Are all airways equal?

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Bronchoconstriction is a cardinal feature of asthma. It involves airway narrowing, increase in airway resistance, impairment of breathing, and can in very severe cases even lead to death. The severe narrowing of the airway lumen during bronchoconstriction is caused by a shortening of the airway smooth muscle in response to agonists or vagal stimulation. However, does a simple stimulus-response relationship, easily observed in isolated airways or tissue strips, apply in vivo equally to all airways?

More than two decades ago, investigators using the multiple inert gas elimination technique (MIGET) showed that bronchoconstriction in asthma resulted in inhomogeneous ventilation-perfusion distributions (2). That suggested that airway lumen narrowing throughout the bronchial tree must have been highly heterogeneous to cause the heterogeneity in ventilation consistent with the measured ventilation-perfusion distributions in asthma. However, it was unclear if such heterogeneity in bronchoconstriction was caused by a random variability in the response of airways and, thus, randomly distributed within the lungs, or if it was predominantly located in contiguous regions of the lungs. During the last decade, pulmonary imaging studies using PET, MRI, and synchrotron CT, found that bronchoconstriction leads to substantial patchy patterns characterized by large areas of ventilation defects (VDefs), e.g., Ref. 1, 4, 7, 8, 10–12. Those results contrasted with in vivo measurements of airway luminal area with CT in large central airways (approximately five airway generations), which failed to show the constriction needed to explain the hypoventilation seen in large VDefs. Taken together, these findings suggested that the primary cause of VDefs was the constriction of smaller airways (12).

In the current issue, Thomas et al. (9) show in an elegant study using \(^{3}{}\text{He}\) MRI imaging in an allergic mouse model that airway inflammation results in significant increases in VDefs in response to an agonist challenge with methacholine (MCh). Most interestingly, at the highest level of airway inflammation, VDefs were even present before MCh challenge. These results are consistent with earlier findings of Bates et al. (3) that showed synergistic interactions between bronchoconstriction and airway wall thickening due to inflammation resulting in excessive narrowing of the airway lumen. The findings of Thomas et al. add that such synergistic interactions, inferred from changes in overall lung oscillatory mechanics, are associated with heterogeneous airway behavior within the lungs and VDefs.

The major ventilation impairment within VDefs compared with ventilation outside of VDefs is caused by severe narrowing or closure of airways along the pathway through the bronchial tree. Thomas et al. found only a moderate constriction of central airways despite large VDefs, which is clear evidence of severe constriction in small airways and for clustering of small airway constriction in large contiguous regions of the lungs. This is similar to recent results of Bayat et al. (4) in healthy animals and adds that airway inflammation does not lead to a major response of the larger central airways.

What limits the constriction of large airways? Does the presence of cartilage in the large central airways prevent their severe constriction? That question has been debated in the past, but Brown and Mitzner (6) demonstrated in vivo that single airways of generation 2–4 could completely close when they were directly stimulated with an agonist. Thus, the presence of cartilage does not seem to be enough to explain the lack of constriction in large airways.

Why did small airways constrict more than large airways, and why was that constriction clustered in VDefs? An answer to these and similar questions likely comes from the integrative behavior of the lung. A computational model of bronchoconstriction that brings together the local behavior of individual airways within a bronchial tree and the global behavior at the organ level during breathing, including airway smooth muscle, interactions among airways and with the parenchyma, predicted the formation of VDefs (12) and other effects of complex airway behavior (14, 15) during bronchoconstriction. Although each airway was allowed to change its radius individually, its behavior was not independent like that of an isolated airway, but integrated within the hierarchical structure of a tree and affected by interactions with other airways. The model included dynamic changes of airflows, pressures, and local tidal expansions of a symmetric airway tree with 12 generations. Each airway of that tree was affected by the local interactions of transmural pressure difference, parenchymal tethering forces, and airway smooth-muscle forces that were modulated during tidal breathing. Simulating acute bronchoconstriction such as a response to MCh challenge in that model resulted in the sudden emergence of VDefs when airway constriction reached a critical point (12, 14). Interdependence among airways led at that point to a combination of continuing constriction, in some airways, and dilation in others (14). In the field of chaotic and complex systems, the emergence of two different modes in behavior at a critical point is referred to as a bifurcation. The interactions among airways lead to a self-organized patchiness of ventilation with severe airway constriction taking place within regions of VDefs (12).

In the integrative model of bronchoconstriction, an increase in airway wall thickness due to airway inflammation led to a shift of the critical point for VDef formation toward lower levels of smooth muscle stimulation (5). Additionally, the baseline level of smooth muscle tone may be elevated due to inflammation. Thus, VDefs could be present even at baseline and increase in size after MCh challenge. This may explain the finding by Thomas et al. that large VDefs were present prior to MCh challenge in the group of animals with the highest level of airway inflammation.
of airway inflammation and that VDef's increased in size after MCh challenge. In fact, their results demonstrate that airway inflammation affects the conditions under which VDef's emerge. If the conditions prior to MCh challenge are above the critical point, interdependence among airways may lead to severe narrowing or closure even with less than occlusive levels of airway inflammation or edema. Also, if airway edema in individual airways was the sole cause of VDef's before MCh the regional level of edema would have to be spread across airways to explain the growth of VDef's. It is, however, possible that airway inflammation was heterogeneous such that, in combination with interdependence among airways, it could have precipitated the emergence of VDef's at lower levels of smooth muscle stimulation compared with homogeneous inflammation.

Severe narrowing exclusively taking place in small airways is also shown by the integrative model of bronchoconstriction (14). The difference between the larger central and the smaller peripheral airways is caused by the higher peak transmural pressures in central airways, which increase the net load on the smooth muscle of central airways compared with that of peripheral airways during breathing. That may also explain why the group of animals with the highest level of airway inflammation in the study by Thomas et al. paradoxically had less constricted large airways after MCh. Also, the presence of $^3$He in a large central airway, proximal to a whole lobar VDef occupying the left lung, suggests that there was no complete closure of all small airways within that lobe because otherwise no airflow would have carried $^3$He into the central airway. This observation would also be consistent with both model prediction and PET measurements of ventilation heterogeneity within VDef's (12). Another interesting observation by Thomas et al. is that of a baseline VDef that became ventilated after MCh while other regions turned into large VDef's and that during recovery the VDef shifted to a different region again. A similar behavior was observed in the model as a result of long-distance interdependence among airways (12), which shows that the location of VDef's may be affected by the history of conditions in the lungs rather than the current conditions only.

Understanding the effects of airway inflammation on severe constriction and closure in small airways may be essential for identifying potential treatments for airway inflammation and exacerbations in asthma. We have illustrated how interpretation of experimental findings, like those of Thomas et al., in the light of a theoretical model of the complex behavior of airways in asthma may provide novel mechanistic insights. Today, computational modeling has become in many fields of science an important tool complementing theory and experiments to study the behavior of systems with complicated networks and interacting elements. Research in physiology may highly benefit from such a modeling approach when systems are too complicated for analytical solutions and/or inaccessible for experimental studies (13). In our case, combining theory, computational modeling, and experimental findings suggest that large and small airways may be equal or similar by design, but their interdependence may force them into very different behaviors.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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