Tracheobronchial Constriction in Asthmatics Induced by Isocapnic Hyperventilation With Dry Cold Air*

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Although it is well known that isocapnic hyperventilation (IHV) with dry cold air produces airway constriction in asthmatic subjects, the site of airway narrowing is unclear. To address this issue, we have quantified the tracheal and bronchial response to IHV with dry cold air in 15 patients with mild asthma and 7 healthy control subjects. We employed the acoustic reflection technique to evaluate changes in airway cross-sectional areas caused by IHV with dry cold air. Airway areas were measured during tidal breathing before and 5 to 10, 30, 60, and 90 min following cold air challenge. For analysis purposes, airway areas were divided into three anatomic segments: extrathoracic tracheal segment, intrathoracic tracheal segment, and main bronchial segment. These segments were assessed at a fixed volume below total lung capacity. Maximal and partial expiratory flow-volume curves were also obtained before each set of area measurements. In normal subjects, IHV with dry cold air caused no significant changes in FEV₁, flow at 30% of the vital capacity in the partial curve (V₃₀p), or airway areas. In asthmatics, at 5 to 10 min after challenge, we found that FEV₁ decreased by 22±5% (mean±SEM) (p<0.0001), V₃₀p by 33±8% (p<0.003), intrathoracic tracheal area by 10.7%±2% (p<0.03), and main bronchial area by 14±3% (p<0.003). At 30 min, tracheal and main bronchial areas were returned to baseline levels; however, FEV₁ and V₃₀p were still significantly decreased, by 13±3% and 16±4%, respectively. We conclude that in asthmatics, IHV with dry cold air causes both tracheal and bronchial constriction, and that recovery seems to occur first in the central airways.

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Key words: acoustic reflections; asthma; bronchi; cold air; trachea

Abbreviations: EIA=exercise-induced asthma; IHV=isocapnic hyperventilation; MEFV=maximal expiratory flow volume; PEFV=partial expiratory flow volume; TLC=total lung capacity; V₃₀p=flow at 30% of vital capacity in the PEFV curves

Isocapnic hyperventilation (IHV) with dry cold air has been employed as a method for detecting non-specific bronchial hyperresponsiveness.¹,² Some investigators have suggested that IHV be regarded as a substitute stimulus in studies examining the pathophysiologic mechanisms of exercise-induced asthma (EIA).²⁻⁴ It is widely accepted that both stimuli trigger bronchoconstriction as a consequence of heat loss and/or a decrease in water content of the intrathoracic airways.²⁻⁵⁻⁷ According to this reasoning, exercise perse does not appear to be essential to the development of EIA and serves simply as the means to increase ventilation and overwhelm the warming and conditioning capacity of the upper airways. Furthermore, drugs that prevent exercise-induced bronchoconstriction (β₂-agonists, corticosteroids, and sodium cromoglycate) provide a similar protection against bronchoconstriction induced by IHV.⁸⁻¹⁰ However, some authors have reported differences between the two stimuli.¹¹⁻¹³ A refractory period has been demonstrated in EIA, but it has not been found consistently following IHV.¹²⁻¹⁴⁻¹⁶ Moreover, release of chemical mediators (such as histamine and neutrophil chemotactic factor) has been detected following EIA, whereas no such mediator involvement has been detected following IHV.¹⁷⁻²⁰ Another difference between the two stimuli may be the site of airway narrowing. Previous studies that have attempted to assess the main site of airway narrowing following exercise have used indirect methods with varying results.²¹⁻²³ Rubinstein et al,²⁴ employing the acoustic reflection technique, demonstrated dilatation of the trachea along with bronchial constriction in a group of asthmatics with EIA. However, little is known about the site of obstruction induced by IHV and whether tracheal dilatation occurs as in EIA.

The purpose of the present investigation was to...
study in asthmatic and healthy subjects the responses of the trachea and bronchi to IHV with dry cold air. To quantify these responses, we used the acoustic reflection technique, which has been shown to be an accurate method to measure changes in cross-sectional areas of the upper and central airways.25,26

**Materials and Methods**

*Subjects*

We studied 15 subjects (8 women and 7 men) aged 34±10 years (mean±SD) who satisfied the American Thoracic Society criteria for asthma27 and had a history of reproducible EIA. They had been free of airway infection in the previous 2 months and had refrained from taking oral bronchodilators 48 h before any study; inhaled bronchodilators were not used for at least 8 h before each study. Treatment with inhaled corticosteroids was not withheld. None of the subjects required regular oral corticosteroids. Seven healthy nonsmoking volunteers (4 men and 3 women) with mean age of 32±7 years (mean±SD) served as control subjects. The study was approved by the University of Toronto Human Ethics Committee and written consent was obtained from each subject.

*Acoustic Reflection Technique*

Measurements of cross-sectional airway areas were performed using the acoustic reflection technique. This method has been described previously in detail.25,26 Briefly, acoustic pulses are generated by a loudspeaker and transmitted into the subject's respiratory tract. As the waves travel through the airways, they are reflected by changes in cross-sectional area. The incident and reflected pulses are recorded by a microphone situated next to the mouth. From the knowledge of the intensities of the incident and reflected waves, the airway area at a given distance from the microphone is computed, and a plot of cross-sectional area as a function of distance is obtained (Fig 1).

Subjects were seated and connected to the echogram system through a scuba-type mouthpiece. They breathed a mixture of 80% He and 20% O2 from a reservoir bag. End-tidal N2 was sampled continuously (Niralyzer 505; Med-Science Electronics; St. Louis) to ensure adequate washout with the He-O2 mixture. When the N2 concentration was less than 10%, measurements of airway cross-sectional areas were carried out every 0.2 s during tidal breathing. Up to 256 measurements of airway areas and simultaneous changes in lung volume were recorded with each echogram. Echograms were obtained at baseline and repeated at 5 to 10, 30, 60, and 90 min after the termination of the challenge.

For analysis purposes, airway areas were divided into three anatomic segments (Fig 1). The glottis was defined as the narrowest area distal to the pharynx, followed by the 2 tracheal segments: the extrathoracic trachea, a 6-cm segment immediately after the glottis, and the intrathoracic trachea, a 12-cm segment distal to the extrathoracic trachea. The main bronchial area was defined as the portion just after the intrathoracic trachea, and ending 50 cm from the mouth. Airway echograms were collected during tidal breathing followed by a complete inspiration to total lung capacity (TLC; Fig 2). The TLC maneuver was performed to establish a volume history and allowed compensation, during subsequent data analysis, for possible shifts in end-tidal volume. Using TLC as the volume standard, a fixed volume below this value was chosen for each subject and used to analyze prechallenge and postchallenge measurements. Below this fixed volume, an approximately 0.5-L window was determined within each subject's tidal volume breathing range. Only area-distance functions acquired within this volume window were used for analysis (Fig 2).
Cold Air Inhalation Procedure

After arrival at the laboratory, subjects were asked to sit quietly for approximately 20 min. Thereafter, six maximal expiratory flow volume (MEFV) and partial expiratory flow volume (PEFV) curves were performed (Med-Science Electronics Wedge Spirometer; St. Louis) and baseline FEV$_1$ and flow at 30% of vital capacity in the PEFV curves ($V_{30p}$) were measured. Sustained (4 min) maximal voluntary ventilation was calculated from the observed FEV$_1$ using the formula of Clark et al.\textsuperscript{28} 4 min maximal voluntary ventilation (L/min, BTPS) = 12.5 FEV$_1$ + 15.4. This value became the target ventilation for the cold air IHV procedure.

The breathing circuit used in this investigation was a modification of that described by Phillips et al.\textsuperscript{59} Subjects were seated and connected through a mouthpiece to a two-way valve (Hans-Rudolph 2700; Kansas City, Mo). They breathed from a tank containing a compressed gas mixture of 21% O$_2$, 5% CO$_2$, and balance N$_2$. This CO$_2$ concentration has been demonstrated to maintain isocapnic conditions at ventilation rates of 30 to 105 L/min.\textsuperscript{28} A device generating dry, subzero gas (Turboaire Challenger; Equilibrated Bio Systems Inc; Melville, NY) was located between the gas source and the inspiratory port of the valve (Hans-Rudolph). This apparatus was able to maintain the temperature of the inspired gas during the challenge between −15 and −20°C. To prevent entrainment of warm room during the challenge, a large-bore tube was attached to the Turboaire outlet port. A thermometer, close to the mouth, continuously monitored the temperature of the inspired gas. A reservoir bag was placed in the expiratory limb between a calibrated rotameter and the valve (Hans-Rudolph). The rotameter was connected to an adjustable vacuum pump to allow emptying of the reservoir at a constant-flow rate determined from the target ventilation.

Once the rotameter was set at the flow rate previously calculated, subjects were required to breathe cold air for 4 min, at the depth and rate necessary to keep the reservoir bag filled. MEFV and PEFV curves were carried out every 3 min until a maximum of 10 min after the test. When FEV$_1$ fell by at least 10%, airway echograms were performed at the time sequence mentioned above. Before each echogram, MEFV and PEFV curves were obtained.

Statistical Analysis

Repeated-measures analysis of variance was used to compare FEV$_1$, $V_{30p}$, and airway areas at baseline, and at 5 to 10, 30, 60, and 90 min. The level of significance was chosen to be <0.05. All statistical calculations were done using a statistical package (SAS version 6.04; SAS Institute, Inc; Cary, NC).

RESULTS

Table 1 shows the age and baseline FEV$_1$ for healthy subjects and asthmatics as well as their medication. Asthmatics had a baseline FEV$_1$ that was 85±15% of predicted compared with the 99±4% of predicted for healthy subjects.

In healthy subjects, IHV with dry cold air resulted in no significant changes in FEV$_1$, $V_{30p}$, or airway cross-sectional areas.

The results in the asthmatics were quite different. At 5 to 10 min, IHV with dry cold air caused a 22±5% (mean±SEM) fall in FEV$_1$ ($p<0.0001$) and a 33±8% decrease in $V_{30p}$ ($p<0.003$). Thirty minutes after the challenge, FEV$_1$ and $V_{30p}$ were still decreased significantly as compared with baseline; 13±3% ($p<0.003$)
and 16±4% (p<0.02), respectively. At 60 and 90 min, FEV₁ and V₃₀₀ values were similar to the baseline.

Cold air inhalation caused a decrease in intrathoracic tracheal cross-sectional area of 10.7±2% (mean±SEM) (p<0.03) and in main bronchial cross-sectional area of 14±3% (p<0.003), 5 to 10 min postchallenge. No significant changes were found in the area of the extrathoracic trachea. At 30, 60, and 90 min, airway areas had returned to baseline. The individual effects of IHV with cold air on intrathoracic and main bronchial areas are displayed in Figure 3. Figure 4 illustrates the time course of the constriction for intrathoracic tracheal and main bronchi segments.

**DISCUSSION**

Our study shows that in asthmatic subjects, IHV with dry cold air elicits a significant decrease in the cross-sectional areas of intrathoracic trachea and main bronchi within 5 to 10 min after the challenge. The recovery of the trachea and main bronchi cross-sectional areas was complete by 30 min; however, a significant decrease in FEV₁ and V₃₀₀ was still present, suggesting that a more peripheral and lasting bronchoconstriction remained.

Eucapnic hyperpnea with cold air has been shown to increase lung resistance in normal and sensitized animals and to cause tracheal constriction in anesthetized and artificially ventilated dogs. In healthy subjects, O’Cain et al reported that IHV with dry cold air resulted in a significant reduction in FEV₁ and V₃₀₀. However, they used higher levels of minute ventilation (123 L/min) than those employed by us (64±8 L/min, mean±SD), proving that airway obstruction can be produced in normal subjects if a strenuous workload is reached. Our finding that IHV has no effect on airway dimensions is in agreement with others who reported little or no change in conventional pulmonary function test results in healthy subjects after IHV with cold air.

In subjects with asthma, Herxheimer was first (to our knowledge) to demonstrate that hyperventilation produces airway constriction. However, little information is available as to the location of this constriction. This is in contrast with EIA, in which several studies have been performed to identify the site of airway narrowing. McFadden et al found that some asthmatics develop predominantly large airway constriction, while others show predominantly small airway narrowing after exercise challenge. By contrast, other investigators demonstrated that the predominant location of narrowing occurs most consistently in the large airways. In all of these studies, the site of airway obstruction was inferred from the measurement of ratios of maximal expiratory flow with air and 80% He-20% O₂. It is possible that the variability of the results reflects the lack of a more accurate method to assess the site of this obstruction. In this regard, Rubinset al used the acoustic reflection technique to measure more directly the effects of EIA on the central airways. These authors demonstrated that bronchi were the main site of airway narrowing. In addition, they found an unexpected dilatation of the trachea following exercise challenge. In a different group of asthmatics, our results showing constriction of the intrathoracic trachea and bronchi with a decrease in FEV₁ and V₃₀₀ suggest that central and peripheral airways are involved in the response to IHV, unlike EIA in which the location of the primary site of airway narrowing has been found to be heterogeneous.

The faster recovery of the asthmatic central airways in comparison to peripherally bronchi might be due to an attenuation of central airway inflammation. Since 10 of the 15 subjects were taking inhaled corticosteroids long term, it is possible that a poor penetration of the aerosol into the peripheral airway could account for a higher degree of inflammation at this level and therefore a more lasting constriction.

Although it is likely that EIA and IHV share an identical trigger (ie, heat/water loss), different mechanisms leading to airway narrowing or dilatation are

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**Table 1—Anthropometric Data, FEV₁₁, and Current Medications for All Subjects**

<table>
<thead>
<tr>
<th>No./Sex/Age, yr</th>
<th>Height, cm</th>
<th>FEV₁, L (% pred)</th>
<th>Medication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/F/38</td>
<td>171</td>
<td>3.2 (94)</td>
<td></td>
</tr>
<tr>
<td>2/M/34</td>
<td>175</td>
<td>4.5 (105)</td>
<td></td>
</tr>
<tr>
<td>3/M/22</td>
<td>173</td>
<td>4.2 (100)</td>
<td></td>
</tr>
<tr>
<td>4/M/36</td>
<td>180</td>
<td>4.3 (95)</td>
<td></td>
</tr>
<tr>
<td>5/M/31</td>
<td>171</td>
<td>4.0 (100)</td>
<td></td>
</tr>
<tr>
<td>6/F/23</td>
<td>161</td>
<td>3.0 (100)</td>
<td></td>
</tr>
<tr>
<td>7/F/40</td>
<td>168</td>
<td>3.1 (100)</td>
<td></td>
</tr>
<tr>
<td>Mean 32</td>
<td>171</td>
<td>3.7 (99)</td>
<td></td>
</tr>
<tr>
<td>SD 7</td>
<td>7</td>
<td>0.6 (4)</td>
<td></td>
</tr>
<tr>
<td>Asthmatic subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/M/21</td>
<td>176</td>
<td>4.4 (100)</td>
<td>β₂</td>
</tr>
<tr>
<td>2/F/24</td>
<td>161</td>
<td>3.2 (107)</td>
<td>β₂</td>
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<td>150</td>
<td>2.1 (92)</td>
<td>β₂, IC</td>
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<tr>
<td>4/M/37</td>
<td>168</td>
<td>3.9 (105)</td>
<td>IC</td>
</tr>
<tr>
<td>5/F/27</td>
<td>157</td>
<td>3.0 (108)</td>
<td>β₂, IC</td>
</tr>
<tr>
<td>6/F/42</td>
<td>156</td>
<td>1.7 (67)</td>
<td>β₂, Th, IC</td>
</tr>
<tr>
<td>7/F/32</td>
<td>155</td>
<td>2.0 (77)</td>
<td>β₂, Th, IC</td>
</tr>
<tr>
<td>8/F/60</td>
<td>152</td>
<td>1.3 (65)</td>
<td>β₂, IC</td>
</tr>
<tr>
<td>9/M/37</td>
<td>166</td>
<td>3.3 (91)</td>
<td>β₂, SG</td>
</tr>
<tr>
<td>10/M/38</td>
<td>170</td>
<td>3.2 (80)</td>
<td></td>
</tr>
<tr>
<td>11/M/40</td>
<td>168</td>
<td>2.6 (72)</td>
<td>β₂, IC</td>
</tr>
<tr>
<td>12/F/25</td>
<td>152</td>
<td>2.0 (80)</td>
<td>β₂</td>
</tr>
<tr>
<td>13/F/29</td>
<td>163</td>
<td>2.1 (67)</td>
<td>β₂, IC</td>
</tr>
<tr>
<td>14/M/37</td>
<td>186</td>
<td>3.7 (74)</td>
<td>IC</td>
</tr>
<tr>
<td>15/M/25</td>
<td>172</td>
<td>3.7 (90)</td>
<td>IC</td>
</tr>
<tr>
<td>Mean 34</td>
<td>164</td>
<td>2.8 (85)</td>
<td></td>
</tr>
<tr>
<td>SD 10</td>
<td>15</td>
<td>0.9 (15)</td>
<td></td>
</tr>
</tbody>
</table>

*β₂—β₂-agonists, Th=theophylline, IC=inhaled steroids, SG=sodium cromoglycate.
possible. Plasma catecholamine levels have been demonstrated to increase in normal subjects and asthmatics following exercise.\textsuperscript{40,41} Conversely, an absence of sympathoadrenal activity has been shown after IHV.\textsuperscript{42} This suggests that catecholamines present during and after exercise, but not during or after IHV, might be the reason for the tracheal dilatation observed in the study of Rubinstein et al.\textsuperscript{24} Other mechanisms due to release of different mediators during EIA vs IHV are possible but remain speculative.\textsuperscript{13,17,19,20} Finally, it is possible that the amount of thermal burden was greater during IHV with dry, cold air than during EIA.
performed at room humidity and temperature, making the trachea more susceptible to the constrictor effects of respiratory heat/water losses.3

In summary, our measurements of the airway cross-sectional areas in asthmatics after IHV with dry cold air showed a significant narrowing of the main bronchi. We also found a significant constriction of the intrathoracic trachea, which along with the main bronchi recovered faster than $FEV_1$ and $V_30_P$, suggesting that the entire tracheobronchial area shares the response to IHV with dry, cold air in asthmatics.

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