Mechanical strain and airway responsiveness: how long does it take, how long will it last?

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AIRWAY HYPERRESPONSIVENESS is a defining characteristic of asthma, and airway smooth muscle function is a critical determinant of this airway responsiveness (7). Current therapies that target airway smooth muscle function in asthma, short- and long-acting bronchodilators, induce relaxation of smooth muscle; their major mode of action targets a symptom, not disease pathogenesis. Other therapies used in the treatment of asthma are targeted toward inflammatory pathways, despite the fact that a substantial proportion of adult asthmatics may actually have little in the way of chronic inflammation (5, 6). The development of treatments specifically targeted toward airway hyperresponsiveness is needed. Developing novel, innovative approaches to target airway reactivity in asthma has the potential to fundamentally change the clinical approach to this disease.

It has been known for many years that acute stretch and mechanical loading of smooth muscle has the potential to modulate airway reactivity; this is impaired in asthma, suggesting a fundamental alteration in airway smooth muscle function in asthma. A deep breath has a potent bronchodilatory effect (8) and protects against induced bronchoconstriction in healthy controls (3). Acute mechanical strain is an important determinant of airway responsiveness in healthy volunteers, and simply reducing mechanical strain by reducing lung volumes induces airway reactivity even in normal healthy volunteers (2). Acute mechanical strain modulates smooth muscle function in health and this acute response to mechanical strain appears to be impaired in asthma, but recent studies suggest that more chronic strain may modulate airway reactivity even in asthmatics (1, 9, 10).

One way to chronically modulate airway muscle strain and alter lung volumes is with the administration of positive end expiratory pressure (PEEP). Prior studies in animals have shown that prolonged PEEP suppresses airway reactivity in rabbits and ferrets, and tracheal segments isolated from these animals even show reduced in vitro responsiveness (9, 10). Chronic mechanical strain appears to have effects on airway structure and function: PEEP can induce changes in airway caliber, and decrease contractility and myosin light chain phosphorylation of airway smooth muscle. On the basis of these prior animal studies suggesting that PEEP could modulate airway reactivity, a small proof of concept study in humans showed that 1 wk of continuous positive airway pressure (CPAP) therapy, administered through a standard set up used in the treatment of sleep apnea, decreased airway responsiveness compared with sham treatment in patients with asthma (1). Currently a large, randomized, multicenter study is underway to evaluate the effects of 12 wk of two different levels of CPAP compared with sham control on airway responsiveness (ClinicalTrials.gov identifier NCT01629823). The results of this study are eagerly awaited, as it could shed light on the role of a noninvasive, nonpharmacological treatment for asthma. Chronic CPAP may prove to be an effective intervention for poorly controlled asthma, but may not be acceptable to many patients, as compliance with CPAP therapy is notoriously difficult in patients with sleep apnea; thus, it is of great interest to know if more acute interventions might modulate airway smooth muscle function.

As such, the results of the study by Xue et al. (11) are particularly exciting and potentially of high clinical relevance. These investigators show that short durations (2 h) of PEEP therapy in mice reduce airway responsiveness both in vivo and in vitro, and remarkably, this effect persisted for at least 6 h after the administration of PEEP. This intervention affected expression of signaling molecules involved in smooth muscle hypertrophy and differentiation (4), suggesting that short periods of PEEP may alter airway smooth muscle structure and function and reduce airway responsiveness.

The current study has a few limitations. First, it was performed in untreated mice, not in a mouse model of asthma. It will be important to understand if similar effects are observed in models of asthma. However, even if this is not seen in an standard asthmatics model, it likely has relevance for patient populations with minimal inflammation in whom chronically reduced lung volume could be contributing to airway reactivity, such as patients with obesity and asthma. Second, effects on airway smooth muscle were considered the sole mechanism of change in airway hyperresponsiveness because only changes in respiratory system resistance were made. It is possible the beneficial effects of PEEP were attributable to overall improved recruitment of lung, although periodic inflations to TLC were performed during the 2-h treatment phase. Additional studies examining changes in respiratory system elastance may provide a better understanding of mechanism. Third, although short periods of PEEP resulted in reduced activation of Akt, it remains unclear what the downstream consequences were on airway smooth muscle, such as changes in the expression and function of contractile proteins. Like all good studies, the current findings by Xue et al. lead to many additional questions, such as determining the minimal duration of PEEP required to effect and sustain reduced airway hyperresponsiveness, how long such an effect may last, and how the effect might change over time or be modulated by changes in BMI and use of inhaled bronchodilators and anti-inflammatory agents. Nevertheless, the current study suggests that very short durations of CPAP therapy might be effective in treating chronic airway responsiveness and this would likely be much more acceptable to many patients than prolonged CPAP treatment.
DISCLOSURES

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AUTHOR CONTRIBUTIONS

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REFERENCES