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

MELISSA L. McLANE, J O ANN NELSON, K. A. LENNER, RANA HEJAL, CHAKRADHAR KOTARU, MARY SKOWRONSKI, ALBERT CORENO, ELIZABETH LANE, AND E. R. MCFA DDEN, J R.

Division of Pulmonary and Critical Care Medicine, University Hospitals of Cleveland, and Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106

McLane, Melissa L., Jo Ann Nelson, K. A. Lenner, Rana Hejal, Chakradhar Kotaru, Mary Skowronski, Albert Coreno, Elizabeth Lane, and E. R. McFadden, J r.

Integrated response of the upper and lower respiratory tract of asthmatic subjects to frigid air. J. Appl. Physiol. 88: 1043–1050, 2000.—To evaluate the influence of cold air hyperpnea on integrated upper and lower airway behavior, 22 asthmatic volunteers hyperventilated through their mouths (OHV) and noses (NHV) while pulmonary and nasal function were determined individually and in combination. In the isolated studies, OHV at a minute ventilation of 65 ± 3 l/min lowered the 1-s forced expiratory volume (FEV1) 24 ± 2% (P < 0.001) and NHV (40 l/min) induced a 31 ± 9% (P < 0.001) increase in nasal resistance (NR). In the combined studies, oral hyperpnea reduced the FEV1 (ΔFEV1 26 ± 2%, P < 0.001) and evoked a significant rise in NR (ΔNR 26 ± 9%, P = 0.01). In contrast, NHV only affected the upper airway. NR rose 33 ± 9% (P = 0.01), but airway caliber did not change (ΔFEV1 2%, P = 0.27). The results of this investigation demonstrate that increasing the transfer of heat and water in the lower respiratory tract alters bronchial and nasal function in a linked fashion. Forcing the nose to augment its heat-exchanging activity, however, reduces nasal caliber but has no effect on the intrathoracic airways.

cold air; asthma; hyperpnea; nasal function; airway function

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_{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 hyperpnea 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_{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.

Isocapnic hyperventilation was performed during mouth and nose breathing at progressively increasing levels of V_{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

http://www.jap.org 8750-7587/00 $5.00 Copyright © 2000 the American Physiological Society


The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Downloaded from http://jap.physiology.org/ by 10.220.33.2 on August 29, 2017
Table 1. Demographic and baseline physiological data

<table>
<thead>
<tr>
<th>Subj No.</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Rhinitis</th>
<th>FEV1, liters</th>
<th>%Pred FEV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>F</td>
<td>–</td>
<td>3.33</td>
<td>122</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>F</td>
<td>–</td>
<td>2.50</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>F</td>
<td>–</td>
<td>3.58</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>F</td>
<td>–</td>
<td>3.82</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>F</td>
<td>–</td>
<td>3.66</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>F</td>
<td>–</td>
<td>2.44</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>M</td>
<td>–</td>
<td>5.58</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>23</td>
<td>M</td>
<td>–</td>
<td>4.10</td>
<td>103</td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>M</td>
<td>–</td>
<td>4.27</td>
<td>102</td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>M</td>
<td>–</td>
<td>4.24</td>
<td>101</td>
</tr>
<tr>
<td>11</td>
<td>24</td>
<td>M</td>
<td>–</td>
<td>5.94</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>24</td>
<td>M</td>
<td>–</td>
<td>3.37</td>
<td>73</td>
</tr>
<tr>
<td>13</td>
<td>23</td>
<td>M</td>
<td>–</td>
<td>2.88</td>
<td>66</td>
</tr>
<tr>
<td>14</td>
<td>27</td>
<td>F</td>
<td>+</td>
<td>2.29</td>
<td>83</td>
</tr>
<tr>
<td>15</td>
<td>28</td>
<td>F</td>
<td>+</td>
<td>2.63</td>
<td>91</td>
</tr>
<tr>
<td>16</td>
<td>28</td>
<td>M</td>
<td>–</td>
<td>3.76</td>
<td>86</td>
</tr>
<tr>
<td>17</td>
<td>50</td>
<td>F</td>
<td>+</td>
<td>2.59</td>
<td>107</td>
</tr>
<tr>
<td>18</td>
<td>27</td>
<td>M</td>
<td>–</td>
<td>2.85</td>
<td>66</td>
</tr>
<tr>
<td>19</td>
<td>21</td>
<td>M</td>
<td>–</td>
<td>5.10</td>
<td>113</td>
</tr>
<tr>
<td>20</td>
<td>25</td>
<td>M</td>
<td>–</td>
<td>3.13</td>
<td>103</td>
</tr>
<tr>
<td>21</td>
<td>29</td>
<td>M</td>
<td>+</td>
<td>4.03</td>
<td>91</td>
</tr>
<tr>
<td>22</td>
<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 V˙E 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 analyzer (Beckman Instruments, Fullerton, CA) (4). The challenge was discontinued when a V˙E of 40 l/min was reached. None of the subjects was able to sustain V˙E 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 equaled 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 ±0.5 l/s and was reported as the mean of five measurements.

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 (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 airway 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 V˙E 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-sided, 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 V˙E 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; S = 0.64, P = 0.53). The mean V˙E 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 $V\dot{E}$. In the nasal trial, resistance rose as $V\dot{E}$ 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 ± 9% ($P = 0.008$) and 31 ± 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 ± 2%, $P < 0.001$), but it was also associated with a decrease in nasal patency ($\Delta NR$ 26 ± 9%, $P = 0.01$). In the converse experiment, nasal hyperpnea induced a 33 ± 9% elevation in NR ($P = 0.01$); however, lung function did not change ($\Delta FEV_1$ 2 ± 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 ± 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 $V\dot{E}$ (Fig. 5). All values except those at 10 l/min ($P = 0.08$) were significantly different from the prechallenge baseline at $P = 0.01$ (overall relationship $F = 11.7$, $P < 0.001$). Even though the prechallenge NR values in this experiment were less than on the control

<table>
<thead>
<tr>
<th>Variable</th>
<th>OHV</th>
<th>NHV</th>
<th>OHV + NR</th>
<th>NHV + PR</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_\text{i}$, °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>3.30 ± 0.20</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>NR, cmH2O·l$^{-1}$·s$^{-1}$</td>
<td>3.48 ± 0.29</td>
<td>3.43 ± 0.43</td>
<td>2.98 ± 0.34</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>$V\dot{E}$, l/min</td>
<td>63 ± 4</td>
<td>40 ± 0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</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 upper and lower airway function; $T_\text{i}$, temperature of inspired air; NR, nasal resistance; $V\dot{E}$ OHV NR, minute ventilation associated with a $\approx 15\%$ decrement in $FEV_1$ in OHV challenge; $V\dot{E}$ NHV PR, maximum ventilation achieved in NHV challenge. Because all subjects in NHV PR challenge achieved 40 l/min, SE = 0.

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

---

Fig. 1. Effect of oral hyperpnea of frigid air on pulmonary mechanics. $FEV_1$, 1-s forced expiratory volume (liters); $V\dot{E}$, minute ventilation (l/min). Values in each panel indicate stimulus-response curves for individual subjects.
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 FEV\textsubscript{1} 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.
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 FEV₁ 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-
plete 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

Fig. 5. Effects of changing breathing patterns on NR. B, baseline data. A: absolute data; B: changes from baseline. Data points are means; error bars are SE.

Fig. 6. Effects of changing breathing patterns on nasal and airway mechanics in 10 subjects. Data points are means; error bars are SE. P values below abscissa reflect baseline-response comparisons.
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 (30); and the increase in NR at any level of ventilation was much greater than in the experiment where a normal pattern was employed.

The prechallenge NR data for the two forms of NHV were statistically dissimilar. However, because each experiment was designed to examine disparate forms of thermal stress in an independent fashion, we do not think that this factor negatively impacted our results. When the variation was eliminated by expressing the data as a percent change from baseline, the differences in the magnitude of the two responses were clearly evident.

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 baselines noted above and could play havoc with long-term experiments, it is unlikely that they were operational 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 is 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 provocation. 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.

The literature has suggested that a cold-induced nasal-pulmonary reflex exists, but the data are inconsistent. Notte and Berger (22) flash evaporated Freon on the nasal mucosa of asthmatic and nonasthmatic subjects and found oscillatory airway resistance to rise only in the former. In contrast, Fontanari et al. (9) found nasal breathing of cold air to increase airway resistance in both groups and subsequently described a relationship between the magnitude of the augmentation in asthmatic subjects and their bronchial responsivity to carbachol (10). Yet, nasal breathing of cold air has no effects on lung function here or actually protects against thermally induced asthma (13, 29). It has not been shown to augment obstruction, as would be expected if there was an added secondary reflex increase in resistance. Given that the reported fluctuations in airway resistance were obtained with relatively inexact techniques (25), the existence of a cold-induced nasal-pulmonary reflex may need to be reevaluated. Alternatively, because the changes were uniformly quite small, they may not have been of sufficient intensity to have influenced the FEV1. Further studies are required to resolve these possibilities.

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.

This study was supported in part by National Heart, Lung, and Blood Institute Grants HL-33791, HL-44920, and Specialized Center of Research Grant HL-37117 and National Center for Research Resources General Clinical Research Center Grant MO1-RR-0088. Address for reprint requests and other correspondence: E. R. McFadden, Jr., Div. of Pulmonary and Critical Care Medicine, University Hospitals of Cleveland, 11100 Euclid Ave., Cleveland, OH 44106-5067 (E-mail: erm2@po.cwru.edu).

Received 5 January 1999; accepted in final form 28 October 1999.

REFERENCES


