Quantitative Computed Tomography in Asthma: For Good Measure

In the past decade, high-resolution computed tomography (HRCT) has provided a wealth of information about airway structure and function in chronic obstructive pulmonary disease (COPD), based on images from large multicenter studies such as COPDGene (Genetic Epidemiology of COPD), CANCOLD (Canadian Chronic Obstructive Lung Disease), ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints), and SPIROMICS (Subpopulations and Intermediate Outcomes Measures in COPD Study). Smaller cohort studies have also identified potentially useful metrics, such as the total airway count (TAC) (1), which has been applied to a larger COPD population (2). The assessment of the number of airways that are discernible on CT to obtain TAC was propelled by micro-CT findings from excised lungs of patients with COPD (3) that demonstrated a dramatic loss of terminal bronchioles. The question then arose as to whether airways could also be missing in more proximal bronchial generations, and whether TAC could be linked to FEV_1 and FEV_1 decline, which appears to be the case in COPD (2).

Recently, HRCT studies have also been performed in patients with asthma to elucidate structure–function links. Dunican and colleagues (4) identified CT-visible mucus plugs, mostly in subsegmental airways, in a majority of their asthma population, and the number of mucus plugs correlated inversely with FEV_1. In a study presented in this issue of the *Journal*, Eddy and colleagues (pp. 923–933) measured TAC in patients with asthma of varying severity, and found that the number of missing airways, mostly at the subsubsegmental level, increased with decreasing FEV_1 (5). An appealing aspect of this study is the additional measurement of ventilation by magnetic resonance imaging (MRI) to explore the link between the missing airways and ventilation defects. Although the quantification of underventilation by MRI is sometimes criticized for being heavily dependent on the choice of thresholds to define what can be graded as more or less well ventilated, the use of "ventilation defect" (ventilated or not) appears to be particularly well suited for searching for a link with TAC (airways missing or not).

Another interesting aspect of this CT-MRI study in patients with asthma (5) concerns the lobar analysis of missing subsubsegmental airways and corresponding ventilation defects. Considered in combination with lobar MRI ventilation data obtained from patients with asthma by Zha and colleagues (6), the right middle lobe was most consistently affected by ventilation defects. In both of these asthma studies, the degree of ventilation defect (2–10%) was rather low, given the number of missing airways that would otherwise be a pathway to relatively large ventilated air spaces. This suggests either that inhaled air is redirected toward the patent airways or that a considerable number of collateral pathways (by convective or diffusive gas transport) are operational. An intriguing finding in Eddy and colleagues' study (5) is that the patients with asthma who displayed a so-called "airway variant" (mostly an accessory subsuperior segment) in fact had fewer ventilation defects than the patients with asthma and a normal airway tree.

The fact that FEV_1 was shown to be inversely related to the number of mucus plugs (4) or the number of missing airways (5) in patients with asthma is not surprising, given that the affected airways are located in proximal bronchial generations. Although the origin and therapeutic implications of either mucus plugs or missing branches remain to be investigated in various asthma phenotypes, such quantitative CT data are extremely useful for the development of lung models. These models can only be as realistic in their prediction of lung function tests as they are realistic in their make-up, and should provide answers to relatively simple questions, such as, what is the quantitative impact of a given number of missing or constricted airways in specific bronchial generations on spirometry-derived FEV_1 (7), forced oscillation–derived resistance (8) and reactance (9), ventilation heterogeneity (10), and aerosol deposition (11)? Such information would pave the way for full-fledged patient-specific quantitative predictions that venture beyond statistical analyses, where causal effects are sometimes difficult to discern.

The interpretation of structure–function studies has long been scaffolded by intuitive reasoning informed by the basic lung mechanical principles laid out by the pioneers who invented the physiological tests that are still, or again, in vogue today. With the various state-of-the-art imaging modalities, it is becoming increasingly clear that the heterogeneous nature of a diseased lung and its ventilation distribution renders intuitive reasoning difficult, and that simple underlying models may no longer suffice to make meaningful estimates of how much a physiological parameter will change in response to a given degree of airway structural change. This is where we probably need to take interpretation to the next level with comprehensive and realistic lung models, where a CT-measured degree of structural abnormality can be translated into its predicted effect on selected lung function indices in COPD (12), cystic fibrosis (13), and asthma (10). Specifically in cases of severe asthma, treatments such as thermoplasty could also benefit from a lung model–guided approach (14), inasmuch as the airway geometry and its variants can be obtained for the patient under consideration for thermoplasty.

When we extract structural data from CT studies to feed them into realistic models, the imaging methods matter and the devil is in the details. For instance, all CT data are obtained with the patient supine, and TAC data may be obtained at lung inflation close to TLC (2) or FRC (5). Both body posture and

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lung inflation affect the degree of airway closure, impacting relationships between supine TAC and upright residual volume/TLC in COPD (2) and asthma (5). Although it is possible for lung models to estimate the posture-dependent effect (15), many physiological tests can be performed in both the upright and supine positions. A practical challenge for future HRCT studies is to reduce radiation exposure, enabling dynamic CT images to investigate the intermittent nature of airway closure in asthma, or the expansion dynamics of the thinned airway walls in COPD (2) and thickened airway walls in asthma (5). On both the image and lung function sides, we owe it to patients with lung disease to make every possible effort to extract as much structural information from the images we have, and to make the lung models that can help us interpret the structure–function link as realistic as possible. This is where morphometric and ventilation data obtained from the same patients (5) can be very helpful. ■

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FSTL-1: A New Player in the Prevention of Emphysema

Emphysema is an incurable destructive lung disease that causes impairment in gas exchange, gas trapping, hyperinflation, and ultimately shortness of breath. Cigarette smoking is a major cause of emphysema, but there are also less common genetic causes of emphysema, such as alpha-1 antitrypsin deficiency (1). The mechanisms underlying the induction and progression of emphysema are believed to involve an imbalance in lung proteases and antiproteases, chronic inflammation and oxidative stress, alveolar wall cell death, and failure of alveolar wall maintenance (2, 3). A better understanding of the cellular and molecular mechanisms that drive emphysema may lead to novel therapeutic strategies to prevent its development or halt its progression, resulting in better health outcomes for patients.

There is a growing body of evidence showing that FSTL-1 (follistatin-like 1) plays an important role in lung development and respiratory diseases, including asthma and pulmonary fibrosis (4–8). In a study presented in this issue of the *Journal*, Henkel and colleagues (pp. 934–945) examined the consequences of reduced FSTL-1 expression on postnatal lung homeostasis (9). For this

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