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Nasobronchial relationship after cold air provocation

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Provocation with cold air in the nose causes broncho-obstruction while warm air causes bronchodilation in patients with asthma, but not in healthy subjects. These findings have suggested the existence of a nasobronchial reflex. The present study aimed to block this effect and evaluate the mechanisms underlying the effect on lung function after cold stimulation of the nose. Lung function, as measured with specific conductance and forced expiratory flow, was reduced after cold stimulation of the nose, but this effect could not be blocked by anesthetizing the nose or by inhaling an anti-cholinergic drug before the provocation. These results confirm the presence of a nasobronchial relationship, but not of a nasobronchial reflex.

Key words: nasal provocation; bronchoconstriction; nasobronchial relationship; paranasal sinus ventilation; nitrogen oxide

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Introduction

Inhalation of cold air is known to induce airway obstruction in sensitive asthmatic patients. This has been attributed to heat and water losses from the airway mucosa causing bronchoconstriction (1–6). Patients often report that the obstruction begins rapidly after exposure to cold air and that damp, cold weather near freezing point causes more breathing problems than colder, dry air. These circumstances appear inconsistent with the heat- and water-loss theory, so this may not be the only mechanism involved in the effects of cold on the airways of patients with asthma.

In an uncontrolled study of 27 patients it was found that a single cold stimulation in the nose of asthmatic patients, but not in healthy controls, induces bronchoconstriction (7). This effect could be blocked by inhaling an anti-cholinergic drug before the cold provocation (7). In another study, nasal inhalation of cold dry air or of dry air alone reduced lung function. These effects were inhibited by anaesthizing the nose or inhaling an anticholinergic drug (8). A reflex from the upper airways, hastening the onset of obstruction, was suggested, but the studies were not controlled and cold air administered via the nose would probably reach the intra-pulmonary airways. Therefore, in a previous study, we evaluated how changes in nasal air temperature affected lung function, when care was taken to avoid the temperature changes in the nose from reaching the lower airways (9). In patients with asthma, but not in healthy ones, cold air administered in and around the nose caused broncho-obstruction and warm air resulted in bronchodilation, while ambient air had no effect. These results are consistent with, but do not establish, the existence of a nasobronchial reflex.

The aim of the present investigation was to evaluate the mechanisms underlying the effect on lung function after cold stimulation of the nose. We studied whether the effect on the lower airways could be blocked by anaesthizing the nose and by inhaling an anti-cholinergic drug before the cold provocation.

Material and methods

Ten patients (six women, four men, 22–44 years, mean 32 years) took part in this study. They all have a history of cold-sensitive asthma, objectively shown in a standardized cold challenge test. All patients had a history of atopy and had earlier shown an increase of at least 20% in FEV_1 after inhaling a β_2-agonist. They were adequately treated (various corticosteroids for inhalation, short- and long-acting β_2-agonists) and had a predicted value of more than 90% FEV_1. On most days, they had no symptoms of asthma and none of them smoked. No medication was taken for a minimum of 12 h before any test. Long-acting bronchodilators were withheld for at least 24 h.

Each patient was provoked with cold air in the nose on two occasions, either after local anaesthesia of the nose combined with inhalation of an anti-cholinergic drug, or after placebo. The order was randomized and the interval was 1–2 weeks. The drugs were given during a rest period of 1 h prior to the provocation. The nasal mucosa was sprayed intermittently with lidocaine (40 mg ml^{-1}), total 5 ml and 5 g EMLA® cream (containing lidocaine and prilocaine;

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Astra, Sweden) was applied to the tip of the nose and in both vestibulum nasi. In addition, the patient inhaled 0·6 mg ipratropium bromide dry powder (Atrovent®; Boeringer, Ingelheim, Germany) by the mouth. Placebos were applied in the same way. The drugs were given in a randomized order by one investigator, while the lung function tests were performed by another, unaware of which drug was used.

The provocations with cold air (about -15°C) were performed on separate days, at approximately the same time each day, in a similar way, as reported elsewhere (9). With each nasal provocation, an airstream (about $0{\cdot}8\,1\,\text{sec}^{-1}$) was blown into one nostril via a nose halter. One provocation consisted of 10 puffs of air of 15 sec duration, each at intervals of 1 min between the puffs. Shortly before each puff of air, the patients took a deep breath and blew into a mouthpiece with a small hole connected to a pressure-meter. Positive intra-thoracic and intra-oral pressures were thereby maintained during the provocation and for a few seconds thereafter. A constant positive mouth pressure excluded any leakage of air from the nose to the lower airways during nasal provocations. The airflow entering one nostril came out through the other, passing the nasopharynx. In the halter, just at the edge of the nose, thermistors recorded the temperature of the inflow and outflow air. The temperatures and the mouth pressure were recorded on a direct writer. The patients kept notes as to whether they had had any difficulty in breathing by using a four-grade symptom-score, where 0 was no symptoms and 3, severe symptoms.

Specific airway conductance (*SG*AW; $1\,\text{kPa}^{-1}\times\text{sec}$) and 1 sec of forced expiratory volumes (FEV_1; l) were determined at the first time when the patients arrived at the laboratory, after resting for 1 h, i.e. just before, and immediately (0 min) and 5, 10 and 15 min after the provocations. *SG*AW was determined in a body plethysmograph (Transmural body box 2800, Sensormedics Co, Iorba LINDA, CA, U.S.A.) and FEV_1 with a spirometer (Vitalograph, Buckingham, U.K.). Recordings of *SG*AW always preceded those of FEV_1 and the recordings were evaluated blindly.

The effects of these provocations were analysed by calculating 'the area under the curve'—i.e. an expression of the overall difference from baseline, by using ANOVA and the Wilcoxon sign rank test. *P*-values less than 0·05 were considered significant. Results are presented as mean ± SE. The study was approved by the local ethics committee.

Results

Both *SG*AW and FEV_1 increased significantly ($P<0{\cdot}01$) during the rest period of 1 h after the patients entered the laboratory. Among patients given active treatment, *SG*AW and FEV_1 increased more, compared to when placebos were given, but the differences were not statistically significant (Table 1).

Stimulation with cold air in the nose induced bronchoobstruction, as measured with *SG*AW and FEV_1 (Figs 1 and 2). The decrease in lung function was statistically significant ($P<0{\cdot}05$), measured with both techniques. However, there was no significant difference between the effect of active treatment, compared to that of placebo.

The symptom scores showed that the asthmatic patients were essentially asymptomatic before the provocations. After provocation with cold air, two patients reported minor breathing problems, while four noted

TABLE 1. Lung function tests were carried out when the patients arrived at the laboratory and after 1 h rest. During this period, local anaesthetic or placebo was applied to the nose and an anti-cholinergic drug or placebo was inhaled.

		Initial	After 1 h rest
*SG*AW	Active substance	3·5 ± 0·5	8·7 ± 3·0
($\text{lkPa}^{-1}\times\text{sec}$)	Placebo	3·4 ± 0·8	5·2 ± 0·7
FEV_1	Active substance	3·2 ± 0·3	3·5 ± 0·3
(l)	Placebo	3·3 ± 0·4	3·5 ± 0·4

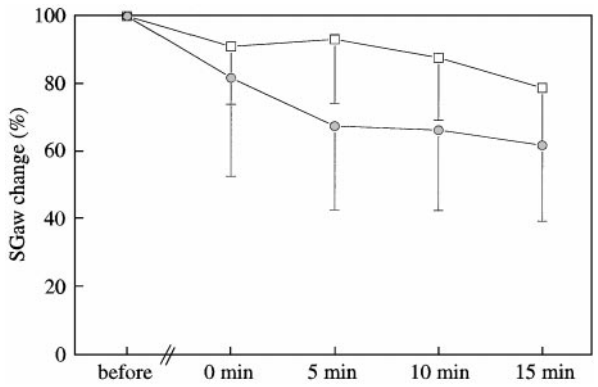

FIG. 1. Changes in *SG*AW after nasal provocations with cold air. The results are shown as mean values and SE expressed in percentage of the preprovocation values. Active treatment (●), placebo (□).

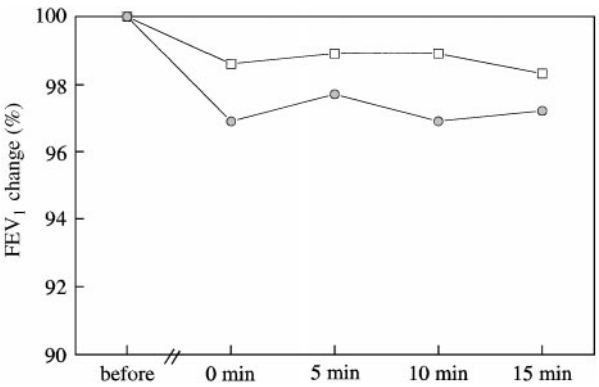

FIG. 2. Changes in FEV_1 after nasal provocations with cold air. The results are shown as mean values expressed in percentage of the preprovocation values. Active treatment (●), placebo (□).

improved breathing. The mean symptom score decreased from 0·7 to 0·5 (NS).

Discussion

An interaction between the nose and the lower airways is confirmed by the present results and by those of the previous study (9). In animal experiments, mechanical stimulation of the nasal mucosa or insufflation of chemical irritating agents into the nose has induced a reduction in airway resistance (10), in others, induced a reduction in minute volume (11) or had no effects on the airways at all (12). In healthy humans, chemical stimuli in the nose and nasopharyngeal area cause an increase in airway resistance (13). Atropine given intravenously prevents this effect, thus indicating a reflex mechanism involving the trigeminal and vagal nerves. Although the existence of a nasobronchial reflex seems likely, it has not been convincingly demonstrated in man. Cooling of the skin of the face or total body seems to trigger bronchoconstriction, both in patients with asthma and healthy subjects (14,15)

As in our previous paper, greater reductions in lung function were measured with body plethysmography than with spirometry (9). The percentage decrease in SG_{AW} after cold provocation was about 25% 10–15 min after the provocation, which accorded with earlier findings. The corresponding figures for FEV_1 were only a few percent. The effect of blocking the sensory system of the nose and pretreatment with an anticholinergic drug did not inhibit the relationship between the nose and the lungs in this study. As anaesthesia was excessive, our findings do not favour a nasobronchial reflex from the sensory nerve system of the nose. Furthermore, we were not able to repeat previous findings that inhalation of an anticholinergic drug or nasal treatment with an anaesthetic before cold stimulation in the nose could block an increase of the resistance in the lower airways of asthmatic patients (7,8). In an additional experiment on a single subject, we infiltrated the area around the nose with an anaesthetic and gave ordinary anaesthesia. However, we found no tendency to inhibition of the effect of cold provocation on the lower airways.

Explanations of our results, other than a nasobronchial reflex, must therefore be considered. Inflammatory mediators released after cold provocation of the nose or a cooling effect of the body might be involved (16). However, cold air had an immediate effect on lung function and it seem unlikely that mediators released in the circulation could act so quickly. In recent years, the effect of nitric oxide (NO) on lung function has been evaluated (17,18). NO is continously produced in human nasal airways, mainly by the paranasal sinuses, which are ventilated by the respiratory cycle (19). Immediately after the provocation, part of the air inspired into the sinuses reaches the lungs via the nasal–sinus ostium. The factors that regulate NO synthesis in the upper airways are still not known, but the ostium might be less open when exposed to cold than when exposed to warm air, resulting in less NO admixture to the inhaled air, due to changes in mucosal congestion (20). Thus, the temperature of the nasal air is presumably important for the amount of NO reaching the lower airways. NO from the sinuses may cause a weak bronchodilation after provocation with warm air and a weak bronchobstruction after cold air in the nose. Support for this theory is that NO can exert a bronchodilatory effect in patients with asthma but not in healthy ones (21).

In our previous study, we found that baseline values of SG_{AW} and FEV_1 varied in patients with asthma, indicating labile lung function even when the patients were asymptomatic (9). However, in healthy normal subjects, the baseline varied less. In the present study, to stabilize the baseline values, the patients rested 1 h before the provocation. During this period, lung function improved considerably and those who were given active treatment improved more, probably an effect of ipratropium bromide. Therefore, they started at a higher level and the percentage reduction in lung function after cold provocation was more pronounced.

In conclusion, as in our previous study, provocation with cold air in the nose caused airflow limitation confirming the existence of an interaction between the nose and the lower airways. This effect could not be blocked by pretreatment with local anaesthesia of the nose in combination with inhalation of impratropium bromide, which provides evidence against a nasobronchial neurogenic reflex. We speculate that the mechanism may be related to reduced ventilation with nitric oxide from the paranasal sinuses.

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