin the use of these metrics in an effort to identify novel phenotypes of asthma by combining airway wall thickness, densitometry, and fractal analysis. Thoracic imaging in asthmatic subjects holds great promise to enrich our understanding of airway wall remodeling, air trapping, and structural complexity in the asthmatic subject and provide novel end points that help identify distinct endotypes that might be driving the disease process when combined with clinical end points. This study adds

to the evidence that quantitative CT offers novel, scientifically relevant biomarkers that expand our understanding of asthma and potentially provide therapeutic end points to reverse airway remodeling.

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