Bronchodilator effects of exercise hyperpnea and albuterol in mild-to-moderate asthma

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EXERCISE-INDUCED BRONCHOCONSTRICTION (EIB) was initially described as an airway narrowing that occurs a few minutes after termination of a short bout of high-intensity constant-load exercise (7, 18). Recent studies have shown that airway narrowing is already initiated during exercise if the duration of exercise is sufficiently prolonged (4, 25, 26). Moreover, because bronchoconstriction does not develop early during exercise, it was proposed that some protective mechanisms are able to transiently oppose airway narrowing. Blocking prostaglandin production (5), β-adrenoceptor activity (24), or nitric oxide synthase (27) may not alter airway responses during exercise, suggesting no role for bronchodilator mediators. An alternative protective mechanism may be an attenuation of airway smooth muscle tone by the increased tidal stretching associated with exercise hyperpnea.

In healthy subjects, induced bronchoconstriction can be attenuated by one or multiple deep inspirations (20, 23), an effect that is attributed to the large cyclic stretching of airway smooth muscle (10, 14). In vitro, Gump et al. (13) documented that tidal stretch is as potent as isoproterenol in relaxing bovine tracheal smooth muscle contracted by various agonists. In asthma, a potent bronchodilator effect of exercise hyperpnea has also been reported (9, 11), although not consistently (4, 25, 26). It is possible that some variability of response to exercise in asthma is due to different degrees of airway narrowing reversibility or baseline lung function between subjects but also to the duration and intensity of exercise.

The present study was designed to quantify the potency of exercise hyperpnea as a bronchodilator stimulus compared with maximal doses of inhaled albuterol and to test the following two hypotheses. First, the magnitude of the bronchodilator effect would increase with ventilation during incremental-load exercise, thus prevailing over the constrictor stimuli of hyperpnea itself. By contrast, a transient bronchodilatation developing early during constant-load exercise would be followed by renarrowing when the constrictor stimuli become predominant. Second, if the effects of hyperpnea and β2-agonists occur by virtue of different mechanisms, then they should be additive.

For the above purposes, two groups of mild-to-moderate asthmatic patients with similar baseline conditions were studied. In one group, the effects of incremental-load exercise and cumulative doses of albuterol on airway caliber were determined during constant-load exercise with or without premedication with albuterol.

METHODS

Subjects

Eighteen mild-to-moderate asthmatic patients (18) from our asthma clinic accepted the invitation to participate in one of two studies. During the preliminary visit, clinical history was reviewed, and physical examinations were performed. Complete lung function was assessed with the use of a body plethysmograph (Vmax 6200 Autobox System, SensorMedics, Yorba Linda, CA) (17, 28) to make sure that the forced expiratory volume in 1 s (FEV1) was between 50% and 80% of predicted and to exclude the coexistence of lung restriction. Each patient was provided with a written personal timetable, which included the days of experiments, the time to suspend bronchoactive medications before each experiment (12, 24, and 72 h for short- and long-acting bronchodilators and leukotriene receptor modifiers, respectively), and a reminder to resume therapy immediately after each experiment. Inhaled steroid treatments were maintained constant throughout the studies. The study was approved by the local Ethics
Committee, and informed consent was obtained before the study commenced.

**Study Design**

The participating subjects were assigned to two groups (Table 1), to reduce to a minimum the number of study days and days without medications for each subject.

**Study 1.** On day 1, 10 subjects attended the laboratory to determine their responses to four doubling cumulative doses of albuterol from 100 to 1,500 µg. On two other occasions, the participants performed an incremental-load exercise test to exhaustion ~20 min after inhaling placebo or albuterol (400 µg) through a spacer in a random order.

**Study 2.** On day 1, eight subjects attended the laboratory to determine their responses to an incremental-load exercise test to exhaustion. On two other occasions, the participants performed a constant-load exercise test at 55% of their maximal workload, after either placebo or albuterol (400 µg) was inhaled through a spacer in a random order.

In both studies, all experiments were carried out in the early afternoon in a conditioned environment at a temperature of ~20°C and relative humidity of ~40%.

**Resting Pulmonary Function Measurements**

A Vmax 6200 Autobox System (SensorMedics) was used for all resting pulmonary function tests. Flow was measured at the mouth by a mass flowmeter and numerically integrated to obtain inspired and expired volumes. FEV1 and forced vital capacity (FVC) were measured according to the American Thoracic Society/European Respiratory Society recommendations (17). Partial flow-volume curves were recorded by asking the participants to expire forcefully from end-tidal inspiration to residual volume (RV) and then to inspire to total lung capacity (TLC) before the FVC maneuver. Partial flow was measured at 30% of control FVC (V\text{part30}). Thoracic gas volume was measured by whole body plethysmography with the subjects panting against a closed shutter at a frequency slightly <1 Hz, with cheeks gently supported by hands (28). TLC was calculated as the sum of thoracic gas volume and the inspiratory capacity taken immediately after the shutter was opened. Functional residual capacity was corrected for any difference in volume between the volume at which the shutter was closed and the four preceding end-tidal volumes. RV was calculated by subtracting the linked slow vital capacity from TLC. Predicted values were from Quanjer et al. (22). For albuterol dose-response curves, FEV1 and V\text{part30} were measured in triplicate at baseline and 15 min after each dose increment.

**Exercise Protocols and Measurements**

Patients sat on an electronically braked cycle ergometer (Rehcor Lode, Lode B.V. Medical Technology, Groningen, The Netherlands), with the trunk in a fairly straight position and wearing a nose clip and breathing through a mass flowmeter with 75-ml dead space (Vmax, SensorMedics) connected to a saliva trap. A12-lead electrocardiogram was continuously recorded. Oxygen uptake (V\text{O2}) and carbon dioxide output were measured breath-by-breath using a rapid gas analyzer (Vmax, SensorMedics). Tidal volume (VT) was obtained by numerical integration of mouth flow, and minute ventilation (V\text{E}) was calculated as VT times breathing frequency.

**Incremental load.** After 6-min resting measurements were completed, the exercise load was increased by 25 W every 2 min, with the subjects cycling at ~60 rpm until exhaustion. Tidal and partial flow-volume curves were recorded at least three times at rest and once over the last 15 s of each step during exercise. The maneuvers consisted of four to six regular tidal breaths with no evident drift of the volume signal, after which the subjects were requested to expire forcefully to near RV and then to take a deep breath to TLC. Then, tidal breathing was resumed. Measurements of V\text{part30} and end-expiratory (EELV) and end-inspiratory (EILV) lung volumes were determined by superimposing flow-volume loops at TLC, which was assumed to be unchanged during exercise.

**Constant load.** After 6-min resting measurements were completed, a workload was imposed approximately equal to 55% of the maximal workload achieved with incremental exercise. Patients cycled at ~60 rpm for at least 20 min or until exhaustion, whatever came first. Measurements of partial flow and operational lung volumes were taken at least three times at rest and once every 2 min as described above.

**Assessment of EIB.** Spirometry was obtained every 5 min for 20 min after cessation of exercise tests. A decrease of FEV1 ≥10% of pretreatment resting value was considered to be indicative of EIB (8).

**Statistical Analysis**

The sample size was determined for V\text{part30} as the primary variable of the study. Based on the mean intra-individual coefficient of variation (15 ± 13%) and the upper 95% confidence limit (0.16 l/s) previously determined in our laboratory (19), we calculated that eight subjects per group were sufficient to detect a difference in V\text{part30} between albuterol and control of at least 0.32 l/s with an α = 0.05. Unpaired t-test, chi-squared, and Fisher’s exact test were used wherever appropriate to assess differences in anthropometric and baseline characteristics between groups. ANOVA was used to assess baseline functional data within and between study days. Two-factor repeated-measures ANOVA with Newman-Keuls post hoc test was used to assess the effects of albuterol and exercise and their interactions. P < 0.05 was considered statistically significant. All values are expressed as means ± SD.

**RESULTS**

Baseline lung function did not differ significantly between studies and experimental days (Table 2).

**Study 1**

**Dose response curve to albuterol.** The FEV1 increased markedly (Fig. 1) with the first dose (100 µg) of albuterol (P < 0.001) and reached a plateau at 300 µg (P > 0.12 for all

### Table 1. Main anthropometric and functional data of the two groups at baseline

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
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</thead>
<tbody>
<tr>
<td>Gender, Male/Female</td>
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<td>6/2</td>
</tr>
<tr>
<td>Age, years</td>
<td>27±5</td>
<td>35±12</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled steroids, n</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Inhaled bronchodilators, n</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Leukotriene modifiers, n</td>
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<td>3</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175±11</td>
<td>176±8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24±3</td>
<td>24±2</td>
</tr>
<tr>
<td>FEV1, liters</td>
<td>2.62±0.67</td>
<td>2.49±0.64</td>
</tr>
<tr>
<td>% of predicted</td>
<td>63±12</td>
<td>63±10</td>
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<tr>
<td>FVC, liters</td>
<td>4.40±0.81</td>
<td>3.92±0.85</td>
</tr>
<tr>
<td>% of predicted</td>
<td>90±8</td>
<td>85±13</td>
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<tr>
<td>TLC, liters</td>
<td>6.93±1.56</td>
<td>6.75±0.76</td>
</tr>
<tr>
<td>% of predicted</td>
<td>103±10</td>
<td>102±3</td>
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<tr>
<td>FRC, liters</td>
<td>3.58±1.30</td>
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</tr>
<tr>
<td>% of predicted</td>
<td>108±37</td>
<td>124±24</td>
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<tr>
<td>RV, liters</td>
<td>2.50±1.14</td>
<td>2.82±0.57</td>
</tr>
<tr>
<td>% of predicted</td>
<td>152±55</td>
<td>155±31</td>
</tr>
</tbody>
</table>

Values are means ± SD. BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; % of predicted, percent predicted value.
comparisons between 300 and 1,500 μg). V\textsubscript{part30} also increased significantly with the first dose (P < 0.001) and reached a plateau at 700 μg (P > 0.26 for comparisons between 700 and 1,500 μg). At the dose of 1,500 μg V\textsubscript{part30} was 2.57 ± 0.86 l/s.

**Incremental-load exercise.** After placebo, peak workload and VO\textsubscript{2} were 72 ± 20% and 73 ± 14% of predicted (Table 3), peak VE was 77 ± 14 l/min, a value corresponding to 79 ± 22% of maximum voluntary ventilation as estimated from FEV\textsubscript{1} multiplied by 40 (29), and peak EELV and EILV were 54 ± 11% and 86 ± 7% of TLC, respectively. The V\textsubscript{part30} increased significantly (P < 0.001) from 0.60 ± 0.24 l/s at rest to 1.54 ± 0.38 l/s at peak exercise (Fig. 2). The V\textsubscript{part30} achieved at peak exercise was 66 ± 29% of the value achieved after 1,500 μg of albuterol (P = 0.02). EIB occurred in four subjects after placebo.

After albuterol, peak workload and VO\textsubscript{2} were 76 ± 22% and 78 ± 18% of predicted, respectively (P = 0.28 and P = 0.13 vs. placebo, respectively). At rest, V\textsubscript{part30} was increased by albuterol to values significantly higher than after placebo (1.76 ± 0.57 vs. 0.60 ± 0.24 l/s; P < 0.001), and this difference was maintained at peak exercise (2.67 ± 0.87 vs. 1.54 ± 0.38 l/s; P < 0.001). Two-factor repeated-measure ANOVA of all V\textsubscript{part30} values from rest to the maximum Ve value achieved by all subjects (60 l/min) showed significant drug (P < 0.01) and Ve (P < 0.001) effects, but no significant interaction (P = 0.69), thus suggesting that hyperpnea was associated with a bronchodilator effect that was similar with or without albuterol and was additive with the effect of albuterol. V\textsubscript{T} was slightly larger (2.39 ± 0.58 liters), and Borg score was significantly lower (2 ± 1 U) than after placebo (P = 0.02 and P < 0.01, respectively). EIB occurred only in one patient (P = 0.14 vs. placebo).

**Study 2**

With constant-load exercise after placebo, Ve increased from 12.8 ± 1.6 l/min at rest to 43.9 ± 13.4 l/min (P < 0.001).

![Fig. 1. Responses in forced expiratory volume in 1 s (FEV\textsubscript{1}) and partial forced expiratory flow at 30% of forced vital capacity (V\textsubscript{part30}) to cumulative doses of inhaled albuterol. Values are means ± SD. *Significantly different from previous dose.](image)

![Fig. 2. Changes in V\textsubscript{part30} vs. minute ventilation (V\textsubscript{E}) during maximal incremental-load exercise with placebo or albuterol. The points connected by continuous lines are those corresponding to Ve values achieved by all participants. The unconnected points (far right) indicate values at peak exercise. Values are means ± SD. See text for statistical analysis.](image)
The duration of exercise was of 17 ± 5 min. \(V_{\text{part30}}\) significantly increased from 0.69 ± 0.38 l/s at rest to a maximum of 1.11 ± 0.31 l/s (\(P = 0.02\)) within 4 ± 2 min and then decreased to 0.59 ± 0.37 l/s at end exercise (\(P < 0.01\) vs. maximal bronchodilatation and \(P = 0.53\) vs. rest), indicating an initial airway dilatation followed by renarrowing (Fig. 3). By the time \(V_{\text{part30}}\) achieved its maximum value, Borg score for dyspnea increased from 2 ± 1 to 3 ± 1 (\(P < 0.001\)), and then, with the return of \(V_{\text{part30}}\) to baseline values at the end of the test, it further increased to 5 ± 1 (\(P < 0.001\)). In contrast, \(V_{E}, V_{T}, EELV,\) and \(EILV\) remained stable between these two time points. Three subjects were unable to complete the 20-min constant-load exercise. EIB occurred in seven patients.

After albuterol, \(V_{\text{part30}}\) was significantly increased at rest from 0.66 ± 0.35 to 1.61 ± 0.67 l/s (\(P < 0.001\)), tended to further increase at maximal bronchodilatation to 2.00 ± 0.79 l/s (\(P = 0.07\)) within 6 ± 6 min, and finally decreased to 1.64 ± 0.63 l/s at end exercise (\(P = 0.04\) vs. maximal bronchodilatation and \(P = 0.88\) vs. rest). At all time points, \(V_{\text{part30}}\) after albuterol was significantly greater than after placebo (\(P < 0.001\) for all comparisons), and no significant interaction was found (\(P = 0.75\)) between treatments and time, which suggests a similar effect of mechanical ventilation and the lack of a potentiating effect with albuterol-induced bronchodilatation. At all of these time points, Borg score increased less than after placebo (from 0 ± 0 at rest to 1 ± 1 at maximal bronchodilatation time and to 2 ± 1 at the end of exercise; \(P < 0.001\) for all time points vs. placebo) with no significant differences between the two last measurements (\(P = 0.38\)). At the end of exercise, EELV, EILV, and Borg score after albuterol were lower than after placebo (56 ± 8 vs. 64 ± 9% of TLC for EELV, \(P = 0.02\); 81 ± 8 vs. 87 ± 8% of TLC for EILV, \(P = 0.08\); and 2 ± 1 vs. 5 ± 1 U for Borg score, \(P < 0.001\)) (Table 4). The three patients who were unable to complete the exercise test after placebo were also unable to complete the exercise test after albuterol. Another patient decreased the endurance time from 20 min after placebo to 18 min after albuterol. EIB occurred in 3 patients (\(P = 0.12\) vs. placebo), but with a significantly less decrement of FEV\(_1\) (9 ± 16% vs. 26 ± 22%; \(P < 0.01\)).

**DISCUSSION**

The main results of the present study are as follows: 1) maximal exercise hyperpnea was associated with a bronchodilatation that was similar to that achieved with albuterol at 400 μg but less than at 1,500 μg; 2) maximum flow increased monotonically with \(V_{E}\) during incremental-load exercise, but only for the first few minutes during submaximal constant-load exercise, and this was followed by renarrowing and occurrence of EIB in most subjects; and 3) the bronchodilator effects of hyperpnea and albuterol were additive.

Before we discuss the present results, some limitations of this study need to be addressed. First, the present results refer to patients with mild-to-moderate asthma and cannot be extrapolated to patients with more advanced disease. As anticipated in the introduction, more severe airflow obstruction may entail a loss of airway-to-parenchyma interdependence, thus reducing the beneficial effects of tidal stretching on airway caliber (20). Second, the maximum work capacity of our participants was slightly below the lower limits of normality and not all participants sustained 55% of their maximal work rate for 20 min. Although we do not have a clear explanation for these findings, we do not believe that they were due to ventilatory constraints because 1) there was still some breathing reserve with either placebo or albuterol at the end of either exercise tests (29), 2) the remarkable increase in \(V_{\text{part30}}\) after albuterol was not associated with any increase in peak \(V_{O2}\) or work rate, and 3) the dyspnea scores were still low at end exercise. We think more likely that these exercise limitations were due to de-conditioning. Therefore, the results of the present study cannot be generalized to subjects with higher than normal exercise capacity.

That hyperpnea is a potent bronchodilator is a well-known phenomenon (16). In healthy subjects and smokers with mild-to-moderate airflow obstruction, exercise is associated with a significant bronchodilatation (1, 21). In patients with asthma, such an effect has been inconsistently reported, although a study by our group documented impressive increments of

![Fig. 3. Mean \(V_{\text{part30}}\) at baseline, before exercise, at maximum bronchodilatation, and at the end of constant-load exercise. Values are means ± SD. *Significantly different from rest; †significantly different from maximal bronchodilatation; ‡significantly different from placebo.](http://jap.physiology.org/.../fig_3.png)
maximum flow at maximum exercise in patients with spontaneous or allergen-induced bronchoconstriction (9). On the basis of the remarkable increase in $V_{\text{part30}}$ at peak exercise with placebo, the present study confirms the potential of hyperpnea in blunting bronchoconstriction in asthma.

There are two mechanisms that may oppose the development of EIB. One is the release of bronchodilator mediators early during exercise. An increase in circulating catecholamines with strenuous exercise could stimulate the $\beta_2$-adrenoreceptors, thus determining bronchodilatation. This hypothesis, however, has never been given sufficient credit because isocapnic hyperpnea is also associated with significant bronchodilatation in the absence of any increase of plasma catecholamines (3) and is also associated with significant bronchodilatation in children (24). Other known bronchodilator mediators are prostaglandins (particularly PGE$_2$) and nitric oxide. However, the inhibition of either cyclooxygenase (5) or NO synthase (27) had no significant effect on airway function during and after exercise in patients with asthma. Hallstrand et al. (15) found the ratio of Cys-leukotrienes/PGE$_2$ to be higher after exercise in patients with EIB than in normal controls. This finding can explain the occurrence of bronchoconstriction during and after exercise but not the biphasic change of airway function, i.e., bronchodilatation followed by renarrowing, as observed in the present study. A second, more likely hypothesis is that bronchodilatation is the result of a mechanical effect of the stretching produced by hyperpnea on airway smooth muscle cell (13, 14). Our findings in humans are consistent with the notion that airway smooth muscle stretching may be a potent bronchodilator, although increased ventilation well above resting values was required to achieve a level of bronchodilatation that was $\sim$60% of that achievable with maximal doses of albuterol. This can be explained by the fact that in asthmatic patients the relaxant effect of tidal stretching is opposed by the effects of bronchoconstrictor mediators possibly released during exercise (2), and the net effect of exercise hyperpnea would depend in vivo on which of these mechanisms prevails. Because the effects of hyperpnea were not investigated independently of exercise, it cannot be said to which extent the bronchodilator effect of airway stretching was blunted by the constrictor stimuli associated with exercise. In any case, the results of our incremental-load study suggest that tidal stretching of progressively increasing amplitude is sufficient to maintain the airways dilated during exercise and prevent the occurrence of airway narrowing in the majority of subjects. This may explain why the number of patients who experienced the occurrence of EIB after incremental exercise was remarkably lower than found with constant-load exercise in this study and similar to other reports in the literature (7).

Another difference between our in vivo and the previous in vitro study (13) is that hyperpnea and albuterol did not show potentiating effects. As a matter of fact, when exercise was preceded by the inhalation of albuterol, the increase in $V_{\text{part30}}$ equaled the sum of those achieved separately with albuterol and hyperpnea at any workload. There are several mechanisms that are operative in vivo but not in vitro to explain this apparent discrepancy. First, it is conceivable that tidal stretching has only a relaxant effect on isolated bronchial tissues, whereas hyperpnea has a mix of bronchodilator and bronchoconstrictor effects in vivo. Second, the magnitude of tidal stretching in asthmatic airways may be reduced because of a decrease in lung elastic recoil, loss of airway-to-parenchyma interdependence, increased airway stiffness, and inhomo-
genous distribution of airflow obstruction (6, 12, 20).

The results of our constant-load study further highlight the complexity of the effects of exercise hyperpnea on airway caliber. In fact, $V_{\text{part30}}$ began to increase with the increase in $V_E$ to peak at $\sim$6 min and then gradually decreased to or even below resting values, even though $V_E$ remained constant up to the end of the test. As discussed above, the initial increase in $V_{\text{part30}}$ was likely due to the bronchodilator effects of hyperpnea but, although $V_E$ soon achieved a steady state, the constrictor stimulus triggered by hyperpnea itself tended to prevail. That this is presumably so is documented by two facts. First, with cessation of exercise and thus reduction of $V_E$, the constrictor stimulus further prevailed over the dilator effect of tidal stretching and EIB occurred in the majority of subjects. Second, when airway smooth muscle was relaxed by albuterol, $V_{\text{part30}}$ remarkably increased during exercise, and the occurrence of EIB was significantly reduced.

In conclusion, the present results confirm that exercise acts as a variable bronchodilator agent in asthmatic patients with airway obstruction at rest. With high-intensity exercise, the bronchodilator effect of tidal deep inspirations on airway smooth muscle seem to prevail over the bronchoconstrictor mechanisms involved in EIB, while the opposite seems to be true during submaximal constant-load exercise. The effects of albuterol and exercise hyperpnea are additive, thus allowing optimal adaptation to exercise in subjects with mild-to-moderate asthma.

REFERENCES


