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Finally More Direct Evidence That Impulse Oscillometry Measures Small Airway Disease

Asthma is an inflammatory airway disease affecting the entire bronchial tree. Although it is now increasingly recognized that the small airways, defined as those with an internal diameter of 2 mm or less, play an important role in asthma, it is notoriously difficult to measure small airway inflammation and/or dysfunction (1). The recent multinational ATLANTIS (Assessment of Small Airways Involvement in Asthma) study performed a variety of physiological tests as well as computed tomography (CT) imaging in 773 patients with asthma and 99 control individuals to investigate the role of small airway disease (2). Small airway disease was shown to contribute importantly to the severity of asthma assessed by GINA (Global Initiative for Asthma) treatment step, asthma control, and history of exacerbations (2). In ATLANTIS, the prevalence of small airway disease varied with the physiological measure used. It was lower with Sacin (19%) and residual volume (RV)/TLC (22%), higher with resistance at 5 Hz (R5) – resistance at 20 Hz (R20) (42%) and forced expiratory flow, midexpiratory phase (FEF_{25–75}), and a decrease in FVC during provocative concentration of methacholine, causing a 20% fall in FEV₁ (PC₂₀) (73%). This was hypothesized to be a result of different small airway disease subtypes, depending on the location in the bronchial tree, with Sacin and RV/TLC reflecting the more peripheral airways and R5 – R20, FEF_{25–75}, and decrease in FVC during PC₂₀ methacholine reflecting the small-sized to mid-sized airways (2). However, the major drawback is that exactly which compartment of the bronchial tree each of the aforementioned tests reflects has never been directly investigated.

Therefore, the findings published in this issue of the *Journal* by Foy and colleagues (pp. 982–991) are important (3). Based on CT imaging data, the researchers reconstructed virtual bronchial trees of 21 patients with asthma and 11 healthy control individuals. To this end, centerlines of the airways were extracted up to generations 6–10, and the remainder of the conducting airways were reconstructed computationally, thus ultimately spanning generations 1–16, including a total of 30,000–100,000 large and small airways (4). Using this model, the resistance for each individual branch was calculated, and then all values were summed up into a simulated measure of R5 – R20. The reliability of this approach was confirmed by the finding that the simulated R5 – R20 values of these 32 subjects were significantly associated with actual measured R5 – R20 outcomes. Because this first step was successful, the authors then used the reconstructed lung model to investigate what the effect of constriction of airways located in

different parts of the bronchial tree (trachea to small airways) would be on R5 – R20 levels. Interestingly, constriction of the small airways (sixth generation and further; average diameter, <1.39 mm) consistently produced larger increases in simulated R5 – R20 values than constriction of the large airways in their model. Using data from a larger clinical asthma cohort and adjusting for possible confounders, the authors then assessed how changes in R5 – R20 would affect the severity of asthma symptoms and demonstrated that narrowing of the small airways by more than 40% would generate clinically important changes in asthma control and quality of life.

The findings of Foy and colleagues are very interesting, as they provide, for the first time to our knowledge, direct evidence on how R5 – R20 reflects airway narrowing in specific locations of the bronchial tree and strengthen the notion that R5 – R20 is a useful tool to measure small airway disease in asthma.

In the study by Foy and colleagues, the association between simulated R5 – R20 and the actually measured values, although statistically significant, was relatively weak. This may have been because the computational modeling to build the bronchial tree was imperfect as a result of certain assumptions, such as the use of a simple constant-phase model (5). Another possible explanation is the imprecision of the actually measured R5 – R20, as the impulse oscillometry technique can also be prone to sources of error (e.g., introduced by variations in patient breathing and upper airway/cheek shunting) (6). Which of the two will be the most relevant to the diagnosis and management of small airway disease remains to be established.

This nice study with very complicated computational models is based on actual CT measurements up to generations 6–10, and essentially on extrapolation from there to the alveoli. The group from Vancouver has added analysis of actual pathology specimens from explanted lungs to further assess the smaller airways, which could be a useful addition for the current technique as well (7, 8). In addition, the modeled sites of constriction from trachea to small airways could perhaps be further validated by actually imposing constriction in patients with asthma in different parts of the bronchial tree (e.g., with small vs. large particle size bronchoprovocation agents) (9).

The authors have been brave to take as their primary correlate of small airway disease asthma control and quality of life, thereby linking small airway disease to what matters to the patient. They showed reasonably good correlations between R5 – R20 and asthma control and also showed that these parameters improve with biologics.

A great opportunity would be to replicate the findings of Foy and colleagues in the larger ATLANTIS cohort. This makes it possible not only to confirm that simulated R5 – R20 is associated with the actually measured outcome but also to assess the respective values of simulated and actual R5 – R20 outcomes in relation to a variety of other small airway measurements, as well

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as to cross-sectional and longitudinal (1-yr) follow-up data on asthma control and exacerbation frequency. In addition, it will be of interest to use the CT-based model to connect changes in airway caliber in different locations of the reconstructed bronchial tree to other small airway parameters such as multiple breath nitrogen washout, FEF, alveolar nitric oxide, and lung hyperinflation. This will improve understanding of how currently available physiological and imaging tests reflect small airway disease in different locations of the bronchial tree, and may identify new small airway disease subtypes with possible clinical relevance in the context of treatment such as biologicals. The ongoing discussion of proving the added value of extra-fine particles, and a range of particle sizes in an administration, could also profit from this new technique. ■

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⊗ Stratifying Bronchiectasis: Getting to within a Zone's Throw

Bronchiectasis is a chronic, progressive, and irreversible dilatation of the airway that exhibits geographic variation, contrasting endophenotypes, and involvement in “overlap” states (1–4). Its clinical heterogeneity and etiological complexity are compounded by our incomplete understanding of its pathogenesis. This leads to difficulties with clinical trials and therefore a lack of evidence-based treatments for patients (5).

The archetype “Cole’s vicious cycle” model of pathogenesis has formed the basis for emerging concepts such as the “vicious vortex,” which offers a more holistic view of the disease, reaffirming its key interrelated components: infection, inflammation, epithelial-

immune dysfunction, and lung destruction (6, 7). All of these components interact and are influenced by one another, perhaps to different extents, in different patients and etiologies and at various disease severities, including exacerbations. Consequently, improving patient stratification and identifying “high-risk” bronchiectasis endophenotypes are key focuses of ongoing research (5, 8).

Although airway infection incites and propagates disease, the immune-inflammatory consequences (even in the absence of infection) have a strong influence on disease outcomes. Neutrophils in particular are the hallmark airway inflammatory cells and a source of protection against infection, but when excessive in number and response, they can induce further airway damage and bronchiectasis. Neutrophils have important roles in severe asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF), where airway-dominant phenotypes are associated with poor disease outcomes. Airway and systemic neutrophils are dysfunctional in bronchiectasis, and although immune dysregulation is a recognized feature in disease, the mechanisms by which neutrophilic inflammation is linked to impaired immunity, particularly in the context of infection, remain poorly understood (1, 5, 9, 10). This is exemplified by the paradoxical strong, cellular-abundant, and sustained neutrophilic response observed with persistence of airway infection. Acute infections in bronchiectasis are cleared by

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