

Nasal histamine challenge in nonallergic and allergic subjects evaluated by acoustic rhinometry

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Nasal patency shows spontaneous variations but is influenced by a number of factors like exercise and allergic conditions. Nasal histamine challenge has been used to define nasal hypersensitivity. We have applied acoustic rhinometry as a new objective method to study the spontaneous variations of the nasal mucosa and its response to histamine challenge in 12 nonallergic subjects and 12 subjects with nasal allergy to pollen, but out of the pollen season. Measurements of the minimum cross-sectional area and the volume of the nasal cavities were done every 15 min for 6 h. More pronounced spontaneous variations, defined by the coefficient of variation of the measurements, were encountered in the allergic than in the nonallergic subjects, especially with regard to the minimum cross-sectional areas in the nasal cavities ($P < 0.02$). Allergic subjects showed increased sensitivity to histamine, as compared with nonallergic subjects, during low-concentration (0.1%) challenge ($P < 0.05$) and a prolonged effect of histamine challenge ($P = 0.01$). Antihistamine (cetirizine) had a significant effect on the histamine-induced symptoms and decrease of nasal dimensions during histamine challenge, but no significant effect on pollen-induced changes. In the allergic group, the decrease in minimum area during allergen provocation correlated with the level of specific IgE ($r = 0.81$; $P = 0.0015$).

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Nasal patency shows spontaneous variations but is influenced by a number of factors like exercise, allergic conditions, or unspecific extrinsic factors. Impaired nasal patency is a prominent feature in individuals with allergic rhinitis when exposed to the specific allergen. However, some allergic patients complain of nasal obstruction out of the pollen season. This may be due to increased sensitivity of the nasal mucosa to extrinsic factors, just as in bronchial hyperreactivity in subjects with asthma. Nasal hypersensitivity has been described (2, 9, 11, 26, 36), although other studies could not find a clinically useful difference between allergic and nonallergic subjects (17, 22, 25) with regard to occlusion (6). In the pollen season, antigen-provoked increase in histamine reactivity is seen (37). Furthermore, hypersensitivity may be present in perennial rhinitis. Histamine challenge has been used for testing methods for evaluation of nasal patency or for drug investigations (7, 10, 13, 39). Other means of challenge are also possible. Bradykinin and serotonin can induce rhinitis symptoms (5, 8, 32, 34). Challenges with cold

dry air and hyperosmolal solutions do not always compare with histamine challenge in response (33).

The effect of antihistamine on rhinitis symptoms is well described in subjective terms, i.e., score analyses in challenge studies (29), but only a few studies (6, 22) have examined by objective measurements whether there is any difference in the protective effect during histamine challenge in allergic and nonallergic subjects. Some authors recommend that both airway resistance and symptom score should be measured (35). The effect of H_1 antihistamines against sneezing, rhinorrhea, and itching is generally accepted, but the effect on nasal obstruction is more dubious, although an effect has been demonstrated in some studies (20, 23, 27). So far, few objective investigations of the action of antihistamine on occlusion have been done. A protective effect of antihistamines during histamine challenge has been described, but this is more dubious during allergen challenge (12). The new nonsedating antihistamine cetirizine has been examined in a primate model (15), but only sporadic studies of the action on oc-

clusion in man have been made (6), and especially few during pollen challenge.

In the present study, we have applied acoustic rhinometry (an objective method for evaluation of nasal passage dimensions) in a group of nonallergic and allergic subjects to investigate the following:

- 1) spontaneous variations in the state of congestion of the nasal mucosa in contrast to the change during and after histamine challenge
- 2) nasal hypersensitivity expressed as increased change of nasal cavity dimensions during histamine challenge in allergic as compared with non-allergic subjects
- 3) the effect of antihistamine (cetirizine) during challenge with histamine and pollen.

Material and methods

Twenty-four subjects were included. The subjects were divided into two groups. One group without any allergic manifestations (six males and six females). The other group (six males and six females) consisted of subjects with typical hay fever symptoms and showing positive skin prick tests against birch and/or timothy.

The inclusion criteria for both groups were age between 18 and 40 years (mean: 25 years for the nonallergic group; mean: 26 years for the allergic group) and not smoking. Exclusion criteria were severe septal deformities, chronic sinusitis, nasal polyposis, or other nasal diseases than allergic rhinitis, and serious diseases of any kind. Subjects were not permitted to use any nasal drugs for a period of 1 month before and during the experimental period.

The normal subjects were studied in two groups of six on separate days during three weekends in the early spring, so that each experimental day was separated by 1 week to avoid interference from the former experiment and eliminate weekly variations. The allergic subjects were similarly studied during five weekends in the late autumn.

The experiment was performed in a climatic chamber at constant temperature and humidity ($22^{\circ}\text{C} \pm 1^{\circ}\text{C}$; RH: $50\% \pm 3\%$), and the subjects were allowed only sedentary activities.

The study was divided into two separate sections.

In the *first part* (day 1), the spontaneous variations of the nasal mucosa and symptoms (nasal scores of itching, secretion, sneezing, and occlusion) were examined. The *second part* was the challenge part. For the nonallergic group, it consisted of 2 days with histamine provocation – 1 day with protection by antihistamine (cetirizine 10 mg) given 3 h before challenge, and the other with placebo. For the allergic group, the second part consisted of 4 days – 2 days with histamine challenge and 2 days similarly with and without antihistamine protection with pol-

len challenge. The experiments were carried out as a double-blind, crossover experiment with the subjects as their own controls.

Each experimental day lasted 6 h and was divided into four periods:

- 1) a rest period of 30 min
- 2) a baseline period of 30 min to establish the actual phase in the nasal cycle with measurements by acoustic rhinometry and nasal scores every 15 min, such a set of measurements defining a run
- 3) spontaneous variations (day 1), histamine provocation (days 2 and 3), and allergen provocation of the allergic subjects (day 4 and day 5), followed by 4 h of measurements every 15 min
- 4) maximum decongestion at the end of the trial to obtain a reference not influenced by the actual state of the mucosa, with measurements every 15 min for 45 min.

The challenge with histamine was done in four steps. A volume of 0.2 ml of histamine hydrochloride was placed on the anterior part of the inferior turbinate in each side. Solutions of 0.1, 1.0, and 10% were used, and finally a small piece (5×5 mm) of filter paper moistened in the 10% solution was applied to the anterior part of the inferior turbinate. The solutions were placed as drops on the inferior turbinate without any instrumental contact with the nasal mucosa. There was a 30-min interval between the stimulations, and the mucosa was gently cleaned with a few milliliters of saline before the next application.

A standardized method for pollen challenge was used (28). Volumes of specific allergen of 0.15 ml in four increasing concentrations of 10, 100, 1000, and 10 000 SQ-E/ml, were applied on the anterior part of the inferior turbinate, just as with the histamine solutions above.

At the end of each experimental day, the nasal mucosa was decongested by filling up each nasal cavity with 0.12% ephedrine solution. After drainage, this was followed by two sprays of xylometazoline hydrochloride (1%; 0.14 ml/spray).

The scores of itching, sneezing, secretion, and occlusion for each side of the nasal cavity (sneezing both sides) were recorded on a visual analog scale (50 mm) with the labels "no symptoms" at one end and "intolerable symptoms" at the other end.

Acoustic rhinometry, described in detail elsewhere (21), was used to determine a curve describing the cross-sectional area of the nasal passage as a function of the distance into the nose. From this area-distance function, the minimum cross-sectional area of the nasal cavity ($A_{\min}$) was calculated. Furthermore, the sum of the volumes of the two nasal cavities was obtained by integration of the area-distance functions from the two nostrils and 7.2 cm into the nasal cavity (Vol). At the end of the experiment,

RAST for specific Ig-E (against timothy and birch) was done.

Statistics

Student's *t*-tests, paired *t*-tests and, Wilcoxon tests were used, depending on the nature of the data and whether they were normally distributed or not. Analysis of variance for repeated measurements was done to analyze the overall effect of medical treatment. A *P* value less than 5% was considered to be significant, and *P* between 5 and 10% to be a tendency.

Results

Mean nasal cavity dimensions and spontaneous variations of nasal mucosa

The results of the analysis are presented in Table 1. Nasal cavity dimensions seemed to be smaller in allergic than nonallergic subjects before decongestion, but not after decongestion. Although there was the same trend for the sum of the nasal cavities, the results were significant only for the smallest side. In this side, the most pronounced difference in the effect of decongestion between allergic and nonallergic subjects is seen. Analysis of variance with repeated measurements showed that this difference was significant ($P < 0.01$).

The spontaneous variations of the nasal mucosa were plotted as the volumes of the right side and the left side, and the total volume of both sides against

Table 1. Volume and minimum area of nasal cavities before and after decongestion of subjects (sum of right and left sides) and for wider and narrower cavities ($\pm$ SEM) (*t*-test or Mann-Whitney test)

	Sum (subjects)		Cavities	
Volume	cm ³		Wider side	Narrower side
Nonallergic	20.44 (1.21)		10.88 (0.76)	9.57 (0.55)
Allergic	18.12 (0.74)		9.94 (0.53)	8.19 (0.40)
<i>P</i> value	0.12		0.32	0.05
Minimum area	cm ²		cm ²	cm ²
Nonallergic	1.25 (0.13)		0.65 (0.07)	0.60 (0.06)
Allergic	1.09 (0.08)		0.58 (0.05)	0.51 (0.05)
<i>P</i> value	0.32		0.40	0.30
Relative decongestion effect				
Volume	Sum		Wider side	Narrower side
Nonallergic	44.5 (3.0)		40.1 (4.5)	48.8 (3.3)
Allergic	56.8 (6.3)		44.7 (6.6)	76.6 (14.6)
<i>P</i> value	0.09		0.56	0.08
Minimum area	%		%	%
Nonallergic	33.4 (5.4)		31.0 (5.2)	37.6 (8.0)
Allergic	44.8 (8.1)		30.3 (7.4)	70.6 (21.6)
<i>P</i> value	0.26		0.93	0.17

Table 2. Spontaneous variation of nasal mucosa. Bilateral value is coefficient of variation for sum of right and left sides. Unilateral value is for right and left sides separately ($\pm$ SEM)

Volume	Subjects sum %	Cavities unilateral %	Wider side %	Narrower side %
Nonallergic	7.7 (0.8)	11.4 (1.0)	11.6 (1.3)	11.2 (1.5)
Allergic	8.6 (0.9)	14.8 (1.3)	14.9 (1.8)	14.7 (2.0)
<i>n</i>	24	48	24	24
<i>P</i> value	0.45	0.04	0.14	0.16
Minimum area	%	%	%	%
Nonallergic	8.2 (0.8)	12.6 (1.1)	12.0 (1.2)	13.2 (1.8)
Allergic	10.7 (0.9)	17.9 (1.9)	16.1 (2.0)	19.7 (3.2)
<i>n</i>	24	48	24	24
<i>P</i> value	0.04	0.02	0.07	0.09

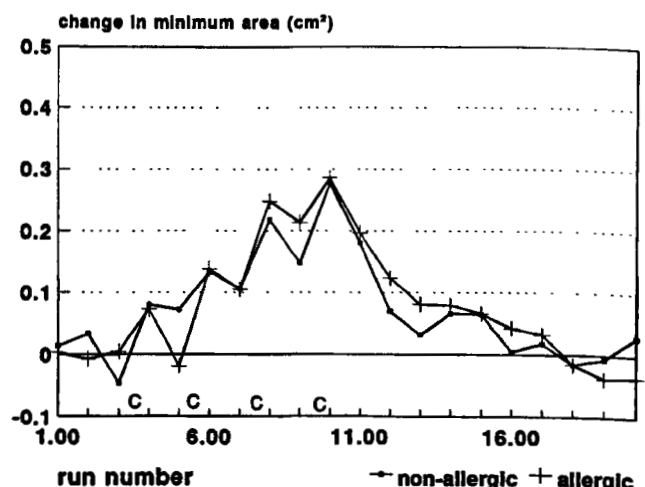
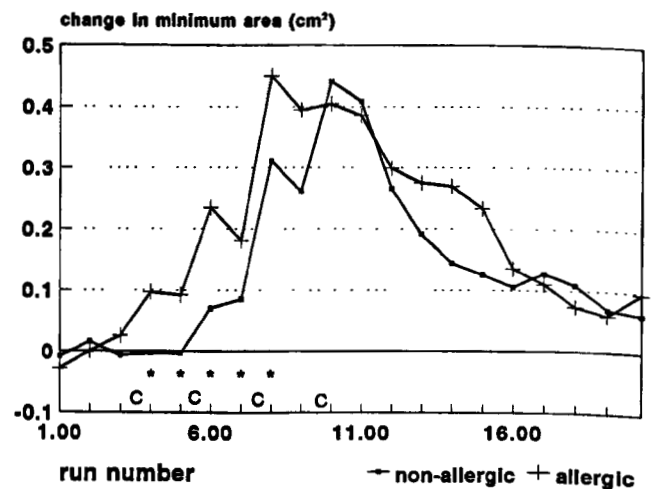


Fig. 1. Change in minimum area of allergic and nonallergic subjects during histamine challenge. C: Four challenge steps. Above: during placebo treatment; below: during cetirizine treatment.

time to determine the variability. The variability of the nasal mucosa for each subject for one side was

calculated as the coefficient of variation of all replicas except those for the decongested state. Correla-

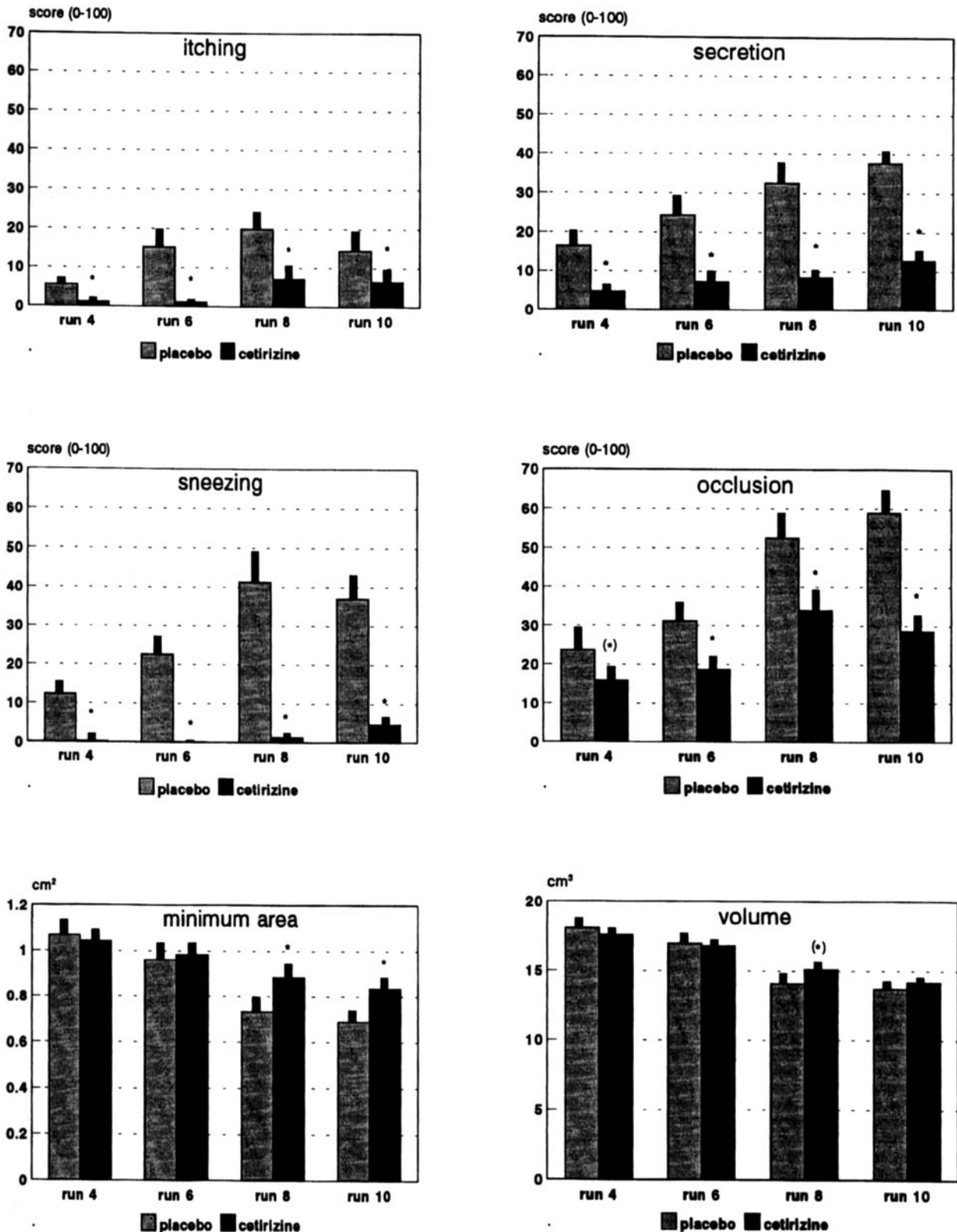


Fig. 2. Effect of antihistamine during histamine challenge for runs 4, 6, 8, and 10 in all subjects. * Significant difference; (*) tendency; error bars = SEM.

tion analyses of the two sides were performed for each subject to determine whether the two sides acted independently. A negative correlation ($P \leq 0.01$) was found in five subjects between right and left side, and a positive correlation in two subjects. Although this reveals a trend, the two sides could be considered to be more or less independent in most of the subjects, at least during the spontaneous variation. Larger variation was seen in allergic than in nonallergic subjects (Table 2). The unilateral variation included the coefficients of variation for the right and left cavities, assuming independence of the two sides. One-side variation (unilateral, wider side or narrower side) seemed to be larger than the variation of the sum of the two sides, and the variation in the narrower side seemed to be larger than in the wider side.

Histamine challenge

The results of the histamine challenge were calculated for the placebo day to examine differences between the allergic and nonallergic groups (Fig. 1, above). Allergic subjects were found to be more sensitive to histamine than nonallergic subjects. During challenge with 0.1% histamine, a significant decrease in nasal dimensions (increase in mucosal volume) was seen in allergic subjects, whereas no effect was seen in nonallergic subjects. Significant differences ($P < 0.05$) between allergic and nonallergic subjects were seen for the challenge with 0.1%, 1%, and 10%, but not with challenge with 10% histamine applied on filter paper.

In the postchallenge period (1½ h after challenge), a prolonged effect of histamine was seen in the allergic subjects ($P = 0.01$ for the minimum cross-sectional area; $P < 0.005$ for the volume). Challenge with histamine during cetirizine treatment revealed no difference between allergic and nonallergic subjects (Fig. 1, below). The return to the prechallenge values was faster and the maximum change at the highest challenge step was less for both allergic and nonallergic subjects.

For all scores, a significant difference or tendency to a difference was found between placebo and cetirizine. For the nasal dimensions, significant differences were found for the two highest challenge steps (Fig. 2).

Effect of antihistamine during pollen challenge

For the allergic group, the effect of antihistamine during pollen challenge was examined. The scores showed a significant effect for itching and sneezing at the two highest challenge steps (1000 SQ-E and 10000 SQ-E) and for secretion at the 10000 SQ-E. No significant effect of cetirizine during pollen chal-

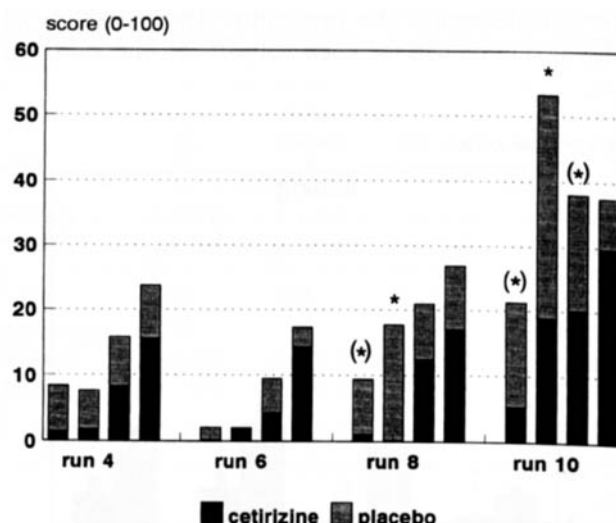


Fig. 3. Effect of antihistamine during pollen challenge for runs 4, 6, 8, and 10. First column at each run: itching; second column: sneezing; third column: secretion; fourth column: occlusion. * Significant difference; (*) tendency.

lenge could be found on nasal occlusion score or nasal dimensions (Fig. 3). The allergic subjects were arbitrarily divided into two groups according to their RAST values: group 0 (five subjects), mean 5.10 PRU/ml (0.2–12.7); group 1 (seven subjects), mean 20.53 PRU/ml (18.3–23.3). The differences in nasal cavity dimensions and scores before and immediately after pollen challenge at the placebo day were calculated. There was a significantly larger change in the minimum area in group 1 ($P = 0.001$). For the volume, $P = 0.026$. The correlation between the individual RAST and change during pollen challenge was highly significant ($P = 0.0015$; $n = 12$; correlation coefficient = 0.81) for the minimum area. Correlations, although less significant, were also found for volume, sneezing, and secretion.

Discussion

Impaired nasal patency is a prominent feature in individuals with allergic rhinitis when exposed to the specific allergen, but some patients also complain of blocked nose out of the pollen season. This could be due to spontaneous variations of the nasal mucosa or high sensitivity to histamine released non-specifically. Some authors find a clear difference in sensitivity to histamine between nonallergic and allergic subjects (11), whereas others are able to demonstrate this nonspecific hypersensitivity of the nasal mucosa only during the pollen season or not at all (2, 22, 25, 35). Several different methods have been used for the nasal challenge (2, 11, 25, 28, 38). This could be partly responsible for the dissimilar results.

The subjectivity in some of the methods, includ-

ing score analyses, for evaluation of changes in the nasal mucosa may be another important factor (2, 11, 17, 23, 28).

In the present study, we applied a new objective method for evaluation of the nasal patency and found a larger spontaneous variation of the minimum cross-sectional area in allergic than in nonallergic subjects. Additionally, it seemed that the allergic subjects out of the pollen season were more sensitive to histamine challenge than the nonallergic subjects. An effect on the nasal mucosa of histamine was observed in the allergic subjects at low-concentration challenge, and a prolonged effect of the challenge was also seen in the allergic subjects, as compared with the nonallergic subjects. These findings may express the non-specific hypersensitivity of the nasal mucosa in allergic subjects described by other authors (11). The fact that the examination of the allergic and nonallergic subjects took place in the late autumn and very early spring was not considered to be of any importance because both were out of the pollen season.

The effect of antihistamine on rhinitis symptoms is well described in subjective terms as score analyses in challenge studies (29), but it has previously not been examined by acoustic rhinometry whether there is any discrepancy in the protective effect during histamine challenge in allergic and nonallergic subjects. In the present study, the effect of antihistamine was clearly seen in the subjective scores and nasal dimensions during histamine challenge, and no differences in effect of challenge between allergic and nonallergic subjects could be recorded during antihistamine treatment. The maximum effect of challenge decreased in both groups during antihistamine treatment. Due to the increased sensitivity to histamine, antihistamine becomes more effective in allergic than nonallergic subjects. Antihistamine abolishes the prolonged effect of histamine in allergic subjects. The increased sensitivity of histamine and the prolonged effect of histamine could be due to an altered binding of histamine to histamine receptors in allergic subjects, as compared with nonallergic subjects.

In the present study, there was a significant effect of antihistamine on the subjective scores of sneezing and itching during the pollen challenge test. There was no effect on the occlusion, measured as changes in total nasal volume of each nasal cavity, or the minimum cross-sectional area, measured by acoustic rhinometry, although a nonsignificant change was observed in the occlusion score. There seems to be a close correlation between occlusion score and the other scores, indicating that other nasal symptoms can influence the feeling of nasal occlusion. In a correlation analysis of the data from the pollen challenge, a higher correlation was found between nasal

occlusion and nasal secretion than between nasal occlusion and nasal dimensions.

Some authors find a significant effect of antihistamine on nasal airway resistance during challenge; others do not (1, 16, 22, 23, 28). In most cases, there is a protective effect of antihistamine during histamine challenge, but not during allergen challenge. This might partly be due to involvement of other mediators than histamine in the normal response to allergens (15, 23). Allergen challenge decreases nasal mucosal blood flow, whereas histamine challenge increases nasal mucosal blood flow (22, 23). In one study, the release of histamine during pollen challenge was not correlated with symptom scores (24). These different findings may explain why antihistamine seemed to act more convincingly during histamine than pollen challenge in the present study.

Some authors have found a correlation between specific IgE and the effect of challenge (14, 18); others have not (3). Similarly, different results are published comparing the skin prick test and nasal challenge (3, 18, 31). It is well known that specific IgE increases during immunotherapy, whereas prick test and nasal challenge responses decrease. This may be due to blocking immunoglobulins (4). The postexperiment RAST in the present study showed that some of the subjects had surprisingly low RAST, despite positive skin prick test and typical hay fever symptoms during the season. The high correlation between specific IgE and change in nasal cavity dimensions during challenge evaluated by acoustic rhinometry and the poorer correlation between IgE and symptoms may indicate that acoustic rhinometry is better able to detect changes than questionnaires. The low RAST in some subjects may partly explain the lack of effect of cetirizine during pollen challenge.

There was no convincing relationship between total symptom score and nasal resistance response to histamine in one study (11), although others did find such a correlation (30). In the present study, nasal occlusion score and the minimal cross-sectional area showed the same trend during the challenges, but total agreement was not seen. Although a previous study also found a correlation between the minimum cross-sectional area and the feeling of impaired nasal patency (19), further studies are required to determine whether other parameters from the area-distance curve than the minimum cross-sectional area and the volume may be useful in the description of changes in the nasal cavity during challenge or interventions involving the nasal cavity.

We may conclude the following:

- 1) Spontaneous variations in the nasal mucosa were more pronounced in allergic than in nonallergic subjects.
- 2) Allergic subjects out of the pollen season showed increased reactivity to histamine challenge, as

compared with nonallergic subjects, in terms of changes in nasal airway dimensions, but further investigations are necessary to establish whether this hypersensitivity may be used in the future for allergic diagnostics.

- 3) Cetirizine protects against nasal occlusion during histamine challenge, but no significant effect during pollen challenge was recorded.
- 4) Changes in nasal airway dimensions measured by acoustic rhinometry during pollen challenge in allergic subjects were proportionate to blood IgE concentration.

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