Exercise-induced Bronchodilation in Asthma*

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Of 34 symptomatic adult asthmatic patients (23 men) aged 51 ± 13 years (mean ± 1 SD) with moderately severe airways obstruction who underwent maximal exercise testing at room temperature (22°C) and humidity (44 percent RH) using a bicycle ergometer, we identified seven male patients aged 56 ± 9 years in whom forced expired volume in one second (FEV₁) increased ≥20 percent over the baseline preexercise value (exercise-induced bronchodilation). At maximal exercise, these patients achieved an O₂ consumption of 1.4 ± 0.4 L/min and a minute ventilation of 56 ± 9 L/min. Baseline FEV₁ was 1.3 ± 0.5 L (SD) (43 ± 12 percent predicted) and increased to 2.1 ± 0.5 L at five minutes after exercise and persisted at least 20 minutes. Exercise was repeated in all seven patients on a separate day one to six months later, and results were similar in six. In these seven patients, three minutes of voluntary isocapnic hyperventilation achieving a minute ventilation comparable to that during maximal exercise led to an increase in FEV₁ of 20 ± 18 percent (range 0 to 54 percent). The Vmaxₐ was 22 ± 30 percent before, and 10 ± 21 percent after maximal exercise and 25 ± 37 percent before, and 11 ± 22 percent after isocapnic hyperventilation. Pre-treatment with acetylsalicylic acid (mean serum concentration 120 ± 64 μg/ml) in the six patients with reproducible bronchodilation completely blocked exercise bronchodilation in one patient and blunted it in four others. Findings suggest that a subset of adult patients with symptomatic asthma may develop bronchodilation after six to eight minutes of exercise, that exercise-induced bronchodilation may in part be reproduced with isocapnic hyperventilation, and that it may be blocked completely or partially by acetylsalicylic acid, implying mediation by prostaglandins.

Postexercise bronchospasm is a well-recognized entity in patients with asthma. It is particularly common in asthmatic children with a reported prevalence of 63 percent, but it has also been widely recognized in adult asthma. Although exercise-induced bronchodilation has been noted in asthmatic children after only one to two minutes of exercise, bronchoconstriction is the characteristic response after a longer duration of exercise (six to eight minutes). We now report data in seven of 34 adult patients with symptomatic asthma who exhibited significant improvement in forced expiratory flow rates after six to eight minutes of maximally tolerated exercise, indicating exercise-induced bronchodilation.

MATERIALS AND METHODS

We studied in detail seven men, aged 56 ± 9 (mean ± 1 SD), who satisfied the criteria for asthma. These seven patients were chosen from a larger group of 34 consecutively studied symptomatic adult asthmatic patients (23 men) aged 51 ± 13 years) who had undergone lung function and exercise studies for evaluation of dyspnea or wheezing as part of a rehabilitation program. These seven patients were selected for further study because they demonstrated an improvement in forced expired volume in one second (FEV₁) following exercise of ≥20 percent above the resting value. All seven patients were lifelong nonsmokers with long-standing history of bronchospastic airways disease characterized clinically by exacerbations and remissions of wheezing associated with chronic cough and sputum production. Pulmonary function studies were obtained in the sitting position and included spirometry before and after two slow deep inhalations of aerosolized metaproterenol (1.5 mg) from a metered-dose inhaler, subdivisions of lung volume, and single-breath diffusing capacity, as previously described. In most of these patients, spirometry had also been performed before and after bronchodilator administration on previous occasion as well. Exercise studies were then carried out on two separate days one to six months apart using an identical protocol. Prior to the first exercise study, only two patients were taking anti-asthma medication, including oral and inhaled beta-adrenergic agonists and a short-acting theophylline preparation. No patient was taking sodium cromolyn and only one patient was receiving corticosteroids (prednisone, 20 mg daily). Prior to the second exercise study, two other patients had begun taking an oral beta-adrenergic agonist and a short-acting theophylline preparation. The subjects were not receiving any other medication concurrently, and none was being treated for any other illness.

On two separate occasions, exercise studies were performed at room temperature (22°C) and humidity (44 percent relative humidity) using the Beckman metabolic measurement cart. No medication was taken for at least six hours prior to testing. After achieving a resting steady state for at least three minutes, the patient exercised on a Tunturi bicycle ergometer; initially, resistances were added every one to two minutes as tolerated until a near-maximal target work rate could be sustained for four to five minutes. Total duration of exercise was from six to eight minutes. Exercise was terminated when the patients could no longer continue due to shortness of breath, wheezing, or fatigue. Minute ventilation, tidal volume, respiratory rate, pulse rate, O₂ consumption, and CO₂ production were measured at baseline, and thereafter, every 30 seconds during the exercise protocol. On a separate occasion, two patients were tested using a similar protocol except that the exercise was submaximal. Spirometry was measured at baseline prior to exercise and was repeated five minutes after the cessation of exercise in each patient and at five to ten minute intervals thereafter for at least 20 minutes.

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following the completion of exercise. Both before and five minutes after exercise, maximum expiratory flow-volume (MEFV) curves were obtained both during air breathing and after breathing an 80 percent helium-20 percent oxygen mixture until expired nitrogen concentration fell to ≤5 percent. The change in maximal flow at 50 percent of the vital capacity (ΔV_{max50}) was measured according to the method of Despas et al.10

On a different day, all seven patients performed voluntary hyperventilation breathing room air, temperature 22°C and humidity 44 percent RH, to achieve a minute ventilation (Ve) comparable to that measured during maximal exercise. Isocapnic conditions were maintained either by the addition of 5 percent CO₂ in oxygen upstream from the mouthpiece (six patients) or by a re-breathing technique in which the rebreathed gas was mixed with CO₂ absorbant using a variable-speed pump (one patient). Isocapnic voluntary hyperventilation was maintained for approximately three minutes. In all seven patients, MEFV curves during air and 80 percent helium-20 percent oxygen breathing were obtained both before and at five minutes after isocapnic hyperventilation.

In three of the patients, maximal and partial expiratory flow-volume curves (during air breathing) were obtained, and maximal expiratory flow was calculated at the last 25 percent of the forced vital capacity from both the complete (ΔV_{max}) and partial (ΔV_{max50}) flow volume curves.11

On a separate occasion, the exercise protocol described above was repeated after the seven subjects had taken 650 to 975 mg acetylsalicylic acid (ASA) approximately every six hours for 48 hours. The last dose of ASA was taken within two hours of exercise testing at which time venous blood was obtained for determination of plasma salicylate concentration.

Data were analyzed by comparing individual values of FEV₁ or forced vital capacity (FVC) following isocapnic hyperventilation and exercise with and without ASA pretreatment using a one-way analysis of covariance in which the baseline FEV₁ or FVC was treated as a co-variate. The t-test matrices were obtained from the analysis of co-variance, comparing the change from baseline after each condition; differences were considered significant for p values <0.05.

**RESULTS**

Of the seven patients who underwent the repeated exercise protocol on a separate day one to six months after the initial study, six reproduced the significant improvement in FEV₁ (>20 percent) noted after the first exercise study (Fig 1). All six of these patients exhibited moderate or severe airflow obstruction at rest without diffusion impairment: FEV₁, 1.5±0.3 L (mean±1 SD) (45±11 percent predicted); FVC 2.9±0.7 L (60±11 percent predicted); TLC 7.7±2.0 L (117±17 percent predicted); and Dco 26±6 ml/min/mm Hg (105±24 percent predicted). On at least one occasion, all subjects demonstrated >15

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**Table 1—Results (Mean±1 SD) of Exercise Physiologic Data in Six Patients with Exercise-Induced Bronchodilation on Two Separate Occasions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ve (L/min) at maximum exercise</th>
<th>RR (min-L)</th>
<th>Vo₂ (ml/kg/min)</th>
<th>FVC₁ (L)</th>
<th>FEV₁₁ (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a exer</td>
<td>p exer</td>
<td>%Δ</td>
<td>a exer</td>
<td>p exer</td>
</tr>
<tr>
<td>E1</td>
<td>59</td>
<td>35</td>
<td>1.5±</td>
<td>17.9±</td>
<td>2.9±</td>
</tr>
<tr>
<td>E2</td>
<td>57</td>
<td>34</td>
<td>0.4</td>
<td>17.6±</td>
<td>2.8±</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>6</td>
<td>0.5</td>
<td>4.2</td>
<td>0.8</td>
</tr>
<tr>
<td>IH</td>
<td>58</td>
<td>36</td>
<td>1.3</td>
<td>16.3±</td>
<td>3.0±</td>
</tr>
<tr>
<td>E/ASA</td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>3.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*Ve is respiratory rate; Ve, minute ventilation; Vo₂, oxygen consumption; a and p exercise, before and after exercise, respectively; E1 and E2, exercise studies performed in same patient on separate days; one to six months apart; E/ASA, exercise study performed after pretreatment with ASA. The percentage of improvement in FEV₁ and FVC after exercise alone was significantly greater than that after isocapnic hyperventilation or exercise after ASA pretreatment (ANCOVA; p<0.05).

†Results shown were obtained 5 minutes after exercise or isocapnic hyperventilation (IH).
percent improvement in FEV₁ after bronchodilator administration. Mean values of FVC and FEV₁ before and five minutes after exercise in the six subjects with reproducible exercise-induced bronchodilation are shown in Table 1. Also included in Table 1 are the values for oxygen consumption, minute ventilation, and respiratory rate measured over a 30-second period at the highest workload achieved during exercise. At maximally tolerated exercise, the patients showed an increase in oxygen consumption that varied between approximately four and seven times the resting value. The minute ventilation at maximal exercise varied between 93 percent and 171 percent of the estimated maximal voluntary ventilation (FEV₁ × 35) at rest. Five minutes following the cessation of the initial exercise study, FEV₁ increased an average of 54 ± 37 (SD) percent (range 21 percent to 125 percent) above the pre-exercise value, and forced vital capacity increased an average of 21 ± 13 (SD) percent (range 5 percent to 50 percent) above the resting value. The bronchodilation observed at five minutes after exercise persisted for at least 20 minutes in each patient and for at least 30 minutes in one patient. The ΔV_{max}, after exercise in the six patients was 10 ± 21 percent compared to the mean pre-exercise value of 22 ± 30 percent (p>0.05). Only two of the six patients noted subjective improvement in their asthma following exercise.

Among the larger group of 34 asthmatic patients who underwent exercise testing at least once, there was a trend toward a relationship between the degree of bronchodilation following exercise and the pre-exercise FEV₁. Of the ten patients whose initial FEV₁ was <50 percent predicted, five exhibited exercise-induced bronchodilation. Although all the patients with demonstrable exercise-induced bronchodilation were men, more than two-thirds of the study population of asthmatic patients were also men. One patient exhibited significant exercise-induced bronchodilation (increase in FEV₁ of 60 percent over the resting value) when initially tested, but failed to reproduce the bronchodilation on the second exercise study (Fig 1). Interestingly, this patient had a markedly improved baseline FEV₁ (2.1 L) prior to the second study when compared to the baseline FEV₁ (1.5 L) on the initial exercise study. This improvement in FEV₁ followed initiation of maintenance bronchodilator medication. The six patients with reproducible exercise-induced bronchodilation on two separate occasions had a similar baseline FEV₁, prior to both exercise studies. The two patients who were also tested before and after submaximal exercise (V̇E during submaximal exercise 33 and 38 L/min) demonstrated postexercise improvement in their FEV₁, but this increase in FEV₁ was <20 percent above the resting pre-exercise value (Fig 1; subjects 1 and 7).

After three minutes of isocapnic hyperventilation, the six patients with reproducible exercise-induced bronchodilation exhibited small but significant mean increases in FVC (10 ± 6 percent) and FEV₁ (13 ± 9 percent) (Table 1). One subject showed no improvement in FEV₁ (although FVC increased by 20 percent), two additional subjects showed only slight increases in FEV₁ (<10 percent), and the remaining four subjects showed greater increases in FEV₁ (12 percent to 54 percent) associated with variable increases in FVC. In only one subject was the improvement in FEV₁, following isocapnic hyperventilation comparable to that noted following exercise. Paradigmatically, this patient exhibited a reduction is isovolume forced expiratory flow rates following a single maximal inspiration (V_{max} = 0.11 L/sec) compared to the forced expiratory flow rates following only a partial inspiratory maneuver (V_{max} (P) = 0.22 L/sec). Interestingly, this 40-year-old man, whose FEV₁ during clinically-stable intervals between attacks of acute asthma was only 33 percent to 45 percent of predicted, had the physical stamina to play tournament tennis and reported that his asthma was subjectively markedly improved whenever he played tennis. In two other subjects in whom partial and maximal expiratory flow volume curves were obtained, maximal inspiration was followed by either no change or a mild reduction (17 percent) in the forced expiratory flow at the last 25 percent of the forced vital capacity. The ΔV_{max} after isocapnic hyperventilation either did not change (three patients) or decreased (four patients).

Pretreatment with ASA for 48 hours yielded plasma salicylate levels of 30 to 220 μg/ml (mean 125 ± 64 SD). Results of the exercise studies performed after ASA pretreatment appear in Table 1 and Figure 1. After ASA pretreatment, mean baseline pre-exercise FVC and FEV₁ and mean maximum ventilation and oxygen consumption achieved during exercise were similar to the values noted during the exercise session without ASA pretreatment (Table 1). In the six patients with reproducible exercise-induced bronchodilation on two separate occasions, ASA completely blocked exercise-induced bronchodilation (and actually induced postexercise bronchoconstriction) in one patient (No. 2), and exercise-induced bronchodilation was blunted after ASA in four patients (Fig 1). There was no significant difference between the degree of inhibition of exercise-induced bronchodilation after ASA pretreatment and the plasma ASA concentration (R = 0.13). The mean percentage of improvement in FEV₁ and FVC after exercise without ASA pretreatment was significantly greater than that after either isocapnic hyperventilation or exercise with ASA pretreatment (ANCOVA; p<0.05).

**Discussion**

Seven of 34 consecutively studied adult asthmatic...
patients with moderately severe airways obstruction developed substantial bronchodilation after six to eight minutes of exercise, and this phenomenon was reproducible in six of these seven patients who underwent exercise testing on two separate occasions. These observations are all the more interesting in view of previous reports which have emphasized exercise-induced bronchoconstriction in asthmatic patients after a similar duration of exercise with the only infrequent occurrence of bronchodilation mainly after exercise of shorter duration (one to two minutes). Moreover, our patients exhibited either no change (one patient), <10 percent increase (two patients), or a 12 percent to 54 percent increase (four patients) in FEV₁ following three mintues of isocapnic hyperventilation (under ambient conditions of temperature and humidity) of a magnitude which matched the increased ventilation of exercise. In contrast, the same procedure when carried out for six to eight minutes with cold, dry air or even air under ambient conditions has been found to produce bronchospasm of a magnitude comparable to that following exercise associated with a similar duration and degree of hyperpnea. It is possible, however, that continuation of hyperventilation in our patients for a longer period of time (six to eight minutes) might have produced different results.

While the effector pathway remains to be elucidated, there is evidence to suggest that either respiratory heat loss or loss of water with subsequent changes in epithelial fluid osmolarity may be responsible for the commonly observed bronchoconstriction seen five to ten minutes after exercise. In contrast to the latter phenomenon, we observed a relatively high prevalence of exercise-induced bronchodilation (approximately 20 percent) in the population of adult asthmatic patients whom we examined compared to previous studies. The reason for this discrepancy may be due to differences in subject characteristics. Specifically, in comparison with most asthmatic patients undergoing exercise challenge who are generally young and asymptomatic, our patients were older and more symptomatic an exhibited more severe resting airways obstruction. Moreover, although the method of exercise challenge we employed was similar to that conventionally used with respect to the duration of exercise, the intensity of the exercise challenge was constrained by the severity of our patients’ pre-exercise airflow obstruction. Thus, although they exercised to a maximally tolerated workload intensity and achieved a maximal minute ventilation during exercise of 93 percent to 171 percent of their estimated resting MVV (baseline FEV₁ x 35), it could be argued that, because of their severe baseline airflow obstruction, this maximally achieved level of minute ventilation during exercise (59 ± 5.1 L) was still too low (under ambient conditions of temperature and humidity) to produce sufficient respiratory heat or water loss to provoke a bronchospastic response. However, five other adult asthmatic patients with similar degrees of obstructive ventilatory impairment whom we studied were noted to develop postexercise bronchoconstriction after achieving a similar or lower minute ventilation during maximal exercise.

Although four of our seven patients with exercise-induced bronchodilation were receiving maintenance bronchodilator medication (a short-acting theophylline, an inhaled beta agonist and/or an oral beta agonist), these medications were withheld for at least six hours prior to exercise testing. Short-acting theophylline preparations should offer little protection against exercise-induced bronchospasm six hours after cessation of therapy, and oral beta-adrenergic agonists have not been shown to be effective in inhibiting postexercise bronchoconstriction five hours after administration.

The mechanism of the airway dilation we observed after six to eight minutes of exercise (seven patients) or three minutes of isocapnic hyperventilation (four patients) is unclear. It is possible that the observed bronchodilation was due to a mechanical effect of the hyperventilation secondary to stress relaxation or length-tension hysteresis of airway smooth muscle similar to the bronchodilation associated with deep inspiration. Although the bronchodilator effect of a single deep breath has been found to be of only short duration (<60 to 90 sec), stress-related relaxation of airway smooth muscle following the repeated deep lung inflations associated with the hyperpnea of exercise or isocapnic voluntary hyperventilation conceivably might be longer lasting in some asthmatic patients. On the other hand, the bronchodilator effect of isocapnic hyperventilation noted in four of our subjects is somewhat paradoxical since most asthmatic patients (including three of the patients reported herein), unlike normal subjects, develop a reduction in forced expiratory flow rates after a single maximal inspiration, the mechanism of which is not clear but probably is not vagally mediated. This phenomenon is thought to be responsible for spirometer-induced bronchospasm which has been reported in some asthmatic patients. By contrast, one of our subjects exhibited the opposite phenomenon, namely that of spirometer-induced bronchodilation with progressively greater improvement in FEV₁, after successive forced vital capacity maneuvers. This observation is all the more interesting (and puzzling) since the same subject responded to a single maximal inflation with a reduction in forced expiratory flow rate \( \bar{V}_{\text{max,typ}} \) measured from the partial flow-volume curve generated just prior to the maximal inspiration.

We noted that the airways dilation produced by
maximal exercise was substantially greater than that following isocapnic hyperventilation or submaximal exercise (Table I). These observations suggest that the exercise-induced bronchodilation reproducibly exhibited by six of our seven patients was at least partially accounted for by factors unrelated to mechanical or other effects of hyperventilation. Such factors, not investigated by us, could include a greater rise in or sensitivity to circulating catecholamines during exercise that has previously been reported in normal subjects and asthmatic patients with exercise-induced bronchospasm.25,26 The bronchodilation previously reported in asthmatic patients after brief periods of exercise (one to two min) has been thought to be due to a sympathomimetic effect of exercise which is subsequently negated by constrictor influences which develop after longer periods of exercise (five to ten minutes).8 It is possible that a supernormal adrenergic drive or sensitivity to adrenergic stimulation made our subjects more responsive to the dilator than the constrictor effects of exercise despite the fact that their duration of exercise was six to eight minutes. Alternatively, the airways of our patients could be unusually sensitive to the bronchodilator effect of prostaglandins (or other mediators) released during deep lung inflation27 as occurs with exercise or voluntary hyperventilation, or repeated deep lung inflation in these patients may stimulate an unusually greater release of bronchodilating substances. The observation that therapeutic levels of acetylsaliclyc acid completely blocked exercise-induced bronchodilation in one of our patients and blunted it in four others suggests that prostaglandins may play a role in mediating the bronchodilation of exercise in a subset of asthmatics.

Since response to a bronchodilator stimulus is in part dependent on the degree of airways obstruction at baseline,29 it is possible that the bronchodilation we noted following exercise may have been related to the greater degree of airways obstruction present at baseline in our subjects, when compared to most asthmatic patients challenged with exercise. On the other hand, the degree of airway narrowing following a constrictor stimulus (such as exercise) would also be expected to be enhanced by the relatively marked airflow obstruction present at baseline.30 In this regard, the baseline FEV1 values of our patients prior to exercise with and without ASA pretreatment were very similar, making it less likely that the apparent inhibition of exercise-induced bronchodilation by ASA was affected by different degrees of baseline airways obstruction.

The lack of change or reduction in ΔVmax following exercise and after isocapnic hyperventilation suggests that the bronchodilator effect of exercise or hyperventilation predominantly involves larger airways, causing a proportionately lesser decrease, or even an increase, in the resistance of the peripheral airways where airflow is relatively independent of gas density.31

In summary, we have identified a subset of patients with asthma who paradoxically developed large airway bronchodilation after six to eight minutes of exhausting exercise. Although the mechanism of the bronchodilation of exercise in these patients is not known, it may be partially related to mechanical or other effects of hyperpnea and may be mediated, in part, by prostaglandins. Since the prevalence and nature of postexercise changes in lung function in symptomatic adult asthmatic patients with moderately severe airways obstruction has not been well studied, it is possible that the occurrence of exercise-induced bronchodilation has been underestimated. Further studies should be directed at determining the prevalence and mechanism of this interesting phenomenon.

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