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VIEWPOINT

Small airways vs large airways in asthma: time for a new perspective

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Is asthma predominately a disease of the large or small airways? The question has vexed these pages for at least 50 years (1–4) and although a consensus appears to be emerging in favor of a substantial role for the small airways, the recent evidence is scarcely more conclusive. Structurally, we now know that airway remodeling may be variable with respect to the involvement of the large or small airways (5). However, this does not necessarily answer the question in terms of function, which ultimately is the answer we seek. Indirect measurements, such as forced oscillation-derived resistance at two different frequencies [e.g., R_5–R_{20} and others (6)] or inferences from flow-volume curves (7, 8)[1] offer some information but the specificity is, by the nature of the measurement, somewhat limited (9).

Advances in imaging methodology increasingly allow direct measurement of substantial numbers of individual small airways in vivo, at least in animal models, and yet the evidence remains seemingly contradictory–for example, synchrotron-source computed tomography (CT) suggests much greater responsiveness in the small airways in response to methacholine (10, 11), whereas tantalum dust and microfocal X-ray show almost precisely the opposite (a predominant role for large airways) (12). Neither approach is possible in humans, and as such direct airway measurements from CT in humans are limited by methodological constraints to the relatively larger airways (13, 14), and generally are interpreted as supporting the conclusion that the smaller airways are the primary site of closure and airflow obstruction (15). On the other hand, hyperpolarized gas MRI studies suggest, from analysis of ventilation distributions, a role for closure of medium- and large-sized airways (15). Leaving aside the methodological differences, let us for the moment take these data at face value. Even with measurements that Ann Woolcock, Jere Mead, and Peter Macklem could scarcely have dreamt of in the late 60s, we are still left without a clear picture. How, despite the attentions of so many talented investigators over so many years, can there yet be no consistent answer to this seemingly innocuous question?

The picture is, of course, further clouded by asthma's status as an umbrella diagnosis encompassing multiple phenotypes (or endotypes). Many readers would happily agree that while the framing as a disease of the large or small airways is oversimplified for asthma as a whole, individual asthma phenotypes may be small or large airway dominated. We would take the argument one step further and suggest that even in the context of a single phenotype, the small versus large airway dichotomy may be unhelpful.

We argue in this *Viewpoint* that "small or large airway?" is the wrong question. Let us start with the premise. Why do we expect a useful delineation between large and small airways? One potential reason is that we observe the structural differences between cartilaginous and noncartilaginous airways, and suspect that this boundary is also relevant in terms of function. Similarly we are constrained by our abilities to observe and measure, much easier in the large airways than the small [i.e., the "Quiet" (16) or "Silent Zone" (2)]. Thus, our thinking coalesces along these lines: the seemingly natural distinction between the large, cartilaginous, measurable airways on the one hand, and the small, noncartilaginous, and difficult-to-measure airways on the other. However, the latter distinction is not relevant to function at all, and the former, although genuine, is perhaps overstated. Fn1

To wit, the conducting airway tree operates in vivo as an interconnected entity without any ready distinction between the large and the small airways (except inasmuch as the mechanical properties of the airways may be altered at the cartilaginous boundary). Indeed, there are remarkable patterns of near-fractal self-similarity in the airway tree (17–20), implicitly arguing against a fundamental distinction between small and large airways. In asthma, in response to a contractile agonist, activation of the airway smooth muscle (ASM) drives airway narrowing; in some airways this leads to closure (or near-closure) and so-called ventilation defects or ventilation heterogeneity, whereas in other airways, paradoxical dilation and hyperinflation is apparent (15, 21, 22). Thus, from a functional perspective we are interested in the distribution of these responses and how it depends on airway size.

As but a single example, consider the compliance of the airways, and how it varies with airway size. Typically, central airways are assumed to be stiff, giving way to increasingly compliant airways toward the periphery (23). Imagine if the difference in compliance between peripheral and central airways is actually less than is generally assumed. How would this alter the response of the airways, as a whole, to a contractile stimulus?

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[1]Because this is a *Viewpoint* and not a comprehensive review, the references and literature review are necessarily limited. Perhaps the readership will agree that such a review is needed and provide one.

We can attempt to address this question using an existing mathematical model of asthma, designed to study the interaction of airway tree structure and function (24) and incorporating airway dynamics and flow-induced instability (25). When the compliance of peripheral airways is exaggerated relative to more centrally located airways, airway narrowing is concentrated in the smaller airways (Fig. 1, red dashed curve), and one would be tempted to conclude that dysfunction manifests due to a susceptibility for closure in small airways. In contrast, when the difference in compliance between peripheral and central airways is reduced, the location of critical airway narrowing shifts toward larger airways (Fig. 1, solid blue curve). In such a case, we might conclude that the large airways dominate. That is not to say that either configuration is necessarily indicative of asthma, but instead that what we might think of as small airway disease, as opposed to large airway-dominated disease, are not so much distinct phenomena but rather variations on a theme. Ergo, although we seem eager to stratify patients into functionally distinct phenotypes, in reality, there may only be subtle differences in terms of structure (or even, potentially, methodological variation).

Compliance is, of course, just one consideration when attempting to isolate the fundamental site of pathology in asthma, and we do not mean to imply by its selection as our example that it is the most important. Similar functional shifts can be brought about by other means of including agonist deposition patterns, postural changes, inflation pressures, lung volume, agonist receptor density, ASM tone, and/or distribution of airway structure, to name but a few. However, compliance is also illustrative in the sense of demonstrating how little we know. The compliance curves are surprisingly poorly studied; although some evidence exists for changes with disease in the central airways (26, 27), direct measurement of the small airways is almost nonexistent. Many representations are based, one way or another, on the study by Lambert et al. (23), in which the small airway compliance was not measured at all but extrapolated from larger airways and expectations about overall flow behavior. A small number of subsequent measurements have suggested that the original extrapolation was surprisingly accurate (28), but the characterization remains far from complete, and is almost nonexistent in terms of disease state, airway remodeling, ASM tone, or variations between animal models. Even for the larger airways, a simple linear notion of compliance is probably insufficient (15).

So, is asthma predominately a disease of the large or small airways? Perhaps the answer is "none of the above". Asthma is a disease of the airways, and the airways function not in isolation but integrated into a complex system whose behavior cannot be readily inferred as the sum of its isolated parts. This may be true not just for asthma as a whole, as a heterogeneous syndrome with multiple subtypes, but even within those subtypes. This leads to different questions, not just about individual airways, but also the interrelationships between the airways. Returning to the role of airway structure, for example, it may not be sufficient to simply know that there is airway remodeling; instead, perhaps the questions that we should be asking relate to the topographical distribution and correlations of structure, and how it varies with airway size. The answers to these questions are not as tidy as the division between large and small airways, but may ultimately prove to be more informative.

DISCLOSURES

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

AUTHOR CONTRIBUTIONS

G.M.D. and P.B.N. conceived and designed research; G.M.D. prepared figures; G.M.D. and P.B.N. drafted manuscript; G.M.D. and P.B.N. edited and revised manuscript; G.M.D. and P.B.N. approved final version of manuscript.

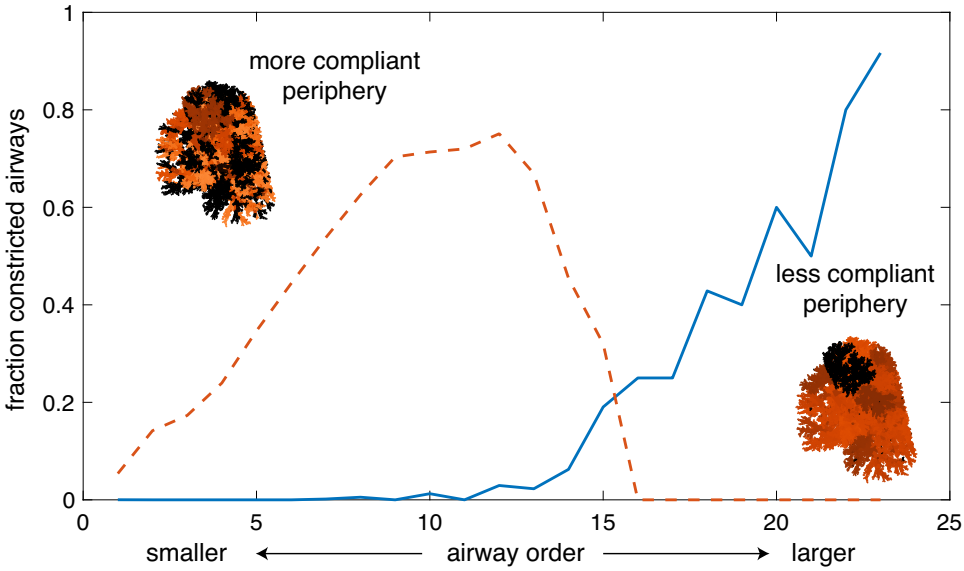

Figure 1. Illustration of concept that apparently distinct functional phenotypes may arise from relatively subtle mechanical differences, in this case altered airway compliance. Insets show patterns of flow (see Ref. 24). Airway compliance was altered by linearly scaling the selection of compliance curves between orders by 50%; for example, an order 10 airway would be made more compliant by using an order 5 compliance curve, or less compliant by using an order 15 curve. All other aspects of the simulation remained fixed.

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