Effect of Cold Air Exposure and Exercise on Nonspecific Bronchial Reactivity*
Tahir Ahmed, M.D., F.C.C.P.; and Ignacio Danta, B.S.

Exercise and eucaic hyperventilation with cold air can produce bronchoconstriction in asthmatic subjects, but their enhancement of nonspecific bronchial reactivity remains unclear. We studied the effect of submaximal exercise and cold air exposure on bronchial reactivity to methacholine in a normal control group (n = 10) and in subjects with bronchial asthma (n = 17). Bronchial provocation testing was performed to determine the provoking dose (PD_{50}) of methacholine that caused a 35 percent decrease in specific airway conductance (Gaw/VL) in the two groups. Each subject was studied on three different occasions to determine the PD_{50} to methacholine on a control day, after ten minutes of submaximal exercise, and after a 30-minute exposure to cold air. Methacholine challenge was performed after the Gaw/VL had returned to the baseline values. In the normal group, neither cold air exposure nor exercise challenge had any significant effect on baseline Gaw/VL, whereas in the asthmatic group, both stimuli caused 20 percent and 15 percent decreases in Gaw/VL, respectively (p < .05). Mean ± SD control PD_{50} was 6.1 ± 11.6 breath units in the asthmatic group, which decreased to 2.2 ± 2.8 after exercise and 3.0 ± 5.0 breath units after cold air exposure (p < .05). In the normal group, control PD_{50} was 73 ± 32 breath units, which was not different from PD_{50} values of 64 ± 75 and 52 ± 64 breath units after exercise and cold air exposure, respectively (p = NS). These data suggest that submaximal exercise and cold air exposure enhance nonspecific bronchial reactivity in asthmatic but not in normal subjects.

Enhancement of nonspecific bronchial reactivity has been observed following upper respiratory tract infection, pollutant exposure, hypoxia, and during pollen season and acute exposure to a specific antigen. Although exercise and eucaic hyperventilation with cold air produce bronchoconstriction, the enhancement of nonspecific bronchial reactivity by these physical stimuli remains controversial. Thus, our purpose was to investigate whether submaximal exercise or exposure to cold air would enhance nonspecific bronchial reactivity in normal subjects and in those with bronchial asthma.

Material and Methods

Subjects

Twenty-seven nonsmokers (12 men and 15 women) without a recent history of upper respiratory tract infection participated in the study. Seventeen subjects had a history of bronchial asthma; their ages ranged from 18 to 39 years (mean, 29). The remaining ten subjects were normal; their ages ranged from 21 to 44 years (mean, 28). Normal subjects had no personal or family history of atopy. The asthmatic subjects were asymptomatic at the time of the study; had normal auscultatory findings; and had not received bronchodilator drugs for at least 24 hours. Informed consent was obtained from all subjects.

Methods

Baseline pulmonary function tests consisted of spirometric study and measurements of airway resistance and functional residual capacity (FRC) by body plethysmography. Specific airway conductance (Gaw/VL) was calculated by dividing the reciprocal of airway resistance by the thoracic gas volume at which airway resistance was measured.

Bronchial Provocation

For bronchial provocation testing, methacholine was delivered to the lungs through a DeVilbis No 42 nebulizer. The nebulizer was attached to a dosimeter, which consisted of a breath-activated solenoid valve and a source of compressed air (20 psi). The solenoid valve was set to remain open for 0.6 s during inhalation to allow the compressed air to flow through the nebulizer, dispersing an average of 0.023 ml of the solution with each breath. The aerosolized material was delivered from FRC position through the course of a submaximal inspiratory effort. After obtaining the baseline measurements of specific airway conductance, the subjects inhaled five breaths of saline diluent, and the measurements were repeated after a ten-minute interval. Methacholine dose-response curves were then established by having the subjects take five inhalations from each of increasing concentrations of methacholine, administered at ten-minute intervals. The first concentration was 0.075 mg/ml, while the concentrations of subsequent doses increased in alternating twofold and fivefold increments, until Gaw/VL decreased by 35 percent or more from the value obtained after breathing the saline diluent (provoking dose, or PD_{50}). If the above decrease did not occur, bronchial provocation was terminated at a concentration of 5 mg/ml. The Gaw/VL was determined at the end of the ten-minute interval after the control diluent and the subsequent methacholine doses were given. The Gaw/VL was then plotted against the cumulative methacholine dose, expressed in breath units, to obtain simultaneous dose-response curves. One breath unit was defined as one inhalation of a 1-mg/ml concentration of methacholine. After completion of bronchial provocation, the subjects took two inhalations of isetharine from a metered-dose inhaler to terminate the methacholine-induced bronchoconstriction. We used Gaw/VL as an indicator of airway narrowing during bronchial provocation to avoid the potential problems associated with deep inspiration, and also because methacholine may cause changes in Gaw/VL and minimal changes in FEV,.

*From the Division of Pulmonary Disease, University of Miami School of Medicine, Mount Sinai Medical Center, Miami Beach. Reprint requests: Dr Ahmed, Mount Sinai Medical Center, 4300 Alton Road, Miami Beach 33140

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Cold Air, Exercise and Nonspecific Bronchial Reactivity (Ahmed, Danta)
Table 1—Comparative Pulmonary Function Tests of Normal and Asthmatic Subjects*

<table>
<thead>
<tr>
<th>Group</th>
<th>TLC</th>
<th>RV/TLC</th>
<th>FRC</th>
<th>FVC</th>
<th>FEV₁</th>
<th>FEV₁/FVC</th>
<th>Raw</th>
<th>Gaw/NL</th>
<th>Gaw/VL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>5.7</td>
<td>0.24</td>
<td>2.63</td>
<td>4.28</td>
<td>3.56</td>
<td>83.9%</td>
<td>1.66</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>(n = 10)</td>
<td>±1.76</td>
<td>±0.07</td>
<td>±1.10</td>
<td>±1.29</td>
<td>±1.02</td>
<td>±8.5</td>
<td>±0.61</td>
<td>±0.08</td>
<td></td>
</tr>
<tr>
<td>Asthmatic</td>
<td>6.23</td>
<td>0.31</td>
<td>3.23</td>
<td>4.18</td>
<td>3.06</td>
<td>75.3%</td>
<td>1.94</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>(n = 17)</td>
<td>±1.92</td>
<td>±0.09</td>
<td>±1.25</td>
<td>±1.13</td>
<td>±0.71</td>
<td>±10.4</td>
<td>±0.71</td>
<td>±0.05</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>&lt;.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;.05</td>
<td>NS</td>
<td>&lt;.05</td>
<td></td>
</tr>
</tbody>
</table>

*Mean ± SD; % predicted in parentheses. RV = residual volume in liters; TLC = total lung capacity in liters; FRC = functional residual capacity in liters; FVC = forced vital capacity in liters; FEV₁ = forced expiratory volume in 1 second in liters; Raw = airway resistance, cm H₂O/L/s; Gaw/NL = specific airway conductance; L/sec⁻¹.

Exercise Challenge

Exercise challenge was performed on the treadmill with a gradually increasing workload until 85 percent of predicted maximum heart rate was achieved. The subjects were then asked to continue exercise at that workload for ten minutes. Measurements of pulmonary functions were obtained before, immediately after exercise, and every ten minutes until Gaw/Vl returned to preexercise values.

Cold Air Challenge

Cold air was generated by passing the compressed dry air through aluminum heat exchanger coiled tubes placed in a large, insulated box filled with dry ice. A one-way valve was placed between the inspiratory and expiratory tubes so that the temperature of inspired and expired air could be measured separately and to avoid contamination from room air. The temperature of inspired air (−20°C ± 2°C) and expired air (±20°C ± 5°C) were measured with probes, connected to thermocouples, which were positioned at a distance of 1 cm from the inspiratory and 1 cm from the expiratory side of the one-way valve. While lying in the supine position, subjects inhaled cold air for 30 minutes at their usual respiratory frequency. Pulmonary function values were obtained before, immediately after cold air exposure, and every ten minutes until Gaw/Vl returned to control values.

Experimental Protocol

Each subject was studied on three occasions separated by at least one week. On experiment day 1, after obtaining baseline pulmonary function test results, a control bronchial provocation test with methacholine was performed to establish the individual's PD₃₅. On experiment day 2, the subjects were exposed to cold air challenge for 30 minutes, and measurements of Gaw/Vl were obtained before and after cold air exposure. Bronchial provocation was performed on Gaw/Vl after cold air exposure had returned to the baseline values, and the PD₃₅ was determined. On experiment day 3, the subjects performed a submaximal exercise on a treadmill. Measurements of Gaw/Vl were obtained before, immediately after exercise challenge, and then every ten minutes until Gaw/Vl returned to baseline. Bronchial provocation test to determine the PD₃₅ was performed soon after the Gaw/Vl had returned to the baseline.

Statistical Analysis

Data were expressed as mean ± SD. The effects of cold air exposure and exercise challenge on Gaw/Vl were analyzed by a paired t test. For PD₃₅, the data were analyzed by a nonparametric test, i.e., the Wilcoxon signed rank test for paired samples. The level of significance was defined at p < .05.

Results

Baseline Pulmonary Functions

These values are shown in Table 1. Asthmatic subjects had evidence of mild airway obstruction as shown by significantly lower Gaw/Vl, FEV₁/FVC ratio, and higher RV/TLC ratio. The Gaw/Vl was comparable on different experiment days within each group. The mean ± SD values of postdiluent Gaw/Vl on control, cold air, and exercise days were 0.19 ± 0.06, 0.18 ± 0.06, and 0.19 ± 0.06 s·cmH₂O⁻¹, respectively, for the normal group, and 0.15 ± 0.06, 0.15 ± 0.04, and 0.15 ± 0.05 s·cmH₂O⁻¹, respectively, for the asthmatic group.

Effect of Exercise and Cold Air on Gaw/Vl

Neither cold air exposure nor exercise challenge had any significant effect on Gaw/Vl or FEV₁ in the normal group (Table 2). In the asthmatic group, both cold air exposure and exercise challenge caused a significant decrease in Gaw/Vl; mean Gaw/Vl decreased by 20 percent and 15 percent after cold air exposure and exercise challenge, respectively (Table 2). Cold air exposure had no significant effect on FEV₁, while exercise decreased it by 8 percent. These values returned to baseline within 30 minutes.

Effect of Exercise and Cold Air on PD₃₅

In the asthmatic group, both cold air exposure and...
Table 3—Effect of Exercise and Cold Air Challenge on Bronchial Reactivity to Methacholine in Normal and Asthmatic Subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Postexercise</th>
<th>Post-Cold Air</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>72.6</td>
<td>± 32.2</td>
<td>64.1</td>
</tr>
<tr>
<td>Asthmatic</td>
<td>6.1</td>
<td>2.2†</td>
<td>3.0†</td>
</tr>
</tbody>
</table>

*Data shown as mean ± SD PD_{20}, i.e., cumulative provoking dose of methacholine in breath units which caused a 35% decrease in specific airway conductance. One breath unit is defined as 1 breath of 1 mg/ml concentration of methacholine.
†Significantly different from baseline, p < .05.

Exercise challenge caused a significant decrease in PD_{20} to methacholine. Mean ± SD baseline PD_{20} was 6.1 ± 11.6 breath units, which decreased to 2.2 ± 2.8 breath units after exercise and to 3.0 ± 5.0 breath units after cold air exposure (p < .05). (Table 3 and Fig 1).

In the normal group, mean ± SD baseline PD_{20} was 73 ± 32 breath units. The PD_{20} values after cold air exposure and exercise challenge were 52 ± 64 breath units and 64 ± 75 breath units, respectively (Table 3 and Fig 2). For the group these changes were not significant. In eight subjects PD_{20} decreased after cold air exposure, while in seven subjects PD_{20} decreased after exercise challenge.

**Discussion**

The results of the present investigation demonstrate that exercise and cold air challenge enhance bronchial reactivity to methacholine in subjects with bronchial asthma. This was shown by a significant decrease in PD_{20} to methacholine after exposure to cold air or exercise. In contrast, cold air or exercise challenge had no significant effect on bronchial reactivity in normal subjects.

Effect of exercise on bronchial reactivity to methacholine has been studied previously in both normal and asthmatic subjects; however, the results are in dispute. Suzuki et al. observed bronchial hyperreactiveness to methacholine 20 minutes after a single exercise challenge in asthmatic subjects. In contrast, Schachter and coworkers did not observe an enhancement of methacholine reactivity after exercise in normal subjects. Similarly, airway responsiveness to methacholine and histamine was unchanged in asthmatic subjects following exercise when inhalation challenge was performed during the refractory period. Some of these differences may be related to the fact that in some studies asthmatic subjects were studied, whereas other studies involved normal subjects. Similarly, in two studies inhalation challenge with histamine or methacholine was performed during the refractory period, which may have masked the enhancement of bronchial reactivity. The results of our study, which show significant enhancement of methacholine reactivity in asthmatic but not in normal subjects, tend to reconcile some of these differences. Although in the normal group no significant changes in PD_{20} were observed after exercise, in seven of ten subjects PD_{20} to methacholine decreased after exercise.
Like the exercise challenge, bronchial reactivity to methacholine after cold air exposure showed differential effects in normal and asthmatic subjects. In the asthmatic group, cold air exposure significantly enhanced the bronchial reactivity to methacholine. Although no significant increases in bronchial reactivity were observed in the normal group, some subjects did show decreases in PD_{50} to methacholine after cold air exposure. In this regard our results are consistent with those of Malo et al.\textsuperscript{17} who observed a slight but significant increase in bronchial reactivity to methacholine in asthmatic subjects after exposure to cold air. However, in contrast to the findings of Suzuki et al.\textsuperscript{18} who observed an increased reactivity to methacholine in normal subjects after cold air exposure, we were unable to find a significant change in PD_{50} to methacholine in the normal group. The reason for these differences is not clear, except that there was a difference in technical procedure. We measured the change in airway reactivity after cold air exposure by estimating the decrease in the provoking dose of methacholine that caused a 35 percent decrease in Gaw/Vt (PD_{35}), whereas Suzuki et al.\textsuperscript{18} assessed the changes in respiratory resistance measured by forced oscillation technique. Changes in lung volume were not measured; thus, respiratory resistance was not corrected for lung volume.

Malo et al.\textsuperscript{11} also observed that increased methacholine reactivity after cold air exposure is of short duration and is not observed 24 hours later. Similarly, the increased airway reactivity in asthmatic subjects after cold air or exercise challenge is peculiar to methacholine and is not observed with histamine.\textsuperscript{15} suggesting that thermal airway stress may modify the parasympathetic modulation of airway tone. In this regard, cold air- and exercise-induced increase in methacholine reactivity is different from increased airway reactivity observed after exposure to antigen, chemical pollutants, and hypoxia.\textsuperscript{1-5} The latter stimuli cause a generalized, prolonged increase in nonspecific airway reactivity, probably related to airway inflammation.

The mechanism of bronchoconstriction or of enhanced airway reactivity to methacholine after exercise or cold air exposure is not known. Excessive respiratory heat loss has been suggested as the basis of exercise-and cold air-induced bronchoconstriction,\textsuperscript{9} however, the initiating role of mast cell degranulation has not been excluded.\textsuperscript{10,19} The release of chemical mediators during exercise\textsuperscript{20} and protective effect of cromolyn sodium suggests a central role of mast cells.\textsuperscript{41} Degranulation of mast cells, which occurs both in allergic and nonallergic reactions,\textsuperscript{22,23} may also play a crucial role in enhancement of nonspecific bronchial reactivity\textsuperscript{4,24} following allergic or nonallergic airway reactions. Nasal challenge with cold, dry air has been shown to release chemical mediators in nasal washings of subjects with allergic rhinitis but not in control subjects.\textsuperscript{25} Thus, it is possible that airway thermal challenge may cause release of chemical mediators only in asthmatic subjects. This is consistent with our observations of enhanced airway reactivity in subjects with bronchial asthma but not in the control group.

REFERENCES

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