

of patients undergoing noninvasive respiratory support due to hypoxemic respiratory failure, to avoid any delay in endotracheal intubation. It is possible that prompt detection of treatment failure prevented muscle exhaustion-induced hypoventilation in failing patients.

Finally, because in some patients (i.e., those with lower inspiratory effort) helmet NIV increased transpulmonary pressure swings, the authors suggest that helmet NIV is less able to limit lung stress than HFNC and that this treatment should be reserved for selected patients as a step-up support. Unfortunately, we fear that it is not possible to draw conclusions regarding this specific aspect from our results. However, global lung stress (estimated by transpulmonary pressure swings) is only one determinant of self-inflicted lung injury, and inspiratory effort seems the most important parameter to be taken into account in this setting. Helmet NIV allows the application of high positive end-expiratory pressure, which reduces inspiratory effort and prevents pendelluft-induced overstretch in the dependent lung, as well as other ventilatory heterogeneities, making spontaneous effort less injurious (7). Importantly, during lung injury, limiting transpulmonary pressure swings cannot prevent injurious inflation patterns or diaphragm injury if inspiratory effort is not reduced as well (5, 8). ■

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Loss of Alveolar Attachments as a Pathomechanistic Link between Small Airway Disease and Emphysema



To the Editor:

Vasilescu and colleagues are the first to provide confirmation that an imaging biomarker, parametric response mapping (PRM), has the ability to differentiate small airway disease (PRM^{SAD}) from emphysema (PRM^{Emph}) in patients with established chronic obstructive pulmonary disease (COPD) (1). This is of utmost importance given the urgent clinical and scientific need to noninvasively detect terminal bronchial pathology.

COPD is characterized by the presence of persistent airflow limitation and respiratory symptoms. Airways smaller than 2 mm in internal diameter are the dominant site of airflow obstruction in patients with COPD. This obstruction is caused by a mixture of pathogenic events (with)in and around the small airways, namely, loss of airways (2, 3), thickening of remaining airway walls (3), luminal obstruction by endobronchial mucus, and loss of bronchiolar-alveolar attachments leading to reduced radial traction.

Emphysema is a key pathological condition in COPD that is defined by an abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by destruction of their walls and without obvious fibrosis. Whereas in an editorial addressing the landmark study of McDonough and colleagues (2), Mitzner (4) questioned whether emphysema formation starts in the small airways or lung parenchyma, accumulating evidence now strongly suggests that small airway disease precedes emphysema formation (2, 3, 5). It has been demonstrated that a significant proportion of terminal and transitional bronchioles are lost in lung samples from patients with COPD without signs of emphysema (2, 3), and that the

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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 Vasilescu 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, Vasilescu 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. ■

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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 detectable 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).

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