

Commentaries on Viewpoint: Airway smooth muscle and airway hyperresponsiveness in human asthma: Have we chased the wrong horse?

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PAUSE FOR DEEP INSPIRATION

TO THE EDITOR: The Viewpoint by Professor Lutchen is timely and appropriate (3). There is now uncertainty as to the importance of airway smooth muscle (ASM) dynamics to normal airway function and whether disruption in the airway-lung dynamic environment contributes to airway hyperresponsiveness (AHR). Seemingly negative findings in airways in vitro, in which simulated tidal breathing failed to provide dominant control of airway responsiveness (1, 2, 4, 5), have led to the trepidation so clearly expressed by Lutchen in assigning too much importance to this dynamic mechanism. Although Lutchen proposes that the “chasm between a tiny piece of excised ASM tissue and a breathing lung inside a human is enormous” we are not sure bronchial tubes do not leave a large gap unbridged. Although bronchial tubes are our own preferred model, can we be sure the “real breathing” matches what happens during a bronchial challenge? How large are the transmural pressures and how much does the ASM stretch if respiratory effort is increased to overcome the added impedance? We also do not share the fear that the literature concentrates too much on ASM dynamics. There is enough information on airway inflammation and innervation in airway disease to fill textbooks many times over, yet no compelling mechanism surfaced to explain AHR. Much could be gained by revisiting early work under more physiologically relevant dynamic conditions. The field has not simply backed one horse. Present and past strategies are to make several wagers, at a greater outlay, but increasing the probability of a win.

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CAN'T DECIDE WHETHER TO CHASE YOUR FAVORITE HORSE? GROOM IT FIRST WITH OCCAM'S RAZOR

TO THE EDITOR: Explaining the airway hyperresponsiveness of asthma has sustained an industry of competing theories for decades, largely due to the plethora of disparate mechanistic possibilities (1). Any claim of preeminence for a particular theory in this complex field should thus raise eyebrows. Lutchen takes aim here (2) at the hypothesis that asthma is all about stretching the airway smooth muscle (ASM). This notion has taken hold in recent years due to numerous studies at the cell and tissue strip levels revealing complex dynamic behavior that invokes various molecular intracellularities within the contractile machinery of ASM (2). Perhaps not surprisingly, the functional significance of these intracellularities has been eagerly extrapolated up to the scale of the whole lung in vivo. But biology can be infuriatingly contrary; just because a particular phenomenon makes its presence strongly felt at one level of length scale, this does not mean that its signature will necessarily manifest in some obvious way at other (higher) levels of scale. Why this happens is a fascinating question in its own right, but one thing is certain—predicting biological behavior at one length scale from that at another is fraught with the danger that you might end up chasing the wrong horse. Identifying the right horse begins in the experimental lab at the pertinent length scale, with the subsequent grooming of theory proceeding under the watchful eye of Occam and Einstein to make sure it is as simple as possible (but no simpler).

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HOLD YOUR HORSES

TO THE EDITOR: The quick action of beta2-agonist in bronchodilation may have given us a wrong impression about the intimacy between airway smooth muscle (ASM) behavior and the function of a living breathing lung. As correctly pointed out by Lutchen (4), many factors other than ASM dysfunction could contribute to the impaired lung function seen in asthma. The cautionary reminder by Lutchen came as a result of some recent findings suggesting that tidal breathing and deep inspirations (DIs) may not impose sufficiently large strains on ASM to reduce its contractility, and therefore DI-induced bronchodilation may have nothing to do with ASM (1, 3). However, before we eliminate ASM as a player in the DI-induced bronchodilation there are at least two issues that need to be addressed. Firstly, we need to know the exact transpulmonary pressure in a contractile-agonist-challenged lung. There is evidence that parenchyma

stiffens when activated by acetylcholine (2). For the same (volume wise) DIs taken with and without bronchial challenge the transmural pressure of airways will be greater in the former, and this needs to be taken into consideration in experiments using airway segments. Secondly, we need to know the degree of ASM activation during bronchial challenges. It is unlikely that ASM cells are maximally activated during a bronchial challenge, especially when epithelial layer of the airways is intact. At submaximal activation, DIs will elicit greater ASM strains. The question is then, with an appropriate oscillation-amplitude of transmural pressure applied to an airway segment, which is submaximally activated, will we see any ASM effect?

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WE BETTER RIDE THE LIVE HORSE

TO THE EDITOR: In his Viewpoint, Dr. Lutchen (4) challenges the concept that a depressed bronchodilator response to a deep inspiration (DI) in asthma is related to the inability of airway smooth muscle (ASM) to lengthen with the increase in lung volume. His arguments are mainly based on in vitro data that appear to be inconsistent with the effects of tidal stretching and DI in vivo. We agree that additional mechanisms regulating airway caliber may confound the effect of stress and strain on ASM. Nevertheless, there are data showing consistent effects of strain in isolated ASM and DI in vivo. Examples are the similar potency of stretching and isoproterenol in relaxing ASM in vitro (2) and similar bronchodilator effects of exercise hyperpnea and maximal doses of albuterol in vivo (4). Also consistent data in vitro and in vivo are that strain rather than stress is the main mechanism underlying the effects of DI on ASM tone (3) and airway caliber (1). Although some effects of strain or DI are not dissimilar between healthy subjects and subjects with asthma, important differences have been reported that are difficult to explain overlooking the role of ASM. For example, reducing strain completely abolished the bronchodilator effect of DI in subjects with asthma but only partially in healthy subjects (1). In conclusion, we concur with Dr. Lutchen that airway narrowing and its reversal by DI is a complex phenomenon, possibly involving several mechanisms. Yet we do not believe that there is currently enough evidence to dismiss the key role of ASM in asthma.

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RESPONSE TO VIEWPOINT: “AIRWAY SMOOTH MUSCLE AND AIRWAY HYPERRESPONSIVENESS IN HUMAN ASTHMA: HAVE WE CHASED THE WRONG HORSE?”

TO THE EDITOR: We agree with Ken Lutchen that “riding only” one “horse” is not an optimal approach to researching a highly complex problem (1). But we have yet to see compelling evidence that periodic lengthening of ASM does not influence contractile function. Working at the in vivo level, we are struck by the finding that a 10-wk rowing exercise program of sedentary, healthy individuals reduces airway responsiveness to methacholine by 50%, in the absence of deep inspirations, with no appreciable changes in baseline lung function (2). In the opposite direction, we see evidence of AHR and impaired DI effects in individuals with obesity who have no asthma (5). We are limited by not knowing what level of ASM lengthening rowing exercise achieves, what level of reduction in lengthening obesity induces, and whether repetitiveness/duration of lengthening is more important than magnitude in achieving contractile changes. We also do not know the potential role of atelectasis, as pointed out by Lutchen. Yet we believe that the lengthening hypothesis is not “out” and that utilizing “nonasthma” conditions, as in our early study (4), is a useful strategy for future research.

In vivo pharmacologic manipulations can also offer significant insights. Dr. Lutchen asks about the role of inflammation. When we used high-dose inhaled corticosteroids in people with mild asthma, it was after removal of inflammation that a strong correlation between methacholine PC₂₀ and DI-induced bronchoprotection was revealed, indicating that the steroid-resistant component of AHR is where DI and airway stretch may be most relevant (3).

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