subgroups, some genes did exhibit opposing expression patterns between sexes (8). It is not clear whether this could explain some of the differences in sex responses to lung injury (12). Additional caveats need to be clarified, such as normalization for menstrual cycle, which could alter macrophage-specific gene profiles. Also, these studies did not include an inflammatory insult, in which the majority of the sex-dependent effects have been observed (13). These studies provide an important foundation to continue to examine the role of sex hormones in regulating macrophage gene expression within the lung.

Taken together, this study provides a concise, well-annotated database for the characterization of lung airspace macrophages from multiple healthy donors. They observed consistent gene expression profiles at a single-cell level between individuals, defining distinct subsets of airspace macrophages with unique profiles. In addition, they provide evidence that there is a constant stream of monocytes into the lungs even in the noninflammatory state. If true, these studies suggest that the airspace macrophage pool is more complex than previously identified, and this reflects a new "normal" that must be considered in human response to injury and chronic disease. ■

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Mucus Plugs in Medium-sized Airways: A Novel Imaging Biomarker for Phenotyping Chronic Obstructive Pulmonary Disease

Multiple studies have already focused on the phenotyping of patients with chronic obstructive pulmonary disease (COPD) by assessing emphysema and airway disease on chest computed tomography (CT). In 2015, the Fleischner Society proposed to differentiate between emphysema-predominant and airway-predominant imaging subtypes based on the presence of at least 5% pulmonary emphysema (1). Additionally, it defined five different subtypes of emphysema-predominant phenotypes based on a visual assessment of the severity and pattern of emphysema (1). More recently, an ancillary study from the COPDGene (Genetic Epidemiology of Chronic Obstructive Pulmonary Disease) study described 10 nonoverlapping CT imaging subtypes by combining visual and quantitative CT imaging features (2). Although emphysema can be simply quantified by measuring the percentage of lung voxels below −950 Hounsfield units (3), the assessment of airway disease is usually more complex. Bronchial airway disease can be estimated

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either visually or automatically by measuring bronchial wall thickness (4). For small airway disease quantification, most previous studies focused on density measurements on expiratory images (5).

In this issue of the *Journal*, Dunican and colleagues (pp. 957–968) propose a novel, simple approach to assess airway disease by quantifying mucus plugs responsible for a complete bronchial occlusion on CT images (6). The evaluated method consists of a bronchopulmonary segment–based scoring system, which was initially developed to study mucus plugs in patients with eosinophilia-related asthma and airflow obstruction (7). A total of 420 participants from the SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD) study were evaluated, including 20 never-smokers and 400 current or ex-smokers with or without airflow limitation. The authors showed that mucus plugs, which occurred in subsegmental medium-sized airways, were highly prevalent in (ex-)smokers, whereas it was relatively rare in nonsmokers. More than two-thirds of patients with COPD had a mucus plug score higher than zero; the mucus plug score was significantly higher in patients with severe and very severe airflow limitation compared with smokers with normal lung function. Importantly, only one-third of smokers with high mucus plugs had symptoms of chronic cough and sputum production, indicating that mucus plugs in medium-sized airways are often asymptomatic. Although mucus plugs and emphysema were both highly prevalent in patients with COPD, they were only weakly correlated, making it possible to explore their relative roles on airflow limitation. In analyses controlling for emphysema, airway wall thickness, and smoking pack-years, both mucus plugs and emphysema were associated with airflow limitation and peripheral oxygen saturation. Interestingly, smokers with mucus plugs had a low post-bronchodilator FEV_1 even when emphysema was absent, and the relationship between mucus plugs and lung function was strongest in smokers with limited emphysema. Compared with smokers with low mucus scores, smokers with high mucus scores had more frequent exacerbations and shorter exercise capacity. A subset of patients had data on sputum cells, and sputum neutrophils (but not sputum eosinophils) were markedly higher in patients with high mucus plug scores compared with those with low scores. Finally, stability of the mucus plugs was examined in a subset of patients by comparing CT scans at baseline and after 1 year: mucus plug scores were rather stable in individual patients, and bronchopulmonary segments with mucus plugs at baseline were usually plugged at 1 year, whereas segments that were free of plugged at baseline generally remained without plugs at 1 year.

The study by Dunican and colleagues is most important as it confirms the importance of mucus plugging in the pathophysiology of COPD. Seminal histopathology studies by Hogg and colleagues have identified anatomical determinants of airflow limitation in patients with COPD, including increased airway wall thickness and mucus plugging in small airways (<2 mm in internal diameter) (8), and their prognostic value (9); emphysema extent and characteristics also contributed to airway limitation via loss of elastic recoil. However, small airways are not directly visible on CT scans (10); although the relationship of CT-defined mucus plugging in medium-sized airways (2–2.5 mm) to pathology-defined mucus plugging in small airways is currently unknown, the study by Dunican and colleagues provides a noninvasive way to examine mucus plugging in living humans and to repeat this analysis over time. An important finding of this study was also that mucus plugging in medium-sized airways often occurs without symptoms of chronic cough and sputum production; this finding is not completely unexpected, as cough receptors are located in large proximal airways, leading to the prediction that plugging in medium and small airways can occur without symptoms (11). Multiple studies have shown a strong relationship between symptoms of chronic cough and sputum production and rates of exacerbations in patients with COPD (12). Whether these findings are independent to CT-defined mucus plugging remains to be established. Furthermore, the findings that patients with high mucus scores have higher COPD assessment test scores is somewhat puzzling, as this is most likely not related to symptoms of cough and sputum.

The score proposed by Dunican and colleagues has the advantage of being simple to implement and reproducible. However, visual quantification remains an obstacle to large-scale studies and clinical use, as it requires time and expertise. Thanks to the development of deep learning applications in thoracic imaging (13), it is nevertheless hoped that the quantification of mucoid impactions can be automated, notably thanks to the improvement of airway segmentation methods (14).

Mucus hypersecretion appears as a therapeutic target for multiple chronic airway diseases, including severe asthma, COPD, cystic fibrosis (CF), and bronchiectasis (15). In CF, highly effective CF transmembrane conductance regulator modulators have been developed for restoring ion transport, and these drugs have beneficial effects on lung function and clinical outcomes (16), presumably by improving mucociliary clearance and reducing mucus plugging in airways (17). Currently available drugs have limited effects on mucus in COPD (18), and CF transmembrane conductance regulator modulators have been proposed for targeting mucus hypersecretion in patients with COPD (19). However, testing for mucoactive drugs has proven challenging in patients with COPD (20) because monitoring airway mucin may require analyses of bronchial biopsies and/or brushing. The study by Dunican and colleagues provides the opportunity to *1*) select appropriate patients (those with high mucus scores) for studies assessing the effects of drugs targeting mucus hypersecretion in multiple airway diseases and *2*) monitor the effects of these drugs on mucus plugging, using a noninvasive technique. The association between sputum neutrophils and mucus plugging is also interesting, as neutrophil proteases are important contributors to mucus production and secretion (11). Novel drugs that target neutrophil serine proteases are under evaluation in patients with bronchiectasis (21), and the present study provides some rationale for evaluating these drugs in patients with COPD.

Overall, the elegant study by Dunican and colleagues demonstrates the effects of mucus plugging on functional impairment in COPD and shows it is independent of that of pulmonary emphysema. The proposed quantification method for mucus plug appears to be a simple, reproducible, and promising new approach for the quantitative assessment of airway disease on CT imaging, complementary to the well-recognized quantification of pulmonary emphysema. ■

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Transpulmonary Pressure–guided Ventilation to Attenuate Atelectrauma and Hyperinflation in Acute Lung Injury

The inherent appeal of using esophageal manometry to guide positive end-expiratory pressure (PEEP) titration lies in its ability to distinguish lung from chest wall mechanics. Transpulmonary pressure (P_L) is calculated as the pressure measured at the airway opening minus the pleural pressure, which is typically estimated via esophageal manometry. Lung injury termed "atelectrauma" may occur from high regional forces generated repeatedly during cyclic closure and reopening of small airways during tidal ventilation (1, 2). Negative P_L values (in which pleural pressure exceeds airway pressure) predispose to small airways closure and cause lung injury that in preclinical models, is attenuated with higher PEEP (3, 4).

In this issue of the *Journal*, Bastia and colleagues (pp. 969–976) highlight the potential for esophageal manometry to estimate P_L even in asymmetric lung injury (5). In their study, invasively ventilated pigs were subjected to unilateral lung injury via surfactant lavage and high tidal stretch instituted with temporary endobronchial blockade, occluding the contralateral lung. After injury was established, the bronchial blocker was removed, and respiratory mechanics were assessed in both hemithoraces at different amounts of PEEP. Pleural pressure was measured directly using air-filled balloon catheters inserted into the ventral and dorsal pleural spaces of the left and right hemithoraces, and it was

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