remaining small airways have thickened walls and narrowed lumens (3). However, it remains to be determined how small airway disease leads to emphysema. Based on Vascilescu and colleagues' study in combination with decades-old research (1, 6), we propose that loss of bronchiolar–alveolar attachments is the most plausible link between small airway disease and emphysema.

Lungs from smokers and lifelong nonsmokers who died suddenly of nonrespiratory causes outside of a hospital, as well as lungs/lobes from smokers who had undergone resection for localized pulmonary lesions, were examined by Saetta and colleagues (6). The internal diameter of the small airways and the alveolar size—as histological measures of small airway disease and emphysema, respectively—did not significantly differ between groups. However, reduced numbers of normal bronchiolar–alveolar attachments were found in smokers compared with never-smokers. Furthermore, the quantity and quality of the bronchiolar–alveolar attachments was related to the level of inflammation in the small airways. Figure 1 of Saetta and colleagues' article, which shows a cross-section of a nonrespiratory bronchiole surrounded by alveoli, probably says more than a thousand words. Inflammation has progressed through the entire airway wall into adjacent alveolar septa, which are relatively thin compared with the much thicker bronchiolar wall and would be the first to succumb to inflammation-induced proteolytic activity.

In a microcomputed tomography analysis, Vascilescu and colleagues showed that $PRM^{SAD}$ was related to an increased number of obstructed terminal bronchioles, decreased terminal bronchial cross-sectional lumen area, and decreased circularity of the terminal bronchioles, whereas $PRM^{Emph}$ was associated with airspace size, alveolar surface area, and the number of alveolar attachments (1). Previously, Labaki and colleagues demonstrated that over a 5-year period, $PRM^{SAD}$ often evolves into $PRM^{Emph}$ (5). Together, these PRM studies suggest that lung areas with small airway disease only transform into emphysema if bronchiolar–alveolar attachments are destroyed (1, 5).

Based on the above findings, we propose the following sequence of pathological steps leading from smoking to emphysema formation: deposition of cigarette smoke particles in small airways→inflammation of small airways→propagation of inflammation through the entire bronchiolar wall into adjacent alveolar septa→destruction of bronchiolar–alveolar attachments→lung parenchyma degradation proceeding from the centers of the secondary pulmonary lobules toward the surrounding interlobular septa.

Disease-modifying therapies should be established to prevent destruction of bronchiolar–alveolar attachments and thus the progression from small airway disease to emphysema. ■

**Author disclosures** are available with the text of this letter at www.atsjournals.org.

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## Reply to Janssen and Wouters

*From the Authors*:

We thank Dr. Janssen and Dr. Wouters for highlighting the importance of our study (1) to validate parametric response mapping (PRM) as an imaging biomarker to identify small airway disease in patients with chronic obstructive pulmonary disease (COPD). We agree with them that our data provide further support for the notion, as previously stated (2), that small airway disease is an important target for COPD therapies. The unique data set and tissues available from our work clearly demonstrate that the number of terminal bronchioles is significantly reduced in lung regions where the airspace size (a surrogate for emphysema) remains below the detectible level of clinical computed tomography, and that these regions are predominantly classified as PRM functional small airway disease. In contrast, the data show that the number of terminal bronchioles is further reduced in regions where PRM emphysema is dominant. However, our data were obtained from patients with severe COPD and cannot unambiguously define whether this pathological process is the same for all patients with COPD. Nonetheless, when these results are combined with the longitudinal imaging data of Labaki and colleagues (3), which demonstrated that in patients with COPD of different degrees of severity, PRM functional small airway disease regions progress to PRM emphysema regions, it becomes evident that initial small airway disease may disseminate into the surrounding tissues, leading to extensive emphysema, as shown by Saetta and colleagues (4). Supporting this mechanism, we previously demonstrated in a cross-sectional study that small airways are lost before loss of alveolar surface area occurs in mild and moderate COPD (5).



Originally Published in Press as DOI: 10.1164/rccm.201911-2154LE on December 5, 2019

Importantly, as the authors point out, a next step is to identify the mechanism by which small airways are lost. The proposed sequential pathological steps, which were first suggested by Saetta and colleagues in 1985 (4) and later revised by Mitzner (6), of "deposition of cigarette smoke particles in small airways→inflammation of small airways→propagation of inflammation through the entire bronchiolar wall into adjacent alveolar septa→destruction of bronchiolar–alveolar attachments→lung parenchyma degradation proceeding from the centers of the secondary pulmonary lobules toward the surrounding interlobular septa" are highly plausible. Support comes from other cross-sectional studies in advanced COPD (7–9). However, we should emphasize that this postulate must be confirmed via rigorous quantitative analyses in earlier COPD stages (10).

Other investigators and we have previously reported that volumetric microcomputed tomography imaging of tissue samples provides a unique opportunity to target specific lesions for histological examination, and therefore to assess the unique properties of the cellular composition within and around a lesion. Tanabe and colleagues demonstrated that the destruction of the alveolar attachments in the preterminal bronchioles could be driven by a B cell–mediated immune response (11). Assessment of the terminal and transitional bronchioles poses greater challenges with regard to analytic imaging techniques, but it is not impossible.

An additional crucial issue is the exact process behind the tissue destruction. What causes the alveolar attachments to "snap"? We believe the most plausible explanation is that the extracellular matrix is remodeled by infiltrating cells, leading collagen and elastin fibers to become deranged to such a degree that they cannot withstand the continual stretching and contraction during breathing. Novel methods, including nonlinear optical microscopy, which was previously applied to study airway remodeling in patients with asthma (12), may shed light on this process.

Hence, performing a targeted analysis of the remodeling, cellular infiltration, and gene expression of the terminal bronchioles, and assessing their association with PRM classifications at earlier disease stages are high research priorities for our group. We are confident that this multipronged approach will shed more light on the mystery of how destruction of the small airways and surrounding tissues occurs. ■

**Author disclosures** are available with the text of this letter at www.atsjournals.org.

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‡F.J.M. is Deputy Editor and J.L.C. and M.K.H. are Associate Editors of *AJRCCM*. Their participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

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## Silica Exposure and Scleroderma: More Bridges and Collaboration between Disciplines Are Needed

*To the Editor*:

We have read with great interest Turner and colleagues' correspondence concerning connective tissue disease



Originally Published in Press as DOI: 10.1164/rccm.201911-2218LE on December 27, 2019