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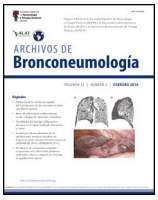

Editorial

Smoking-Induced Small Airway Dysfunction. An Early Marker of Future COPD?☆

La disfunción de las pequeñas vías aéreas inducida por el tabaco ¿podría ser un marcador precoz de una futura EPOC?

Despite legal restrictions, smoking continues to be a major health problem in our setting, causing a significant number of diseases of the respiratory tract and other organs. In fact, it is estimated that at least 25% of smokers will develop chronic obstructive pulmonary disease (COPD) over their lifetime.[1] Early identification of smokers at high risk of COPD is therefore important for reinforcing smoking cessation interventions. The presence of chronic respiratory symptoms in smokers without airflow limitation (AFL) also has a significant clinical and prognostic impact by decreasing quality of life and exercise tolerance, while the rate of respiratory infections and chronic bronchitis in patients without AFL is similar to that of mild COPD patients.[2,3]

In view of this situation, and thanks to a better understanding of the pathophysiological disorders of the disease, it is logical to ask what functional changes can be detected early in smokers with an increased risk of COPD and, in particular, how they can be determined. From a pathophysiological perspective, it is important to consider the possible early functional impact of both the loss of pulmonary parenchymal traction caused by the development of emphysema, and small airway obstruction. Loss of parenchymal traction can be manifested by alterations in gas exchange. In fact, lung diffusion capacity (DLCO) is reduced in approximately 25% of smokers with normal spirometry and is associated with an increased risk of incidental COPD.[4] With respect to small airway obstruction, exposure to tobacco smoke has been shown to induce edema, epithelial metaplasia, inflammation, and remodeling of the bronchiolar wall, which causes small airway dysfunction (SAD) in up to 75% of symptomatic smokers with normal spirometry.[5]

An assessment of the small airways may provide some advantages over DLCO, as SAD is known to precede the development of emphysema. Morphometric studies in patients with COPD have shown that, compared to control subjects, patients with mild small airway involvement have a marked reduction in both the number and luminal area of terminal or transitional bronchioles, with little or no evidence of lung parenchymal damage.[6–8] Furthermore, data from the COPDGene study confirm that SAD is associated with low DLCO in smokers without AFL or with mild-moderate COPD,[9] supporting the notion that the SAD could precede parenchymal damage and constitute the onset of pathogenic alterations leading to COPD.

The MESA population-based cohort study recently reported that a reduced number of distal airways modulates the genetic risk of COPD.[10] This finding raises the interesting possibility that an inherited deficit in distal airway development combined with smoking could contribute to the development of SAD before the manifestation of other structural alterations of COPD.[10] There are also biological reasons to suspect that exposure to tobacco smoke has a specific effect on the small airways. Analysis of the transcriptomic profiles of the epithelium of different regions of the tracheobronchial tree has shown that the distal transcription pattern is suppressed in the epithelial cells of the distal airways of smokers without AFL, leading to the acquisition of a transcription phenotype similar to that of the proximal airways, mainly due to increased signaling of the epidermal growth factor receptor in the basal cells.[11]

Finally, it is important to bear in mind that SAD appears to be more sensitive to smoking cessation than DLCO. In a group of smokers with normal spirometry, the conduction function of the distal airways improved within 1 year after quitting smoking, while no modifications were detected in acinar airway function or in DLCO,[12] suggesting that SAD caused by smoking could be reversible. It should be noted, however, that the information currently available on the potential utility of SAD as a risk factor for COPD is mainly derived from small cross-sectional studies, so information from the longitudinal follow-up of larger cohorts of smokers with normal spirometry is essential for proper assessment.

Now that the potential relevance of SAD in COPD risk assessment has been recognized, the next question is how to evaluate it routinely. Although computed tomography (CT) has gained progressive importance in the evaluation of COPD patients, it should be noted that the analysis of attenuation densities in inspiration and expiration and the measurement of the caliber of the segmental and subsegmental bronchi only provide indirect evidence of SAD. Furthermore, accessibility to CT is obviously limited, and the added radiation risk must be taken into consideration.

Compared to other more complex lung function techniques, oscillometry is a simple, reliable, low-cost procedure for assessing the smoking population.[13] It can be used to detect an increase

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in respiratory resistance and a decrease in respiratory reactance in smokers who have not yet developed AFL,[13] which is related to a greater symptomatic burden and a loss of quality of life.[14] Oscillometry also predicts loss of lung function better than spirometry in smokers with high-risk occupational exposures.[15] Therefore, identification of SAD by oscillometry could reinforce motivation and interventions to quit smoking in smokers with normal spirometry and, as an ongoing clinical trial is currently exploring, may support the prescription of specific pharmacological interventions.

However, it should be noted that the reliability of SAD diagnosed by oscillometry to identify smokers at high risk of COPD has not yet been confirmed in longitudinal studies. Therefore, before the generalized use of this technique for the systematic evaluation of COPD risk in smokers can be recommended, progress is still needed in understanding the medium- to long-term consequences of changes in the various oscillometric parameters, and some technical aspects of the examination, such as standardization and the unification of interpretation criteria, should be clarified.

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