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VIEWPOINT

Last Word on Viewpoint: Small airways vs. large airways in asthma: time for a new perspective—Size does not matter: airway interactions determine respiratory dys(function)

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TO THE EDITOR: The range of responses to our Viewpoint (1) calling for a re-evaluation of how airway size is scrutinized in asthma has helped to clarify several important points. Although there appears to be relative consensus that the dichotomy between "small" and "large" airways is not particularly useful, it is less clear what paradigm should replace this in either a research or clinical context. Drs. Lutchen and Winkler (2) pose the question not in terms of generic behavior based on airway size, but rather the specific airways involved in each patient. This, we think, is the right question, but without a straightforward answer. Dr. Bayat (2) describes the potential role of functional imaging in service of this goal, and indeed, the relative stability over time of hyperpolarized gas MRI ventilation distributions (e.g. Ref. 3) supports the notion of specific structural defects largely determining the functional outcomes. The obstacle, as outlined by Drs. Bossé and Winkler (2), is complexity within a subject or patient. Indeed, recent efforts to identify specific airways for treatment using functional imaging (4) has demonstrated that although this approach has promise, mapping functional defects to specific structural abnormalities is challenging (5) because airways do not function in isolation, but instead are coupled by airflow and parenchymal interdependence. Hence, trying to interpret the results of functional assays in terms of specific, localized structural abnormalities may carry a substantial error margin.

We acknowledge and support the need for any new perspective to propagate to the clinic, as called for by Drs Verbanck, Brusasco, O'Sullivan, and colleagues, and Thamrin and colleagues (2). As but one example, it is unclear if prioritizing aerosol delivery to the "small" airways is appropriate if we cannot be certain that the origin of the defect lies within the lung periphery. There is an urgent need to understand the outputs of new diagnostic methods, such of those offered by Dr. O'Sullivan and colleagues, and Drs. Foy and Siddiqui (2), and adopt those with adequate diagnostic power into clinical practice.

Finally, several authors took up our call regarding the uncertainty of airway compliance and how it varies across the airway tree. The modeling outputs (1) were based on relatively small changes in the compliance difference between the peripheral and central airways; however, Dr. Eskandari (2) goes further and suggests that the relationship may be inverted (i.e., peripheral airways are stiffer than the central airways—at least in pigs). If so, this would certainly have notable functional consequences; we can only hope that we will soon have the data to better resolve this important question.

DISCLOSURES

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

AUTHOR CONTRIBUTIONS

G.M.D. and P.B.N. drafted manuscript; edited and revised manuscript; and approved final version of manuscript.

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