

## Acute effects of inspiratory pressure threshold loading upon airway resistance in people with asthma

Stephen C. How<sup>a,\*</sup>, Lee M. Romer<sup>b</sup>, Alison K. McConnell<sup>b</sup>

<sup>a</sup> Department of Sport & Exercise Sciences, University of Gloucestershire, Oxstalls Lane, Gloucester GL2 9HW, UK

<sup>b</sup> Centre for Sports Medicine and Human Performance, Brunel University, Uxbridge, Middlesex UB8 3PH, UK

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### ABSTRACT

Large inspiratory pressures may impart stretch to airway smooth muscle and modify the response to deep inspiration (DI) in asthmatics. Respiratory system resistance (Rrs) was assessed in response to 5 inspiratory manoeuvres using the forced oscillation technique: (a) single unloaded DI; (b) single DI at 25 cmH<sub>2</sub>O; (c) single DI at 50% maximum inspiratory mouth pressure [MIP]; (d) 30 DIs at 50% MIP; and (e) 30 DIs at 50% MIP with maintenance of normocapnia. Rrs increased after the unloaded DI and the DI at 25 cmH<sub>2</sub>O but not after a DI at 50% MIP ( $3.6 \pm 1.6$  hPa L s<sup>-1</sup> vs.  $3.6 \pm 1.5$  hPa L s<sup>-1</sup>;  $p = 0.95$ ), 30 DIs at 50% MIP ( $3.9 \pm 1.5$  hPa L s<sup>-1</sup> vs.  $4.2 \pm 2.0$  hPa L s<sup>-1</sup>;  $p = 0.16$ ) or 30 DIs at 50% MIP under normocapnic conditions ( $3.9 \pm 1.5$  hPa L s<sup>-1</sup> vs.  $3.9 \pm 1.5$  hPa L s<sup>-1</sup>;  $p = 0.55$ ). Increases in Rrs in response to DI were attenuated after single and multiple loaded breaths at 50% MIP.

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### 1. Introduction

The ability of a deep inspiration (DI) to modify lower airway calibre has been known for a number of years. Nadel and Tierney (1961) were the first to demonstrate a marked decrease in airway resistance (bronchodilation) in healthy subjects after a DI during a period of induced bronchoconstriction. They suggested that increased stretching of airway smooth muscle, caused by greater transmural airway pressures, induced a change in the airway lumen diameter. The response to DI in people with asthma differs from that of healthy people. Typically, in people with asthma, DI results in either a diminished or absent bronchodilation or even an increase in airway resistance (Kapsali et al., 2000; Brown et al., 2001; Salome et al., 2003). The bronchoconstriction seen after DI may be explained by changes in the excitation–contraction mechanism of the airway smooth muscle (Fredberg et al., 1997). Slowly cycling cross bridges may become ‘latched’, stiffer and possess low hysteresis. Under such conditions the airway is less responsive to stretch and, if airway hysteresis is low relative to parenchymal hysteresis, further airway narrowing after DI is likely (Burns et al., 1985).

Another factor that may contribute to the magnitude of airway re-narrowing after a DI is the extent to which the airway dilates in response to the pressure generated by DI. In support of this Jensen

et al. (2001) demonstrated that not only did the airways of patients with asthma dilate less after DI, they also re-narrowed more. It has previously been proposed that the opening of narrowed airways in people with asthma may require negative pressures in excess of those generated by DI (Gunst et al., 1988). Recently it has been demonstrated that positive pressure inflation is able to reduce airway obstruction in asthma patients who are unable to do so with an active DI (Slats et al., 2008). The authors suggest that the positive pressures may have applied a greater stretching force on the airway than that which could be achieved under physiological conditions (Slats et al., 2008).

An alternative method of increasing airway stretch may be to breathe against an inertial inspiratory load, which may lead to a temporal dislocation between intra-airway pressure and pleural pressure as the inertial load is overcome. Studies of pressure threshold inspiratory muscle training have observed improvements in FEV<sub>1</sub> (Weiner et al., 1992) and peak expiratory flow rate post-IMT (Lima et al., 2008). In addition, medication usage has been shown to reduce, suggesting an improvement in the severity of disease per se (Weiner et al., 2002). These data are therefore consistent with the notion that pressure threshold loading may impart a unique stretching stimulus to the airway. If this is the case, acute inspiratory loading may modify the bronchoconstrictor response to DI in people with asthma.

The aim of this study was to determine the acute effect of DI and various inspiratory loads upon respiratory system resistance (Rrs) in people with moderate asthma. We hypothesised that inspiratory loading, combined with DI would elicit either no change, or an acute decrease in Rrs.

\* Corresponding author. Tel.: +44 0 1242 715317.  
E-mail address: [show@glos.ac.uk](mailto:show@glos.ac.uk) (S.C. How).

**Table 1**  
Descriptive characteristics of the subjects.

Parameter	Mean $\pm$ S.D.	%Predicted
n (male/female)	8/1	–
Age (y)	38 $\pm$ 15	–
Stature (m)	1.75 $\pm$ 0.07	–
Body mass (kg)	85.4 $\pm$ 18.8	–
FEV <sub>1.0</sub> (L)	3.18 $\pm$ 0.72	82 $\pm$ 12
FVC (L)	5.10 $\pm$ 1.13	109 $\pm$ 12
FEV <sub>1.0</sub> /FVC	63 $\pm$ 6	78 $\pm$ 7
FEF <sub>25–75</sub> (L s <sup>-1</sup> )	1.90 $\pm$ 0.60	43 $\pm$ 10
PEF (L s <sup>-1</sup> )	8.48 $\pm$ 2.0	93 $\pm$ 16
MIP (cmH <sub>2</sub> O)	123 $\pm$ 40	124 $\pm$ 33

FEV<sub>1.0</sub>, forced expiratory volume in 1.0 s; FVC, forced vital capacity; FEF<sub>25–75</sub>, forced expiratory flow between 25 and 75% of FVC; PEF, peak expiratory flow; MIP, maximum inspiratory mouth pressure. Predicted values for lung and respiratory muscle function were determined from the equations derived by [Quanjer et al. \(1993\)](#) and [Wilson et al. \(1984\)](#), respectively. Values are group means  $\pm$  S.D.

## 2. Methods

### 2.1. Participants

After local ethics committee approval and written informed consent, 9 non-smoking adults (1 female) with a physician diagnosis of asthma and a history of respiratory complications volunteered to participate in the study. Participants were being prescribed with medication to control their asthma symptoms. All of the participants demonstrated an obstructive ventilatory defect as defined by a reduced FEV<sub>1</sub>/FVC ratio below the 5th percentile of the predicted value ([Pellegrino et al., 2005](#)). Spirometry was undertaken after treatment withdrawal of 24 and 48 h for short- and long-acting medication, respectively. The severity of lung function impairment was classified as “moderate” based on the FEV<sub>1</sub> expressed as a percentage of the predicted value ([Pellegrino et al., 2005](#)). Participants were selected from a group that had previously demonstrated either no response or an increase in airway resistance in response to a DI. Descriptive characteristics of the participants are shown in [Table 1](#).

### 2.2. Procedures

#### 2.2.1. Lung and inspiratory muscle function

Lung function measurements were conducted in the sitting position using an electronic spirometer (Microloop, Micro Medical Ltd., Rochester, Kent, UK) connected to a PC running Spida 5 software (Micro Medical Ltd.). Measurements were performed and interpreted according to ATS/ERS guidelines ([Miller et al., 2005](#); [Pellegrino et al., 2005](#)). Inspiratory muscle function measurements were also conducted in the sitting position using a portable hand held mouth pressure meter (Micro RPM, Micro Medical Ltd., Chatham, Kent, UK). Maximum inspiratory mouth pressure (MIP) was determined from residual volume (RV). The maximum average pressure sustained over one second from three manoeuvres that varied by less than 10% was recorded ([Green et al., 2002](#)).

#### 2.2.2. Airway resistance

Respiratory system resistance (Rrs) was measured using the forced oscillation technique (FOT; Quark i2m, Cosmed, Rome, Italy) in accordance with ERS recommendations ([Oostveen et al., 2003](#)). A low amplitude pseudorandom multi-frequency pressure oscillation (4–48 Hz) was applied at the mouth during quiet tidal breathing. Participants wore a nose clip and supported their cheeks and floor of the mouth with their hands to minimise upper airway shunt due to compliance of these structures during the measurement. Equipment was calibrated before each session, using a calibration cylinder of known resistance, according to manufacturer’s guide-

lines. Measurements at the 8 Hz frequency were recorded as this frequency is most representative of changes in airway resistance (Raw; [Jensen et al., 2001](#)).

#### 2.2.3. Inspiratory manoeuvres

Participants performed one of five different inspiratory manoeuvres at each visit. All manoeuvres were performed from RV and participants were instructed to inspire forcefully to fill their lungs as close to total lung capacity (TLC) as possible. Upon reaching TLC participants then relaxed to allow lung volume to return to functional residual capacity. Inspiratory manoeuvres were designed to assess the influence of a typical IMT protocol (50% MIP), as well as a low absolute inspiratory load (25 cm H<sub>2</sub>O). One condition also controlled for the direct influence of hypocapnia upon the airway. Accordingly, the manoeuvres consisted of: (1) a single unloaded DI; (2) a single DI against a load of 25 cm H<sub>2</sub>O; (3) a single DI against a load equivalent to 50% MIP (62  $\pm$  20 cm H<sub>2</sub>O); (4) 30 DIs at 50% MIP; (5) a repeat of trial 4 under conditions designed to maintain end-tidal carbon dioxide (PETCO<sub>2</sub>) within the normocapnic range. Specifically, normocapnia was maintained by enclosing the inspiratory and expiratory ports of the threshold loading device within a 10L re-breathing bag. A number of perforations were made in the bag to allow participants to re-breathe a mixture of atmospheric and expired air. A familiarisation session served to individualise the number of perforations required for each participant. During the 30 DI protocol, expired gas composition was analysed breath-by-breath using a metabolic measurement system (Oxycon Pro, Jaeger, Hoechberg, Germany). The effectiveness of this method was determined by paired-samples *t*-test, which revealed no significant difference between resting and loaded breathing PETCO<sub>2</sub>. Loaded breathing was undertaken using a calibrated pressure threshold device (POWERbreathe<sup>®</sup>, HaB Ltd, Southam, UK; [Caine and McConnell, 2000](#)).

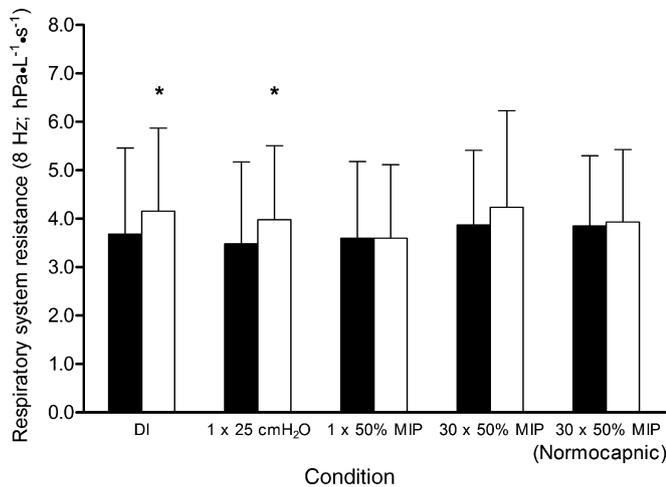
#### 2.2.4. Protocol

Prior to testing, participants abstained from using their bronchodilator inhaler for 24 and 48 h for short- and long-acting medication, respectively. Measurements were made with the airway in its normal basal state of tone, i.e., not after induced bronchoconstriction. The DI and inspiratory loads were randomised and carried out on separate days. Tests were arranged to ensure that abstention from medication did not exceed 48 h, with a minimum of 48 h between consecutive tests. The same time of day was used for all tests to minimise the effect of circadian influences upon airway function ([Mortola, 2004](#)).

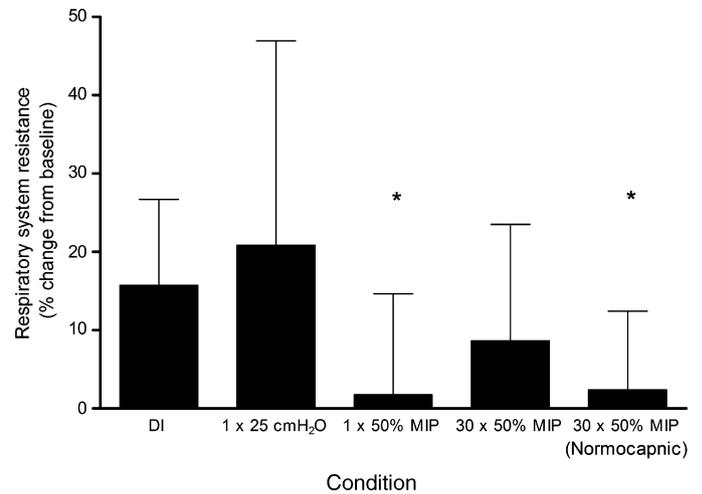
Prior to the baseline measurement of Rrs, lung volume history was monitored for 5 min by asking participants to breathe quietly on a mouthpiece connected to the electronic spirometer, whilst refraining from taking any DIs. Tidal volume loops were visually inspected in real time on the interfaced PC. Any evidence of DI during this period resulted in the 5 min period restarting. Only when participants had breathed for 5 min in the absence of DI were the baseline measurements made. Respiratory system resistance was measured immediately after the 5 min period and this was followed by either an unloaded DI, or a DI against one of the four loads. Respiratory resistance was measured immediately after each of the manoeuvres to determine any effect. The protocol was repeated three times using the same load, each separated by a 5 min period of quiet breathing with no DIs.

### 2.3. Data analyses

Stability of baseline respiratory system resistance (8 Hz) over all trials was assessed with one-way repeated-measures analysis of variance (ANOVA). Test–retest correlations were derived from the ANOVA as intraclass correlation coefficients (ICCs).



**Fig. 1.** Respiratory system resistance (Rrs) in response to various inspiratory manoeuvres. Closed bars = baseline Rrs; open bars = post-manoeuve Rrs.  $p < 0.05$ , significantly different from baseline. Values are group means  $\pm$  S.D.



**Fig. 2.** Percent change from baseline in respiratory system resistance (Rrs) in response to various inspiratory manoeuvres  $p < 0.05$  significantly different from DI. Values are group means  $\pm$  S.D.

Repeated measures ANOVA was used to examine for group mean differences in Rrs (8 Hz) between “inspiratory load” (single unloaded DI; single DI at 25 cm H<sub>2</sub>O; single DI at 50% MIP; 30 DIs at 50% MIP; 30 DIs at 50% MIP [normocapnic]) and “response to load” (pre-DI, post-DI). Mauchly’s sphericity test was used to check homogeneity of covariance and violations of this assumption were corrected using the Greenhouse-Geisser adjustment. Following significant main effects, planned pairwise comparisons were made using the Bonferroni method. Statistical significance was defined as  $p \leq 0.05$ .

### 3. Results

#### 3.1. Baseline respiratory system resistance and response to acute inspiratory loading

Repeated-measures ANOVA revealed no significant between-trial differences in baseline Rrs. Test–retest reliability revealed an intraclass correlation coefficient of 0.87 (95% likely range: 0.71–0.96). Rrs increased by  $15.7 \pm 11.0\%$  in response to DI ( $3.7 \pm 1.8$  hPa L s<sup>-1</sup> vs.  $4.2 \pm 1.7$  hPa L s<sup>-1</sup>;  $p = 0.016$ ) and  $20.8 \pm 26.1\%$  in response to a single inspiration at 25 cmH<sub>2</sub>O ( $3.5 \pm 1.7$  hPa L s<sup>-1</sup> vs.  $4.0 \pm 1.5$  hPa L s<sup>-1</sup>;  $p = 0.03$ ). No increase was observed in response to a single inspiration at 50% MIP ( $3.6 \pm 1.6$  hPa L s<sup>-1</sup> vs.  $3.6 \pm 1.5$  hPa L s<sup>-1</sup>;  $p = 0.95$ ), to 30 inspirations at 50% MIP ( $3.9 \pm 1.5$  hPa L s<sup>-1</sup> vs.  $4.2 \pm 2.0$  hPa L s<sup>-1</sup>;  $p = 0.16$ ) or to 30 inspirations at 50% MIP under normocapnic conditions ( $3.9 \pm 1.5$  hPa L s<sup>-1</sup> vs.  $3.9 \pm 1.5$  hPa L s<sup>-1</sup>;  $p = 0.55$ ) (Figs. 1 and 2).

### 4. Discussion

The finding of increased Rrs after DI agrees with previous studies in people with asthma (Brown et al., 2001; Salome et al., 2003). The attenuation of this response, seen after both a single loaded breath at 50% MIP and 30 loaded breaths at 50% MIP, is new. Furthermore, the magnitude of the latter response appears to be modulated by changes in airway carbon dioxide during loaded breathing. The attenuated response to DI was not seen during a single breath at 25 cmH<sub>2</sub>O. These data confirm our hypothesis, but suggest that the pressure threshold required to modify the response to DI in people with asthma must exceed 25 cmH<sub>2</sub>O. Further, they suggest that there is a confounding influence of airway carbon dioxide upon the response to loaded breathing.

Baseline Rrs did not differ between trials, which supports the effectiveness of our volume history control prior to each of the measurements. We chose to monitor tidal breathing for 5 min, which is shorter than some previous studies (20 min; Scichilone et al., 2001), but longer than others (1 min; Burns and Gibson, 2001). Those studies that have monitored volume history for longer than 5 min have done so to minimise the impact on their measurement of a preceding forced ventilatory manoeuvre. Although our measurements were not preceded by forced manoeuvres we chose to be cautious and extend our monitoring of volume history beyond that normally recommended, i.e., 3 min (Oostveen et al., 2003).

The response of Rrs to DI in people with asthma differs from that of healthy people (constriction vs. dilation, respectively). As has been observed previously, our participants showed an increase in Rrs in response to DI (Kapsali et al., 2000; Brown et al., 2001; Salome et al., 2003). The mechanisms underpinning this abnormal response of airway smooth muscle to DI are unknown, but it has been suggested that the airway smooth muscle (ASM) of people with asthma adopts a so-called ‘latched’ state (Fredberg et al., 1999), in which it is stiffer and less compliant, resulting in a less distensible airway. This renders the airway less responsive to the stretching influence of the surrounding parenchyma during lung inflation. Under these conditions the forces generated by normal lung inflation are thought to be insufficient to elicit ASM relaxation in response to DI, with the ability to dilate the airway related to the severity of the asthma symptoms (Jensen et al., 2001). In addition, it has also been shown that the extent of airway re-narrowing after DI is inversely correlated with the extent to which the airways are able to dilate (Salome et al., 2003).

Evidence to support this notion was provided by an elegant series of experiments in which intra-breath airway resistance was measured using a modified forced oscillation technique. Jensen et al. (2001) noted that the minimum airway resistance achieved by people with mild/moderate and severe asthma at TLC during a DI was significantly lower in people with asthma, compared to healthy people. There was also an inverse dose response relationship between the Raw at TLC and the severity of asthma. Furthermore, in the presence of a bronchoconstrictor, this difference between groups (healthy, mild/moderate asthma, severe asthma) increased, and after a bronchodilator, the difference diminished. Thus, in both health and disease, the ability to stretch the airways during a DI appears to be dependent upon the baseline level of airway stiffness due to the contractile state of the airway smooth muscle.

In this respect it has recently been demonstrated that positive pressure inflation reduces airway obstruction in asthma patients who are unable to do so with an active DI (Slats et al., 2008). The authors suggest that the positive pressures may have applied a greater stretching force on the airway than that which can be achieved under physiological conditions (Slats et al., 2008). The positive pressure model is also suggested to prevent airway wall oedema, which may occur during negative pressure inflation. Burns and Gibson (2002) suggest that the increase in resistance seen in their subjects may have been a result of fluid leaking into the airway wall with a consequent reduction in airway calibre. An alternative explanation, however, is that the increase in resistance was due to acute airway hypoxaemia after the repeated DIs, something we controlled for in our study.

This functional approach to examining the influence of DI upon the ability to stretch the airways supports the notion that a normal DI provides an inadequate stimulus to the stiffened airway smooth muscle of people with asthma. Our data are consistent with this notion; both DI and a loaded breath at 25 cmH<sub>2</sub>O were associated with bronchoconstriction, whilst a moderate (50% MIP) pressure threshold load abolished the bronchoconstrictor response to DI.

Whilst our study is not the first to examine the effect of added resistances upon the response to DI, it is the first to do so in people with asthma. Two previous studies on healthy people have examined the influence of elastic inspiratory loads in the form of chest wall strapping (CWS; Duggan et al., 1990; Torchio et al., 2006). In the first of these, Duggan et al. (1990) demonstrated that the bronchodilatory effect of DI was dependent upon either, achieving an inspiratory tidal volume ( $V_T$ ) > 68% of total lung capacity, or by combining a smaller  $V_T$  (56% of TLC) with the increased transpulmonary pressure generated by CWS. The authors also noted a slightly greater response to fast DI than to slow DI (though not significant), which would be consistent with the production of slightly elevated transmural airway pressure at raised inspiratory flow rates. The authors concluded that the primary determining factor for the magnitude of the response to DI was the resultant transmural airway pressure (Duggan et al., 1990). In contrast, a more recent study by Torchio et al. (2006) observed a concomitant reduction in the bronchodilator effect of DI under conditions of CWS, which occurred in the presence of equivalent transpulmonary pressure (albeit at a lower end inspiratory lung volume (EILV)). The discrepancy between the findings of these two studies is most likely explained by the differing severity of CWS employed by each. For the participants in the Torchio study, the strapping resulted in a decrease in TLC of only around 12%, whereas the strapping imposed in the Duggan study reduced TLC by 43%. Accordingly, the transpulmonary pressures achieved in the Duggan study were almost twice those of the Torchio study (~11 cmH<sub>2</sub>O vs. ~19 cmH<sub>2</sub>O).

The importance of attaining a critical transpulmonary pressure in order to elicit a bronchodilatory response to DI is supported by evidence from a canine model (Brown and Mitzner, 2001). Varying magnitudes of lung inflation were imposed upon anaesthetised, paralysed dogs receiving methacholine by continuous infusion. The authors noted that lung inflations generating airway pressures less than 35 cmH<sub>2</sub>O induced bronchoconstriction, whilst inflation generating airway pressures of 45 cmH<sub>2</sub>O induced bronchodilation. However, since EILV was proportional to inflation pressures, it is difficult to separate the influence of airway stretch due to differences in lung volume, and the effects of differing transpulmonary pressure in this model.

In the absence of an externally imposed load, transpulmonary pressure is a function of inspired volume. Salerno et al. (2005) examined the influence of differing inspired volumes upon the response to DI in healthy participants under the influence of methacholine-induced bronchoconstriction. They noted that, despite a non-linear relationship between transpulmonary pres-

sure and EILV, the response to DI was related linearly to EILV. They argued that this provided evidence that the primary stimulus to the influence of DI upon ASM was stretching, and not transpulmonary pressure. To our knowledge, our study is the first to impose a resistance at the mouth, but in common with Brown and Mitzner's (2001) dog model, we found the bronchoconstrictor response to DI was only modified by a load in excess of 25 cmH<sub>2</sub>O. Since higher threshold loads are associated with lower EILV (because of the length-tension relationship of the inspiratory muscles), our data are consistent with those of Duggan et al. (1990), suggesting that transmural pressure and airway stretch (resulting from volume-related parenchymal pull on the airways) have discrete influences, acting in concert to generate ASM relaxation.

The inverse relationship of lung volume and airway resistance has long been known, with higher airway resistance seen at lower lung volumes (Briscoe and Dubois, 1958). Indeed, a reduction in FRC after the unloaded DI may explain the increase seen in airway resistance for this experimental condition. However, a change in operating lung volume of approximately 2 l would be required to explain the absence of this response after a 50% MIP load (Brown et al., 2007). It therefore seems very unlikely that changes in FRC explain any of our observations.

Overall, our data suggest that in the presence of spontaneous airway tone, people with moderate asthma are unable to elicit a bronchodilation in response to DI; indeed, they show a bronchoconstrictor response. However, when transpulmonary pressure is increased by imposition of an adequate inspiratory load (50% MIP), and combined with a DI, the response of the ASM is shifted towards normality, i.e., there is neither bronchodilation nor constriction.

The nature of the pressure threshold load utilised in the present study is worthy of brief comment, since its inertial properties may be central to the nature of the distorting influence imposed upon the ASM. The pressure threshold valve does not open until intrathoracic pressure equals the valve opening pressure. This means that there is a brief period at the onset of the inspiratory effort, before the valve opens, when there is intrathoracic gas decompression, which presumably applies a brief stretching influence upon the airways. Once the valve opens, air enters the airways and lung inflation occurs; the dynamics of these changes in relation to the mechanical forces exerted upon the ASM are unknown, but worthy of further exploration, as they may provide a potent method of distorting ASM and inducing relaxation.

One of the original rationales for our study was to assess whether improvements in FEV<sub>1</sub> in people with asthma after inspiratory muscle training (Weiner et al., 1992) might be due to the chronic effect of inspiratory pressure threshold loading upon the latched state of the ASM. Accordingly, we assessed the response to single loaded breaths, as well as multiple breaths that simulated a typical inspiratory muscle training protocol. We found that the response to 30 breaths at the 50% MIP load was modulated by the prevailing airway carbon dioxide, such that hypocapnia attenuated the effect of the inspiratory load. The bronchoconstrictive effect of hypocapnia is well known (see Bruton and Holgate, 2005), and when hypocapnia was prevented during the 30-breath condition, the attenuation of the bronchoconstrictor effect of DI was enhanced. Our data therefore suggest that hypocapnia exerts an independent effect upon ASM, which can reduce the beneficial effect of raised transmural airway pressure generated by pressure threshold loading at 50% MIP. This observation may be important in terms of the hypothesised effect of inspiratory muscle training upon the latched state of ASM, i.e., the influence of the raised transmural airway pressure induced by the inspiratory loading upon ASM may be dependent upon maintenance of normocapnia. It is also noteworthy that the acute effect of 30 loaded breaths was no greater than the effect of 1 breath.

In summary, we have shown that the spontaneous bronchoconstrictor tone of people with moderate asthma is increased by DI, and by an externally imposed inspiratory load of 25 cmH<sub>2</sub>O. This bronchoconstrictor response was abolished when the load was increased to 50% of MIP. Finally, during multiple loaded breaths at 50% of MIP that simulated an inspiratory muscle training session, the attenuation of the bronchoconstrictor response was enhanced when airway carbon dioxide was controlled by re-breathing.

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