EDITORIAL

Seeking for the links between biochemical markers of remodeling and structural changes in chronic obstructive pulmonary disease: where are we?

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Although numerous antitobacco campaigns resulted in a decreased prevalence of some smoking-related diseases, chronic obstructive pulmonary disease (COPD), for which smoking remains the main risk factor, is still a major health problem worldwide. COPD was the world's sixth leading cause of death in 1990 and is estimated to rank fourth by 2030.[1] According to the World Health Organization, approximately 3 million people die every year as a consequence of COPD.[2] Hence, all measures aimed at a better understanding of COPD pathogenesis, the course of the disease, and limitations in treatment efficacy seem critically important not only for individual patients but also for global health.

COPD is a heterogeneous disease characterized by local and systemic inflammatory response that develops as a result of exposure to inhaled noxious particles and gases. Airway remodeling (mainly bronchial wall thickening) and destruction of lung parenchyma are the hallmark of the disease. The structural changes within the lungs and airways contribute to fixed airway obstruction and air trapping leading to lung hyperinflation. It should be emphasized, however, that despite some common features, the clinical course of the disease may differ among patients with COPD. Thus, in the recent years, various COPD phenotypes have been extensively studied in order to explain the differences in structural and functional alterations, which may eventually help optimize management strategies. It has been well documented that patients with COPD differ in terms of disease exacerbation frequency, predominant type of inflammatory response (including the cells and proinflammatory cytokines involved), degree of airway obstruction reversibility, and, last but not least, the relative contribution of the structural changes in the airways and lung parenchyma.[3] In the context of COPD-related alterations in lung architecture, experts distinguish, among others, the emphysema and non-emphysema phenotype[4] and emphysema with or without bronchial thickening.[5] This important approach based on morphological changes calls for reliable imaging methods that would allow a reliable assessment of airway wall remodeling and emphysema severity. For years, COPD-related inflammation and remodeling could have been evaluated exclusively in autopsy and bronchoscopic biopsy studies. The introduction of high-resolution computed tomography (HRCT) enabled the quantitative and qualitative analysis of emphysema. HRCT is also useful in the assessment of bronchial wall thickness (BWT).[6] In the last few years, several studies have shown that a new bronchoscopic technique, namely, endobronchial ultrasound (EBUS), may be used for the evaluation of airway remodeling in obstructive lung diseases.[7-9] Of note, there is a significant contribution of a research group from Cracow, Poland, to the development of the method and to the promotion of its application in respiratory research.

In the June issue of the *Polish Archives of Internal Medicine* (*Pol Arch Med Wewn*), the same group presented an interesting attempt to translate the contribution of biomarkers of inflammation and remodeling to changes in lung structure and pulmonary function impairment in patients with COPD.[10] The authors used both EBUS and HRCT to correlate the airway wall structural parameters as well as the so called emphysema score with the levels of selected biomarkers in the bronchoalveolar lavage fluid (BALF) and pulmonary function assessed in spirometry and body plethysmography. The evaluated biomarkers included matrix

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metalloproteinase 9 (MMP-9), tissue inhibitor of metalloproteinase 1, transforming growth factor β_1 (TGF-β_1), neutrophil elastase, and eosinophil cationic protein, all of which are recognized markers of airway inflammation, remodeling, and destruction of lung parenchyma.[11,12] The authors found some interesting correlations between the BALF biomarkers and both BWT and forced expiratory volume in 1 second (FEV_1). The thickness of the mucosal, submucosal, and smooth muscle layers correlated weakly but significantly with TGF-β_1 concentrations in BALF. Patients with higher levels of MMP-9 in BALF had lower FEV_1. These are important findings, which may support the role of these proteins in airway remodeling. No such relationships with emphysema were found. Moreover, there were no correlations between the emphysema score and indices of hyperinflation (percentage of predicted residual volume, residual volume to total lung capacity ratio), neither did the score correlate with BWT.

Besides its unquestionable scientific value, the study by Górka et al[10] is an excellent example for methodologic challenges in the research on the relationships between structural changes in the lungs and biomarkers of inflammation and remodeling in COPD. In HRCT, the whole area of both lungs as well as the bronchial tree to the level of the segmental or even subsegmental bronchi may be assessed. However, its use is limited by a considerable radiation exposure. Furthermore, BWT measurement in HRCT may be affected by the angle between the long axis of the bronchus and cross-sectional plane of the computed tomography image, as well as by the presence of mucus adjacent to the airway wall, which may be particularly important in patients with COPD. In contrast, EBUS is not associated with radiation exposure, although it requires bronchoscopy. In addition, EBUS seems to be more accurate than HRCT in the assessment of the airway wall, allowing even to discriminate its particular layers.[9,10] Indeed, a very recent study showed that EBUS may be more precise than HRCT in the measurement of BWT.[13] However, it must be emphasized that the evaluation of the features of the airway wall by EBUS is usually limited to a single segmental bronchus. This is in contrast to HRCT, which provides data on BWT from various generations of the bronchi, including those at the subsegmental level. This limited local assessment of bronchial wall parameters with EBUS may have important implications for studying the relationships between the markers of inflammation and remodeling in BALF and structural alterations in the bronchial wall.

In the study by Górka et al,[10] the analysis of BALF provided mainly data from peripheral airways, while BWT was measured by EBUS in proximal airways. Therefore, it cannot be excluded that the lack of correlations between BWT and some investigated BALF biomarkers was, at least to some extent, associated with the different sites evaluated. To the authors' knowledge, comparative data on EBUS-measured BWT in the bronchi of different calibers and locations are not available to date. Can we really correlate parameters derived from materials coming from different compartments and anatomical regions? If BWT was measured in the segmental bronchus of the posterior basal segment of the right lower lobe, then perhaps this segment should have been lavaged and the emphysema score should have been determined for the lower right lobe only? Such an approach would presumably increase the probability of finding potential correlations between any analyzed parameters. However, the "local" strategy would limit the application of pulmonary function testing, which reflects the "global" consequences of structural changes in the lungs and airways in such studies. On the other hand, COPD is not a local disease and affects the lungs and bronchial tree as a whole. Hence, although the answers to the above questions might be a matter of discussion, there is no doubt that the study by Górka et al[10] adds interesting data and indicates new challenges for future research on COPD.

The ultimate aim of the research on COPD is the improvement in treatment efficacy. Even though experts suggested that pulmonary function parameters should not be the most important criterion for the selection of a given treatment option, the strategy of COPD management has long been based on the value of FEV_1. It was only several years ago when the traditional Global Initiative for Chronic Obstructive Lung Disease classification of COPD severity based on the value of postbronchodilator FEV_1 was replaced by 4 disease categories, which differ not only in the degree of airway obstruction, but also in patient-reported symptom severity and disease exacerbation rate.[1]

More recently, it has been proposed that even more parameters should be evaluated in patients with COPD.[14] Agusti et al[15] further suggested that therapeutic strategies in COPD should be based on clinical, functional, biological, and imaging features of the disease and focus on the so called "treatable traits" reflecting the needs of the individual patient rather than numerical indices such as FEV_1.[15] This approach shows that lung and airway imaging may potentially be included in future phenotyping of COPD.

The search for the optimal imaging technique for COPD-related remodeling is not limited to HRCT and EBUS. Data from recent studies show a high precision of optical coherence tomography in the assessment of the bronchial wall.[16] The analysis of COPD-related structural changes in the airways and lung parenchyma not only adds relevant scientific value to the knowledge on the pathophysiology of COPD, but may also have clinical applications. HRCT is already applied in the selection of patients for endoscopic lung volume reduction with bronchial valves, for which emphysema heterogeneity and lung fissure integrity are qualifying criteria. BWT may yet be another potential parameter that could be useful in the

selection of therapeutic options in COPD, serving as an index for a specific COPD phenotype with a particularly favorable response to a selected treatment, regardless of the clinical course of the disease. New compounds targeting disease-related structural changes may be developed.

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