Inhaled β₂-Agonist and Positive Expiratory Pressure in Bronchial Asthma

Influence on Airway Resistance and Functional Residual Capacity

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Introduction: Positive expiratory airway pressure seems to dilate narrowed or collapsed airways, but this may be accompanied by a maintained and harmful increase in resting lung volume in obstructive pulmonary disease.

Purpose: To evaluate the influence of inhaled terbutaline and positive expiratory pressure (PEP) on airway resistance (Raw) and functional residual capacity (FRC) in bronchial asthma.

Design: Randomized crossover design, single blind with regard to inhaled medication, open with regard to PEP (PEP can be felt).

Material and Methods: Ten patients with bronchial asthma inhaled placebo and terbutaline in doses of 0.125 mg, 0.5 mg, and 1.5 mg by spacer combined with a facemask, giving 0, 10, or 15 cm H₂O PEP on separate days. FRC and Raw were measured by body plethysmography before and after inhalations. Data were analyzed by analysis of variance with terbutaline dose and PEP as factor levels.

Results: The effect of terbutaline: Raw decreased significantly (p<0.0001) after 0.125 mg and 1.5 mg. The FRC did not change significantly. The effect of PEP: Raw decreased, but significantly only when the dose of 1.5 mg terbutaline was excluded from the analysis. Raw decreased with PEP 10 and 15 cm H₂O, mean 0.6 (95 percent CI: −1.1, −0.2) and 0.9 (95 percent CI: −1.3, −0.4) cm H₂O/L/s. The FRC did not change significantly with the PEP level.

Conclusion: PEP only had influence on Raw when insufficient doses of terbutaline were inhaled, whereas once an efficient dose of terbutaline was administered, significant bronchodilation was achieved with or without PEP. Positive expiratory pressure did not increase FRC.

(Chest 1993; 104:1108-13)

ANOVA = analysis of variance; CPAP = continuous positive airway pressure; CI = confidence interval; PEEP = positive end-expiratory pressure; PEFR = peak expiratory flow rate; PEP = positive expiratory pressure; PLB = pursed-lip breathing; Raw = airway resistance

In bronchial asthma the airways are obstructed due to increased bronchial muscle tone, inflammatory edema in the bronchial wall, and mucus in the airways lumen. During expiration positive pressure within the airways contributes to keep them open, but in diseases with airflow limitation, the airways tend to collapse during expiration. Airway collapse theoretically can be counteracted by externally applied expiratory positive pressure, which can be achieved in different ways: by pursed-lip breathing (PLB) used spontaneously by some patients with chronic obstructive pulmonary disease (COPD), or by mechanical devices such as positive end-expiratory pressure (PEEP) during mechanical ventilation, as continuous positive airway pressure (CPAP) during spontaneous breathing, and finally simple positive expiratory pressure (PEP) can be given by devices acting as resistance to flow of exhalation during spontaneous breathing. Since Barach and Swenson first introduced treatment with positive airway pressure, the possible beneficial and/or harmful effects of PLB, PEEP, CPAP, and PEP in diseases with airflow limitation have been a matter of controversy, and recently have gained renewed interest. Few controlled studies have been performed. The dilemma arises because positive expiratory airway pressure keeps the airways open and decreases airway resistance; however, this may be accompanied by an increase in resting lung volume, which might be harmful in patients whose lungs are already hyperinflated as in obstructive pulmonary disease.

If PEP decreases airway resistance, it may improve the effect of inhaled bronchodilator. In a crossover study, we showed that inhaled terbutaline combined with PEP improved peak expiratory flow rate (PEFR) compared with terbutaline alone and PEP alone in home treatment of bronchial asthma. A similar device was shown beneficial for inhalation of corticosteroid in treatment of recurrent wheezing in children.

With this background we found it of interest to study the effects of PEP combined with inhaled β₂-agonist on airway resistance and resting lung volume in patients with increased airway resistance due to bronchial asthma. To avoid the risk of bronchospasm or bronchodilation by procedures, including forced inspiration and expiration, we used the body plethysmographic determination of FRC and expiratory airway resistance (Raw) to measure the effects. In the present study we evaluated subtherapeutic and therapeutic doses of terbutaline combined with 0, 10, and
15 cm H₂O PEP.

**Material and Methods**

Fourteen polyclinic patients were included. All had a history of bronchial asthma, with wheezing and dyspnea relieved by bronchodilator, hyperresponsive airways, allergy, and/or eosinophilia. They were never-smokers or had stopped smoking for more than 5 years. They all needed daily bronchodilator treatment with β₂-agonist and/or oral theophylline, and all patients used daily inhaled corticosteroid. They had all previously showed an increase in forced expiratory volume in the first second (FEV₁) of at least 15 percent predicted after inhalation of 1.25 mg of terbutaline. On the study days, treatment with oral bronchodilators was withheld for 12 h and inhaled bronchodilator for 6 h before each study day commencing at 8 AM. Inhaled corticosteroid therapy was continued.

The study design was a randomized crossover trial. The study was single blind concerning inhaled medication, and open concerning PEP, because PEP can be felt. The patients were studied on 3 days separated by at least 72 h. On each study day, increasing doses of terbutaline, 0 mg (placebo), 0.125 mg, 0.5 mg, and 1.5 mg were given at 8:30 AM, 10:30 AM, 12:30 pm, and 2:30 PM. In random order, PEP was applied at pressure levels 0, 10, and 15 cm H₂O (PEP 0, PEP 10, and PEP 15) on separate days. Furthermore, the study was planned to include a fourth day on which placebo and PEP of 0 cm H₂O was given at the time points as above, except for the 1.5-mg terbutaline dose. This study day, however, could only be completed by a few patients, because of worsening of symptoms and lung function on that day.

The inhalation of terbutaline was performed through a cone spacer (Nebuhaler, Draco, Sweden) combined with a PEP mask (Astra-Meditec, Denmark; a Nebuhaler-PEPmask) (Fig 1). This consisted of a 750-ml volume cone spacer where the mouthpiece was removed and instead connected to the inspiratory tube of a one-way valve in a PEP mask. Connections with different diameters could be applied to the expiratory tube, thus creating a positive pressure only during expiration. Each inhalation was started with an inspiration followed by ten breaths through the device. The pressure achieved with the PEP mask is dependent on flow, so the participants were trained before the test to breathe through the device to achieve the intended pressure. Pressure was continuously monitored between the expiratory tube and the tube connection by a pressure transducer (ÄKH Medics Pressure Transducer, Århus, Denmark) connected to an XY-recorder (HP 7041 A, Hewlett Packard, Calif). This site was chosen for measurement to avoid leaks on the inspiratory tube.

The FRC and expiratory Raw were measured with constant-volume body plethysmography (Siregnost FD 91, Siemens, Germany) according to the recommendations from European Community for Coal and Steel Working Party. The patients were seated in the box with their nose clipped. Gas flow at the mouth measured by pneumotachograph (Fleisch, Switzerland) and box pressure was measured, and a minimum of three pressure-flow curves were obtained. Afterwards changes in box pressure were recorded as a function of changes in the mouth pressure measured when the airways were briefly closed off by a shutter. Again at least three curves were obtained. Measurements were done just before and after each inhalation. The patients were instructed to breathe at their usual frequency, around 20/min. All participants were familiar with the procedures in the body plethysmograph before entering the study. The mean value of three measurements was used in the calculations of Raw and FRC as recommended.

**Statistical Methods**

Analyses of variance (ANOVA) were used to analyze both the influence of terbutaline dose and PEP level and to avoid the risk of multiple tests of significance. Results are presented in mean and range or 95 percent confidence intervals (CI). If the CI for a difference does not include zero, the mean difference is significantly different from zero. The CI furthermore gives information about the magnitude of the difference. The data analysis from the day with repeated placebo inhalations was made separately because fewer patients completed this day. Based on calculations of type 2 error with 20 percent risk to overlook a true difference corresponding to one standard deviation, the study was planned to include 15 patients.

**Ethics**

The study was approved by the Ethical Committee of Aarhus and was in accordance with the Helsinki Declaration II. The patients consented after verbal and written information.

**Results**

Of the 14 patients included, 4 patients had severe exacerbation of their disease during the study days, probably because the doses of terbutaline during the initial hours were small, and the test procedures had to be interrupted. The four patients not completing the study had a mean age of 35 years (range, 18 to 55 years), FEV₁ of 1.73 L (0.85 to 3.05 L) corresponding to 51 percent (24 to 84 percent of predicted), and FEV₁/FVC = 0.45 (0.32 to 0.60). Of the remaining ten patients, one patient missed the day with PEP 10, and due to technical problems, the measurements after the two last doses on the day with PEP 10 are missing for another patient. Only five patients were able to perform the study day with placebo inhalations and PEP 0. Summary of the data for the ten patients completing the study is given in Table 1.

The actual pressure achieved was mean 10.6 and 16.0 cm H₂O on the day with PEP 10 and PEP 15 (Table 2). The total ranges of expiratory pressures are given for each patient, but the minimum and maximum values were reached only a few times, most often at the beginning of the inhalation procedure. On the day with PEP 0, the actual pressure measured was 0 cm H₂O, because it was measured at the expiratory side.
of the one-way valve. Functional residual capacity and Raw before each dose are shown in Table 3, and no differences were found between the 0, 10, and 15 PEP days.

The differences in FRC, FRC after minus FRC before each inhalation (ΔFRC) and in Raw, Raw after minus Raw before each inhalation (ΔRaw) on the study days are shown in Figures 2 to 4.

The results from the day with repeated placebo inhalations (Fig 2) are described separately: (1) no significant changes in FRC were found, but FRC tended to decrease after 1.5 mg terbutaline, and (2) Raw tended to increase during the day after the placebo inhalations, but decreased significantly after terbutaline 1.5 mg (mean ΔRaw = −5.2, CI = −7.1, −3.3 cm H₂O/L/s).

The results from the three study days are shown in Figures 3 and 4 and Table 4. From the ANOVA, the influence of the terbutaline dose and of the PEP level was analyzed.

**The Effect of Terbutaline**

Terbutaline had significant influence on ΔRaw (p<0.0001, ANOVA). This was mainly due to decrease in Raw after 0.125 mg with mean ΔRaw = −0.9 cm H₂O/L/s (CI = −1.4, −0.3) and 1.5 mg of terbutaline with mean ΔRaw = −1.9 cm H₂O/L/s (CI = −2.4, −1.3) (Table 4, Fig 3). These decreases were significant because zero was not included in the 95 percent CI for the differences. The mean decrease after 0.5 mg of terbutaline was minor and not significant (Table 4).

Terbutaline did not significantly influence ΔFRC (p = 0.75, ANOVA), but FRC decreased significantly after placebo (mean ΔFRC = −0.29 L, CI = −0.51,
Table 3—FRC and Raw Before Each Dose on the Study Days

<table>
<thead>
<tr>
<th></th>
<th>PEP 0 (Placebo)*</th>
<th>PEP 0</th>
<th>PEP 10</th>
<th>PEP 15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 5</td>
<td>n = 10</td>
<td>n = 9</td>
<td>n = 10</td>
</tr>
<tr>
<td>FRC, L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>4.08 (3.10-5.06)</td>
<td>4.30</td>
<td>4.20</td>
<td>3.65</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.34 (3.36-5.32)</td>
<td>3.79</td>
<td>3.69</td>
<td>3.69</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.24 (3.36-5.22)</td>
<td>3.90</td>
<td>3.86</td>
<td>3.54</td>
</tr>
<tr>
<td>1.500 mg terb</td>
<td>4.14 (3.16-5.12)</td>
<td>3.85</td>
<td>3.86</td>
<td>3.54</td>
</tr>
<tr>
<td>Raw, cm H$_2$O/L/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>8.3 (6.15-10.2)</td>
<td>6.6</td>
<td>7.0</td>
<td>6.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.9 (6.0-9.7)</td>
<td>6.5</td>
<td>6.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.1 (5.3-10.0)</td>
<td>6.1</td>
<td>7.8</td>
<td>6.7</td>
</tr>
<tr>
<td>1.500 mg terb</td>
<td>10.1 (8.5-12.0)</td>
<td>6.6</td>
<td>7.4</td>
<td>6.8</td>
</tr>
</tbody>
</table>

*Mean (95 percent confidence interval), PEP = positive expiratory pressure. PEP 0 = PEP of 0 cm H$_2$O; PEP 10 = PEP of 10 cm H$_2$O; PEP 15 = PEP of 15 cm H$_2$O. Terb = terbutaline. PEP 0 (placebo) refers to the study day with placebo inhalations except for the last dose; this day was not included in the analysis. One-way analysis of variance for PEP 0, 10, and 15 cm H$_2$O demonstrated no significant differences.

FRC = functional residual capacity; Raw = airway resistance.

− 0.08, Table 4), mainly with PEP 0.

The Effects of PEP

With PEP 10 and PEP 15, Raw decreased with mean ΔRaw − 0.6 cm H$_2$O/L/s (CI −1.1, −0.2), and mean ΔRaw − 0.9 cm H$_2$O/L/s (CI −1.3, −0.4) (Table 4), but these decreases were considerably smaller than the decrease after 1.5 mg of terbutaline. PEP 0 did not change Raw significantly, mean ΔRaw − 0.3 cm H$_2$O/L/s (CI −0.7, +1.7), and as − 0.7 is included in CI for ΔRaw after both PEP 10 and PEP 15, the differences in ΔRaw between the placebo levels were not statistically significant in the ANOVA (p = 0.15). The decrease in Raw with PEP 0 was mainly due to the pronounced decrease after 1.5 mg of terbutaline. On all study days there was a major and highly significant decrease in Raw after 1.5 mg of terbutaline (Fig 3), and when this dose was excluded from the ANOVA, ΔRaw was significantly different according to the PEP levels (p = 0.04, ANOVA).

With PEP 0 and PEP 10, FRC decreased with mean ΔFRC − 0.27 L (CI −0.45, −0.09) and with mean ΔFRC − 0.22 L (CI −0.42, −0.02) (Table 4), and after PEP 15, FRC tended to decrease but not significantly (ΔFRC − 0.12 L, CI −0.30, +0.07). Thus, overall FRC did not change significantly with PEP levels (p = 0.45, ANOVA) (Fig 4). It should be noted that the dose of 1.5 mg of terbutaline did not influence the pattern of ΔFRC. The largest increases in FRC seen in individual patients were 1.04 L without PEP (patient 3, after placebo), 0.45 L with PEP 10 (patient 7, after 0.125 mg of terbutaline), and 0.78 L with PEP 15 (patient 7, after 0.5 mg of terbutaline).

**DISCUSSION**

The interpretation of this study is complicated because it did not show a typical dose-response pattern with decreasing Raw after increasing doses of terbutaline. The 0.5-mg terbutaline dose did not decrease Raw significantly, whereas the doses of 0.125 and 1.5 mg did. The dose of 0.5 mg of terbutaline is recommended in treatment of stable bronchial asthma, but...
Table 4—Terbutaline Dose-Response and PEP Level-Response on Raw, FRC

<table>
<thead>
<tr>
<th>Dose</th>
<th>ΔRaw, cm H₂O/L/s</th>
<th>ΔFRC, L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>+0.4 (-0.1, +1.0)</td>
<td>-0.29 (-0.51, -0.08)</td>
</tr>
<tr>
<td>0.125 mg</td>
<td>-0.9 (-1.4, -0.3)</td>
<td>-0.14 (-0.36, +0.08)</td>
</tr>
<tr>
<td>0.500 mg</td>
<td>-0.1 (-0.7, +0.4)</td>
<td>-0.15 (-0.37, +0.01)</td>
</tr>
<tr>
<td>1.500 mg</td>
<td>-1.9 (-2.4, -1.3)</td>
<td>-0.21 (-0.43, +0.01)</td>
</tr>
<tr>
<td>PEP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>-0.3 (-0.7, +1.7)</td>
<td>-0.27 (-0.45, -0.09)</td>
</tr>
<tr>
<td>10</td>
<td>-0.6 (-1.1, -0.2)</td>
<td>-0.22 (-0.42, -0.02)</td>
</tr>
<tr>
<td>15</td>
<td>-0.9 (-1.3, -0.4)</td>
<td>-0.12 (-0.30, +0.07)</td>
</tr>
</tbody>
</table>

*ANOVA, mean and 95 percent confidence interval. PEP = positive expiratory pressure; Raw = airway resistance; FRC = functional residual capacity; ANOVA = analysis of variance; Δ = difference.

in the present study it did not relieve bronchospasm sufficiently, which indicates that bronchospasm was considerable. Bronchoconstriction probably was provoked by withdrawal of the usual morning dose of inhaled and oral bronchodilator and the bronchoconstriction apparently gradually worsened during the day, as indicated by the pattern of increasing Raw in the five patients given repetitive placebo doses. This could explain the paradox that the dose of 0.125 mg of terbutaline decreased Raw, whereas 0.5 mg of terbutaline did not. Clinically all patients worsened during the day, and 4 of the initial 14 patients could not accomplish the study due to worsening of their disease during the days. Furthermore, the hyperresponsiveness of the airways was reflected by the increases in Raw after the initial placebo inhalation and PEP 0, probably caused by a reaction to the propellants in the sprays. In summary, these patients with no or moderate chronic pulmonary obstruction shown by FEV₁ and FEV/FVC prior to the study had considerable bronchoconstriction on the study days. The purpose of this study, however, based on our previous observations in a home study of stable moderately severe bronchial asthma, was to evaluate the effects of PEP and inhaled β₂-agonist in airways with actual bronchoconstriction; thus, the airways had to be responsive and not stable.

In this study, minor decreases in Raw were observed with PEP 10 and 15. Although, the influence of PEP on Raw reached statistical significance only when 1.5 mg of terbutaline dose was excluded from the analysis. The influence of PEP on Raw was minor, and the influence of PEP level on ΔRaw was seen especially after inhalation of placebo and less clearly after 0.5 mg of terbutaline. With 1.5 mg of terbutaline, PEP did not further decrease Raw. The more pronounced decrease in Raw after 1.5 mg of terbutaline on the placebo day is explained by the gradual increase in Raw during the day. In summary, PEP had influence on Raw only when insufficient doses of terbutaline were inhaled, whereas once an efficient dose of terbutaline was administered, significant bronchodilation was achieved with or without PEP.

The decrease in Raw with PEP was not accompanied by a significant increase in FRC. On the contrary, we found a tendency toward decreasing FRC. Ten of the 14 patients completed the study. This increased the type 2 error from a planned 20 percent to 30 percent, and increased the risk to overlook a true difference in FRC. We chose not to include more patients in the study because of the withdrawal of several patients due to exacerbation of their asthma during the study days. The pronounced decrease in FRC after placebo on the day with PEP 0 was partly explained by two patients with particularly high FRC at the start of that study day showing great decreases after the initial inhalation.

Airway resistance and FRC might be different during the inhalation with PEP, but we were not able due to technical reasons to make measurements during the inhalation, and we found it of major interest to study the lasting effects after these treatments given during spontaneous breathing.

Only a few studies have been published concerning the effect of externally applied expiratory pressure on airway caliber and resting lung volume in obstructive lung diseases. Part of the studies concern PEEP during assisted or controlled mechanical ventilation of sedated and paralyzed patients. The airways in patients with COPD are characterized by regional differences in airway caliber. They have a tendency for airway closure and collapse during expiration to a greater extent than airways in healthy subjects. Positive end-

Figure 4. Difference in functional residual capacity, ΔFRC = FRC after-FRC before each dose; p = placebo. Mean and 95 percent confidence interval.

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expiratory pressure can dilate flow limited airways by increasing the airway pressure and recruit closed airways to participate in ventilation. These effects would decrease resistance without any appreciable increase in end-expiratory lung volume. Positive expiratory pressure might similarly decrease airway collapse during expiration, and our results point toward similar effects of PEP as the hypothesized effects of PEEP in COPD.

Continuous positive airway pressure giving both positive airway pressure during inspiration and expiration is used in spontaneous breathing. The first study of CPAP showed 1- to 2-mm increase in the widths of small and medium-sized bronchi revealed by contrast radiograph in seven patients with asthmatic dyspnea. Continuous positive airway pressure was given with inspiratory pressure of 5 cm H₂O and expiratory pressure of 8 cm H₂O and compared with no CPAP. In the 1960s, studies concentrated on the effect of PLB, which has similarities with PEP, though PLB creates only a small pressure of 2 to 5 cm H₂O. Most studies were uncontrolled or open crossover studies on COPD patients, and the hypothesis of decreased airway collapse was supported. In a more recent study, CPAP of 12 cm H₂O increased FRC by mean 0.27 L (SD = 0.12 L) in 8 patients with induced bronchial asthma. Pulmonary resistance during CPAP fell dramatically, but rose immediately after the release of CPAP, although not to pre-CPAP level. Shivaram et al found symptomatic relief with low levels of CPAP in acute asthma. Continuous positive airway pressure was beneficial for weaning from mechanical ventilation in 7 COPD patients and estimated end-expiratory volume increased moderately and most with 15 cm of CPAP and preliminary results indicated that CPAP may help to avoid intubation in patients with acute respiratory failure in COPD.

The influence of PEP on airways in bronchial asthma has, to our knowledge, been reported in only two controlled studies. Positive expiratory pressure applied by expiration against a water column reduced exercise-induced bronchoconstriction measured by FEV₁ and PEFR in a crossover study. In a crossover study of home treatment of moderate bronchial asthma with a cone spacer PEP mask, we showed that the combination of inhaled terbutaline (0.5 mg) and PEP improved PEFR compared with terbutaline alone and with PEP alone; however, the differences in PEFR were small.

Opposite to this, PEP in the present study was not found to improve airway dilation when combined with efficient doses of inhaled bronchodilator in patients with considerable bronchoconstriction due to bronchial asthma. The decreases in Raw with PEP alone (with placebo inhalations) and with inefficient doses of terbutaline (0.5 mg), however, indicate dilation of airways by PEP *per se*, but of minor magnitude compared with efficient doses of inhaled terbutaline. The evidence of airway dilation with PEP *per se* suggests a beneficial influence in obstructive pulmonary diseases, although the clinical significance seems negligible with this simple form of PEP in patients with acute bronchoconstriction. Other forms of PEP, such as CPAP, might be more appropriate in acute bronchial asthma and acute exacerbation of COPD, as indicated by a few studies because CPAP combines the expiratory pressure with an inspiratory flow, but controlled studies are needed to elucidate this question.

ACKNOWLEDGMENT: Thanks to Draco, Denmark, for providing the sprays and to Astra-Medic, Denmark, for providing the Nebulizer-PEP-masks.

REFERENCES
1. Barach AL, Swenson F. Effect of breathing gases under positive pressure on lumens of small and medium-sized bronchi. Arch Intern Med 1939; 63:946-48
5. Martin JC, Shore S, Engel LA. Effect of continuous positive airway pressure on respiratory mechanics and pattern of breathing in induced asthma. Am Rev Respir Dis 1982; 126:512-17
7. Tuxen DV. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. Am Rev Respir Dis 1989; 140:5-9