

Airway remodeling: Shifting the trigger point for exacerbations in asthma

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Obstructive airway disease involves a wide spectrum of clinical phenotypes, including mild-to-moderate asthma, severe asthma, asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome, and COPD. But, early identification of phenotypes with the aim to prevent progressive changes in the airways and a decline in lung function remains a significant challenge, limiting efforts for a precision medicine approach to targeted treatment. For better identification of treatable traits specifically related to airway remodeling and functional decline even across clinical diagnostic groups, novel combined structural and functional phenotyping methods are urgently needed. Now, writing in the *Journal of Allergy and Clinical Immunology*, Krings et al¹ show for the first time that baseline measurements of airway wall area and other imaging-derived parameters obtained by using computed tomography (CT) are epidemiologic predictors of the rate of future exacerbations and lung function decline in severe asthma.

The phenotypes of obstructive airway disease are the result of complex interactions among hereditary, developmental, environmental, and aging-associated factors. A variety of factors related to asthma and impaired lung functional development have been identified in early life.² Similarly, lung functional growth trajectories during childhood may, for example, affect COPD risk in the elderly.³ In adults with asthma, enhanced loss of lung function over time has been reported in groups of patients with asthma in longitudinal prospective and retrospective studies. Not all patients show accelerated decline in lung function, but young age, male sex, ethnicity, longer duration of disease, low lung function, low serum 25-hydroxyvitamin D levels, more prominent eosinophilic airway inflammation (based on fractional exhaled nitric oxide level), asthma exacerbations, smoking, and air pollution are described risk factors.

To address all these aspects, a multivariable statistical approach needs to be chosen. The latter is challenging, however, because

the effect sizes of each contributing factor are typically small, there are interdependencies such as host-environment interactions and structure-function interactions, and there are additional developmental and temporal effects. There are uncertainties with respect to the involved mechanism and factors contributing to irreversible progression of functional decline. On the basis of the association of the age-related functional decline with fractional exhaled nitric oxide levels and inhaled corticosteroids use, it has been hypothesized that an active underlying inflammatory process could contribute to the rapid functional decline, as well as to the rate of exacerbations. Young age and longer duration of disease, on the other hand, suggest the involvement of a long-lasting disease process. Both considerations raise the interest in structural airway remodeling following inflammation as a complementary aggravating and persistent mechanism.

Now, Krings et al show in patients with severe asthma (in the SARP3 study) that baseline CT measurements of more severe airway remodeling, more small airway disease and hyperinflation, and less pointwise regional change in lung volumes are associated with the rate of future exacerbations and lung function decline.¹ Interestingly, their study shows that the baseline wall area percent was associated with the average number of subsequently occurring asthma exacerbations and functional decline of lung function (change in FEV₁ value per year) with age.

The novel epidemiologic relationship is consistent with the hypothesis that wall area percent as a measure of airway remodeling affects future exacerbations and lung function decline. In this editorial, we focus on the mechanistic understanding of the pathophysiologic mechanisms of exacerbations and lung functional decline because the relatively large variation among the individuals shows the need for a better understanding of the complexity of the involved structure-function mechanism. Although the association of airway remodeling and airway obstruction has long been described, the pathophysiology of airway remodeling and susceptibility to asthma exacerbation are less evident. Exacerbations, as prolonged bronchoconstriction, are a cardinal feature of severe asthma. Airway remodeling is associated with increasing severity of the disease and lung functional decline with age. The fluctuating nature of environmental stimuli and the dynamic behavior of airways, both leading to high variability in the exacerbation rate, further complicate the study of this relationship.

Airway behavior in asthma is characterized by reversible bronchoconstriction, and the response to bronchodilators demonstrates the involvement of airway smooth muscle. In the past, it was suspected that bronchoconstriction causes some heterogeneity in ventilation, but pulmonary imaging revealed major regional ventilation defects (VDefs) rather than randomly scattered heterogeneity in ventilation.⁴ Remarkably, mathematical modeling of the bronchoconstriction in an airway tree demonstrated that positive feedback in airway behavior can explain the avalanche-like emergence of self-organized clustering of severe airway

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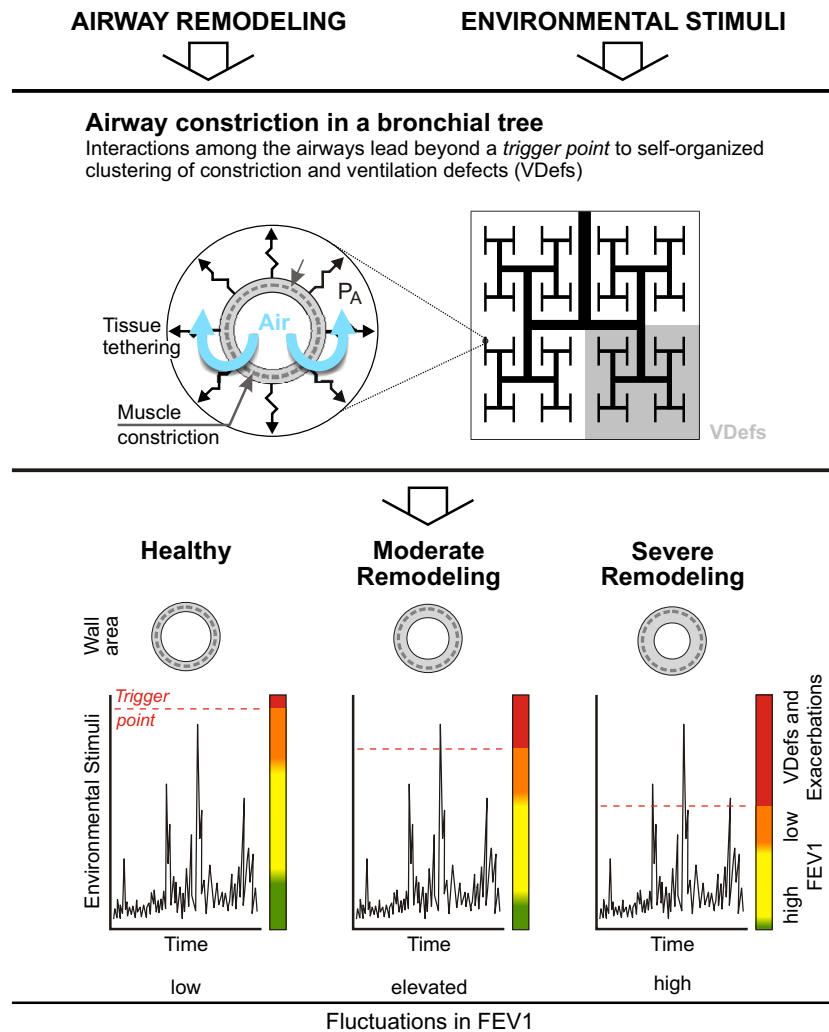


FIG 1. Conceptual overview over how airway remodeling shifts the trigger point for severe airway constriction and VDefs so that environmental stimuli may trigger exacerbations more frequently. Highly relevant for the interaction among airways during bronchoconstriction in an airway tree is the fact that the airflow through the airway affects the alveolar pressure (P_A) and the tissue tethering counteracting the force of the airway smooth muscle. An increase in wall area shifts the trigger point beyond which an environmental stimulus causes VDefs and (potentially) exacerbations, thereby increasing the frequency of exacerbations. Additionally, narrowing the airway lumen results in higher fluctuations in FEV₁ value.

constriction, which is causing VDefs,⁴ and several other phenomena of airway behavior.⁵ The key mechanism of the feedback, which can be explained by using a single airway bifurcation for simplicity, is that a lower airflow in 1 daughter airway results in lower parenchymal tethering, leading to an increase in smooth muscle constriction and airway resistance (Fig 1). When this positive feedback is triggered, it results in an avalanche-like airway narrowing to severe constriction. In contrast, the higher airflow in the other airway results in higher regional tethering forces preventing further constriction. An important aspect of this positive feedback causing VDefs is that it occurs only beyond a *tipping point* in airway narrowing, also referred to as a *critical point*, triggering the feedback. Thus, minor stimuli of the airway smooth muscle do not lead to VDefs. However, an increase in wall thickness shifts the tipping point such that lower than normal stimuli can trigger the emergence of VDefs.⁶ The finding of Krings et al¹ that subjects with an increased baseline wall area percent

showed more subsequent frequent exacerbations in parallel with functional decline is consistent with this hypothesis. Similar observations related to the temporal behavior in symptom exacerbations have been made in healthy infants,⁷ who typically show no remodeling but naturally have very narrow airways and thus quickly reach the critical trigger point.

Krings et al¹ report the average airway wall area of a few central airways, which is relatively common in the literature. But, an excellent postmortem study has shown that airway remodeling occurs only in a fraction of airways, whereas other airways appeared to be normal.⁸ Is it relevant if airway remodeling is heterogeneous? Is it perhaps an advantage if not all airways are affected? In the aforementioned mathematical model, an increase in airway wall thickness and, thus, in area shifted the tipping point for the emergence of VDefs to a lower stimulus compared with the control.⁶ Interestingly, a heterogeneous increase in wall thickness resulted in a higher sensitivity to stimuli than a homogeneous

increase did. This may seem surprising, but the heterogeneity in airflow within the bronchial tree affects the overall tipping point and the locations of VDefs. It should be noted that these are generalized mechanistic insights into bronchoconstriction in a bronchial tree based on a model that includes the relevant physiologic mechanisms.

Exacerbations are triggered by environmental stimuli that are highly variable in time and location. The stimuli can trigger airway smooth muscle constriction, immune responses, and airway inflammation. We speculate that the fluctuations in the stimuli affect the dynamic airway behavior by stimulating the airway smooth muscle, immune response, airway inflammation, and increased mucus secretion such that larger stimuli lead to airway narrowing beyond the tipping point, triggering the avalanche-like clustering of severe constriction and the emergence of VDefs. An increase in wall area shifts the trigger point for the emergence of VDefs toward a lower concentration for the stimulus so that exacerbations should on average become more frequent, which may explain the relationship found by Krings et al,¹ including the high variability at the individual level. We hypothesize that treatments with corticosteroids, biologics, or other drugs may potentially reverse the inflammatory component of the wall area and the shift of the tipping point, decreasing the risk for exacerbation.

The computational model predicts that even in the absence of ongoing type II inflammation, airway remodeling phenomena can theoretically have an effect on enhanced airway fluctuations and exacerbations. If patients with severe airway remodeling are exposed to fluctuations in stimuli below the tipping point, it should cause increased fluctuations in lung function parameters such as FEV₁ and clinical exacerbation rates. These predictions are consistent with recent findings in patients with severe asthma and COPD from the BIOAIR cohort that have been published in the *Journal of Allergy and Clinical Immunology* and show that this distinct functional fluctuation phenotype can be independent of type II inflammatory parameters, related to biomarkers of remodeling, and partly independent of clinical diagnosis.⁹ Future directions could include combining CT-based assessment of the degree of airway remodeling with fluctuation analysis of FEV₁ or peak airflow for assessment of the exacerbation risk¹⁰ so as to identify treatable traits related to remodeling and lung functional decline.

In summary, the epidemiologic association between airway wall area and the rate of future exacerbations reported by

Krings et al¹ and the relationship with lung function decline are important advances in our understanding of both severe asthma and obstructive airway disease in general. This editorial hypothesizes that the latter phase of asthma with substantial remodeling may be a complementary aggravating mechanism causing further progression of not only the functional decline but also the increased risk for exacerbation. Airway remodeling could therefore become a mechanism that transforms the mild asthma phenotype from an episodic, reversible process into a more severe, self-perpetuating persistent process with both accelerated functional decline and increased exacerbation rate. The latter phase with substantial remodeling may need different therapeutic approaches. As a proof of concept of these considerations, future studies may have to show that patients with asthma with normal age-related functional decline show no or little airway remodeling and exacerbations.

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