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Neil C. Thomson, M.D.*
University of Glasgow
Glasgow, United Kingdom

*Corresponding author (e-mail: neil.thomson@glasgow.ac.uk).

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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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J. Alberto Neder, M.D.
Juan Pablo de-Torres, M.D.
Denis E. O'Donnell, M.D.*

Queen's University and Kingston Health Sciences Centre, Kingston, Ontario, Canada

*Corresponding author (e-mail: odonnell@queensu.ca)

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Pre–Chronic Obstructive Pulmonary Disease: Toward the Limits of the Spirometric Funnel

To the Editor:

In the February issue of the *Journal*, Han and colleagues (1) introduced the term "pre-COPD" to refer to individuals in whom spirometry is unable to detect airflow obstruction but who are at risk of subsequently developing chronic obstructive pulmonary disease (COPD) with a reduced FEV_1/FVC ratio. The authors adopt the concept of predisease status as in prediabetes or preeclampsia. The latter condition is not a predisease model but a serious complication during pregnancy, which is characterized by sharp rise in blood pressure, albuminuria, and edema. Recent data also suggest that prediabetes is not a robust diagnostic entity, at least not in older age (2). After the suggestion of the authors that chronic cough and phlegm stand apart as so-called nonobstructive chronic bronchitis, the authors refer to physiological variables (low to normal FEV_1, D_{LCO} and/or accelerated FEV_1 decline) and/or radiographic abnormalities as emphysema or airway abnormalities. Considering that alveolar abnormalities are part of the definition of COPD, at least the presence of emphysema (assessed by imaging or using surrogate markers as D_{LCO}) fulfills the criterion of structural disorder as formulated by the GOLD initiative, as well as by Criner and colleagues and Scadding and colleagues (3–5). Interestingly, the recently reported COPD Gene data illustrate that imaging in combination with symptoms and/or spirometry was predictive for COPD progression (6). Considering the wide availability of computed tomography, we urgently need to delineate the subtype of emphysema, referring to the original conclusions of the CIBA symposium dealing with the definitions and classification of chronic pulmonary emphysema and related conditions (7). As for other so-called predisease conditions, it must be realized that a new clinical category of pre-COPD will engender costs and disutilities related to self-image. The main driver for transformation could only be scientific evidence. A clear operational definition of pre-COPD and validation of cutoff points are needed to assess whether the problems of such a new label outweigh the benefits. The authors focus in particular on the development of airflow limitation using FEV_1/FVC ratio cutoff values. Based on new insights of lung function trajectories and the impact of dysanapsis on the variation of FEV_1/FVC ratio, it can be questioned whether the current physiological cutoff of airflow limitation is a marker of a disease condition, particularly in the absence of accelerated decline in FEV_1 (8, 9). Before introducing a new label as a window of opportunity for early intervention and prevention, nosology of chronic respiratory diseases must dynamically integrate the new scientific discoveries offered by new physiological and imaging facilities for correct identification of abnormalities. Therefore, it will become important to engage the scientific community regarding the development of a new taxonomy for these chronic respiratory disease conditions instead of the current concept of pre-COPD. ■

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Emiel F. M. Wouters, M.D., Ph.D.*
Ludwig Boltzmann Institute for Lung Health
Vienna, Austria
and
Maastricht University Medical Center
Maastricht, the Netherlands

*Corresponding author (e-mail: woutersemiel@gmail.com).

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