Changes in airway resistance induced by nasal inhalation of cold dry, dry, or moist air in normal individuals

PIERRE FONTANARI, HENRI BURNET, MARIE CAROLINE ZATTARA-HARTMANN, AND YVES JAMMES
Laboratoire de Physiopathologie Respiratoire Intégrée et Cellulaire, Unité de Recherche Associée, Centre National de la Recherche Scientifique 1630, Institut Jean Roche, Faculté de Médecine, Université de la Méditerranée, 13916 Marseille cédex 20, France

Fontanari, Pierre, Henri Burnet, Marie Caroline Zattara-Hartmann, and Yves J ammes. Changes in airway resistance induced by nasal inhalation of cold dry, dry, or moist air in normal individuals. J. Appl. Physiol. 81(4): 1739–1743, 1996.—Nasopulmonary bronchomotor reflexes elicited by mechanical or irritant stimulation of the nose have been described in animals and asthmatic patients. However, few studies were devoted to the consequences of nasal breathing of cold and dry air or of only dry or only moist air on the bronchomotor control in normal individuals. The present study reported changes in interruption resistance (Rint) measured during eupneic breathing of moderately cold (−4 or −10°C) and dry (0.3% relative humidity (RH)) air or of room air at 23°C that is either dry (0.3% RH) or moist (97% RH). Nasal inhalation of cold (−4°C) dry air or of only dry air significantly increased baseline Rint value (17 and 21%, respectively) throughout the 15-min test periods. The response to cold was significantly accentuated when the air temperature was lowered to −10°C (42%). After nasal anesthesia or inhalation of a cholinergic antagonist, cold air did not induce a change in Rint. Nasal inhalation of moist room air had no effect. No Rint changes were measured during oral breathing of the three test agents. It is concluded that the activation of cold receptors or osmoreceptors in the nasal mucosa induces protective bronchoconstrictor responses in normal individuals.

nose; cold receptors; osmoreceptors; bronchomotor control; humans

THE ATTENTION of respiratory physiologists has been often focused on pulmonary reflexes elicited by the stimulation of lower airways, but upper airways, namely the nose, seem to play key roles in the control of ventilation and bronchomotor tone. The nose constitutes the first line of defense of the respiratory system against the penetration of airborne particles and irritant chemicals and also plays a major role in temperature and water-content conditioning of inspired air. The existence of nasopulmonary reflexes elicited by nasal irritation is suspected in normal subjects (5, 9, 10, 17) as well as in patients suffering from asthma and/or rhinitis (14, 18, 21). Animal studies suggest the presence of cold receptors in the nasal mucosa (12, 20), and the existence of nasal osmoreceptors is evoked in humans (19).

Fresh air (2 or 25°C) inhalation through the nose changed the ventilatory pattern with decreased minute ventilation, whereas warm air breathing had no effect (1, 13, 15). Except for the studies by Nolte and Berger (14) in asthmatic patients and by Le Merre et al. (11) in normal individuals, no data were found in the literature on the consequences of nasal breathing of cold or warm air on pulmonary mechanics. Nolte and Berger (14) reported bronchoconstriction in response to a Freon spray into the nose, whereas Le Merre et al. (11) found no change in airway resistance (Raw) after nasal single deep inspirations (sniff) of freezing air (−40°C). However, Le Merre et al. measured Raw between cold tests, i.e., when subjects breathed room air. Thus their results could not preclude the occurrence of transient changes in bronchomotor tone elicited by the activation of nasal cold receptors. No studies were found on the pulmonary consequences of varying the air humidity during nasal breathing. Indeed, Togias et al. (19) limited their study to a score of nasal symptoms after instillation of hyperosmolar mannitol solution into nostrils.

The aim of the present study conducted during eupneic nasal ventilation in normal subjects was to analyze the changes in interruption resistance (Rint) in response to three test agents (cold and dry air, dry air, or moist room air). A temperature range was chosen to reproduce environmental conditions often found in Mediterranean countries (from 23 to −4°C), and in some individuals the effects of cooler air (−10°C) were also studied. To evaluate the respective roles played by the activation of nasal and oropharyngeal receptors, tests were also randomly repeated during mouth breathing. In the most reactive individuals, the cold challenges were repeated after local anesthesia of the nasal mucosa or oral inhalation of a cholinergic antagonist to suppress the afferent or efferent arm of the suspected nasopulmonary reflex arch, respectively.

METHODS

Subjects

Twelve healthy subjects (3 women and 9 men) volunteered to participate in the present study. Their mean age was 42 ± 4 yr. None had antecedent symptoms of asthma and rhinitis. Table 1 shows that their pulmonary function was normal and also that airway hyperreactivity to carbachol was absent; a dose-response curve was obtained in each individual by plotting the value of Raw measured in a body plethysmograph by the method of Dubois et al. (4), against cumulative doses of carbachol in the range 200–1,800 µg. None of the subjects had a twofold increase in Raw with a carbachol dose of <1,200 µg. In eight subjects, no change in Raw could be detected with the highest dose, i.e., 1,800 µg (Table 1). As mandated by the Institutional Human Subjects Committee, the subjects were fully informed of all procedures and written consent was obtained, but they remained naive as to the purpose of the study.
Morphological characteristics, pulmonary function, and airway response to carbachol inhalation of subjects

Table 1.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>VC, liters BTPS</th>
<th>FEV$_1$/VC, %</th>
<th>RV/TLC, %</th>
<th>Raw, cmH$_2$O·l$^{-1}$·s$^{-1}$</th>
<th>Rint, cmH$_2$O·l$^{-1}$·s$^{-1}$</th>
<th>Sensitivity to Carbachol, µg</th>
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<tr>
<td>1</td>
<td>M</td>
<td>50</td>
<td>62</td>
<td>167</td>
<td>3.97</td>
<td>76</td>
<td>43</td>
<td>1.58</td>
<td>1.82</td>
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<tr>
<td>2</td>
<td>M</td>
<td>23</td>
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<td>176</td>
<td>5.62</td>
<td>90</td>
<td>15</td>
<td>2.32</td>
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<td>&gt;1,800</td>
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<tr>
<td>3</td>
<td>M</td>
<td>29</td>
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<td>172</td>
<td>4.97</td>
<td>90</td>
<td>29</td>
<td>1.78</td>
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<td>4</td>
<td>M</td>
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<td>85</td>
<td>26</td>
<td>1.03</td>
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<td>5</td>
<td>M</td>
<td>31</td>
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<td>173</td>
<td>5.48</td>
<td>75</td>
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<td>2.24</td>
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<td>4.18</td>
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<tr>
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<td>51</td>
<td>157</td>
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VC, vital capacity; FEV$_1$/VC, ratio of forced expiratory volume in 1 s to VC; RV/TLC, ratio of residual volume to total lung capacity; Raw, central airway resistance (plethysmographic measurement); Rint, interruption resistance; sensitivity to carbachol, dose-doubling baseline Raw value.

Measurements of Respiratory Variables

Measurements were always performed when the subjects were comfortably seated. In all cases they inhaled −4 or −10°C cold dry, dry 24°C, or moist 24°C air via a two-way valve (dead space 5 ml) so that contamination of inspired air by expired gas was avoided. During nasal breathing, the subjects wore a mask (dead space 140 ml) firmly adjusted to the nose. During oral breathing, they were connected to a rigid mouthpiece and they wore a noseclip.

Rint. The subjects breathed through the mouth in a grid pneumotachograph connected to the interrupting device, consisting of a throttle valve with electromanometer to measure mouth pressure (Masterscreen, Hellige-Jaeger, Switzerland). After every two breaths, a single 100-ms occlusion was performed at 50% of expired tidal volume. We were aware of the fact that the interrupter technique had poorer sensitivity for detecting bronchoconstriction than the standard techniques that use an esophageal balloon or body plethysmograph, as clearly shown by Phagoo et al. (16). However, the interrupter technique was more convenient in our protocol to measure the airway response during periods of inhalation of conditioned air and required minimal subject cooperation.

Inlet pressure. Inlet pressure was measured in the nose mask or in the mouthpiece by using an electromanometer (±20 cmH$_2$O; Schlumberger).

Gas temperature. Temperatures were measured with type-K chromel-alumel thermocouples (time constant 0.1 s). Inspired temperature was measured just before the two-way valve.

Oropharyngeal temperature was also measured in two individuals by introducing a thermocouple into the mouth and positioning its tip on the bottom of the tongue. Simultaneous measurements of inspired and oropharyngeal temperatures evaluated the efficiency of the nasal heat exchanger during nasal inhalation of conditioned air. Temperatures could be read on a digital voltmeter.

Relative humidity (RH). A thermohygrometer (time constant 3 s; Quick Novo, Bioblock Scientific, Strasbourg, France) was placed in the inspiratory line of the circuit. RH values were read on a digital voltmeter.

Experimental Setup Used to Modify Inspired Air Temperature and/or Humidity

Compressed air at a flow rate of 30 l/min could be either 1) conditioned at 23 ± 1°C and totally humidified (RH 97 ± 1%; Bennett heat-water exchanger), 2) conditioned at 23 ± 1°C and then dried (RH 0.3 ± 0.02%) after passing through a calcium chloride column, or 3) dried and then cooled at −4 ± 1°C and in some cases at −10 ± 2°C. Thus air was insufflated in a circuit with a spiral of copper tubing (ID 4 cm, total volume 6 liters) immersed in a glycol bath in a commercial freezer. Total resistance of this circuit was 0.3 cmH$_2$O·l$^{-1}$·s$^{-1}$ when inspired flow rate was 1 l/s. A four-way stopcock allowed diversion of conditioned air to the inspiratory circuit or the room. Subjects could inhale room air (mean temperature 23 ± 1°C, RH 34 ± 1%), moist, dry, or cold dry conditioned air. In all cases we took care that mask or mouth pressure changes were <1 cmH$_2$O when the stopcock was turned to the compressed-air circuit. Conditioned air was inspired through the two-way valve. Expired air was exhaled through the two-way valve and low-resistance T tube into the room. During room air breathing or inhalation of conditioned air, the subjects breathed in time with a metronome at 15 breaths/min. This minimized mechanical artifacts due to changes in breathing pattern and expiratory lung volume during cold or dry gas inhalation. Ten successive Rint values were measured during room air breathing (control Rint). Measurements were repeated at 5, 10, and 15 min during the 15-min period of nasal or oral inhalation of conditioned air. A 15-min recovery period of room air breathing separated two successive presentations of moist, dry, or cold dry air. During nasal inhalation of test agents, the subjects were asked to breathe one time via the nose and two times via the mouth through the grid pneumotachograph and throttle valve to maintain nasal stimulations between two successive Rint measurements. Five Rint values were then measured. During oral inhalation of test agents, the subject was disconnected from the air conditioning circuit and Rint measurements were performed for four consecutive breaths. Two consecutive Rint values were measured at 5, 10, and 15 min. Nasal and oral inhalations of conditioned air were randomly performed, but the effects of dry air were always studied before those of moist air.

In six subjects, the changes in Rint in response to nasal inhalation of −10°C cold dry air were compared with those measured at −4°C, and the order of appearance of the two temperatures was randomized. In these individuals we tested the hypothesis that two repeated cold air challenges produced the same result. This was performed before the study to determine the consequences of local anesthesia of nasal mucosa on cold-induced Rint changes. Local anesthesia was induced by nebulization plus instillation of 1 ml of a 5%
Xylocaine solution. Baseline Rint values were measured 5 min after anesthesia. Nasal cold challenges were begun immediately after that.

In five subjects, nasal cold dry air challenges were repeated 30 min after oral inhalation of a cholinergic antagonist (ipratropium bromide; Atrovent, Boehringer Ingelheim). This was made in an attempt to elucidate the mechanisms of cold-induced changes in Rint, which could result not only from a bronchospasm but also from laryngeal constriction or decreased expiratory lung volumes because of reflex changes in the breathing pattern.

Statistical Analysis

After assessment of data normality (Kolmogorov-Smirnov test), repeated-measures analysis of variance (ANOVA) was used to test for differences in the effects of a series of experimental conditions on the same group of subjects by examining the changes in each individual. When ANOVA indicated the existence of a significant difference within experimental conditions, we used Dunnett's method as a post-ANOVA multiple-comparison test. Paired t-test was used to compare mean change in Rint measured in the same individuals when cold air challenges were repeated twice or when two different temperatures were tested.

RESULTS

Cold Dry Air Breathing

In the two subjects in whom oropharyngeal temperature was measured repetitively during the 15-min periods of nasal breathing of room air or −4°C cold dry air, mean inspired temperature values were 35.4 ± 0.3 and 34.9 ± 0.3°C, respectively. Thus the nasal heat exchanger was very efficient during eupneic breathing of moderately cold air. Figure 1 shows the mean Rint changes measured in the 12 subjects during nasal inhalation of −4°C cold dry air and the 15-min recovery period. A significant (P < 0.001) and consistent Rint increase (17%) was measured 5 min after the test began, and then the response plateaued. Rint returned to control values within 5 min after cessation of cold air inhalation. Nasal inhalation of cooler dry air (−10°C) significantly accentuated the Rint increase (42 ± 4%; P < 0.001) compared with the response to −4°C cold air measured in the same individuals (25 ± 5%). Figure 2 shows that Rint changes were not significantly different when −10°C cold air challenges were repeated twice (first test: ΔRint = 38 ± 4%; second test: ΔRint = 33 ± 5%). The comparisons between individual mean change in Rint induced by nasal breathing of cold dry air before and after anesthesia of the nose or oral inhalation of the cholinergic agonist (Fig. 3) show no significant Rint increase after anesthesia or inhalation of the bronchodilator.

As shown in Fig. 1, oral inhalation of cold dry air did not significantly increase Rint values.

Dry or Moist Air Breathing

Figure 4 shows mean Rint values measured during nasal inhalation of dry or moist air in six individuals. Rint increased significantly (21%; P < 0.01) at the beginning of dry air test, and the response persisted throughout the 15-min test period. No Rint changes were measured during inhalation of moist air or during oral inhalation of dry or moist air.
DISCUSSION

The present study shows that nasal inhalation of cold dry air elicited significant increases in Rint values, proportional to the magnitude of air cooling, which persisted throughout the challenge and disappeared in <5 min during the recovery period. The airway response was not found after local anesthesia of the nasal (and also pharyngeal) mucosa or after the administration of a cholinergic antagonist. It was not observed when cold dry air was inhaled through the mouth. Our data indicate the existence of a nasopulmonary reflex in response to the activation of temperature-sensitive nerve endings in the nasal mucosa. The magnitude of bronchoconstriction was perhaps underestimated by the use of interrupter technique, as recently shown by Phagoo et al. (16), but the use of an esophageal balloon was not authorized by the Institutional Human Subjects Committee, and Raw measurement by body plethysmography was difficult to perform during periods of inhalation of conditioned air.

The observation that the use of a cholinergic antagonist suppresses the Rint response to nasal inhalation of cold air demonstrates the existence of a bronchoconstrictor reflex and not upper airway narrowing, which may be also suspected. Indeed, Jounieaux et al. (8) have reported that normal awake subjects breathing room air develop vocal cord adduction during positive nasal pressure breathing. However, they did not measure lower airway resistances and attributed most of the upper airway response to hypocapnia and not to a reflex initiated by activation of nasal receptors. The present observations of a bronchoconstrictor reflex to nasal inhalation of cold air agree with those of Nolte and Berger (14) in asthmatic or laryngectomized patients. However, their cold air test consisted of a single spray of Freon-propelled aerosol containing a mixture of mono- and difluorodichloromethane and tetrafluorodichloroethane. They measured a 25% increase in oscillatory resistance that began immediately after the application of cold into the nose and reached a peak within 10 s. Our observations demonstrate the existence of a nasopulmonary bronchoconstrictor reflex in response to cold dry air in healthy individuals under realistic circumstances of eupneic inhalation of moderately cold air. Animal experiments indicate that cold receptors in the nose were activated at 0°C (12), and in the study of humans by Togias et al. (19) symptoms of nasal obstruction occurred when the inspired temperature ranged between −3 and −10°C.

Rint changes during −4°C cold air inhalation were of the same magnitude as those during room temperature dry air breathing through the nose. Thus the possibility that cold-sensitive units may in fact be osmosensitive living in the nasal mucosa is not excluded.
receptors cannot be excluded. Indeed, the observations of Togias et al. on the nasal consequences of instillation of hyperosmolar mannitol solution into the nostrils support the existence of osmoreceptors in the nasal mucosa. The observation that Rint response to cold air was roughly proportionate to the decrease in air temperature suggests strongly that the nasopulmonary bronchoconstrictor reflex to cold results from the activation of cold-sensitive and not osmosensitive units in the nasal mucosa. Thus this reflex may be elicited by the activation of cold receptors or osmoreceptors in the nose.

No Rint changes were noticed during nasal inhalation of moist room air. Increasing the water content in inspired gas has the same biophysical consequences as warming the airway mucosa. Animal studies by Wallois et al. (20) have confirmed that increasing the temperature of the air jet through the nose from 20 to 35°C had no effect on the trigeminal unit discharge.

In the present study, oral inhalation of dry or cold dry air did not change Rint values. This suggests the absence of cold-sensitive and/or osmosensitive nerve endings in the mouth and the oropharynx. The absence of changes in pharyngeal temperature during nasal inhalation of cold air indicates that pharyngeal cold receptors are not activated after nasal inhalation. In fact, subjects did not hyperventilate, and thus the temperature in laryngeal and tracheal mucosa had no reason to vary. It has been previously shown in cats that cold-sensitive units were present in the superior laryngeal nerve innervating the larynx and the cervical trachea (7), but these receptors were not found in pulmonary vagal branches innervating intrapulmonary airways (3). A unique circumstance for the occurrence of cold-induced bronchospasm during eupneic oral breathing in normal subjects is deep underwater diving. Elevated air pressures increase gas density, and the use of dilutant gases as helium and/or hydrogen that have high specific heat and thermal conductivity coefficients produced bronchoconstriction, presumably due to increased heat loss from the airways. This bronchoconstriction increases with depth (2, 6).

The existence of bronchospasm in response to nasal inhalation of cold and/or dry air may be considered as a protective mechanism that tends to reduce the airflow rate in the upper airways and cervical trachea and limits the penetration of insufficiently conditioned inspired air into the lungs. However, it must be pointed out that oropharyngeal temperature did not vary during our conditions of eupneic nasal breathing of moderately cold air. We speculate that this nasal bronchomotor reflex may be accentuated during nasal breathing of freezing air, a circumstance where the nasal heat and water exchanger may be insufficient. This reflex appears to only originate in the nose because oral inhalation of cold and/or dry air did not induce a bronchoconstrictor response. The question is now whether the responses may be different in allergic rhinitis or asthmatic subjects.

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Address for reprint requests: Y. Jammes, URA, CNRS 1630, Faculté de Médecine, Blvd. Pierre Dramard, 13916 Marseille cédex 20, France.

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