Commentary

Airway obstruction in asthma: does the response to a deep inspiration matter?

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Abstract

Airway hyperresponsiveness in asthma may not be a problem of too much airway smooth muscle strength. Rather, it may be a problem of too little of the factors that oppose muscle shortening. The weight of available evidence seems to support the idea that loss of the dilating response to a deep inspiration may play a central role in this process, and that the locus of the response is within the airway smooth muscle cell. Bridge dynamics and plastic reorganization of the smooth muscle cytoskeleton are the focus of this commentary; how these factors interact and details about underlying mechanisms remain unclear.

Keywords: bronchospasm, hyperresponsiveness, myosin, plasticity

Introduction

Smooth muscle surrounding the airway shortens when it is activated, and as the muscle shortens the airway narrows. In normal individuals subjected to challenge with non-specific contractile agonists, the extent of airway narrowing is limited and this limited response is reflected by a plateau of the dose–response curve corresponding to only modest levels of airway narrowing. Asthmatic individuals, by contrast, are hyperresponsive. Compared with the response in the normal subject, the plateau of the dose–response curve in the asthmatic is markedly elevated, or abolished altogether, indicating that airway smooth muscle (ASM) shortening is limited only by airway closure. It is the marked elevation of this plateau, or its absence altogether, that makes asthma such a serious disease [1].

It is presently unclear if the elevated or absent plateau in asthma is attributable to fundamental changes in the phenotype of the smooth muscle, structural and/or mechanical changes in the non-contractile elements within the airway wall, or alterations in the mechanical coupling of the airway wall to the surrounding lung parenchyma. Current evidence suggests that ASM has the force-generating capacity to close every airway, even in the normal lung [2,3]. Given the modest level of the plateau response in the normal lung, it follows that there must be mechanisms at work that act to limit smooth muscle shortening. Furthermore, it follows that those mechanisms might become compromised in the asthmatic lung, thereby accounting for an elevated plateau.

Might the response of the airway to a deep inspiration (DI) fit into this picture? Maximally activated ASM is subjected to time-varying mechanical strains associated with tidal lung inflations and spontaneous DIs. Consequently, activated ASM must become equilibrated within a dynamic microenvironment [4]. It is now believed that the dynamic pattern of muscle stretch that occurs during spontaneous

ASM = airway smooth muscle; DI = deep inspiration.

breathing engenders a potent dilating effect, and that it is this dilating effect that accounts for the limited degree of narrowing that can be attained in the healthy airway during maximal bronchial provocation [5–8]. The static elastic load against which the muscle must shorten is appreciable, especially at high levels of lung inflation [9]. At modest levels of lung inflation, however, in the absence of tidal loading, this static load seems to be insufficient by itself to prevent airway closure [2,3,10]. There exists also a bronchoprotective effect of DIs that is perhaps even more important than the bronchodilating response; a DI prior to agonist exposure blunts the subsequent contractile response [11].

Dynamically equilibrated states

We breathe all the time and we sigh at the rate of about 10 times per hour. The expected physiologic range of tidal muscle stretch during breathing is from about 4% of muscle length during spontaneous breathing at rest to 12% during a sigh, and greater still during exercise. In comparison, the tidal stretch of ASM corresponding to 3% of muscle length is enough to inhibit force generation by 50% and is equipotent in that regard with concentrations of isoproterenol, a potent relaxing agonist, in the range 10^{-7} to 10^{-5} M [12]. In healthy volunteers who inhale bronchoconstricting substances such as histamine there is a reflex increase in the frequency and depth of spontaneous sighs, and these DIs cause prompt and nearly complete dilation of the airway [6,13]. In studies of the canine lung, Loring *et al* have shown that the locus of the decrease of lung resistance caused by a DI is within peripheral airways rather than central airways or the lung tissue [14].

Deep inspirations: friend or foe?

These bronchodilating and bronchoprotective effects of a DI fail in the asthmatic [8,11,15]. Ingram provides functional evidence to show that, if anything, DIs only serve to make matters worse during a spontaneous asthmatic attack [13], and this conclusion has been reinforced by recent high resolution computed tomographic reconstructions of airway geometry in mild asthmatics before, during and after a DI [16]. It is not clear, however, what fraction of that response might be myogenic. Orehek *et al* speculated about the existence of a vicious circle in which asthmatic airway obstruction causes a reflex increase in the frequency of DIs, and DIs in turn make the obstruction worse [6]. Fish *et al* observed that airway obstruction in asthma behaves as if it were caused by an inability of DIs to dilate constricted airways, as opposed to an increased responsiveness of the airway itself [5]. Remarkably, Salter had come to the much the same conclusion more than 120 years earlier [17].

Failure of the airway to stretch due to mechanical uncoupling?

This impairment of the bronchodilating effect of a DI was long thought to be a characteristic of only spontaneous asthmatic obstruction and the late-phase response to allergen challenge [13,18]. Nonetheless, a similar impairment is easily induced in healthy subjects merely by prohibiting DIs. Prohibition of DIs was first undertaken as a rough model of mechanical uncoupling of ASM from the mechanical loads attributable to parenchymal tethering and lung elastic recoil [8]. Several laboratories have subsequently confirmed that, if healthy non-asthmatic, non-allergic subjects do nothing more than to voluntarily refrain from DIs but otherwise maintain normal tidal volume, minute ventilation and functional residual capacity, their airways become hyperresponsive [8,15,19,20]. When DIs are eventually reinstated, the subsequent ability of DIs to dilate the airways becomes impaired, as it does in spontaneous asthmatic obstruction [8,19,20]. Prohibition of DIs during bronchial challenge of healthy subjects, however, makes their dose–response curves similar but not equivalent to that of asthmatic subjects [15,21]. As shown clearly by Brusasco *et al* [15], airway hyperresponsiveness is not just a problem of lack of dilation with a DI.

It's about time

King *et al* showed that responsiveness of healthy subjects continue to increase for up to 15 min after prohibition of DIs [20]. Data obtained in isolated smooth muscle shows, similarly, that muscle responses to imposed load fluctuations (simulating the mechanical action of tidal breathing) become dynamically equilibrated with a time constant in the order of 10 min. The data also show that isotonic shortening is not completed for many tens of minutes after muscle activation [4]. Myosin binding is slow to become dynamically equilibrated in a dynamic microenvironment, certainly orders of magnitude slower than in an isometric contraction [4]. Thus, if the muscle is to become so stiff that it fails to respond to a DI, it must take a relatively long time to attain that frozen contractile state [4].

The issue of time also comes into play with considerations of cytoskeletal plasticity. The cytoskeleton of ASM is continuously adapting to its dynamic microenvironment, and these cytoskeletal-remodeling events seem to play out over a wide range of time scales. Gunst and Wu [22] have shown that muscle force can display an almost immediate sensitivity to the length history, whereas Pratusevich *et al* have shown that other remodeling processes play out for at least many tens of minutes [23,24].

How much does ASM stretch *in vivo*?

Do differences in ASM stretch account for differences in the response to a DI? The ability of lung inflation to stretch ASM versus its failure to do so has been suggested as a likely mechanism to account for bronchodilating versus bronchoconstricting effects of a DI, but it now seems that this may not be the case. Recent data from two laboratories have confirmed that healthy subjects challenged with a spasmogen display substantial bronchodilation following

a DI, whereas asthmatics either fail to dilate their airway in response to a DI or, more often, exhibit further bronchoconstriction [16,19]. These new data imply, however, that peak mechanical strains in the airway wall during the DI are in excess of 50% in both the normal and the asthmatic subject, even when the smooth muscle is activated. If transient strains of that magnitude were actually transmitted undiminished from the airway wall to the contractile units within ASM cells, then all bridges would surely be disrupted, even in the asthmatic airway. One potential explanation for the absence of a dilatory response in the asthmatic might be that myosin bridges never see strains that large. This is perhaps because the majority of the mechanical strain in the asthmatic airway during a DI is taken up by increased extensibility of the extracellular matrix, by the intracellular series elastic component, or by the cytoskeletal scaffolding within which the myosin motor operates. At present, however, there are no data available that can address this possibility.

Conclusion

The potent dilating response to a DI observed in normal individuals fails in asthmatics. Bridge dynamics and plastic reorganization of the cytoskeleton are surely important factors, but how they interact and details about underlying mechanisms remain unclear. Muscle shortening velocity also seems to be an important factor [4,25,26]. In addition, Permutt and colleagues have suggested that the bronchodilating and the bronchoprotective effects of DIs may be connected to the release from non-adrenergic, non-cholinergic nerves of an endogenous dilating substance such as nitric oxide [11]. Taken together, the weight of available evidence seems to support the idea that loss of the dilating response to a DI may indeed play a central role in airway obstruction in asthma. However, no clear picture has yet emerged to account for the constellation of curious findings that is associated with responses of the airways to DIs.

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