Airway smooth muscle stretch and airway hyperresponsiveness in asthma: Have we chased the wrong horse?

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WHY DO HUMANS WITH ASTHMA have hyperresponsive airways? About 20 years ago, a delightfully simple hypothesized mechanism emerged that lack of stretch on the airway smooth muscle (ASM) can be causal to hyperresponsive airways as it occurs in asthma. On the face of it, this mechanism seemed to bridge the gap between two ends of biological length scales associated with hyperreactivity: the ASM and the whole organ level response. But was the relationship between these data coincidental, and have we spent two decades chasing the wrong horse?

Starting as early as 1981 (10), comparison of maximum versus partial flow volume maneuvers suggested that unlike patients with asthma, healthy subjects can dilate their airways in a sustained fashion after a deep inspiration (DI). But was the depressed DI response a cause or an effect of having airways that are hyperresponsive? Because only the airway smooth muscle can invoke constriction, some studies suggested that the asthmatic ASM had a distinct phenotype. The results are mixed (9, 14), but even if so the core question is how did the ASM become distinct?

Then, in 1995, a clever experiment by Skloot et al. (29) indicated that if healthy humans purposely refrained from taking a DI prior to a challenge, they subsequently displayed evidence of amplified reactivity to methacholine. At about the same time other studies showed that if one isolated an ASM strip, its contractile response was dependent on the dynamics of externally applied force/length changes (11). Specifically, when undergoing force/length oscillations the isolated ASM shortened less and generated less force than if it was excited while under static conditions. Also, oscillations imposed after stimulating a static ASM tended to cause relengthening. The enticing hypothesis was that airway hyperresponsiveness is caused by phenomena that remove or greatly diminish the capacity of a human to continuously and periodically lengthen the ASM surrounding their airways.

The flood gates opened, drawing in me and a sea of experienced and new investigators at both length scales chasing the notion that the observed effect of stretch on the isolated ASM and the response of the whole organism were fundamentally linked in a fashion causal of asthma. Scores of studies were done imposing a plethora of gymnastics on isolated ASM strips (11, 25, 30), isolated ASM cells (1, 22), and intact animals and humans (6, 7, 17, 19, 27, 28). Creative methods were advanced to monitor indices of airway caliber in real time (17, 18, 26). Computational models were created ranging from advancing comprehensive biophysics of ASM during dynamic forcing to multiscale structurally consistent models of the whole lung (3, 23). Most of these were variations on the same theme, but some 20 years hence, although many were consistent with the hypothesis, none of them could inextricably prove it while also excluding alternative viable hypotheses.

The chasm between a tiny piece of excised ASM tissue and a breathing lung inside a human is enormous, and the behavior at one scale does not easily nor necessarily translate to become functionally and/or clinically critical at longer length scales. Experiments and models are needed to connect these scales, and about 5 years ago a few laboratories examined preparations at the level of a single airway. Experiments were done on excised airways from bovine and human airways (20, 24) and precision cut human lung slices (21) and with careful controls of the conditions so as to mimic real breathing. The data are compelling in that force-induced length modulations that would be achievable in situ for typical breathing forces did not play an important role to either bronchoprotect the airways from subsequent exposure to an agonist nor bronchodilate after exposure. Now, in 2013 Harvey et al. (15) and Ansell et al. (2) show that the impact of oscillations on a constricted airway are proportional to the degree to which one can strain the airway wall. After constriction, Harvey showed that tidal stretches resulted in little strain, and hence, recovery and pressure oscillations simulating a DI with every breath were required to achieve even 50% recovery. It is worth noting that at FRC, and unlike the parenchyma, most airways are already near the flattened (stiff) portion of their pressure-area curve, which fortuitously ensures that they experience little strain and that the preponderance of a tidal breath enters the more compliant alveoli. So, it is not that the behaviors seen in isolated ASM were in conflict or inconsistent with those for the intact airway, but rather that the conditions necessary to invoke them at levels that would have functional impact were likely not routinely achieved during breathing by humans.

Were we predisposed to supporting the original hypothesis? Did we exhaustively test it against legitimate alternative hypotheses? For example, Black et al. (4) showed that after a long time of withholding DIs, a healthy human’s lung was more responsive, but when they finally take a deep breath postchallenge they seem to dilate their airways in a fashion similar to what they had at baseline. Perhaps in healthy lungs a long prohibition of the DI simply caused a substantial portion of the lung to become atelectatic and the DI simply reopened these areas. In other words, the amplified reactivity in the whole lung after prolonged DI could have had nothing to do with any “transition” within ASM of their airways; rather perhaps one was exciting a smaller lung. Black provided some evidence for this in that dynamic elasance dropped during the course of
withholding a DI but recovered after a DI. Indeed, since the Skloot study several laboratories (4, 8) have now shown that withholding a DI does not subsequently lead to a depressed DI response in healthy humans akin to patients with asthma. Shen et al (28) showed reduced reactivity for intact rabbits as the tidal volume imposed during excitation increased. First, perhaps an increased tidal volume distributes the same dose of agonist over a larger surface area, thereby reducing the effective dose per unit area of airway wall and ASM. Also, such increase in tidal volume necessarily increases the mean transmural pressure load against which the airways would constrict. Finally, perhaps the conditions throughout the airway tree of a patient with asthma amplify the heterogeneity of its response when provoked compared with a healthy lung (12). These are all perfectly plausible alternative explanations having nothing to do with the central hypothesis of force-induced length fluctuations altering the ASM in situ. In short, explicit (and quantitative) extrapolation to and from in vitro and in vivo and at distinct length scales is fraught with complexities.

So why do some patients with asthma respond differently to a DI, even those that are not in the midst of an attack? Some 20 years after the Skloot study this question remains as open as it was then. Perhaps patients with asthma have stiffer airway walls as a consequence rather than a cause of increased muscle tone or other changes that amplify reactivity? A 2011 study by Grainge et al. (13) suggests that remodeling that would amplify wall stiffness can occur as a consequence and not the cause. Whether such remodeling in turn could amplify or protect airways is an open question. Perhaps just a bit extra ASM per wall area is all that is needed to stiffen the wall while amplifying responsiveness (16). We need to ask ourselves the following chicken and egg question: Is there evidence confirming that excessive airway stiffness is the root cause rather than the consequence of amplified reactivity?

Remarkably, few of these “impact of stretching” studies bring up the issue of abnormal levels of inflammation or other mediators that can stimulate contraction. I find it compelling that the only effective approach for asthma management (except perhaps for some with severe asthma) is to minimize airway inflammation. Could patients with asthma have some background level of excitatory mediators or abnormally amplified neural tone that keeps these airways closer to the edge so that when they are exposed to something they react more quickly? Recent studies by Bossé et al. (5) amplifies this point. We do not have the tools to provide sufficient resolution for measuring inflammation or neural tone in situ and across a sufficient cross section of the airway tree to answer this, especially because some airways constrict far more than others during an attack.

In closing, many challenging studies over these last two decades no doubt provide fascinating new insights on ASM and on airway/lung structure-function and even evidence for a distinct ASM phenotype in patients with asthma. Many understandably chased a compelling desire to connect how the changes in the contractile function of ASM caused by periodical lengthening leads to the excessive airway narrowing that is characteristic of patients with asthma. But, with respect to advancing why humans develop asthma and how to best treat it I urge the community to consider if we want to continue riding only this “horse” or saddle up some others and focus on how they all interact within and across length scales to create an asthmatic lung.

DISCLOSURES
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AUTHOR CONTRIBUTIONS
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