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Asthma with a Smoking History and Pre–Chronic Obstructive Pulmonary Disease

To the Editor:

The Perspective article by Hans and colleagues proposes the term "pre-COPD" to describe current and former smokers with normal spirometry who are at risk of developing chronic obstructive pulmonary disease (COPD) ($FEV_1/FVC < 0.7$) (1). Factors considered helpful in identifying individuals with pre-COPD who are likely to progress to COPD include symptoms, particularly nonobstructive chronic bronchitis, and lung function and imaging biomarker abnormalities (1). Although not discussed in the article, data suggest that asthma in adults with a smoking history and normal spirometry COPD (pre-COPD) is a risk factor for COPD development. Selective studies supporting a role of asthma in smoking-related pre-COPD are briefly outlined below. First, asthma commonly occurs in adult smokers without spirometric COPD because of the high prevalence of cigarette smoking and asthma in many populations worldwide (2). Current smoking in asthma is frequently associated with poor symptom control, corticosteroid insensitivity, and type 2 low airway inflammation (2). The diagnosis of asthma may be uncertain in some symptomatic smokers with normal spirometry because of an overlap in chronic respiratory symptoms among smokers with and without asthma. Second, general population–based surveys and observational cohort studies of current and former smoking volunteers used to investigate smoking-related pre-COPD frequently include individuals with a history of asthma. For example, among symptomatic middle-aged and older current or former smokers with normal spirometry results included in the SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) (3) cohort, more than one-quarter reported a history of asthma. Third, chronic bronchitis is a common symptom among cigarette smokers with asthma (2, 4) and may contribute to the development of COPD in this subgroup. Fourth, longitudinal population-based studies have shown accelerated decline in lung function in adult smokers with asthma (2, 4), some of whom develop chronic persistent airflow obstruction. Individuals with specific phenotypes of asthma, such as smokers with late-onset asthma (5) and/or nonatopic asthma, may be at greater risk of developing COPD. Finally, data on computed tomographic imaging in current smokers with asthma, although limited, provide some evidence of radiological abnormalities, including reduced segmental airway lumen area, particularly in those with chronic bronchitis, and occasionally emphysema (6). Collectively, these findings suggest that asthma with a smoking history and pre-COPD should be included as a risk factor for developing COPD. Future research should establish whether the natural history and management of current and/or former smokers with pre-COPD differs in those with or without asthma. ■

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Exposing Pre–Chronic Obstructive Pulmonary Disease: When Physiology Matters!

To the Editor:

We read with great interest a recent Pulmonary Perspective on the early manifestations (i.e., before the development of airflow obstruction on spirometry) of chronic obstructive pulmonary disease (COPD) (1). The authors outline some convincing pieces of evidence indicating that the identification of smokers at higher risk of developing COPD (called "pre-COPD") is not only feasible but also of substantial societal and economical relevance. It called our attention, however, that their keen interest in structural abnormalities signaling toward pre-COPD was not paralleled by a similar enthusiasm concerning more detailed physiological measurements. Although the authors do list "low lung diffusing capacity for carbon monoxide (D_{LCO})," "hyperinflation," "small airways obstruction," and "accelerated forced expiratory volume in one second (FEV_1) decline" as functional markers of pre-COPD in their Figure 2 (1), only the latter topic is adequately supported by published evidence. For instance, a single study is cited to endorse some potential value of an isolated low D_{LCO} to point out pre-COPD; regrettably, however, no mechanistic insights are provided to justify why D_{LCO} might decrease before the FEV_1/FVC ratio crosses the 0.7 threshold.

In this context, our research group has investigated in detail the physiological characteristics of subjects in the transition from "pre-" to "established" COPD (2–4). The following two features consistently stood out in smokers with largely preserved FEV_1 who were dyspneic on exertion: a reduced D_{LCO} and excessive ventilation at low exercise intensities. What does a low D_{LCO} tell us about the nature of pre-COPD? D_{LCO} (or, more properly, the transfer factor) is influenced not only by the surface area for gas exchange but also by ventilation distribution and ventilation/perfusion (mis)matching. Apart from any incipient emphysema (sometimes below the limits of resolution of conventional computed tomography [CT]) (5), impaired perfusion due to microvascular dysfunction in emphysema-free areas may decrease D_{LCO} (6). The tenuous small pulmonary vessels might also be compressed by patchy areas of localized gas trapping due to small airway dysfunction. A low D_{LCO} might also be a consequence of a reduced accessible V_A due to early ventilation distribution inhomogeneities; of note, we did find a reduced V_A/TLC (by body plethysmography) ratio in these subjects. Regardless of the contributing mechanisms, a low D_{LCO} signals high ventilation/perfusion. Indeed, we found that increased "wasted" ventilation underpins the excessive ventilation observed in subjects with low D_{LCO} (2–4). Breathlessness is the sensory translation of an increased neural drive to breathe secondary to such high ventilatory demands. Closing the loop, the report of activity-related dyspnea may precede the diagnosis of COPD in smokers (1).

How do small airway dysfunction and gas trapping fit into this scenario? Dynamic hyperinflation develops at a faster rate *1*) the slower the expiratory flows through the smaller airways and *2*) the higher the volume at which they close on tidal breathing. These assertions explain why dyspneic smokers may show low midexpiratory flows and increased residual volume (RV) and/or RV/TLC ratio, respectively (2). When these abnormalities conflate with high ventilatory demands (predicted by a low D_{LCO}), critically high operating lung volumes are reached earlier during exercise. To avoid the uncomfortable respiratory sensations associated with activity, smokers with pre-COPD adopt a sedentary lifestyle that fuels the downward spiral of deconditioning and worsening breathlessness.

In summary, integrative respiratory pathophysiology has much to contribute to the understanding of "incipient" pre-COPD. Using a Bayesian approach that considers symptoms and abnormal CT features, the pulmonologist should look for early marks of disrupted physiology despite preserved FEV_1/FVC (decreased D_{LCO}, decreased midexpiratory flows, and increased RV and/or RV/TLC ratio) to identify smokers who are in the process of eventually developing airflow obstruction consistent with COPD. We echo the authors of this Pulmonary Perspective that such a proactive approach may enable early therapeutic interventions with the potential to modify the course of the disease (1). ■

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