

# A novel hypothesis to explain the bronchoconstrictor effect of deep inspiration in asthma

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**Background:** In healthy subjects deep inspiration transiently dilates the airways, while many asthmatic subjects show bronchoconstriction by a mechanism which is incompletely understood. We hypothesised that the negative intrathoracic pressure associated with deep inspiration occurring in the context of increased leakiness of the airway vasculature may temporarily increase airway oedema and thus reduce luminal diameter in subjects with asthma.

**Methods:** The effects of non-forced deep inspiration and forced deep inspiration through resistance (generating enhanced negative intrathoracic pressure) on specific airway conductance (sGaw) were compared in 10 asthmatic and 11 healthy subjects. Each performed two respiratory manoeuvres: (1) sGaw was measured immediately after three deep inspirations without added resistance, each performed at a predetermined rate (equal to that when performed maximally through resistance); and (2) sGaw was measured immediately after three forced inspirations through resistance.

**Results:** Compared with deep inspiration without added resistance, sGaw was significantly reduced after deep inspiration through resistance in the asthmatic group by a mean (SD) of  $-13.5$  (11.0)% ( $p=0.003$ ) but was unchanged in the control group ( $-0.5$  (12.4)%,  $p=0.67$ ).

**Conclusions:** Given the similar time-volume relationship in the two manoeuvres, the reduction in sGaw is unlikely to be due to differences in smooth muscle behaviour. It is suggested that the enhanced negative intrathoracic pressure acting across the airway capillaries increases airway wall oedema and reduces airway calibre. Such a mechanism operational during normal rapid deep inspiration might contribute to bronchoconstriction after deep inspiration in subjects with asthma.

Several studies have shown that the functional response to deep inspiration is different in asthmatic and healthy subjects.<sup>1-10</sup> Most studies report a bronchodilating response to deep inspiration in healthy subjects.<sup>2-5,8-10,11</sup> In asthmatic subjects, while those with milder disease display a more limited bronchodilator response, severe asthmatics show frank bronchoconstriction following deep inspiration.<sup>1,4,12,13</sup>

The bronchodilatation following deep inspiration in healthy subjects is generally attributed to a reduction in airway smooth muscle tone, but the mechanism underlying the bronchoconstriction observed after deep inspiration in some patients with asthma is not fully established.

In the inflamed asthmatic airway wall, fluid flux across leaky capillaries between the intravascular and extravascular compartments in response to changes in hydrostatic pressure is likely to be greater than in a healthy non-inflamed airway. We therefore hypothesised that the large negative intrathoracic pressure generated during a rapid deep inspiration would cause extravasation of fluid into the asthmatic airway wall, increasing its thickness and reducing the lumen, while in the healthy airway with no inflammatory changes such an effect would be absent or insignificant.

We have tested this hypothesis by comparing the bronchoconstricting effect of deep inspiration in asthmatic and healthy subjects when inspiration was performed both with and without added resistance. Inspiration against added resistance was used to enhance the negative intrathoracic pressure during deep inspiration. Our hypothesis predicted that asthmatic subjects would show greater than normal airway narrowing following deep inspiration against resistance compared with resistance free inspiration.

## METHODS

Ten subjects with mild asthma and 11 normal subjects were studied (table 1). None of the asthmatic subjects was taking

**Table 1** Characteristics of study subjects

	Asthmatic subjects (n=10)	Healthy subjects (n=11)
Age (years)	32.8 (5.1)	30.2 (5.0)
M:F	5:5	6:5
FEV <sub>1</sub> (% predicted)	90.8 (27.8)	97.5 (10.5)
FEV <sub>1</sub> /FVC	0.72 (0.14)	0.80 (0.07)
sGaw (before deep inspiration)	0.094 (0.037)	0.154 (0.048)

Values are mean (SD). sGaw measured in  $\text{cm H}_2\text{O}^{-1} \cdot \text{s}^{-1}$ .

more than 400  $\mu\text{g}$  of inhaled steroid (beclomethasone) per day. Normal subjects were all hospital employees who reported no symptoms of asthma, had never received a diagnosis of asthma from a physician, and had normal spirometric volumes. All subjects were non-smokers and had had no recent upper respiratory tract infection. Approval was obtained from the local ethics committee and written informed consent was obtained.

All respiratory function tests were performed with the subject seated and breathing via a mouthpiece attached to a flow sensor (Sensormedics), the output of which was integrated to give volume. Lung volume and specific airway conductance (sGaw) were measured by plethysmography.<sup>14,15</sup> sGaw was measured during panting at functional residual capacity (FRC).

**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; sGaw, specific airway conductance; RV, residual volume; TLC, total lung capacity; FRC, functional residual capacity; VC, vital capacity.

Additional resistance for inspiration was provided by the attachment in series to a standard mouthpiece of an orifice 3 mm wide and 3.4 cm long.

### Preliminary studies

A pilot study was conducted in 10 subjects to confirm the practicability of this degree of resistance and the time to inspire a full breath through it. In each subject we measured the time (t) to perform a forced maximal inspiration from residual volume (RV) to total lung capacity (TLC) through resistance and the inspiratory vital capacity (IVC) during unencumbered breathing. This study showed that t approximated to a linear function of IVC:  $t = 2.12 \times IVC - 0.05$  ( $R^2 = 97\%$ ,  $p < 0.0005$ ). Inspiratory times varied between 5 and 14 seconds.

In a second pilot study the magnitude of the intrathoracic pressure generated during the two manoeuvres was assessed in four subjects after swallowing an oesophageal balloon. The subjects performed the two inspiratory manoeuvres that were to be performed in the main study. Maximum (negative) pleural pressure during forced inspiration against resistance was achieved early in inspiration and was sustained for most of the duration of the inspiration. During the controlled resistance free inspiration the negative pressure generated gradually increased throughout inspiration, achieving its maximal (negative) value at the end of inspiration. The peak (negative) pressure generated during forced inspiration against resistance was significantly greater than the peak (negative) pressure during controlled resistance free inspiration (mean  $-62.9$  cm  $H_2O$  v  $-23.1$  cm  $H_2O$ ,  $p = 0.019$ ).

### Study protocol

The full study was performed at a later date. A series of respiratory manoeuvres was performed in the following sequence:

#### (1) Inspiratory vital capacity (IVC)

Following two or three tidal breaths, subjects exhaled to RV and then performed a non-forced inspiration to TLC. The best of three technically good manoeuvres was recorded and used to predict the inspiratory time (t) through resistance using the previously derived equation:  $t = 2.12 \times IVC - 0.05$ . Subjects then rested for 5 minutes.

#### (2) sGaw before deep inspiration

The manoeuvre before deep inspiration began with tidal breathing for 1 minute. The volume-time trace was monitored on screen to ensure that no deep breaths occurred. After a 1 minute deep inspiration free period, sGaw, TLC, FRC, and RV were measured. The sequence was repeated at least twice more after at least 1 minute of tidal breathing on each occasion. The mean of three technically good measurements was calculated and recorded as the sGaw before deep inspiration.

#### (3) sGaw after deep inspiration without resistance (sGaw<sub>DI</sub>)

Using the same apparatus, after two or three tidal breaths subjects performed a non-forced expiration to RV. From RV they inspired slowly (at a steady rate) to TLC. The inspiratory rate was such that the entire inspiration took t seconds. This precise timing was achieved by practice and an audible second count '1, 2, ..., t' during inspiration. The actual time taken was measured to ensure parity with the time (t) predicted for the inspiration performed against resistance. From TLC subjects performed a swift but non-forced expiration to RV. The manoeuvre was repeated twice more and, following the third timed inspiration to TLC, subjects returned to FRC. Panting at FRC as before allowed calculation of sGaw. The mean of three technically good measurements was calculated and recorded as the sGaw<sub>DI</sub>.

**Table 2** Specific airway conductance (sGaw) and functional residual capacity (FRC) after deep inspiration with and without resistance in asthmatic and healthy subjects

	Asthmatic subjects (n=10)	Healthy subjects (n=11)
sGaw <sub>DI</sub>	0.084 (0.036)	0.141 (0.041)
sGaw <sub>DI RES</sub>	0.071 (0.031)	0.138 (0.039)
% change	-13.5 (11.0)*	-0.5 (12.4)*
p value	0.003	0.67
FRC <sub>DI</sub> (l)	4.3 (1.4)	3.7 (1.2)
FRC <sub>DI RES</sub> (l)	4.1 (0.9)	3.5 (1.1)
p value	0.23	0.02

Values are mean (SD). \*p=0.02. sGaw measured in  $cm H_2O^{-1} \cdot s^{-1}$

#### (4) sGaw after deep inspiration against resistance (sGaw<sub>DI RES</sub>)

Using the same apparatus, subjects began by performing two or three tidal breaths without added resistance. They then performed a non-forced expiration to RV, followed by inspiration with maximum effort through resistance to TLC. Subjects were required to achieve a full inspiration as quickly as possible. The time taken was noted to ensure the accuracy of the predicted time (t) and thus matching with the time of the earlier controlled resistance free inspiration. From TLC subjects performed a swift but non-forced expiration to RV against no resistance. The manoeuvre was repeated twice more. Following the third maximal inspiration to TLC subjects returned to FRC. Panting at FRC as before allowed calculation of sGaw. The mean of three technically good measurements was calculated and recorded as the sGaw<sub>DI RES</sub>.

### Analysis of data

In order to assess the effect of the negative intrathoracic pressure generated by forced inspiration against resistance we compared sGaw<sub>DI RES</sub> with sGaw<sub>DI</sub> in each subject group. The % change from sGaw<sub>DI</sub> to sGaw<sub>DI RES</sub> in each subject was calculated and compared between the two groups. FRC<sub>DI RES</sub>, the lung volume at which sGaw<sub>DI RES</sub> was measured, and FRC<sub>DI</sub>, the lung volume at which sGaw<sub>DI</sub> was measured, were also compared within each group.

The time taken to inspire when inspiration was performed at a voluntarily controlled rate without additional resistance ( $t_{DI}$ ) was compared with the calculated time to inspire with maximal force performed against added resistance ( $t_{DI RES}$ ).

Within group results were compared using a paired *t* test and between group comparisons were made using a non-paired *t* test.

### RESULTS

All results are expressed as mean (SD) values. Subject groups were of similar mean age and sex distribution (table 1). The asthmatic subjects had mild airways obstruction.

In asthmatic subjects sGaw following forced inspiration against resistance (sGaw<sub>DI RES</sub>) showed a consistent small decline compared with sGaw measured following the voluntarily controlled deep inspiration against no added resistance (sGaw<sub>DI</sub>) and was, on average, 13.5% lower (table 2). This difference was statistically significant ( $p = 0.003$ ). In healthy subjects there was no difference in the sGaw following the two types of inspiratory manoeuvre. The % change from sGaw<sub>DI</sub> to sGaw<sub>DI RES</sub> was significantly different between the two groups. In the asthmatic subjects there was no statistically significant difference between FRC<sub>DI</sub> and FRC<sub>DI RES</sub>, although in healthy subjects a difference of similar average magnitude was statistically significant.

There were no differences in the mean (SD) inspiratory time when measured at the voluntarily controlled rate

without added resistance in asthmatic and normal subjects (9.5 (2.3) s v 10.5 (3.1) s) and the calculated time to inspire with maximal force performed against added resistance (9.5 (3.0) s v 10.2 (2.9) s).

## DISCUSSION

The different responses of asthmatic and healthy airways to deep inspiration probably reflect a fundamental feature of asthmatic pathophysiology. Studies in healthy subjects consistently show a bronchodilating response to deep inspiration,<sup>2 5-8 10 11</sup> but in subjects with asthma the response is more variable.<sup>12 13 16-19</sup> While milder asthmatics simply display a more limited bronchodilator response, subjects with more severe asthma show bronchoconstriction after deep inspiration. Indeed, some studies have identified an inverse relationship between the bronchodilating effect of deep inspiration and severity.<sup>1 4 12 13</sup> The bronchodilatation after deep inspiration in healthy subjects is largely attributable to a reduction in airway smooth muscle tone. This explanation is consistent with the enhanced bronchodilating effect of deep inspiration seen in the context of methacholine induced bronchoconstriction in both asthmatic<sup>13 17 18</sup> and healthy subjects,<sup>6 20</sup> and with diminution of the bronchodilating effect of deep inspiration following administration of  $\beta_2$  sympathetic agonists.<sup>12 18 21</sup>

The mechanism underlying the bronchoconstriction observed after deep inspiration in some asthmatics is not fully established. A diminution of the bronchodilating effect of deep inspiration can be explained by a reduction in the degree of stretch imposed on smooth muscle by deep inspiration in asthmatic subjects.<sup>22</sup> An additional mechanism, however, is required to explain the observed bronchoconstrictor response. Hysteresis within the parenchyma resulting in lower lung recoil pressure following deep inspiration and a diminished retractive force on the airway wall has been proposed as such a mechanism, with the net effect on airways after deep inspiration being a balance of the hysteresis within the airways and parenchyma (the "relative hysteresis hypothesis").<sup>5 11 17 21 23</sup> This mechanism explains many reported findings, but it does not account for the increase in isovolumic forced expiratory flow following deep inspiration seen in conjunction with a reduction in sGaw in two studies of asthmatic subjects.<sup>10 17</sup>

We therefore propose the following mechanism which, together with the stretching effect of deep inspiration on airway smooth muscle, would account for all the published observations.

A large proportion of the increased thickness of the airway wall in asthma is due to inflammation, which includes increased vascularity, increased mucosal blood flow,<sup>24</sup> leaky capillaries, inflammatory exudate, and oedema.<sup>25</sup> Even in stable situations the equilibrium of intra/extravascular fluid flux is dynamic and delicately balanced. This equilibrium would be disturbed by a change in hydrostatic pressure. The markedly negative intrathoracic pressure generated during a rapid deep inspiration would lead to a pressure gradient across the capillary wall. In the context of the leaky low pressure capillary bed of a more vascular asthmatic airway, this would cause extravasation of fluid into the airway wall, increasing its thickness and reducing its lumen (and thus reducing sGaw). The increased interstitial fluid would also render the airway wall more turgid, reducing its compliance, and the airway would therefore be less susceptible to compressive forces during the subsequent forced expiration.<sup>10</sup> It has been shown that relatively small changes in airway wall oedema can potentiate the bronchoconstricting effect of smooth muscle constriction<sup>26 27</sup> and lead to significant airway narrowing. Thus, relatively small net movements of fluid could be responsible for the observed changes. In healthy subjects without inflammatory changes such a mechanism would be absent or insignificant.

In the current study we have tested this hypothesis by comparing the bronchoconstricting effect of deep inspiration (reduction in sGaw) in asthmatic and healthy subjects both with and without added resistance. The inspiratory manoeuvres were designed to be identical in their time-volume relationship in order to minimise differences in the behaviour of smooth muscle or any other element in which intrinsic tone varies in response to stretch, including factors contributing to both airway and parenchymal hysteresis. Inspiration against added resistance enhanced the negative intrathoracic pressure during deep inspiration. Thus, the only difference between the two types of inspiratory manoeuvre was the change in intrathoracic pressure. The fluid flux hypothesis predicts enhanced airway narrowing in asthmatic subjects following deep inspiration against resistance compared with resistance free inspiration. In healthy subjects without airway inflammation the hypothesis predicts substantially less sensitivity to changes in intrathoracic pressure and a smaller difference in sGaw following the two types of inspiratory manoeuvre. Our results are entirely consistent with this hypothesis.

This study suggests that the changes in airway function observed after deep inspiration in asthmatic subjects result, not only from changes in airway and parenchymal components of the lung which are subject to the stretch/relaxation phenomenon (already extensively studied), but also from the effects of transient changes in intrathoracic pressure on the inflamed asthmatic airway wall.

Further testing is required to investigate the full implications of this mechanism. The potential to influence airway wall oedema by manipulation of the intrathoracic pressure could have clinical benefits. Positive pressure applied by non-invasive ventilation, for example, could have the effect of reducing airway wall oedema. If effective, such interventions could have a role in clinical management in the acute setting.

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