Integrated response of the upper and lower respiratory tract of asthmatic subjects to frigid air

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The ability of the respiratory tract to regulate heat and water losses to the environment plays a critical role in allowing mankind to function in climatic extremes without fear of dehydration or thermal damage to the lungs (5, 15, 34). In the process of conditioning the inspired air, the upper and lower airways act in series, and heat and water move to and from the airstream in a longitudinally distributed fashion as a function of the respective gradients that exist (5, 15, 34). Although the mouth offers less resistance to flow, the nose is the more efficient heat exchanger, and it is the usual route by which the inspirate enters the lungs (24, 26, 33). During tidal breathing through the nose, the inspired air is close to body temperature and fully humidified by the time it reaches the posterior pharynx, and the intrathoracic airways play little role in the conditioning process, even in frigid environments (5, 15, 26, 34). When there is a need to move large volumes of air, however, the pattern of respiration shifts, and at minute ventilations (V\textsubscript{E}) at or near 40 l/min, mouth breathing commences (33). Now the intrathoracic airways are forced to contribute a significant amount of the thermal energy required to bring the inspirate to full saturation at core temperature (17–20).

In normal humans, these adaptations proceed without adverse clinical consequence (7, 23), but this is often not the case in those with respiratory tract illnesses (1, 7, 21). For example, it is well documented that oral hyperventilation (OHV) of cold air can result in bronchoconstriction in asthmatic subjects and in some individuals with bronchitis (1, 7). The influence of thermal stress on nasal function, however, is far less established. Cold air hyperventilation can certainly induce rhinorrhea in some subjects (21), but it is controversial as to whether nasal resistance rises (27, 30). It is also unclear whether the events in the nose have any clinical impact on the airways and vice versa.

The purpose of the present study was to provide data on these issues by characterizing the individual responses of the upper and lower respiratory tract of asthmatic subjects to systematic increases in V\textsubscript{E} while they breathed frigid air. We also examined whether the imposition of large thermal burdens on one component of the system could influence the physiology of the other. Our observations form the basis of this report.

MATERIALS AND METHODS

Twenty-two asymptomatic asthmatic volunteers [12 men and 10 women, 27 ± 2 (SE) yr] served as our subjects (Table 1). All the participants were nonsmokers, and four had rhinitis. None used antihistamines, nasal decongestants, glucocorticoids, cromolyn sodium, or long-acting bronchodilators. All refrained from employing short-acting agents for 12 h before any study day. The Committee on Human Investigation of University Hospitals of Cleveland approved the protocol, and informed consent was obtained from each participant.

Isoacapnic hyperventilation was performed during mouth and nose breathing at progressively increasing levels of V\textsubscript{E} while the subjects inhaled frigid air through a heat exchanger. Expired air was directed into a reservoir balloon that was constantly evacuated at a known rate through a

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Table 1. Demographic and baseline physiological data

<table>
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<th>Subj No.</th>
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<th>FEV1, liters</th>
<th>%Pred FEV1</th>
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<td>22</td>
<td>M</td>
<td>+</td>
<td>3.13</td>
<td>73</td>
</tr>
</tbody>
</table>

Mean ± SE 27 ± 2 3.60 ± 0.22 93 ± 3

M, male; F, female; FEV1, 1-s forced expiratory volume at entrance into study; %Pred FEV1, FEV1 expressed as a percentage of predicted values.

calibrated rotameter (11, 19, 20). The subjects were coached to keep the balloon filled, and, in so doing, their VE could be controlled at any desired level. Previous experiments have documented the accuracy of this approach (19). End-tidal Pco2 during hyperventilation were monitored with an LB-2 analyzer (Beckman Instruments, Fullerton, CA), and sufficient CO2 was added to the inspiratory port of the exchanger to maintain end-tidal Pco2 at eucapnic levels. Recovery took place on room air in all trials. The water content of the inspirate during hyperpnea was <1 mgH2O, which, for the purposes of this study, was considered to be zero. As has been standard procedure (7, 11–13, 19, 20, 23), each bout of hyperventilation lasted 4 min. During the mouth breathing trial, the challenge was stopped when the 1-s forced expiratory volume (FEV1) decreased ≥15% from its prechallenge value. The VE at this point was then used in the subsequent studies on integrated function.

Maximum-forced exhalations were performed in triplicate with use of a waterless spirometer before and 10 min after cessation of each bout of hyperpnea. This point has been previously shown to correspond to the maximum response (7, 11–13). The curves with the largest FEV1 were chosen for analysis. After the maximum VE had been reached, the FEV1 was followed serially for 30 min.

The protocol for the upper airway trials was similar to that for the mouth breathing trials, except the subjects inspired from the heat exchanger through a heavily insulated small-volume nasal mask (neonatal anesthesia mask) and exhaled into the rotameter-balloon system. Before and 10 min after each period of hyperpnea, the resistance to flow through the nose was measured by posterior rhinometry (G. M. Instruments Computerized NR 9 Rhinomanometer, Life-Tech, Houston, TX) (4). The challenge was discontinued when a VE of 40 l/min was reached. None of the subjects was able to sustain VE beyond this point. As with spirometry, nasal resistance was serially followed for 30 min after the maximal challenge.

Nasal resistance was computed by relating airflow from a pneumotachograph, mounted in a facemask, to the pressure drop recorded by a tube placed through the mouth, which lay at the back of the tongue, in the pharynx. The subjects were asked to close their lips around the tube and breathe through the nose. In so doing, the pressures developed in the mouth equalized those behind the nasal passages (4). The outputs of the pressure and flow transducers were fed into an analog-to-digital converter and stored in a desktop computer. The subjects were coached to inhale and exhale through the nares at fixed efforts, producing flows of 1–2 l/min, and the resulting pressure-flow relationships were displayed on a calibrated screen on the computer monitor to provide visual feedback to the subject and technician. Resistance was computed electronically by measuring the slopes of the curves at flows between 0 and ±0.1 l/s and was reported as the mean of five measurements. Results

The experimental protocols were performed at the same hour on 5 test days. On one occasion, stimulus-response relationships to isocapnic hyperventilation of frigid air were obtained during mouth breathing, and lung function was assessed (nose hyperventilation (OHV)); on another, these relationships were recorded for the nose, and nasal resistance was measured (nasal hyperventilation (NHV)). The order of study was randomized. When this information was in hand, the participants returned on 2 more days, when OHV and NHV were undertaken at the respective maximum levels, then upper and lower airflow responses were assessed [OHV + nasal response (NR) and NHV + pulmonary response (PR)]. Several hours after the NHV + PR challenge, the subjects also hyperventilated orally, at the VE applied to the upper airway, to determine whether this thermal burden would independently change bronchial caliber. In the combination studies, nasal resistance was measured at 10 min after hyperpnea and then immediately thereafter by spirometry.

After completion of the main body of experiments, the subjects came to the laboratory on a fifth occasion and hyperventilated frigid air while inhaling through the nose and exhaling through the mouth. Nasal resistance was measured before and after challenge, as described above. In 10 subjects the FEV1 was also recorded before and after the breathing paradigm was changed.

The data were analyzed by two-factor repeated-measures ANOVA, one-factor ANOVA, and paired t-tests. All P values were two-tailed, and P ≤ 0.05 was considered significant.

RESULTS

The mean values for the temperatures of the inspired air for each experiment, along with the relevant prechallenge values for the FEV1 and NR, in the four main experiments are presented in Table 2. The mean VE is also provided. The temperatures ranged between 15.3 and 19.5 °C (F = 1.72, P = 0.17). The FEV1 before the OHV trial was 90 ± 3% of predicted normal and varied <10% between experiments (range 3.46 ± 0.16 to 3.28 ± 0.25 liters, F = 0.25, P = 0.78). The data for NR fell within published ranges (14, 28) and differed little from trial to trial (range NR 2.98 ± 0.34 to 3.48 ± 0.29 cmH2O·l−1·s−1, F = 0.64, P = 0.53). The mean VE used in the OHV + NR and NHV + PR trials were 63 ± 4 and 40 ± 0.1 l/min, respectively.

The individual stimulus-response curves during oral and nasal hyperpnea are presented in Figs. 1 and 2, respectively. In the oral experiment, the FEV1 decreased an average of 24 ± 2% from control (P < 0.001)
at the maximum $\dot{V}_E$. In the nasal trial, resistance rose as $\dot{V}_E$ increased ($F = 7.12, P < 0.001$). The values after the 30 and 40 l/min trials were significantly different from baseline but not each other [$\Delta NR = 32 \pm 9\% (P = 0.008)$ and $31 \pm 9\% (P = 0.005)$ at 30 and 40 l/min, respectively]. The effect of inhaling frigid air through the mouth on combined upper and lower airway function is shown in Fig. 3. As in the control experiment, oral hyperpnea not only produced airway obstruction ($\Delta FEV_1 = 26 \pm 2\%, P < 0.001$), but it was also associated with a decrease in nasal patency ($\Delta NR = 26 \pm 9\%, P = 0.01$). In the converse experiment, nasal hyperpnea induced a $33 \pm 9\%$ elevation in NR ($P = 0.01$); however, lung function did not change ($\Delta FEV_1 = 2 \pm 2\%, P = 0.27$; Fig. 4). Hyperventilation at 40 l/min through the mouth, however, caused the $FEV_1$ to decrease 0.55 liter ($17 \pm 3\%, P < 0.001$).

Changing the pattern of breathing materially enhanced the consequences of cold air on the nose. When the subjects inhaled through the nares and exhaled through the mouth, NR increased markedly at each level of $\dot{V}_E$ (Fig. 5). All values except those at 10 l/min ($P = 0.08$) were significantly different from the prechallenge baseline at $P \leq 0.01$ (overall relationship $F = 11.7, P < 0.001$). Even though the prechallenge NR values in this experiment were less than on the control

Table 2. Inspired temperatures, prechallenge mechanical data, and threshold ventilations

<table>
<thead>
<tr>
<th>Variable</th>
<th>OHV</th>
<th>NHV</th>
<th>OHV + NR</th>
<th>NHV + PR</th>
<th>$P$</th>
</tr>
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<tbody>
<tr>
<td>$T_i$, °C</td>
<td>-15.3 ± 1.1</td>
<td>-19.1 ± 1.4</td>
<td>-19.5 ± 1.8</td>
<td>-18.6 ± 1.7</td>
<td>0.17</td>
</tr>
<tr>
<td>$FEV_1$, liters</td>
<td>3.46 ± 0.16</td>
<td>3.28 ± 0.20</td>
<td>3.43 ± 0.43</td>
<td>2.98 ± 0.34</td>
<td>0.78</td>
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<tr>
<td>NR, cmH$_2$O·l$^{-1}·s$</td>
<td>3.48 ± 0.29</td>
<td>3.30 ± 0.20</td>
<td>2.98 ± 0.34</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>$\dot{V}_E$, l/min</td>
<td>63 ± 4</td>
<td>40 ± 0</td>
<td></td>
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</table>

Values are means ± SE. OHV, isocapnic hyperventilation performed through the mouth followed by an assessment of lower airway function; NHV, isocapnic hyperventilation performed through the nose followed by an assessment of upper airway function; OHV + NR, oral isocapnic hyperventilation followed by an assessment of upper and lower airway function; NHV + PR, nasal isocapnic hyperventilation followed by an assessment of lower and upper airway function; $T_i$, temperature of inspired air; NR, nasal resistance; $\dot{V}_E$ OHV + NR, minute ventilation associated with a $>15\%$ decrement in $FEV_1$ in OHV challenge; $\dot{V}_E$ NHV + PR, maximum ventilation achieved in NHV challenge. Because all subjects in NHV + PR challenge achieved 40 l/min, SE = 0.

Fig. 1. Effect of oral hyperpnea of frigid air on pulmonary mechanics. $FEV_1$, 1-s forced expiratory volume (liters); $\dot{V}_E$, minute ventilation (l/min). Values in each panel indicate stimulus-response curves for individual subjects.

Fig. 2. Inspiratory temperatures, prechallenge mechanical data, and threshold ventilations.
day (ΔNR 34%, *P* = 0.008), the observed effect on NR was significantly larger than that seen with the normal paradigm of inhaling and exhaling through the nose (*F* = 9.6, *P* < 0.001). As shown in Fig. 6, even increases in NR of this magnitude had no effect on lower airway function. Nasal resistance rose 88% from control (*P* < 0.001), but the FEV₁ changed <1% (*P* = 0.24).

**DISCUSSION**

The results of the present study demonstrate that the upper and lower airways of asthmatic subjects exhibit a complex pattern of response to hyperpnea with cold air. Short, isolated exposures of the lower respiratory tract to large thermal loads result in bronchial narrowing and an increase in nasal resistance, whereas similar events in the upper respiratory tract have a different outcome. Forcing the nose to increase its heat-exchanging activity reduces nasal patency but has no direct or indirect consequences on the caliber of the intrathoracic airways.

Our findings with OHV on lung function were expected and are consistent with extensive literature on the subject (1, 7, 18). To our knowledge, however, the effects of OHV of frigid air on nasal geometry that we observed have never been reported. Such an occurrence is presumably reflex in origin and likely represents a teleological adaptation to improve the efficiency of the conditioning of inspired air (see below). Previous attempts at examining integrated upper and lower airway function have been limited to studying strenuous exercise in combination with cold air breathing. In these circumstances, bronchial narrowing develops, but nasal resistance typically falls through the vasoconstrictor effects of circulating norepinephrine and epinephrine (6, 12, 31). Hence, in this type of challenge, any tendency toward nasal constriction is abolished by the systemic hormonal consequences of physical exertion. In contrast, although the intrathoracic thermal profiles with isocapnic hyperventilation are identical to exercise (11), the catecholamine levels do not increase...
consequently, the underlying nasal events can manifest themselves. The suggestion of the presence of oral-nasal reflexes is not new. Bundgaard and associates (2) and Yap and Pride (35) gave histamine aerosols orally to asthmatic subjects and noted falls in \( FEV_1 \) and nasal conductance. A major impediment to interpreting these works was the difficulty in excluding histamine absorption from the lung with systemic delivery to the nose. Because the converse readily occurs (i.e., airway distribution from nasal deposition) (16), the presence of reflex physiology was uncertain. In the present study, because it was impossible for the cold air in the lower airways to have reached the nose, the existence of such a reflex is more firmly grounded.

There has been uncertainty as to how the nose responded when called on to condition large volumes of cold air. Early works uniformly recorded an increase in nasal resistance (6, 27, 32), but more recent studies have not been confirmatory (3, 30). Most of the latter investigations used relatively short exposures, which may not have provided sufficient thermal stress to induce an effect. During hyperpnea, thermal losses in the nose progressively rise with time because of incom-

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**Fig. 3.** Effect of oral hyperpnea on frigid air on airway and nasal mechanics. Data points are means; error bars are SE. \( P \) values below abscissa refer to baseline (B)-response (R) comparisons.

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**Fig. 4.** Effects of nasal hyperpnea of frigid air on nasal and airway mechanics. A and B: effects of nasal hyperventilation of 40 l/min on combined upper and lower airway function. C: effects of oral hyperventilation (HV) at same level of \( \dot{V}_E \) on lower airway function. Data points are means; error bars are SE. \( P \) values below abscissa refer to baseline-response comparisons.
ple recovery of the heat and water released from the mucosa during inspiration (17, 26). The colder the incoming air, the less its water content, the greater the transfers, and the more the deficits. When losses become critical, nasal blood volume increases secondary to engorgement of the venous sinuses in the submucosa (26). This adaptation brings more heat and water to the surface to meet the increased demands and protects the tissue from evaporative damage. By congesting the air passages, it also promotes turbulence to aid in air-surface contact, thus improving thermal exchange (26). The down side is that the individual must now overcome an increase in resistance and excessive fluid production, which, if severe enough, may shift breathing to the mouth (21, 33).

The precise time course for these events has not been determined, but at normal tidal ventilation, 45 min may be required (21). With hyperpnea, the duration is shorter and our data suggest that, with progressive cumulative stress, as little as 4–8 min may be all that is needed (Fig. 2). If, however, recovery of the heat and water transferred during inspiration is prevented, congestion may develop even more rapidly (30). Thus the changes in nasal resistance observed at any given
moment appear to be a function of the cumulative energy expended to that point. If losses are small, little narrowing develops; as they increase, nasal flow becomes progressively limited. These concepts are nicely exemplified by contrasting the two forms of hyperventilation depicted in Fig. 5. Inhaling through the nose and out of the mouth forced the continued loss of heat and water and produced rapid engorgement of the nasal mucosa of asthmatic and normal subjects and their bronchial responsivity to carbachol (10). Yet, nasal breathing of cold air has no effects between the magnitude of the augmentation in asthmatic subjects and their bronchial responsivity to carbachol. In contrast, Fontanari et al. (9) found nasal oscillatory airway resistance to rise only in the former. In summary, the effects of cold air hyperpnea on the respiratory tract of asthmatic subjects are complex, and the results appear to depend on the site of stimulation. During oral hyperpnea, the upper and lower airways respond. Nasal resistance rises when local heat and water losses are large; however, clinically significant nasal-pulmonary reflexes do not appear to be part of the physiological response to such exposures.

We recognize that NR varies temporally (15) and that there can be cyclic fluctuations in resistance between nostrils (8). Although it is possible that events such as these may have been responsible for the differences in baseline in our studies. The changes in NR are typically random occurrences with long periods between them (8, 15). Our measurement technique recorded the resistance in both nostrils simultaneously, and all our interventions were acute with short-lived responses.

What of the influence of nasal stimulation with cold on lower airway function? In the NHV + PR trial (Fig. 4), NR rose significantly after hyperpnea, but the FEV1 did not change. Because the same ventilatory load applied to the nose induced bronchial narrowing when given orally, our results did not derive from an insensitivity of the intrathoracic airways to the provocations. Rather, they appear to be related to a lack of an adverse interaction between upper and lower events. The data in Fig. 6 further support this conclusion by demonstrating that even maximal changes in NR did not induce bronchoconstriction.

REFERENCES


