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Multiscale Lung Imaging Provides New Insights into Disease Progression in the Chronic Obstructive Pulmonary Disease Lung

The early disappearance of terminal bronchioles in the sequelae of events associated with chronic obstructive pulmonary disease (COPD) was observed in what is now considered to be a landmark publication of McDonough and colleagues using both multi-detector row computed tomography (MDCT) and micro-computed tomography (microCT) to study the lungs of subjects with panlobular (PLE) and centrilobular (CLE) emphysema (1). In comparison with control subjects, McDonough and colleagues found a reduction of airway segments detected at the limits of resolution of MDCT in both PLE and CLE (1). These reductions in the 2- to 2.5-mm inner diameter airways observed on MDCT were accompanied by a reduction in the number of terminal bronchioles in PLE and more so in subjects with CLE studied by microCT. In this issue of the *Journal*, Tanabe and colleagues (pp. 630–638) extend the observations of McDonough and colleagues by assessing, in an expanded set of lung samples, the anatomic characteristics of the preterminal airways of PLE, CLE, and control subjects (2). The observations include a demonstration of an increased wall thickness and wall area percentage in CLE compared with subjects with PLE and control subjects.

One of the most interesting features of this study is that it allowed airways to be integrally studied, from branch point to branch point, cross-section, and length. This resulted in the paradoxical finding that, compared with control subjects, the length of preterminal bronchioles is reduced by 28 and 48% in CLE and PLE, respectively, whereas the lung volumes are increased by 33 and 46%, an observation that needs some explanation. However, it is only paradoxical if one assumes that the emphysema pathology affects both the acinar structures and the airways homogeneously, but this is hardly the case. Integrity of lung structure is essentially ensured by the complex fiber continuum that extends from the pleura through the septal fiber nets of the acini and along the airway tree to the hilum (3). This system has the characteristics of a tensegrity structure (4, 5): when one fiber of the tensed network is snapped, the entire structure becomes deformed. In the case of emphysema, the acinar fiber networks are partly disrupted, which reduces the tensile forces they exert on the proximal structures, mainly on the (pre)terminal airways that will retract toward the larger more central airways; at the same time they will withdraw from the acinar structures, thus increasing the acinar space, the hallmark of emphysema.

The observation that total wall volume of preterminal bronchioles was not maintained but reduced, despite the

observation of cross-sectional thickening, in both CLE and PLE, suggests an upstream loss of airway structure coincident with the previously observed (2) disappearance of terminal airways. With this current observation of wall volume reduction in the preterminal bronchioles, there is emerging a picture of wall reduction along the length of the airway tree. Smith and colleagues have recently demonstrated that, if one is careful to assess spatially matched airway segments, on average, subjects with COPD have thinner airway walls compared with a nonsmoking control population (6). It should be noted, as discussed by Smith and colleagues, that the observation of thinned airway walls is based on a population average and is not to say that wall thickening is absent from a portion of the COPD population (6). There seems to be at least a subset of the COPD population with an airway phenotype that includes airway wall thinning starting as centrally as the segmental airways and possibly extending to the periphery, whereby the terminal bronchioles are lost.

The emergence of new imaging methodologies holds great promise for the continued exploration of this and other COPD phenotypes, and, through the ability to follow these phenomena longitudinally, disease etiologies will begin to be better understood. Although it is observed that the terminal bronchioles are reduced in length (2), it would seem difficult to know whether or not the length observed in a cored and preserved sample is truly reflective of the state of the bronchioles within the intact lung. A microCT methodology using interior tomography has been introduced (7), whereby large tissue samples can be imaged with a region of interest set to reconstruct pulmonary acini with a spatial resolution down to 1 to 2 μm . This methodology allows for the detailed comparison of airway and acinar anatomy ranging from the subpleural regions to the lung core (8), and airway paths can be traced from the acinus to the segmental bronchi.

Advances in MDCT allow for the imaging of the lung with a spatial resolution two to three times that of previous CT methodologies (Siemens SOMATOM Force; Siemens, Forchheim, Germany), and iterative reconstruction methods provide low-noise images with X-ray doses down to 0.1 mSv or the dose associated with a pair of chest films (9). Novel new hyperpolarized gas methods for magnetic resonance imaging provide the tools to longitudinally follow indices associated with the terminal bronchioles (10–12). Dual-energy CT has allowed for the assessment of peripheral distributions of perfused blood volume, a surrogate for parenchymal perfusion, leading to the exploration of vascular

dysfunction and its role in smoking-associated emphysema (13). Prototypes of the next generation of CT scanners have emerged, which use photon counting rather than energy integration to generate the projection images used in the image reconstruction process (14). By counting photons passing through the body and binning them into their various energy levels, one can image multiple contrast agents simultaneously by reconstructing various scan data using only a range of detected photon energies, leading to the possibility of imaging ventilation, perfusion, and inflammation simultaneously through the delivery of, for example, krypton gas, gadolinium, and gold-labeled autologous neutrophils. Leng and colleagues demonstrate imaging via photon counting with an in-plane pixel dimension down to 200 μm (14). With photon counting, image artifacts such as beam hardening should be eliminated. Jorgensen and colleagues have recently demonstrated the ability of photon counting CT to image alterations in perfusion to the vasa vasorum of the carotid artery wall, leading to the expectation that such methodologies will allow for the assessment of perfusion to the airway walls, providing a means of exploring the possible link between vascular dysfunction and bronchial wall thinning (15). Through the use of interior microCT (7, 8) for the imaging of select regions within larger specimens (with local resolution down to 1–2 μm), structural details can be matched to associated *in vivo* image data, as demonstrated by Kumar and colleagues (16). This provides the means of understanding the mechanical interactions occurring in the most peripheral regions of the lungs by taking the strain fields generated by matching multiple *in vivo* lung volumes together and then applying the resultant strain fields to the volumetric microCT data set.

Through the exploration of anatomic changes in the lung at the level of the preterminal bronchioles, Tanabe and colleagues (2) provide the link between prior microCT-based studies demonstrating the early disappearance of the terminal bronchioles and the emerging understanding provided by Smith and colleagues (6) showing that more central airways, on average, thin in a replicate pair of COPD cohorts. With careful attention to the development of and adherence to the use of imaging methodologies embedded into multicenter studies of COPD (17), the ability to link *in vivo* imaging and *ex vivo* imaging methodologies are likely to provide the insights needed to better define what are likely multiple etiologies of COPD and to begin to develop targeted interventions. ■

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