Letter To The Editor

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Reply to Noble, Hernandez, Mitchell, and Janssen

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The Pressure-Controlled Intact Airway System as a Powerful Tool in Unraveling the Mystery of Airway Hyperresponsiveness

TO THE EDITOR: We are not at all surprised by the reaction of Noble et al. (9) to our recent study (7), and we suspect several others will have similar reactions. Because force fluctuations on airway smooth muscle (ASM) in isolation can mitigate ASM responsiveness (12), the prevailing hypothesis is that the same happens in vivo and is likely a major factor controlling airway hyperresponsiveness (6). Unfortunately, our study provides strong experimental evidence that the hypothesis is not highly relevant for an intact airway. Whenever a set of new experiments refutes a sensibly derived preconceived notion (e.g., from isolated ASM), there is a natural inclination to question the new data rather than the validity of the hypothesis. We too were rather stunned at first. Nevertheless, it has become increasingly clear that responses at the level of isolated ASM may not directly scale up to macroscopic function of the intact airway (1). To address the seemingly contradictory data raised by Noble et al., we focus on how methodological differences in both isolated ASM and intact airway studies may propagate to misleading inferences of data.

First, we agree with Noble et al. that there are some indisputable imaging data in which intact airways in vitro (8) and in vivo (4) dilate transiently from a single deep inspiration (DI). However, these airways re-constrict with a short time constant of ~30 s, and similarly, transient dilations to DIs occurred in our recent study (*protocol 1*). The DIs were ultimately insufficient to sustain a reduction in airway responsiveness as would be required to compare breathing fluctuations to a potent bronchodilator (6). More importantly, Noble et al. refer to studies in which length-controlled or volume-controlled oscillations are imposed on isolated ASM or intact airways. Oscillatory mechanical strain results in sustained reductions in active force (5) or active pressure (11) although there remain discrepancies (10).

How is it possible that our recent study (7) shows that intact airway responsiveness, measured directly as airway caliber, is not largely impacted by physiological pressure-controlled oscillations? We pose the following questions: Should maximal isometric force in the ASM's bell-shaped active force-length curve correspond to maximal shortening that occurs under auxotonic loading? Should maximal isovolumetric active pressure correspond to maximal airway narrowing under pressure-controlled conditions? Finally, should reductions in active force/pressure during length/volume-controlled oscillations correspond to airway dilation during pressure-controlled oscillations? If the ASM in situ is a simple force generator acting against a passive load, then the answers would all be "yes." Noble et al. and many others likely concur and extrapolate results from length/volume-controlled conditions to infer how airway caliber should change during pressure-controlled conditions. However, the activated ASM in situ is likely not this simple since active cytoskeletal processes occur concurrently with, but distinct from, actin-myosin cross bridging (13). Furthermore, during induced constriction in our system, the transmural pressure (Ptm) oscillations remain constant while both the airway radius and oscillatory airway wall stress decrease (via LaPlace's law). In contrast, active ASM contraction during volume-controlled oscillations results in increased amplitude Ptm oscillations that become unphysiologically large as the airway wall becomes stiffer (11). Interestingly, the impact of these volume oscillations was largely attenuated when Noble et al. purposely prevented excessive amplitude Ptm oscillations (11). Perhaps more importantly, the inability of the airway to narrow during the volume-controlled experiment may actually prevent active ASM processes from occurring. Seow's group (2) has shown that isolated ASM can adapt to its current length by altering its fundamental "passive" mechanical properties over time (3). This suggests that ASM within an intact airway that is required to maintain its resting caliber (i.e., volume-controlled) could be structurally different from the ASM in the same airway that is allowed to narrow and length adapt to its decreasing diameter during pressure-controlled oscillations. It is thus conceivable that the functional responses to breathing fluctuations are different under the two experimental conditions.

In summary, data from multiple length scales under a variety of loading conditions are emerging to study airway hyperresponsiveness, but it is not evident how to extrapolate to intact airway function during realistic physiological conditions. Although each experiment likely provides an important piece of the puzzle, none in isolation can reveal the full solution. In addition, it has yet to be determined how to map microscopic-level mechanisms (ASM cells and extracellular matrix) to macroscopic-level function (constriction and dilation) in any one species. Invoking interspecies differences may be convenient to explain discrepancies, but we believe that the community should first vigilantly evaluate fundamental mechanisms at and across length scales and in the context of experiment design. Our recent study (7) applied an advanced tool and has allowed a previously unsuspecting and hidden piece of the puzzle to be revealed in the mystery of airway hyperresponsiveness.

DISCLOSURES

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

REFERENCES

1. **Bates JHT.** The multiscale manifestations of airway smooth muscle contraction in the lung. *J Appl Physiol* (May 27, 2010). doi:10.1152/japplphysiol.00535.2010.
2. **Bosse Y, Sobieszek A, Pare PD, Seow CY.** Length adaptation of airway smooth muscle. *Proc Am Thorac Soc* 5: 62–67, 2008.
3. **Bosse Y, Solomon D, Chin LY, Lian K, Pare PD, Seow CY.** Increase in passive stiffness at reduced airway smooth muscle length: potential impact

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on airway responsiveness. *Am J Physiol Lung Cell Mol Physiol* 298: L277–L287, 2010.
4. **Brown RH, Mitzner W.** Airway response to deep inspiration: role of inflation pressure. *J Appl Physiol* 91: 2574–2578, 2001.
5. **Fredberg JJ, Inouye D, Miller B, Nathan M, Jafari S, Raboudi SH, Butler JP, Shore SA.** Airway smooth muscle, tidal stretches, and dynamically determined contractile states. *Am J Respir Crit Care Med* 156: 1752–1759, 1997.
6. **Krishnan R, Trepat X, Nguyen TT, Lenormand G, Oliver M, Fredberg JJ.** Airway smooth muscle and bronchospasm: Fluctuating, fluidizing, freezing. *Respir Physiol Neurobiol* 163: 17–24, 2008.
7. **LaPrad AS, Szabo TL, Suki B, Lutchen KR.** Tidal stretches do not modulate responsiveness of intact airways in vitro. *J Appl Physiol* (April 29, 2010). doi:10.1152/japplphysiol.00107.2010.
8. **LaPrad AS, West AR, Noble PB, Lutchen KR, Mitchell HW.** Maintenance of airway caliber in isolated airways by deep inspiration and tidal strains. *J Appl Physiol* 105: 479–485, 2008.
9. **Noble PB, Hernandez JM, Mitchell HW, Janssen LJ.** Deep inspiration and airway physiology: human, canine, porcine, or bovine? *J Appl Physiol*. doi:10.1152/japplphysiol.00631.2010.
10. **Noble PB, McFawn PK, Mitchell HW.** Intraluminal pressure oscillation enhances subsequent airway contraction in isolated bronchial segments. *J Appl Physiol* 96: 1161–1165, 2004.
11. **Noble PB, McFawn PK, Mitchell HW.** Responsiveness of the isolated airway during simulated deep inspirations: effect of airway smooth muscle stiffness and strain. *J Appl Physiol* 103: 787–795, 2007.
12. **Oliver MN, Fabry B, Marinkovic A, Mijailovich SM, Butler JP, Fredberg JJ.** Airway hyperresponsiveness, remodeling, and smooth muscle mass: right answer, wrong reason? *Am J Respir Cell Mol Biol* 37: 264–272, 2007.
13. **Zhang W, Gunst SJ.** Interactions of airway smooth muscle cells with their tissue matrix: implications for contraction. *Proc Am Thorac Soc* 5: 32–39, 2008.