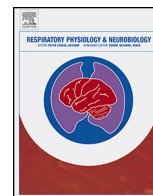




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Invited commentary

Disruption of the bronchodilatory response to deep inspiration in asthma – Extrinsic or intrinsic to the airway smooth muscle?

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The bronchodilatory response to regular deep inspiration (DI), studied by Hulme and colleagues (Hulme et al., 2013), is considered an innate protective mechanism maintaining airway calibre, one that appears disrupted in patients with asthma, even in mild disease as the authors demonstrate. Still, the significance of reduced bronchodilation to DI in asthma remains uncertain, unlike airway hyper-responsiveness (exaggerated airway narrowing, AHR) which has important clinical correlates such as predicting the rate of decline in lung function or response to treatment (Brutsche et al., 2006; Leuppi et al., 2001). The fascination with DI in asthma instead stems from the belief that it may be a precursor/contributor to AHR (Skloot and Togias, 2003) and therefore the mechanisms underlying the failure in the response to DI become important to revealing mechanisms producing AHR.

Broadly speaking, disruption in the response to DI may occur at a level that is extrinsic or intrinsic to the airway wall and/or airway smooth muscle (ASM). There is a large body of literature demonstrating that transient mechanical stretch of the ASM layer decreases active force production (Gump et al., 2001; Shen et al., 1997), which theoretically explains the bronchodilatory response to DI. Any mechanism thereby reducing the stretch of the ASM during DI (an extrinsic mechanism) can be implicated as an abnormality responsible for reducing the bronchodilatory response to DI. Disease processes limiting the mechanical stretch of the ASM include airway wall stiffening (Brown et al., 2007; Ward et al., 2001) and uncoupling of the airway wall from distending parenchymal forces that are responsible for maintaining airway patency (Macklem, 1991). However, the present study provides convincing evidence to suggest that the capacity to stretch the airway wall and in turn the ASM is not the reason for the failure of the response to DI in asthma, favouring other explanations intrinsic to the airway wall.

Hulme and colleagues (Hulme et al., 2013) studied a group of healthy and mild asthmatic subjects and used the forced oscillation technique to probe changes in airway calibre, which corresponds to resistance measures at 6 Hz in the frequency spectrum. While the capacity to dilate the airway during the DI was not altered in subjects with asthma (i.e. airways expanded to the same degree as in the normal airway), immediately after the DI there was persisting bronchodilation in the healthy group (referred to as residual dilation by the authors), but not in subjects with asthma. Further, in the healthy group expansion during DI correlated with residual bronchodilation after DI, yet there was no such relationship in subjects with asthma. Seemingly, it is not the amount of stretch on the airway wall, rather, how the airway responds to the mechanical stimulus which determines the benefit after DI, or lack thereof, in subjects with asthma.

The study by Hulme and colleagues, returns to the spotlight an earlier study by Brown and colleagues (Brown et al., 2001) who used high resolution computed tomography (HRCT) to directly measure airway lumen cross sectional area before and after DI. Findings by Brown resemble those by Hulme: the capacity to open the airway lumen during DI was not different between groups, but only airways from healthy individuals remained open after DI. In comparison, airways from individuals with asthma returned to the same calibre present prior to DI, and in some instances, additional bronchoconstriction was observed. Together these findings suggest that the mechanical stretch of the airway wall in asthma is adequate, indeed sufficient to produce lasting (residual) bronchodilation in a healthy individual, but the response to the applied mechanical stretch is impaired. It is comforting that the different physiological levels agree, that is, the integrated lung response to DI assessed by FOT (Hulme et al., 2013), and single generation airways viewed by HRCT (Brown et al., 2001).

The question then becomes whether there is something intrinsically different about how the airway wall responds to mechanical stretch during DI in patients with asthma? In an ontogeny study (Wang et al., 2005), differences in the airway wall response to

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mechanical stretch were demonstrated with maturation. Force production in tracheal rings from mature guinea-pigs was inhibited by mechanical stretch, and also initially in immature animals. In contrast, immature animals exhibited a striking enhancement in ASM force once the early length-induced force depression resided. Such studies provide necessary proof of concept that the response to mechanical stretch is modifiable and will impact airway function. In the guinea-pig airway the maturational effect on the response to mechanical stretch was attributed to release of a contractile prostanoid (Wang et al., 2005), however in asthma, it's possible that the phenotype of ASM is altered such that it responds uniquely to a mechanical stimulus.

The idea that there may be a difference in the phenotype of the ASM in asthma is by no means a new concept. There has been an arduous and timely search for a change in the contractile phenotype of the ASM in asthma, particularly with respect to force production. Numerous studies examining the mechanical response of ASM tissue in vitro can be cited and when the literature is viewed as a whole there is simply no consistent evidence to suggest that the contractile phenotype is altered in asthma (Pascoe et al., 2012). On the other hand a phenotype that determines the ASM cells response to mechanical stretch is a comparatively new question and one that is sure to be further addressed in future studies (see below).

As discussed, there are an abundance of studies that previously looked to establish changes in contractile properties of the ASM in asthma. Unfortunately early studies on ASM tissue in vitro were limited by low sample size or other technical related issues such as failure to correct for the amount of muscle in the airway specimen. Moreover, as our understanding of ASM mechanics has evolved, methods and protocols to study the ASM in vitro have improved (Bai et al., 2004) and we are now better placed to reliably characterise ASM contractile properties in asthma. Recently Chin et al. (2012) published the most comprehensive study to date, examining an array of mechanical properties including passive and active length-tension relationships, stress, shortening, length adaptation, and of relevance here, the response to length oscillation. Yet these meticulously performed experiments revealed very little. For the most part the ASM from subjects with asthma was not special, with the notable exception that the response to length oscillation differed. Length oscillation produced force inhibition in both the healthy and asthmatic groups but the effect was blunted in the latter.

A reduced response to length oscillation in ASM from asthmatic patients may at least contribute to reduced bronchodilation after DI. The DI itself represents the applied length change to the ASM, whereas the bronchodilatory response that follows is analogous to force inhibition seen in the isolated ASM, but to a lesser extent in the asthma group. Another possible change to the ASM (an intrinsic mechanism) that could reduce the response to DI is increased velocity of shortening. There is some evidence that the rate of re-narrowing after DI is increased in subjects with asthma (Salome et al., 2003), meaning that any bronchodilation to DI is likely to be short lived. Whether the much sought after defect in ASM involves a greater shortening velocity is certainly worthy of study (Ijpmma et al., 2012) although the focus on shortening velocity is essentially driven by a failure to identify changes more intuitively relevant to AHR, force or shortening (Fredberg, 2002). The above study by Chin et al. (2012), also measured shortening capacity and there was no difference in the degree of or velocity of shortening in ASM from healthy and asthmatic subjects.

It is necessary to point out that a reduced response to mechanical stretch demonstrated in isolated ASM strips excised from subjects with asthma is not proof alone for a change in cell phenotype. Factors that alter the transmission of force at the cell level would be expected to reduce the ASM response to a given length change. For instance, compositional changes to the ASM layer in asthma involving a shift in the fraction of extracellular matrix may impact

cellular mechanical strain. The available evidence argues against any such compositional change to the ASM layer in asthma. A large stereological study on the ASM layer found no difference in the composition of the ASM layer in subjects with and without asthma (James et al., 2012). Irrespectively, future mechanistic studies are required to demonstrate a phenotype defined by its response to mechanical stimuli and to then assess its relevance in asthma.

There remain conflicting studies that still in essence support an extrinsic mechanism for a reduced response to DI in asthma. Observations of reduced airway distensibility in asthma (Brown et al., 2007; Ward et al., 2001) are not supported in the present study by Hulme. The answer may lie in the known increase in wall stiffness brought about by contractile activation (Ansell et al., 2013; Noble et al., 2007). The extent of airway wall stiffening to an agonist such as methacholine (used by Hulme) is expected to be large to the point that any differences in airway distensibility observed prior to induced bronchoconstriction may become trivial in the presence of sufficient ASM tone. Remodelling events that favour increased ASM activation are perhaps more detrimental to wall mechanics than those which alter passive wall properties. In short, differences in airway distensibility observed prior to induced bronchoconstriction may not necessarily be apparent after a bronchial challenge.

A final potentially complicating study is in fact from my own laboratory. We observed no difference in the response of the excised bronchial wall to physiological inflationary pressures in airways from subjects with and without a history of asthma (Noble et al., 2013), suggesting that the airway (and ASM) retains a normal response to mechanical stretch. The field is of course appropriately guided by the weight of numbers and time will show which in vitro approach is most relevant to the in vivo environment and similarly which in vivo technique and protocol is the most informative. Nonetheless the evidence is mounting (in vivo and in vitro) that a reduced response to DI is not simply due to greater wall stiffness in asthma. Instead, it seems entirely feasible the defect may well be intrinsic to the airway and ASM.

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