Enhanced airway dilation by positive-pressure inflation of the lungs compared with active deep inspiration in patients with asthma

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The functional response of the airways to deep inspiration is different between healthy subjects and patients with asthma (27, 41). In healthy subjects deep inspirations reverse induced bronchoconstriction almost to baseline level (4, 32, 39). In patients with mild asthma, however, dilation of constricted airways by deep inspiration is impaired (16, 38, 44). The impairment of this bronchodilatory effect is related to asthma severity and disease status (28, 40). Restoring this physiological mechanism that reverses airways obstruction in patients with asthma might reduce the need of current asthma treatment.

During a deep inspiration the transpulmonary pressure is transmitted through the parenchymal tissue and distends all intrapulmonary structures, including the airways (42). Airway wall thickening by chronic inflammation in asthma would decrease the strain transmission from the parenchyma to the airway wall, thereby reducing airway distension. Using a mathematical model it has been shown that peribronchial inflammation decreases both the load and the slope of the relationship between peribronchial and pleural pressure (30). Furthermore, Burns and Gibson (12) showed that adding a resistance during deep inspiration, to enhance the subatmospheric intrathoracic pressure, decreased airway conductance (gaw) in asthmatic patients. They concluded that the large subatmospheric pressures during deep inspiration may lead to extravasation of fluid in the inflamed asthmatic airway wall, thereby enhancing airway wall thickness. However, two studies using fast intravenous infusion of saline, resulting in airway wall thickening by edema and fluid flux (9, 11), showed no effect on deep inspiration-induced bronchodilation (37).

On the other hand, the inflammation-induced remodeling processes in chronic asthma (13, 25) may increase the airway wall stiffness (5) and make it more resistant to imposed stretch by deep inspiration (17, 33, 35, 47). Using high-resolution CT scans, Brown and Mitzner (8) demonstrated in mechanically ventilated dogs that increased airway wall stiffness by smooth muscle tone resulted in impaired dilation of the airways by positive pressure compared with relaxed airways. Even though it has been observed that the airways of asthmatic patients dilated to the same extent as those of healthy subjects by a deep inspiration, the airways of the patients with asthma constricted following the deep inspiration (10). The latter may be a result of altered smooth muscle function in asthma leading to impaired bronchodilation by deep inspiration (2).

It can be postulated that airway wall distension can be improved by manipulation of the intrathoracic pressures by passive lung inflation in patients with asthma. Mechanical inflation of the lungs would induce stretch of the airways without large subatmospheric intrathoracic pressures and could therefore prevent extravasation of fluid in inflamed airways. In addition, the inflated volume may open closed airways, thereby redistributing tethering forces of the parenchyma on the airway wall.

Therefore, we hypothesized that positive-pressure machine-assisted lung inflation will reduce the level of airways obstruction in patients with asthma who do not feature bronchodilation following active deep inspiration. To that end, we developed a...
computer-controlled syringe, which can inflate the lungs with a predetermined individual volume and inspiration time for each subject. This was connected to a forced oscillation device, which measured resistance (Rrs) and reactance (Xrs) of the respiratory system continuously during the breathing maneuvers.

The aim of this study was to compare changes in Rrs and Xrs in response to active or positive-pressure (syringe inflated) deep inspiration maneuvers in asthmatic patients who have an intact or an impaired bronchodilatory response to active deep inspiration while provoked with inhaled methacholine.

METHODS

Subjects. For this study we recruited 24 patients with mild to moderate persistent asthma (32a). All patients had a history of wheezing, breathlessness, or cough. They were all atopic, as demonstrated by a positive skin reaction to 1 of 10 common aeroallergen extracts (HAL, Haarlem, The Netherlands) and were hyperresponsive to methacholine [provocative concentration of methacholine inducing > 50% increase in Rrs (PC20 Rrs) < 8 mg/ml] (7). The subjects were clinically stable and used β2-agonists on demand only or in combination with inhaled corticosteroids. Short- and long-acting β2-agonists were stopped, respectively, 8 and 24 h before the challenges. None of the participants had a recent upper respiratory tract infection or other relevant diseases. The Medical Ethics Committee of the Leiden University Medical Center approved the study, and the subjects gave their written informed consent before entering the study.

Study design. Clinical status, atopy, and hyperresponsiveness to methacholine were assessed during a screening visit. The initial response of the airways to an active deep inspiration was measured at the end of the methacholine challenge of the screening visit. The response determined whether the subject was included in group A (intact response to deep inspiration, the "intact DI response group") or group B (impaired response to deep inspiration, the "impaired DI response group") (see also Statistical analysis). On two subsequent randomized visits two additional methacholine challenges were performed to measure the response of the airways to either an active deep inspiration or a positive-pressure inflation performed by the computer-controlled motor-driven syringe (Fig. 1).

Methacholine challenges. The response of the airways to methacholine was measured using the forced oscillation technique (FOT) at 8 Hz (44). At baseline, forced expiratory volume in 1 s (FEV1) was measured three times following saline inhalation. One minute later, three measurements of Rrs during 30 s of tidal breathing were performed. The mean of these three measurements was used as baseline Rrs. Serial doubling doses of methacholine bromide (0.03–9.6 mg/ml) in normal saline were aerosolized and inhaled for 2 min by baseline Rrs. Serial doubling doses of methacholine bromide (0.03–20 mg/ml) were used in randomized order.

Statistical analysis. Mean Rrs and Xrs were calculated from all data points during three tidal inspirations (Rrsinsp and Xrsinsp) and three tidal expirations (Rrsexp and Xrsexp) separately. The response of the airways was calculated as the difference between Rrs and Xrs following and preceding the deep inspiration. An impaired response to deep inspiration was defined as a decrease in Rrs < 2 SDs of Rrsexp preceding the deep inspiration, whereas an intact response to deep inspiration was defined as a decrease in Rrs < 2 SDs of Rrsinsp (Fig. 3).

The sample size of 12 patients per group was based on our data with regard to Rrs measurements (44), allowing the detection of a 1 cmH2O·l−1·s−1 difference within and between the groups, if α = 0.05, and 1 − β = 0.80. Between-group differences were analyzed using Mann-Whitney U-tests. Within-group differences were explored using Wilcoxon signed-rank tests. Correlations were examined using Spear-
man’s rank correlation coefficients. We used SPSS version 12.01 for all analyses (SPSS, Chicago, IL). *P* values $< 0.05$ were considered statistically significant.

**RESULTS**

All patients performed the measurements without any personal or medical problems. The patient characteristics are given in Table 1. The groups were not significantly different with regard to sex, age, steroid usage, lung volumes (VC, ERV, IC), or lung function (FEV$_1$% predicted). A methacholine-induced increase of more than 50% in Rrs could not be reached in all patients. This occurred in 6 of 24 patients: 2 in the intact DI response group, and 4 in the impaired DI response group.

The challenge was then stopped if apparent breathlessness or wheezing occurred in combination with a further decrease in Xrs. FEV$_1$ dropped by more than 20% in all cases (Table 1). We calculated mean resistance and reactance over tidal inspirations (Rrs$_{insp}$, Xrs$_{insp}$) and tidal expirations (Rrs$_{exp}$, Xrs$_{exp}$) separately. However, the parameters showed the same results, indicating that deep inspiration and positive-pressure inflation altered both parameters in the same way. We have therefore only presented the results of Rrs$_{exp}$ and Xrs$_{exp}$.

**Baseline measurements.** Baseline Rrs$_{exp}$ and Xrs$_{exp}$ were not significantly different between the groups at both visits ($P > 0.1$). Active deep inspiration significantly decreased Rrs$_{exp}$ at baseline in the intact DI response group (mean change $\pm$ SE: $-0.12 \pm 0.06$ cmH$_2$O·l$^{-1}$·s, $P = 0.04$) but not in the impaired DI response group ($+0.05 \pm 0.10$ cmH$_2$O·l$^{-1}$·s). Positive-pressure inflation had no effect on baseline Rrs$_{exp}$ in both groups ($P = 0.9$). Xrs$_{exp}$ was not significantly changed by either deep inspiration or positive-pressure inflation ($P > 0.2$).

**Methacholine-induced changes.** Methacholine significantly increased Rrs$_{exp}$, and decreased Xrs$_{exp}$, in both groups ($P < 0.01$; Fig. 4, A and B) at both visits. Both Rrs$_{exp}$ and Xrs$_{exp}$ were not significantly different between the groups following methacholine inhalation before deep inspiration or positive-pressure inflation ($P > 0.11$). The changes in Rrs$_{exp}$ and Xrs$_{exp}$ by methacholine and deep inspiration or positive-pressure inflation are summarized in Table 2.

**Active deep inspiration.** Active deep inspiration significantly decreased Rrs$_{exp}$ in the intact DI response group ($P = 0.003$, Fig. 4A) but not in the impaired DI response group ($P = 0.9$), which confirmed the findings from the screening visit. Also the change in Rrs$_{exp}$ by active deep inspiration was significantly larger in the intact DI response group compared with the impaired DI response group ($P < 0.01$), which resulted in a significantly lower Rrs$_{exp}$ during the three tidal expirations following the active deep inspiration in the intact DI response group ($P < 0.01$). Interestingly, Xrs$_{exp}$ was significantly increased by active deep inspiration in both groups ($P < 0.02$;
positively by positive-pressure inflation was significantly different between the groups (*P = 0.02), and the change induced by the positive-pressure inflation was not significantly different between the groups (P = 0.8).

Also, Xrsexp was significantly increased by positive-pressure inflation in both groups (P < 0.01; Fig. 4B) with no significant differences between the groups. Notably, the change induced in Xrsexp by the positive-pressure inflation was significantly larger than the change induced by active deep inspiration (P = 0.002) in the impaired DI response group, but not in the intact DI response group (P = 0.18) (Table 3).

The changes in Xrsexp induced by both active deep inspiration and positive-pressure inflation were not significantly different between the groups (P = 0.38). Also in the impaired DI response group no significant difference was seen in the change induced in Xrsexp by either active deep inspiration or positive-pressure inflation (P = 0.48).

Inspiratory volumes. VC, ERV, and IC were measured at baseline to calculate the volume to be inflated by the machine. Also, the actual inspired volume during both the active and positive-pressure inflation was measured. Using these values...
we calculated the percentage inspired volume of baseline inspiratory capacity during the maneuvers following methacholine inhalation. The percentage inspiratory volume of the active deep inspiration following methacholine inhalation was significantly lower in the impaired DI response group (mean ± SD: 71 ± 13%) compared with the intact DI response group (82 ± 12%, \( P = 0.027 \)) and was significantly increased by positive-pressure inflation (mean change ± SD: 15 ± 14%; \( P = 0.011 \)). Notably, although the reduction in Rrs exp was not related to the percentage inspiratory volume (\( P > 0.1 \); Fig. 5), the increase in percentage inspiratory volume by positive-pressure inflation correlated with the increase in reduction of Rrs exp by positive-pressure inflation (\( P < 0.01 \); Fig. 6).

**DISCUSSION**

This study shows that airways obstruction can be reduced by positive-pressure inflation in the lungs in asthma. Interestingly, this could also be achieved in patients with asthma who were not capable of reducing respiratory resistance by an active deep inspiration. These results suggest that influencing transpulmonary pressures by mechanical inflation of the lung can restore the beneficial bronchodilatory effects of lung inflation in patients with asthma.

To our knowledge this is the first study that used a computer-controlled syringe to inflate the lungs of conscious subjects in the upright position, and at the same time continuously measure the change in airways obstruction by lung inflation by the positive-pressure inflation. The mean reduction in Rrs exp in all patients by the active deep inspiration was 0.7 cmH2O l/s, which is in line with our previous data measured by FOT showing a reduction of 0.6 cmH2O l/s (44). Our data further extend the findings by Burns and Gibson (12, 19), who showed that deep inspiration through an added resistance, compared with a regular deep inspiration, resulted in lower airway conductance in patients with asthma, but not in healthy subjects. They proposed that inflation by positive pressure could prevent the occurrence of edema. And indeed, positive-pressure inflation of the lungs resulted in an improvement of bronchodilation in these patients with asthma.

In our study we included 24 patients with mild to moderate persistent asthma. However, only in 12 patients was Rrs exp

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**Table 2. Rrs and Xrs values during tidal breathing and deep inspiration or positive-pressure inflation**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-methacholine</th>
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<tbody>
<tr>
<td></td>
<td>Intact DI</td>
<td>Impaired DI</td>
</tr>
<tr>
<td></td>
<td>ADI PPI</td>
<td>ADI PPI</td>
</tr>
<tr>
<td>3 Tidal exp (pre-DI)</td>
<td>3.5±0.3 3.6±0.3</td>
<td>4.3±0.5 4.2±0.4</td>
</tr>
<tr>
<td>At TLC</td>
<td>1.7±0.3</td>
<td>1.4±0.1</td>
</tr>
<tr>
<td>At FRC (post-DI)</td>
<td>2.7±0.2 2.9±0.3</td>
<td>3.1±0.3 3.5±0.3</td>
</tr>
<tr>
<td>3 Tidal exp (post-DI)</td>
<td>3.4±0.3 3.6±0.3</td>
<td>4.3±0.4 4.2±0.4</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. All the Rrs and reactance of the respiratory system (Xrs) data measured at baseline and following methacholine inhalation (Post-methacholine), during active deep inspiration (ADI) and positive-pressure inflation (PPI), are shown for each group separately. Rrs at total lung capacity (TLC) could not be measured during PPI due to valve switching at that time point. Exp, expiration; FRC, functional residual capacity; pre-DI, before deep inspiration; post-DI, after deep inspiration.

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**Table 3. Changes in Rrs and Xrs induced by methacholine and deep inspiration**

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<thead>
<tr>
<th></th>
<th>ADI PPI</th>
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<tbody>
<tr>
<td></td>
<td>Rrs exp Xrs exp</td>
<td>Rrs exp Xrs exp</td>
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<tr>
<td>Intact DI response group</td>
<td></td>
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<tr>
<td>Change by methacholine</td>
<td>2.1±0.3 -1.8±0.3</td>
<td>2.4±0.2 -2.0±0.4</td>
</tr>
<tr>
<td>Change by DI</td>
<td>-1.0±0.3* 1.0±0.2</td>
<td>-0.6±0.2 0.9±0.3</td>
</tr>
<tr>
<td>Impaired DI response group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change by methacholine</td>
<td>1.9±0.3 -2.9±0.5</td>
<td>2.3±0.3 -3.0±0.5</td>
</tr>
<tr>
<td>Change by DI</td>
<td>0.03±0.2 0.8±0.3</td>
<td>-0.6±0.1 0.9±0.2</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE in cmH2O l/s. Rrs exp, Rrs measurements during tidal expiration; Xrs exp, Xrs measurements during tidal expiration. The change in Rrs exp by ADI was significantly larger in the intact DI response group compared with the impaired DI response group (*\( P = 0.006 \)). The change in Rrs exp by PPI was significantly larger than by ADI in the impaired DI response group (†\( P = 0.002 \)).
significantly reduced by active deep inspiration. We questioned whether this difference was due to either limited dilation of the airways or to a difference in the response of the airways to stretch. Therefore, we calculated the Rs at the TLC and FRC level. We found that Rs at TLC was not significantly different between the groups (mean ± SE: impaired DI response group 2.1 ± 0.2 cmH2O·L−1·s; intact DI response group 1.9 ± 0.1 cmH2O·L−1·s; P = 0.6), but tended to be higher at FRC in the impaired DI response group (3.8 ± 0.1 vs. 3.5 ± 0.4 cmH2O·L−1·s; P = 0.09). Following active deep inspiration Rs was significantly higher in the impaired DI response group (Table 2). This suggests that positive pressure and active deep inspiration dilated the airways to the same extent, but following active deep inspiration airways reconstricted more in the patients form the impaired DI response group.

Our data are in line with the results by Brown et al. (10) using high-resolution CT scans. They demonstrated that distension of constricted airways (>3 mm) by deep inspiration is not significantly different between healthy subjects and patients with mild asthma. However, following deep inspiration, the airways of healthy subjects remained dilated, whereas bronchoconstriction occurred in the asthmatic patients. These data, together with ours, suggest that the airway-parenchyma interdependence is not the reason for impaired bronchodilation following deep inspiration in patients with mild asthma. Other studies that used the FOT also demonstrated rapid renarrowing of airways following deep inspiration in mild asthma (38). A reduction in dilation of airways was only demonstrated in severe asthma (26). Therefore, airway distension during deep inspiration may become impaired with increasing asthma severity, whereas the airway response following deep inspiration is already impaired in mild asthma. This is also observed with the loss of bronchoprotection (41, 43); therefore these two phenomena could clearly be linked.

We succeeded in safely inflating the airways of conscious sitting patients with a volume and inspiration time specific for each patient, and measured Rs and Xrs continuously during these measurements. We used 8 Hz to measure impedance of the respiratory system, because this is close to the resonance frequency (34) and thus would represent airway caliber predominantly. Respiratory resistance is frequency dependent. At lower frequencies (0.1–2 Hz) inhomogeneity and tissue resistance may increasingly affect impedance (constant-phase model) (24). However, these frequencies are too close to the breathing frequency. The changes in RsXexp and Xrsexp by deep inspiration and positive-pressure inflation were different. Possibly, the changes in Xrsexp represent opening of closed airways (4, 14) or a change in compliance of the airway wall (36).

Our data are in line with the results by Brown et al. (10) for the reduction in Rsxexp and percentage inspiratory volume by positive-pressure inflation. We calculated the changes in % inspiratory volume (of baseline inspiratory capacity) and bronchodilation (reduction in Rsxexp) as induced by positive-pressure inflation compared with active deep inspiration. This figure shows the correlation between the changes in the percentage inspiratory volume and the changes in bronchodilation (reduction of Rsxexp) (Spearman rho = 0.6, P = 0.04; ρ = −0.029x + 0.151). Thus an increase in the percentage inspiratory volume by positive-pressure inflation was associated with more bronchodilation.
be due to leakage of air between the lips and mouth piece, early start of the apparatus, or an increased ERV. Surprisingly, the positive-pressure inflation actually reached a higher percentage of baseline IC than an active deep inspiration in the impaired DI response group. Therefore, we do believe that the inflated volume was enough to dilate the airways adequately.

How could positive-pressure inflation of the lungs induce bronchodilation in patients who cannot achieve this by an active deep inspiration? First, positive-pressure inflation may have opened closed airways that could not be opened by active deep inspiration (3, 29). Indeed, the improvement in reduction of airways obstruction by positive-pressure inflation over active deep inspiration was related to an increase in the percent inspired volume (Fig. 6). However, the reduction in $R_{nexp}$ by active deep inspiration was not related to the percentage inspired volume. In addition, both active deep inspiration and positive-pressure inflation led to a significant increase in $R_{nexp}$ in the impaired DI response group. Both observations may therefore not represent a causal relationship, but parallel consequences of the positive-pressure inflation. However, in both cases increased inspired volume by positive-pressure inflation may have led to an increase in tethering of the alveolar attachments, thereby improving the distension of the intraparenchymal airways.

On the other hand, positive-pressure inflation may have led to an increase in stretch of smooth muscle within the airway wall. Using high-resolution CT scans Brown and Mitzner (8) showed in dogs that airways, with increased smooth muscle tone, cannot be dilated to their maximal diameter by transpulmonary pressures of up to 25 cmH₂O. This suggests that under physiological conditions it may be impossible to stretch constricted airways to the maximal diameter. This may be augmented by increased stiffness of the airway wall in patients with asthma as a result of chronic inflammation and remodeling (5). Many in vitro and in vivo animal studies have shown that length oscillations of smooth muscle cells are necessary to reduce stiffness and contractility of the cells (18, 22, 23). Positive-pressure inflation may have induced greater stretching forces on the airways, and thereby increased stretch of smooth muscle cells and thus reduced airway wall stiffness.

What may be the clinical implication of our study? Although we developed the ALFG in an experimental setting, noninvasive mechanical ventilation is a realistic treatment option in asthma at the emergency department (15, 31, 46). Especially during exacerbations of asthma it has been shown that deep inspirations can induce bronchoconstriction (28). Whether this is due to altered smooth muscle function that further constricts on stretch, or to acute inflammatory edema enhanced by large subatmospheric pressures during deep inspiration, remains unclear. However, in both conditions occasional inflation of the lungs (mimicking a deep inspiration) may perturb the ongoing pathophysiological process and act synergistically with pharmacological bronchodilators to reduce the airway narrowing (21). In the intensive care setting is has been shown that high-volume ventilation recruits closed airways, and prevents closure in combination with positive end-expiratory pressures at the mouth (1, 19, 20). Further studies are required before the use of positive-pressure deep inspirations could be implemented as an actual additional treatment option in the clinical setting.

In conclusion, positive-pressure inflation of the lungs can significantly enhance the reduction in airways obstruction compared with active deep inspiration in patients with asthma. In addition, the inspired volume during the active deep inspiration was significantly lower in patients who were not capable of reducing airways obstruction by deep inspiration compared with patients with an intact bronchodilatory effect of deep inspiration. This suggests that the tethering forces of the parenchyma during active deep inspiration, possibly in relation to the magnitude of the inspired volume, are not strong enough to adequately stretch the airway wall, which may be overcome by positive-pressure inflation.

**REFERENCES**


**GRANTS**

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AIRWAY DILATION BY POSITIVE-PRESSURE INFLATION IN ASTHMA


