Invited Editorial on “Measurement of intraindividual airway tone heterogeneity and its importance in asthma”: How does an airway and subsequently the lung become hyperresponsive?

Kenneth R. Lutchen
Boston University, Boston, Massachusetts

Submitted 12 May 2016; accepted in final form 12 May 2016

THE ANSWER TO THIS QUESTION is fundamental to understanding the root cause of asthma. The question can be expanded as follows: What must change within an otherwise healthy airway and/or the airway tree, so as to cause elevated constriction and/or a constriction pattern at a lower dose of airway smooth muscle (ASM) agonist, and in a fashion that stays constricted after our attempts to dilate these airways with a deep breath? Both must occur to cause a sustainable asthma attack.

If one googles the question, “What causes asthma?,” unsurprisingly you will get an extraordinary number of hits, but none directly answers the question—they dance around it. Many will say asthma is thought to be a disease associated with airway inflammation, and of course, in the majority of cases it is. However, the presence of inflammatory compounds in and of itself does not explain why an airway around which inflammation exists hyperconstricts compared with a corresponding airway in a healthy lung or how the lung as a whole in asthma patients more easily transitions to a state where breathing becomes difficult and function is severely compromised.

Most of us would agree that a person does not become and remain an asthma patient after a single inflammatory episode, say, due to pneumonia. Moreover, asthma patients can hyperrespond to methacholine without evidence of standing inflammation (2). Several studies (7, 10) report that airway walls of asthma patients have remodeled (e.g., thicker ASM layer, altered ECM, etc.), but how do these changes lead to hyperresponsiveness? There has been some focus on whether reductions in the periodic lengthening of the ASM surrounding an airway might result in transition of the ASM to a state capable of hyperresponsiveness. However, there is now ample evidence in the literature (5, 9) that disproves this notion, i.e., an otherwise healthy airway will not become hyperreactive simply by prohibiting periodic breathing-like pressure fluctuations. While lack of dynamics will not transition an airway to being more responsive, lack of an ability to stretch an airway after one stimulates its ASM facilitates a sustained constricted state. However, again, why did it overconstrict in the first place?

This issue of the Journal of Applied Physiology includes a study by Brown and Togias (1) that provides some new exciting hints as to critical alterations that need occur in asthmatic lungs that conspire to insure hyperresponsiveness, perhaps even in the absence of inflammation. In comparing healthy and asthmatic humans using high-resolution computed tomography and oscillatory mechanics, they show that asthmatic airways have a tendency to have higher resting tone, and more so, the intrasubject heterogeneity of the tone in asthma patients is higher with strong statistical significance. They also found that the higher the baseline tone, the greater the degree of heterogeneity of tone within an individual. Also, the higher the tone (and hence heterogeneity of tone), the less the asthmatic subjects were able to distend their airways by taking a deep breath from functional residual capacity (FRC) to total lung capacity (TLC). Finally, the walls of the asthma patients were thicker at FRC compared with healthy subjects. Taken together, these data could reflect a pathway that connects individual airway alterations that conspire not just to cause “hyperconstriction” at a single-airway level but also to create a dangerous pattern or heterogeneous constriction that serves to amplify and sustain lung hyperresponsiveness regardless of attempts of a deep inspiration (DI) to mitigate the constriction (3).

The data of Brown and Togias (1) are consistent with the following trajectory. Consider conditions (i.e., no one single one) that are capable of causing periodic and frequent increase in airway tone (such as chronic inflammation). This will result in repeated and/or sustained amplification of abnormal mechanical forces (stresses) on various constituents of the airway wall. It is well understood by now that the normal functioning of adherent cells is intricately tied to the mechanics of its environment (6). Most recently, it has been shown that altered mechanical environment alone can cause healthy human airways to remodel and transition to being hyperreactive without any evidence of sustained inflammation (4). What if the resulting changes in ECM and ASM properties cross some threshold such that (1) the muscle layer can generate more force at a given stimulus, so as to hyperconstrict the airway compared with when healthy; 2) the entire wall after constriction is so stiff that the constriction cannot easily be relieved by a DI attempt; and 3) the remodeling is heterogeneous, so as to facilitate a highly heterogeneous pattern?

We and others have shown that constriction in asthma is heterogeneous and that a heterogeneous pattern can greatly amplify the reduction in lung function beyond what might be expected at the single-airway response level (3, 8). If the constriction is heterogeneous [which the increased heterogeneity of tone as Brown and Togias (1) report would facilitate], then a DI is even less likely to stretch the airways that do constrict because the forces distending the lung will preferentially expand the less stiff airway walls that have constricted less (and parenchyma distal to them), thereby sustaining the asthmatic “attack.” Moreover, in principle, it would not take remodeling of a huge fraction of airways to create this “hyperresponsive” lung so long as the remodeling facilitated such a heterogeneous pattern.
We need to be much more sensitized and inquisitive as to what changes in the constituents of the walls of asthma patients represent hints as to causes vs. consequences of asthma. Just finding a difference does not constitute cause. One wonders if some differences (e.g., unjamming of epithelial cells or late stage upregulation of molecules that can impact ASM function) are even relevant to the genesis of airway hyperresponsiveness rather than simply the epigenetic consequences of it. Similarly, at the genomic levels, most agree that there are no specific genomic signatures at birth that necessarily lead to asthma. While some distinctive genomic signatures or upregulation of molecules may be found in asthma patients, no one can be certain whether these are epigenetic (consequence) rather than a cause. This is not to say identified distinctions in the wall of asthma patients may not lead to ideas for treatments for asthma patients, but they do not lead to a deeper understanding of how the lung became hyperresponsive in the first place.

Asthma is a disease that likely needs to evolve from some healthy state at birth or some point in life. We need to start generating and testing hypotheses to understand what changes need to occur to the airways of a previously healthy lung such that they now have hyperresponsive lungs associated with clinical asthma. The data of Brown and Togias (1) reveal differences in tone and even bigger differences in heterogeneity of tone in asthmatic airways. When we ask the “so what?” question, it triggers a trajectory hypothesis, articulated above, that may be consistent, not only at the single-airway level but also at the whole lung level, as to how hyperresponsiveness at the organ level consistent with human asthma may emerge from remodeling of the airway wall. Now our challenge is to test this hypothesis. Searching for differences in airways or their constituents is an interesting task. However, we also are responsible for designing experiments that can irrefutably determine if these differences are important to airway and whole lung function and if they reveal a cause or consequence and how.

ACKNOWLEDGMENTS
The author thanks Dr. Hari Parameswaran for his feedback in composing this editorial.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
K.R.L. drafted manuscript; K.R.L. edited and revised manuscript; K.R.L. approved final version of manuscript.

REFERENCES