Improvement in Bronchodilation Following Deep Inspiration After a Course of High-Dose Oral Prednisone in Asthma*

Annelies M. Slats, MD; Jacob K. Sont, PhD; Rik H.C.J. van Klink, MD; Elisabeth H.D. Bel, MD; and Peter J. Sterk, PhD

Background: Bronchodilation following deep inspiration is usually impaired in patients with asthma. This might be due to changes in airway mechanics in the presence of inflammation or structural changes within the airways. Although inhaled corticosteroid treatment has been shown to improve airway responses to deep inspiration in patients with asthma, airway inflammation can persist despite inhaled corticosteroid treatment, and thus could still influence the airway mechanics during deep breaths. We hypothesized that oral steroid treatment further optimizes deep inspiration-induced bronchodilation in clinically stable asthmatic patients who are receiving therapy with inhaled corticosteroids.

Methods: Twenty-four atopic patients with mild-to-moderate persistent asthma (FEV₁, > 70% predicted; provocative concentration of methacholine causing a 20% fall in FEV₁ [PC₂₀], < 8 mg/mL), who were treated with 250 to 2,000 μg of beclomethasone-dipropionate or equivalent, participated in a parallel-design, double-blind study. Before and after treatment with 0.5 mg/kg/d prednisone or placebo for 14 days, a methacholine challenge was performed. Deep inspiration-induced bronchodilation was measured by the ratio of flow at 40% of FVC on the flow-volume curve after maximal inspiration/flow at 40% of FVC on the flow-volume curve after partial (60% of FVC) inspiration (M/P ratio).

Results: The M/P ratio significantly increased from a mean of 1.31 (range, 1.0 to 1.7) to 1.49 (range, 1.1 to 2.3) in the prednisone group. Interestingly, the improvement in the M/P ratio did not correlate with an accompanying significant increase in PC₂₀ for methacholine (mean change, 1.02; SD doubling dose, 0.97) and a decrease in exhaled nitric oxide (mean change, 14 parts per billion [ppb]; SD, 33.4 ppb).

Conclusions: Systemic antiinflammatory treatment in addition to maintenance therapy with inhaled corticosteroids increases bronchodilation by deep inspiration in patients with mild-to-moderate persistent asthma. This suggests that residual inflammation impairs airway mechanics in asthma patients.

(CHEST 2006; 130:58–65)

Key words: airway inflammation; bronchial hyperreactivity; deep inspiration-induced bronchodilation; glucocorticoid treatment; nitric oxide; prednisone

Abbreviations: M/P ratio = ratio of flow at 40% of FVC on the flow-volume curve after maximal inspiration/flow at 40% of FVC on the flow-volume curve after partial (60% of FVC) inspiration; Mslope = slope of the linear regression line of all values of flow at 40% of FVC on the flow-volume curve after partial (60% of FVC) inspiration against all values of flow at 40% of FVC on the flow-volume curve after maximal inspiration during the challenge test; NO = nitric oxide; PC₂₀ = provocative concentration of a substance causing a 20% fall in FEV₁; PC₄₀V₄₀M = provocative concentration of a substance causing a 40% fall in partial flow at 40% of FVC; ppb = parts per billion; TLC = total lung capacity; V₄₀M = flow at 40% of FVC on the flow-volume curve after maximal inspiration; V₄₀P = flow at 40% of FVC on the flow-volume curve after partial (60% of FVC) inspiration

Asthma is a chronic inflammatory disorder of the airways, which is associated with excessive airway narrowing in response to stimuli that have no or little effect on healthy subjects. Interestingly, the degree of airway narrowing appears to be related to the response of the airways to deep inspiration.1 In healthy subjects deep inspirations can protect against airway narrowing (bronchoprotection) and also can

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response of the airways to deep inspiration in asthma patients have yet to be unraveled, but seem to be a key for understanding the pathophysiology of the disease and possibly for the development of truly effective therapy.

The uncoupling of the mechanical airway-parenchyma interdependence has been hypothesized as one of the mechanisms that is responsible for the impaired responses of the airways to deep inspiration in asthma patients. Uncoupling can be a result of inflammatory changes within the airways, such as edema, thereby thickening the peribronchial airway wall and thus decreasing the radial forces acting on the airways during a deep inspiration. Indeed, some studies have shown beneficial effects of antiinflammatory treatment on the bronchodilatory effect of a deep inspiration. Systemic corticosteroid treatment of spontaneous asthma exacerbations improved the airway responses to deep inspiration as lung function recovered. Treatment with inhaled corticosteroids, on the other hand, improved deep inspiration-induced bronchodilation in steroid-naïve patients with mild asthma in two studies but had no effect on bronchodilation following deep inspiration in a recent article. It has been previously shown that airways inflammation can persist in asthmatic patients despite treatment with inhaled corticosteroids. It may therefore not be surprising that deep inspiration-induced bronchodilation is still deficient in some asthmatic patients whose conditions are being clinically well-controlled with inhaled steroid therapy.

We hypothesized that systemic antiinflammatory therapy, when added to regular treatment with inhaled corticosteroids, reduces any ongoing inflammation in clinically stable patients with persistent asthma, and therefore optimizes the bronchodilatory effect of deep inspiration. The aim of this study was to examine the effect of a course of high-dose oral prednisone on the degree of deep inspiration-induced bronchodilation at a given level of airway narrowing in patients with mild-to-moderate asthma who were already treated with inhaled steroids. In order to estimate the effect of the treatment on airway inflammation, which is a noninvasive marker of airway inflammation, exhaled nitric oxide (NO) was added as a secondary outcome parameter.

**Materials and Methods**

**Subjects**

Twenty-four nonsmoking, atopic subjects with mild-to-moderate persistent asthma, according to Global Initiative for Asthma guidelines, participated in this study. All subjects had experienced symptoms of episodic chest tightness or wheezing within the previous 12 months, had a baseline FEV₁ of >70% of predicted, and had a provocative concentration of methacholine causing a 20% fall in FEV₁ (PC20) of <8 mg/mL. All patients were atopic, which was determined by a positive skin-prick test (wheal size, ≥3 mm) to ≥1 of 10 common airborne allergen extracts (ALK; Abello; Nieuwegein, the Netherlands), and all patients were asked to avoid overt allergen exposure during the study. The patients were clinically stable, indicating that there had been no change in their clinical condition or medication use within the previous 6 weeks. They were all receiving inhaled corticosteroid treatment (i.e., beclomethasone-dipropionate, 500 to 2,000 µg daily or equivalent) in combination with short-acting or long-acting β₂-agonists and had no history of a recent (i.e., ≤2 weeks) upper respiratory tract infection or other relevant diseases. None of the subjects had used oral corticosteroids within 3 months prior to the study. The patient characteristics are shown in Table 1. The study was approved by the institutional review board, and the subjects gave their written consent before entering the study.

**Study Design**

The study had a placebo-controlled, double-blind, parallel design. The 24 patients were randomly assigned to receive either prednisone treatment or placebo. The patients received therapy with prednisone, 0.5 mg/kg/d (rounded to the nearest tenth) once daily for 14 days, in addition to their regular inhaled corticosteroid treatment (i.e., beclomethasone-dipropionate). The study consisted of the following two visits: visit 1 at day 0; visit 2 at day 14 or 15. On both visits, the Juniper Asthma Control Questionnaire, exhaled NO level, FEV₁, partial and maximal flow-volume curves, and airway responsiveness to methacholine were measured. The degree of bronchodilation following deep inspiration was measured at baseline and at a given level of airway narrowing in response to methacholine. All tests were performed after adequately stopping bronchilator therapy (for >8 h for short-acting β₂-agonists and >24 h for long-acting β₂-agonists).

**Maximal and Partial Flow-Volume Curves**

The effect of a deep inspiration on airways obstruction was measured by partial and maximal expiratory flow-volume curves. First, baseline FVC was measured. The mean of three
technically satisfactory FVC measurements was used to calculate the starting point of the partial flow-volume curve throughout all measurements during that visit, including the methacholine challenge. Since total lung capacity (TLC) does not change during a methacholine challenge, this point was used to calculate 60% or 40% of FVC above the baseline residual volume. Each measurement was therefore preceded by an inhalation to TLC. Forty-five seconds after inhaling to TLC, the patients performed a forced expiratory maneuver starting at 60% of baseline FVC (partial flow-volume curve), marked off from TLC, directly followed by a forced expiratory maneuver starting from TLC (maximal flow-volume curve). Expiratory flow was measured at 40% of the baseline FVC (marked off from TLC) on both the maximal flow-volume curve (V40M) and partial flow-volume curve (V40P). The effect of a deep inspiration on airways obstruction was expressed as the ratio between V40M and V40P (M/P ratio). An M/P ratio of >1 indicates bronchodilation following deep inspiration, as the flow on the curve after inspiration to TLC is higher than the flow on the curve after a partial inspiration, whereas an M/P ratio of <1 indicates bronchoconstriction. The values of V40M and V40P at a 40% fall in V40P were obtained by linear interpolation between the values before and after a 40% fall in V40P, and the M/P ratio was calculated from these interpolated values. MPslope was determined as slope of the linear regression line of all values of flow at 40% of FVC on the flow-volume curve after partial (60% of FVC) inspiration against all values of flow at 40% of FVC on the flow-volume curve after maximal inspiration during the challenge test.

**Airway Hyperresponsiveness**

Methacholine challenge was performed by a standardized methodology, using methacholine bromide in a normal saline solution.Serial double concentrations of methacholine (0.15 to 40 μmol/L) were aerosolized (DeVilbiss; Somerset, PA) and were inhaled by tidal breathing for 2 min at 5-min intervals with the nose clipped until FEV1 dropped 20% from baseline. The response was expressed as the PC20 and as the provocative concentration of methacholine causing a 40% fall in flow of the partial flow-volume curve at 40% of FVC (PC40V40P).

**Exhaled NO Measurements**

Exhaled NO was measured online with an expiratory flow rate of 50 mL/s according to American Thoracic Society guidelines and European Respiratory Society, and was analyzed with a chemiluminescence analyzer (NIOX; Aerocrine AB; Solna, Sweden). NO concentrations were determined at a 5-s plateau and

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**Table 1—Patient Characteristics and Posttreatment Values of FEV1, Airway Hyperresponsiveness, M/P Ratio, and Exhaled NO Levels**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline</th>
<th>Posttreatment</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>27.6 (7.3)</td>
<td>0.8 (0.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>Asthma Control Questionnaire score</td>
<td>1.1 (0.6)</td>
<td>91.8 (14.0)</td>
<td>0.36</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>90.1 (13.7)</td>
<td>0.64 (1.76)</td>
<td>0.004</td>
</tr>
<tr>
<td>PC20, mg/mL</td>
<td>0.24 (1.04)</td>
<td>0.43 (1.53)</td>
<td>0.07</td>
</tr>
<tr>
<td>PC40V40P, mg/mL</td>
<td>At baseline‡</td>
<td>1.12 (0.9–1.6)</td>
<td>1.14 (0.8–1.7)</td>
</tr>
<tr>
<td>M/P ratio</td>
<td>At PC40V40P‡</td>
<td>1.31 (1.0–1.7)</td>
<td>1.49 (1.1–2.3)</td>
</tr>
<tr>
<td>Exhaled NO,§ ppb</td>
<td>At PC20‡</td>
<td>1.71 (1.2–2.9)</td>
<td>1.81 (1.1–3.0)</td>
</tr>
<tr>
<td></td>
<td>MPslope</td>
<td>0.89 (0.23)</td>
<td>0.87 (0.30)</td>
</tr>
<tr>
<td>Placebo group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
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<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>31.6 (11.6)</td>
<td>1.0 (0.6)</td>
<td>0.7</td>
</tr>
<tr>
<td>Asthma Control Questionnaire score</td>
<td>1.0 (0.6)</td>
<td>85.6 (11.2)</td>
<td>0.20</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>87.6 (8.7)</td>
<td>1.75 (1.75)</td>
<td>0.10</td>
</tr>
<tr>
<td>PC20, mg/mL</td>
<td>0.74 (1.91)</td>
<td>1.29 (1.29)</td>
<td>0.43</td>
</tr>
<tr>
<td>PC40V40P, mg/mL</td>
<td>At baseline‡</td>
<td>1.19 (1.0–1.6)</td>
<td>1.15 (1.0–1.3)</td>
</tr>
<tr>
<td>M/P ratio</td>
<td>At PC40V40P‡</td>
<td>1.45 (1.1–1.9)</td>
<td>1.41 (1.1–1.9)</td>
</tr>
<tr>
<td></td>
<td>At PC20‡</td>
<td>1.59 (1.2–3.0)</td>
<td>1.57 (1.2–2.9)</td>
</tr>
<tr>
<td>Exhaled NO,§ ppb</td>
<td>MPslope</td>
<td>0.97 (0.23)</td>
<td>0.94 (0.23)</td>
</tr>
</tbody>
</table>

*Values are given as the mean (SD), unless otherwise indicated.
†Values are given as the geometric mean (SD in doubling doses).
‡Values are given as the geometric mean (range).
§Values are given as the median (range).
were expressed as parts per billion (ppb). During the measurements the subject inspired “NO-free” air (ie, NO level, < 2 ppb). Three successive recordings were made, and the mean value was used in the analysis.

Statistical Analysis

The sample size of 12 patients per group was based on previous data from our laboratory with regard to partial and maximal flow-volume curves, allowing the detection of a change in the M/P ratio of 0.2 within and between groups, if \( \alpha = 0.05 \) and \( 1 - \beta = 0.80 \). M/P ratios and PC\(_{20}\) values were log-transformed before analysis. Within-group and between-group differences were analyzed using Student paired and unpaired \( t \) tests. NO values were tested by the Wilcoxon signed rank test and the Mann-Whitney \( U \) test. Pearson correlation was used to examine the relationship between the changes in M/P ratio and PC\(_{20}\) and PC\(_{40V_{40P}}\). Spearman rank correlation was used to examine the correlation between the changes in exhaled NO and M/P ratio, PC\(_{20}\), and PC\(_{40V_{40P}}\). A \( p \) value of < 0.05 was considered to be statistically significant.

Results

All patients completed the study. There were no baseline differences between the two treatment groups with respect to age, sex, medication use, FEV\(_1\), exhaled NO levels, and M/P ratio (Table 1). However, there was a significant difference in the PC\(_{40V_{40P}}\) for methacholine at baseline between the two groups (\( p = 0.016 \)), and a trend toward a difference in the PC\(_{20}\) for methacholine (\( p = 0.057 \)). Furthermore, there was no significant difference in the Asthma Control Questionnaire score between the groups, which ranged from 0.3 to 2. According to the Global Initiative for Asthma classification, there were three patients with mild persistent asthma, six patients with moderate persistent asthma, and three patients with severe persistent asthma in the prednisone group, and there were five patients with mild persistent asthma, four patients with moderate persistent asthma, and three patients with severe persistent asthma in the placebo group.

The M/P ratio at a 40% fall in \( V'_{40P} \) improved significantly in the prednisone group (geometric mean at baseline, 1.41; range, 1.1 to 1.9) after treatment (geometric mean, 1.49; range, 1.1 to 2.3; \( p = 0.006 \)). No significant change was observed in the placebo group (geometric mean at baseline, 1.45; range, 1.1 to 1.9) after treatment (geometric mean, 1.41; range, 1.1 to 1.9; \( p = 0.46 \)). Moreover, the change in M/P ratio at a 40% fall in \( V'_{40P} \) in the prednisone group was significantly different from the change in M/P ratio in the placebo group (\( p = 0.006 \)) [Fig 1, Table 2].

![Figure 1](image)

**Figure 1.** Individual values of M/P ratio measured at a 40% fall in \( V'_{40P} \) to methacholine before (pre) and after (post) 2 weeks of treatment in the placebo-treated and prednisone-treated group. The data are expressed as the ratio between the flow on the maximal and partial flow-volume curves at 40% of FVC. The geometric mean is depicted as a horizontal bar. At baseline, there was no difference in the M/P ratio between the treatment groups. In the prednisone group, the M/P ratio improved significantly (\( p = 0.006 \)). Furthermore, the change in M/P ratio was significantly different between the prednisone-treated and the placebo-treated groups (\( p = 0.006 \)).

The PC\(_{20}\) increased significantly in the prednisone group compared to baseline (mean change in doubling dose, 1.02; SD, 0.97; \( p = 0.004 \)) [Fig 2, left, A], whereas no significant changes were found in the placebo group. Furthermore, the PC\(_{40V_{40P}}\) increased in the prednisone group (mean change in doubling dose, 0.84; SD, 1.21), but this did not reach significance (\( p = 0.07 \)) [Fig 2, right, B]. Moreover, the changes in hyperresponsiveness, both the PC\(_{20}\) and PC\(_{40V_{40P}}\), were significantly different between the treatment groups (Table 2).

Two weeks of treatment did not significantly change the level of exhaled NO either within the

**Table 2—Changes in Airway Hyperresponsiveness, Degree of Bronchodilation Following Deep Inspiration at a Given Level of Airway Obstruction, and Exhaled NO Values Between the Prednisone-Treated Group and the Placebo-Treated Group**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Prednisone</th>
<th>Placebo</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta PC_{20} )†</td>
<td>1.02 (0.97)</td>
<td>-0.44 (0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>( \Delta PC_{40V_{40P}} )‡</td>
<td>0.84 (1.21)</td>
<td>-0.29 (1.21)</td>
<td>0.05</td>
</tr>
<tr>
<td>( \Delta M/P ) ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At PC(<em>{20})( V'</em>{40P} )‡</td>
<td>1.14 (0.95–1.45)</td>
<td>0.97 (0.74–1.17)</td>
<td>0.006</td>
</tr>
<tr>
<td>At PC(<em>{40V</em>{40P}})‡</td>
<td>1.06 (0.85–1.58)</td>
<td>0.98 (0.74–1.12)</td>
<td>0.31</td>
</tr>
<tr>
<td>( \Delta ) Exhaled NO, ppb</td>
<td></td>
<td>-14.0 (33.4)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Values are given as the mean change (SD), unless otherwise indicated.
†Values are given as the mean change (SD) in doubling dose.
‡Values are given as the fold change (range).
prednisone group (mean change, −14.0 ppb; SD, 33.4 ppb) or within the placebo-treated group (mean change, 9.7 ppb; SD, 12.8 ppb) [Table 2]. However, the changes in exhaled NO were significantly different between the two treatment groups (p = 0.03, Fig 3). Notably, within the prednisone group there were no significant correlations between the changes in M/P ratio at 40% fall in V/40P, and those in PC40V/40P and exhaled NO (p > 0.15) [Fig 4].

**Discussion**

The results of this study demonstrate that a course of high-dose oral prednisone therapy improves the degree of deep inspiration-induced bronchodilation at a given level of airways obstruction in stable patients with asthma who are receiving regular treatment with inhaled corticosteroids. It appears that this improvement is not related to concurrent reductions in airway hyperresponsiveness or to changes in the level of exhaled NO. These findings indicate that the degree of bronchodilation following a deep breath in clinically stable asthmatic patients is still impaired, presumably based on the level of residual airway inflammation while receiving regular treatment with inhaled corticosteroids. Our data suggest that the optimizing of deep inspiration-induced bronchodilation by the use of systemic steroids occurs partially independent of improvements in hyperresponsiveness and the level of exhaled NO.

To our knowledge, the improvement in M/P ratio in asthma patients by the use of systemic steroid treatment on top of maintenance therapy with inhaled steroids is a novel finding. The present results extend the previous findings by Corsico et al12 and Bel et al13 who observed an increase in deep inspiration-induced bronchodilation after 4 weeks of treatment with inhaled corticosteroids in steroid-naïve asthmatic patients. However, recently Sciclone et al14 found no effect of inhaled corticosteroids on the bronchodilatory effect of a deep inspiration in a study with asthmatic patients with mild-to-severe airway hyperresponsiveness. The methods of assessing the airway responses to deep inspiration differed among these three studies, as well as the dose and type of inhaled steroids used. In a post hoc analysis, we have also calculated the slope of the linear regression line of all values of flow at 40% of FVC on the flow-volume curve after partial (60% of FVC) inspiration against all values of flow at 40% of FVC.
on the flow-volume curve after maximal inspiration during the challenge test (MPslope), as introduced by Pellegrino et al,3 but found no significant differences within or between the groups after 2 weeks of treatment. This discrepancy might be explained by the fact that M/P ratio and MPslope represent different features, representing the level and relative change in deep breath responses, respectively.

Apparently, there is still significant room for improvement in the response of asthmatic airways to a deep breaths by adding systemic steroids to their regular controller medication therapy. This is also discernible from the changes in our secondary outcome parameters, which are in line with previous observations. The decrease in hyperresponsiveness achieved by prednisone therapy confirms the findings by Meijer et al26 in a group of asthmatic patients two thirds of whom were receiving therapy with inhaled steroids. In their study, this was accompanied by reductions in both the sputum and serum levels of eosinophils. Similarly, the reduction in exhaled NO by adding prednisone to maintenance therapy with inhaled steroids extends the findings by Payne et al27 in children with difficult asthma. Therefore, it appears that the deep inspiration-induced bronchodilation follows other functional characteristics in asthmatic patients in not being optimized by the currently recommended regular therapy.

In this study, we recruited patients with mild-to-moderate persistent asthma using inhaled corticosteroids as maintenance treatment.18 These patients are representative of a large group of patients who can reach adequate clinical control by using the currently recommended controller medication. The patients were selected based on the use of inhaled corticosteroids as part of their regular asthma treatment, and based on the fact that no change in clinical condition or medication use had occurred during the previous 6 weeks. As a result, the maintenance treatment in some patients included in the study may not have been optimal. However, at baseline there was no significant difference between the two groups in terms of Asthma Control Questionnaire score. Furthermore, there was a significant difference in airway hyperresponsiveness between the two treatment groups at baseline. However, the baseline PC20 and PC40V changed significantly after 2 weeks of treatment with pred-

![Figure 4. Relationship between the change in M/P ratio at a 40% fall in V₄₀P and (left, A) the change in PC₄₀V₄₀P (prednisone group, r = -0.44; p = 0.15; placebo group, r = -0.04; p = 0.91) and (right, B) the change in exhaled NO (prednisone group, r = 0.13; p = 0.73; placebo group, r = 0.07; p = 0.86). The absence of a relationship between the change in the bronchodilatory effect of a deep inspiration and airway hyperresponsiveness or exhaled NO suggests that these changes occur independently. ○ = placebo group; ● = prednisone group.](image-url)
nisonone, but not the M/P ratio at a 20% fall in FEV₁.

The difference between these two parameters is that the latter was based on a measurement of airway responsiveness that implicitly includes a deep breath. Inducing a fall in FEV₁ implies that the deep inspiration itself can no longer prevent the airways obstruction. Apparently, prednisone only increased deep inspiration-induced bronchodilation for a measure that was not directly preceded by a deep inspiration.

How can we interpret these results? Inflammation is thought to play a role in deep inspiration-induced bronchodilation by uncoupling the airways and the parenchyma as a result of airway wall thickening and/or peribronchial edema. Tidal breathing, and occasional deep inspirations, provide load fluctuations on airway smooth muscle that are necessary to keep the airway smooth muscle in a flexible and less contractile state. Glucocorticosteroids exert anti-inflammatory effects, resulting in decreased inflammatory cell counts in sputum, and bronchial biopsy specimens, and the inhibition of cytokine expression and production. Furthermore, steroids can decrease bronchial blood flow, particularly under inflammatory conditions, and they inhibit vascular permeability and edema in the capillaries and postcapillary venules. Therefore, the improvement in deep inspiration-induced bronchodilation observed in the present study could be a result of the effects of glucocorticosteroids on peribronchial inflammation and edema, thereby reducing airway wall thickness and restoring airway-parenchyma interdependence.

In the presence of inflammation, changes in the airway smooth muscle function itself may also play a role in the reduced airway response to deep inspiration in asthma. First, adjustment of the contractile apparatus of the airway smooth muscle cell to length changes (plasticity) enables the cell to optimize its contractility to the mechanical conditions under which it is activated. Second, an increase in shortening velocity enables the airway smooth cell to reshorten much faster after being stretched. In vitro studies have shown direct effects of corticosteroids on airway smooth muscle contractility. Airway smooth muscle cells exposed to tumor necrosis factor-α and interleukin-1β show an increased asthma-like contractility to a constrictor agent, which can be prevented by pretreatment with dexamethasone. Improvements in deep inspiration-induced bronchodilation could therefore also be a result of changes in airway smooth muscle function by corticosteroid treatment, reducing the force generation and recontraction after being stretched. However, since the change in deep inspiration-induced bronchodilation was not related to the change in airway responsiveness (ie, PC<sub>40</sub>V<sub>40</sub>P or PC<sub>20</sub>), one could speculate that prednisone therapy predominantly influenced the ability to stretch the airways or smooth muscle rather than restoring the effect of stretch on the contractility of the airway smooth muscle cell per se.

What are the clinical implications of this study? Patients with asthma, who are regularly treated with inhaled corticosteroids, can have residual airway inflammation that impairs the mechanical properties of the airways even during clinically stable episodes. This may have implications during exacerbations when physiologic protective mechanisms, such as deep inspiration-induced bronchodilation, become of vital importance. Patients with impaired airway responses to deep inspiration, although being clinically stable, may therefore be more at risk for the development of exacerbations. As airway responses to deep inspiration tend to be related to asthma severity and the severity of breathlessness, long-term studies are required in order to address the prognostic implications of impaired responses of the airways to deep inspiration in asthma patients.

We conclude that adding systemic antiinflammatory treatment to regular therapy with inhaled corticosteroids improves the dilation of preconstricted airways by deep inspiration in patients with mild-to-moderate persistent asthma. Since it is obvious that prednisone cannot be recommended as maintenance therapy in clinically stable asthma patients, other interventions specifically targeting the mechanisms of impaired deep-breath responses in asthma patients need to be explored.

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Chest 2006;130;58-65
DOI: 10.1378/chest.130.1.58
This information is current as of August 1, 2006

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