

Pathophysiological Features of the Nasal Mucosa in Patients with Idiopathic Rhinitis Compared to Allergic Rhinitis

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Key Words

Idiopathic rhinitis · Vasomotor rhinitis · Acoustic rhinometry · Pathophysiology · Cold stimulation · Vasomotor response · Nasal mucosa

Abstract

Background: The literature on abnormality of vasomotor responses of the nasal mucosa to cold stimulation of the skin in idiopathic rhinitis is conflicting. The objective of this study was to elucidate pathophysiological features of the nasal mucosa in idiopathic rhinitis compared to allergic rhinitis. **Methods:** The following were studied in patients with idiopathic rhinitis and allergic rhinitis and in normal controls: (1) threshold of the nasal reaction to histamine; (2) inflammatory cells in nasal lavage and scraped nasal mucosal epithelium, and (3) nasal vasomotor response to cold stimulation of the feet evaluated by acoustic rhinometry. **Results:** Inflammatory cells were not found to be involved in idiopathic rhinitis. Nasal reactivity to histamine was significantly enhanced in patients with idiopathic rhinitis compared to normal controls, but was significantly lower compared to those with allergic rhinitis. The most prominent finding in idiopathic rhinitis was nasal mucosal swelling induced by cold stimulation of the feet. While in normal controls, cold stimulation of the feet caused mucosal contraction due to sympathetic excitation, sympathetic nasal vasomotor response in idiopathic rhinitis patients

was significantly inhibited and caused mucosal swelling and enhanced nasal secretion. Mucosal reactions observed in allergic rhinitis were between those observed in idiopathic rhinitis and in normal controls. Cold stimulation of the feet increased systolic blood pressure by 5–15 mm Hg, but the degree of increase observed in the 3 groups was almost equal. **Conclusions:** The above findings indicate that patients with idiopathic rhinitis have abnormalities that inhibit sympathetic reactions and enhance parasympathetic vasomotor response at peripheral levels, possibly in the nasal mucosa.

Introduction

Patients who show hyperreactive nasal symptoms, characterized by sneezing and watery rhinorrhea with or without nasal obstruction, are classified into allergic rhinitis, idiopathic rhinitis (vasomotor rhinitis) and nonallergic rhinitis with eosinophilia syndrome (NARES), according to the diagnostic criteria in the guideline for treatment of allergic diseases [1] established by the Japanese Society of Allergy (table 1). The diagnosis of idiopathic rhinitis is based on exclusion. However, the number of patients with idiopathic rhinitis and NARES has apparently decreased following the introduction of clear diagnostic criteria and progress in antigen detection methods. Idiopathic rhinitis accounted for only 3.2% of 866 patients with hyperreactive

nasal symptoms, consisting of sneezing and watery rhinorrhea with or without nasal obstruction, who visited the nasal allergy clinic of Chiba University Hospital and 2 associated hospitals between January 1994 and October 1995 (table 2).

According to the International Consensus Report on the diagnosis and management of rhinitis [2], rhinitis is classified into allergic rhinitis, infectious rhinitis and nonallergic noninfectious rhinitis. Nonallergic noninfectious rhinitis is further subclassified into idiopathic rhinitis, NARES, occupational rhinitis, hormonal rhinitis, drug-induced rhinitis including drug intolerance to aspirin or other nonsteroidal anti-inflammatory substances, and others. In the present study, the term idiopathic rhinitis was used as a synonym for vasomotor rhinitis described in the above guideline [1]. The generally held assumption concerning the etiology of vasomotor rhinitis had been an imbalance of the autonomic nerve supply to the nasal mucosa with excessive parasympathetic or reduced sympathetic activity. However, with increased knowledge on neuropeptidergic innervation of the nasal mucosa, the above assumption has recently been questioned [3].

The literature regarding the mode of vasomotor response of the nasal mucosa induced by cold stimulation of the skin in patients with hyperreactive nasal symptoms is conflicting [4–6]. In all of these previous reports, patients with idiopathic rhinitis were not separated from those with allergic rhinitis, but they were combined for comparison with normal controls. Furthermore, the first of the previous studies [4] recorded the surface temperature of the nasal mucosa to monitor vasomotor response, Ralston and Kerr [5] recorded pressure changes in a balloon inserted into the nasal cavity, and Drettner [6] used posterior rhinomanometry. We can now utilize acoustic rhinometry which measures the cross-sectional area of the nasal cavity and/or nasal volume using acoustic reflection [7–9], by which we can monitor vasomotor response of the nasal mucosa within a minute, without imposing much psychophysiological disturbance on the subjects.

The objective of the present study was to evaluate pathological and pathophysiological differences between idiopathic rhinitis and allergic rhinitis, and to determine the features of vasomotor response of the nasal mucosa to cold stimulation of the feet and of the nasal mucosa in patients with idiopathic rhinitis. The following were studied in patients with idiopathic rhinitis, with allergic rhinitis and in normal controls: (1) the threshold of nasal reaction to histamine; (2) inflammatory cells in nasal lavage and scraped nasal mucosal epithelium, and (3) vasomotor response of the nasal mucosa to cold stimulation of the feet and of the nasal mucosa.

Table 1. Diagnostic criteria to differentiate allergic rhinitis from idiopathic rhinitis and NARES among patients who complain of sneezing and watery rhinorrhea with/without nasal obstruction

Allergic rhinitis	> 2 positive reactions: positive nasal eosinophilia, antigen skin test (or IgE RAST) and nasal antigen provocation test
Idiopathic rhinitis (vasomotor rhinitis)	Negative reactions to the above 3 tests
NARES	Only positive nasal eosinophilia with negative skin test (or IgE RAST) and negative nasal antigen provocation test

Table 2. Classification of 866 patients who visited the nasal allergy clinic of Chiba University Hospital and 2 associated hospitals from January 1994 to October 1995 complaining of sneezing and watery rhinorrhea with/without nasal obstruction

	Patients n	%
Perennial allergic rhinitis	310	35.8
Pollinosis	380	43.9
Perennial allergic rhinitis combined with pollinosis	130	15.0
Idiopathic rhinitis	28	3.2
NARES	14	1.6
Pollinosis combined with idiopathic rhinitis	2	0.2
Pollinosis combined with NARES	2	0.2

Subjects and Methods

Subjects

Table 2 shows the classification of 866 patients who visited the nasal allergy clinic of Chiba University Hospital and 2 associated hospitals complaining of sneezing and watery rhinorrhea with or without nasal obstruction between January 1994 and October 1995. Diagnosis was based on the diagnostic criteria shown in table 1. In patients with idiopathic rhinitis, the ratio of males to females was 6 to 22, while the ratio was 174 to 136 in patients with perennial allergic rhinitis and 5 to 9 in NARES. Idiopathic rhinitis was significantly more prevalent among females than males ($p < 0.01$). The mean age of onset of hyperreactive nasal symptoms was 39.3 ± 14.9 years in patients with idiopathic rhinitis, compared to 15.1 ± 10.2 years in perennial allergic rhinitis and 41.7 ± 10.7 years in NARES.

The investigations outlined below were conducted in 18 randomly selected patients with idiopathic rhinitis (mean age 40.5 ± 18.2 years), 25 patients with perennial allergic rhinitis (mean age 31.4 ± 8.5 years) who were allergic to house dust and mite and had more than moderate hyperreactive nasal symptoms defined in the guideline [1], 8 patients with NARES (mean age 40.8 ± 11.4 years), and 25 normal

Table 3. Symptom scores and threshold of nasal responses to histamine in patients with allergic rhinitis, idiopathic rhinitis and NARES compared with normal controls

	Symptom scores			Threshold of nasal responses to histamine	
	sneezing	rhinorrhea	nasal obstruction	sneezing	rhinorrhea
Normal controls, n = 25	0	0	0	4.1±0.8	4.5±0.7
Allergic rhinitis, n = 25	2.6±0.7	2.2±0.8	1.8±0.9	2.6±0.8*	2.6±0.8*
Idiopathic rhinitis, n = 18	1.8±0.8 ¹	1.6±0.6 ¹	1.1±0.6 ¹	3.3±0.9*,**	3.4±0.8*,**
NARES, n = 8	2.6±0.7	2.1±0.9	1.6±0.7	2.4±1.3	3.4±1.1

*p<0.05 compared to controls; **p<0.05 compared to allergic rhinitis.

¹ Differences not significant compared to allergic rhinitis and NARES.

controls (mean age 40.4±9.7 years) who gave informed consent to participate in this study. Any subject who had seasonal allergic rhinitis or drug intolerance to aspirin or anti-inflammatory substances was excluded from the study.

Symptom scores of sneezing, watery rhinorrhea and nasal obstruction, evaluated according to the guideline [1] in which each symptom was graded as not notable (0), mild (1), moderate (2), or severe (3), were 1.8±0.8, 1.6±0.6 and 1.1±0.6, respectively, in patients with idiopathic rhinitis, 2.6±0.7, 2.2±0.8 and 1.8±0.9, respectively in patients with allergic rhinitis, and 2.6±0.7, 2.1±0.9 and 1.6±0.7, respectively, in patients with NARES. Symptom scores were lower in patients with idiopathic rhinitis compared to those with allergic rhinitis and NARES, although the differences among the 3 groups were not statistically significant (table 3). 15 out of 18 patients with idiopathic rhinitis had complaints of aggravation of hyperreactive nasal symptoms on exposure to cold air or cold water in daily life, while 17 out of 25 patients with allergic rhinitis and 5 out of 8 patients with NARES had similar symptoms with no significant difference among the 3 groups.

Study Items and Methods

Measurement of Threshold of Nasal Mucosal Reactivity to Histamine

Histamine dichloride was dissolved in phosphate-buffered saline (pH 7.2) to prepare histamine solutions of 10, 10², 10³, and 10⁴ µg/ml. 20 µl each of the histamine solution of the lowest concentration was dropped onto the medial surface of the left and right inferior turbinates near its anterior tip under direct vision using a micropipet. The subjects were asked to slightly tilt their head anteriorly, and the frequency of sneezing was counted for 10 min. Rhinorrhea flowing out of the anterior nostrils was lightly wiped off with previously weighed tissue paper. Ten minutes later, the subjects were asked to blow their nose using the same tissue paper, and the weight of the nasal secretion was measured. The histamine concentration was then sequentially increased at 10-min intervals in order to determine the thresholds to induce >0.5g/10 min nasal secretion and >1 sneezing/10 min.

Counting of Eosinophils in Nasal Lavage and Scraped Epithelium of the Inferior Turbinate Mucosa

The following were determined in nasal lavage and scraped epithelium of the inferior turbinate mucosa in order to evaluate the role of inflammatory cells, especially activated EG2-positive eosinophils, in the pathogenesis of idiopathic rhinitis: (1) the numbers of desquamated epithelial cells, eosinophils and neutrophils in nasal lavage; (2) the ratio of eosinophils to neutrophils and the percentage of EG2-positive cells in entire eosinophils in nasal lavage, and (3) the ratio of eosinophils to epithelial cells and the percentage of EG2-positive cells in entire eosinophils in scraped epithelium of the inferior turbinate mucosa.

Collection of Nasal Lavage

A nozzle connected to a 20-ml syringe and a silicone tube was closely inserted into each anterior nostril while keeping the patients in a sitting position with a slight anterior flexion of the neck. The left and right nasal cavities were then lavaged using 10 ml each of normal saline. Ten pushes of the syringe were made into each nasal cavity, about 1 ml/push every 2 s. Part of the saline introduced into one anterior nostril which flowed out of the contralateral anterior nostril was received in a funnel above a measuring cylinder and combined with the saline in the syringe to calculate the recovered volume. The recovery rate of lavage was 90.3±3.9%. The recovered nasal lavage was filtered through a nylon mesh (No. 200) to remove mucin and centrifuged at 400 g for 20 min at 4°C. Inflammatory cells and desquamated epithelial cells were counted using a counting chamber after staining with Türk staining for neutrophils, monocytes and desquamated epithelial cells and Hinkelmann staining for eosinophils. The lavage was also sprinkled over slide glasses using a Cytospin, and the cells were counted after staining.

Vasomotor Response of the Nasal Mucosa to Cold Stimulation of the Feet and the Nasal Mucosa

Acoustic Rhinometry. An acoustic rhinometer (MADAP, ARI-19, G.M. Instruments, UK) was used for evaluation of vasomotor response of the nasal mucosa. This device consists of a sound source (loudspeaker) mounted at the distal end of a wave tube with a recording microphone located at the proximal end of the tube. The acoustic pulse generated by the loudspeaker is propagated along the wave tube, and the pulse passes through the microphone and enters the

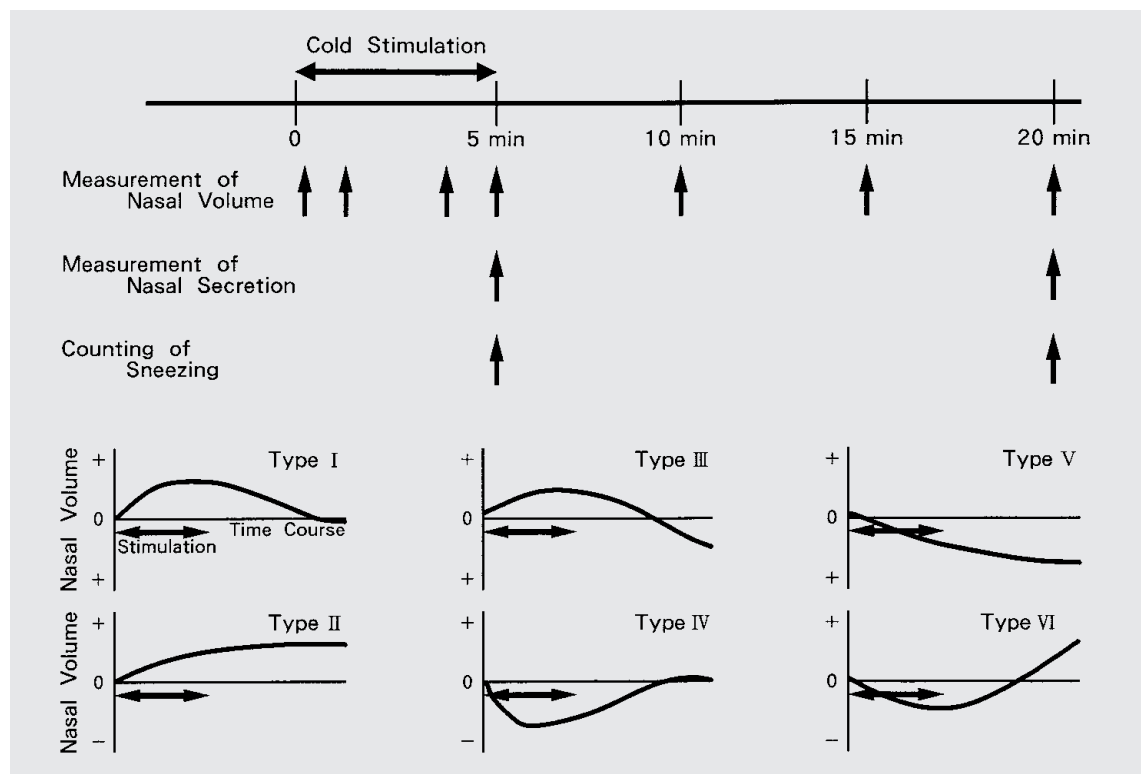


Fig. 1. Time schedule of the experiment to evaluate vasomotor and glandular responses of the nasal mucosa to cold stimulation of the feet and the nasal mucosa, and the patterns of time course changes in nasal volume observed during and after stimulation. Nasal volume was not measured during direct stimulation of the nasal mucosa with dry cool air. The patterns which could not be classified into any of the above 6 types were classified as type VII (see also results for characterization of types).

nasal cavity. Acoustic reflections (pressure signals) from the nose are sensed by a microphone and analyzed with an analog-to-digital converter by a computer. This information is processed to determine the minimal cross-sectional area of the nasal cavity and nasal volume as a function of distance from the nasal aperture [7–9]. During measurement, utmost care was taken to maintain control of the respiratory pattern, angle of incidence of the acoustic wave into the nasal cavity, palate position and nosepiece seal quality. Each measurement was repeated 3 times, and the mean value from 3 estimates was taken as the final estimate. Readings were taken at the suspension of respiration which took only a few seconds.

Cold Water Stimulation of the Feet and Dry Cool Air Stimulation of the Nasal Mucosa. We evaluated vasomotor and glandular responses of the nasal mucosa to cold stimulation of the feet and of the nasal mucosa in 8 patients with idiopathic rhinitis and compared to 14 patients with perennial allergic rhinitis and 15 normal controls. As informed consent to cold stimulation of the feet and of the nasal mucosa was obtained in only 3 of 8 patients with NARES, patients with NARES were not included in this part of the study. Cold stimulation was done by cooling of the feet and stimulation of the nasal mucosa with dry cool air.

The tests were conducted in a room kept at 20–28°C between 1.00 and 4.00 p.m. after keeping the patients in a sitting position for at least

30 min. The test schedule is shown in figure 1. First, both legs were put into water of 13°C up to above the ankles to give cold stimulation for 5 min. This temperature is close to the upper limit at which subjects can tolerate the procedure for 5 min. Almost all the subjects in the present study complained of pain and showed increases in systolic blood pressure. To monitor vasomotor response of the nasal mucosa, the nasal volume 2–4 cm from the anterior nostril was measured with an acoustic rhinometer before and 1, 3 and 5 min after starting cold stimulation. The nasal volume was measured 5, 10 and 15 min after taking the feet out of the water. The amount of nasal secretion which was measured by the tissue paper method and the frequency of sneezing were also determined throughout the study period.

After a rest for 2 h, the nasal mucosa was stimulated by allowing the subjects to inhale dry cool air of 13°C through the nasal nozzles fitted to the bilateral anterior nostrils for 5 min while the subjects breathed through their mouth. The dry cool air was obtained by passing compressed dry air through a metal tube in a box filled with ice and salt with a flow velocity of 4 l/min. The nasal volume was measured immediately before starting, upon completion, and 5, 10 and 15 min after the 5-min stimulation. The amount of nasal secretion and the frequency of sneezing were measured upon and 15 min after completion of the 5-min stimulation period.

Table 4. Number of inflammatory cells and desquamated epithelial cells in nasal lavage and in scraped epithelium of the inferior turbinate in patients with allergic rhinitis, idiopathic rhinitis and NARES

	Nasal lavage					Scraped epithelium of the inferior turbinate	
	epithelial cells × 10 ² /ml	eosinophils × 10 ² /ml	neutrophils × 10 ² /ml	eosinophils/ neutrophils	EG ₂ -positive cells in total eosinophils, %	eosinophils/ epithelial cells	EG ₂ -positive cells in total eosinophils, %
Normal controls, n = 25	24.3±17.5	6.3±5.1	8.4±5.4	0.38±0.27	13.2±13.0	0.06±0.03	14.2±25.1
Allergic rhinitis, n = 25	23.6±12.8 ¹	20.7±10.2*	10.8±6.7 ¹	2.13±1.31*	53.2±25.4*	0.44±0.41*	55.1±24.6*
Idiopathic rhinitis, n = 18	10.8±8.4 ¹	3.9±6.1 ¹	4.1±7.2 ¹	0.78±0.59 ¹	2.0±5.9 ¹	0.06±0.06 ¹	11.9±20.2 ¹
NARES, n = 8	16.4±6.4 ¹	8.1±7.5 ¹	5.2±6.4 ¹	2.38±1.68*	77.1±16.2*	0.61±0.30*	77.9±9.1*

*p<0.01 compared to controls.
¹ No differences compared to controls.

Statistical Analysis

Data were shown as means ± standard deviations. One-factor ANOVA, Scheffé’s F test and the χ^2 test were used to determine the statistical significance. p<0.05 was considered to be statistically significant.

Results

Threshold of Nasal Reactivity to Histamine

The thresholds (expressed as power exponents) to induce >0.5 g/10 min nasal secretion were 2.6±0.8 in nasal allergy. 3.4±0.8 in idiopathic rhinitis, and 3.4±1.1 in NARES compared to 4.5±0.7 in normal controls. The thresholds to induce >1 sneezing/10 min were 2.6±0.8 in allergic rhinitis, 3.3±0.9 in idiopathic rhinitis, and 2.4±1.3 in NARES compared to 4.1±0.8 in normal controls (table 3). The thresholds to induce both nasal secretion and sneezing were significantly lower in patients with idiopathic rhinitis and NARES than in normal controls (p<0.05). However, they were significantly higher in patients with idiopathic rhinitis than in patients with allergic rhinitis (p<0.01).

Desquamated Epithelial Cells and Inflammatory Cells in Nasal Lavage and Scraped Nasal Mucosal Epithelium

Number of Desquamated Epithelial Cells in Nasal Lavage

There were no significant differences in the number of desquamated epithelial cells in nasal lavage in patients with

idiopathic rhinitis (1,080±840 cells/ml), allergic rhinitis (2,360±1,280 cells/ml), NARES (1,640±640 cells/ml), and normal controls (2,430±1,750 cells/ml) (table 4).

Number of Eosinophils in Nasal Lavage

The number of eosinophils in nasal lavage was comparable in patients with idiopathic rhinitis (390±610 cells/ml) and normal controls (630±510 cells/ml), while it increased significantly in patients with allergic rhinitis (2,070±1,020 cells/ml) compared to normal controls (p<0.01) (table 4). No significant differences were observed in patients with NARES (810±750 cells/ml) compared to normal controls and patients with allergic rhinitis due to the great variability.

Number of Neutrophils in Nasal Lavage

The number of neutrophils in nasal lavage was 410±720 cells/ml in patients with idiopathic rhinitis, 1,080±670 cells/ml in allergic rhinitis, 520±640 cells/ml in NARES and 840±540 cells/ml in normal controls. There were no significant differences among these 4 groups (table 4).

Ratio of Eosinophils to Neutrophils in Nasal Lavage

The ratio of eosinophils to neutrophils in nasal lavage was 0.78±0.59 in patients with idiopathic rhinitis, compared to 2.13±1.31 in allergic rhinitis, 2.38±1.68 in NARES and 0.38±0.27 in normal controls. The ratio significantly increased in patients with allergic rhinitis and NARES compared to normal controls (<0.01), whereas there were no significant differences between patients with idiopathic rhinitis and normal controls (table 4).

Percentage of EG2-Positive Cells in the Total Number of Eosinophils in Nasal Lavage

Percentages of EG2-positive cells in the total number of eosinophils in specimens prepared using a Cytospin were determined as a marker of eosinophilic activation in nasal lavage. The percentage was $2.0 \pm 5.9\%$ in patients with idiopathic rhinitis, compared to $53.2 \pm 25.4\%$ in allergic rhinitis, $77.1 \pm 16.2\%$ in NARES and $13.2 \pm 13.0\%$ in normal controls. There were no significant differences between patients with idiopathic rhinitis and normal controls. The percentages in patients with allergic rhinitis and NARES were significantly increased compared to normal controls ($p < 0.01$) (table 4).

Ratio of Eosinophils to Epithelial Cells in Scraped Epithelium of the Inferior Turbinate Mucosa

The ratio of eosinophils to epithelial cells in scraped epithelium of the inferior turbinate mucosa was 0.06 ± 0.06 in patients with idiopathic rhinitis, compared to 0.44 ± 0.41 in allergic rhinitis, 0.61 ± 0.30 in NARES and 0.06 ± 0.03 in normal controls (table 4). While there were no significant differences between patients with idiopathic rhinitis and normal controls, significant increases were observed in patients with allergic rhinitis and NARES ($p < 0.01$) compared to controls.

Percentage of EG2-Positive Cells in the Total Number of Eosinophils in Scraped Epithelium of the Inferior Turbinate Mucosa

The percentage of EG2-positive cells in the total number of eosinophils in scraped epithelium of the inferior turbinate mucosa was $11.9 \pm 20.2\%$ in patients with idiopathic rhinitis, compared to $55.1 \pm 24.6\%$ in allergic rhinitis, $77.9 \pm 9.1\%$ in NARES and $14.2 \pm 25.1\%$ in normal controls (table 4). While no significant increases were observed in patients with idiopathic rhinitis compared to normal controls, patients with allergic rhinitis and NARES showed significant increases compared to normal controls ($p < 0.01$).

Vasomotor and Glandular Response of the Nasal Mucosa to Cold Stimulation of the Feet and of the Nasal Mucosa

Cold Water Stimulation of the Feet

Changes in Nasal Volume. Time-course changes in the nasal volume observed during and after cold stimulation of the feet were classified into the following 7 patterns (fig. 1): type I in which the nasal volume transiently increased 1–3 min after starting cold stimulation due to nasal mucosal contraction caused by sympathetic nasal reflex but de-

creased gradually thereafter and returned to baseline 15 min after completion of the stimulation; type II in which increases in nasal volume lasted for 15 min after completion of the stimulation; type III in which the nasal volume increased after cold stimulation, but decreased thereafter due to nasal mucosal swelling; type IV in which the nasal volume decreased immediately after starting stimulation due to mucosal swelling but returned to baseline 15 min after completion of the stimulation; type V in which decreases in the nasal volume persisted throughout the study; type VI in which the nasal volume increased due to nasal mucosal contraction after transient decreases, and type VII in which time course changes in the nasal volume could not be classified into any of the above 6 types.

The incidence of each pattern of time course changes in nasal volume upon cold stimulation of the feet is shown in table 5. Type I was the pattern most commonly seen in normal controls (8/15). The remaining normal controls showed either type II (4/15) or III (2/15). This finding indicates that in a great majority of normal controls contraction of the nasal mucosa due to sympathetic excitation occurred in response to cold stimulation of the feet. In contrast, no patient with idiopathic rhinitis showed type I or II, and only 2 showed type III time-course changes. Six of the 8 patients with idiopathic rhinitis showed mucosal swelling due to cold stimulation of the feet. In patients with idiopathic rhinitis, the incidence of vascular contraction of the nasal mucosa during cold stimulation of the feet was significantly lower than in normal controls, and cold stimulation of the feet rather caused nasal mucosal swelling ($p < 0.002$). In patients with allergic rhinitis, a distribution pattern between normal controls and patients with idiopathic rhinitis was observed, with 2 each of the 14 patients showing types I and II, and 4, 4 and 2 showing types III, V and VII, respectively.

The magnitude of changes in nasal volume 1 and 5 min after starting cold stimulation of the feet is shown in table 6. 1 min after cold stimulation of the feet, the nasal volume decreased to $0.35 \pm 0.61 \text{ cm}^3$ in patients with idiopathic rhinitis, while it increased to $0.18 \pm 0.78 \text{ cm}^3$ and $0.45 \pm 0.68 \text{ cm}^3$, respectively, in those with allergic rhinitis and in normal controls, indicating that sympathetic vasomotor response of nasal mucosa was significantly inhibited in patients with idiopathic rhinitis compared to normal controls and to patients with allergic rhinitis ($p < 0.05$). There were no significant differences between normal controls and patients with allergic rhinitis in this respect (fig. 2).

5 min after starting cold stimulation of the feet, the nasal volume decreased to $0.04 \pm 0.78 \text{ cm}^3$ in patients with idiopathic rhinitis, while it increased to $0.03 \pm 1.48 \text{ cm}^3$ and $0.31 \pm 0.66 \text{ cm}^3$, respectively, in those with allergic rhinitis

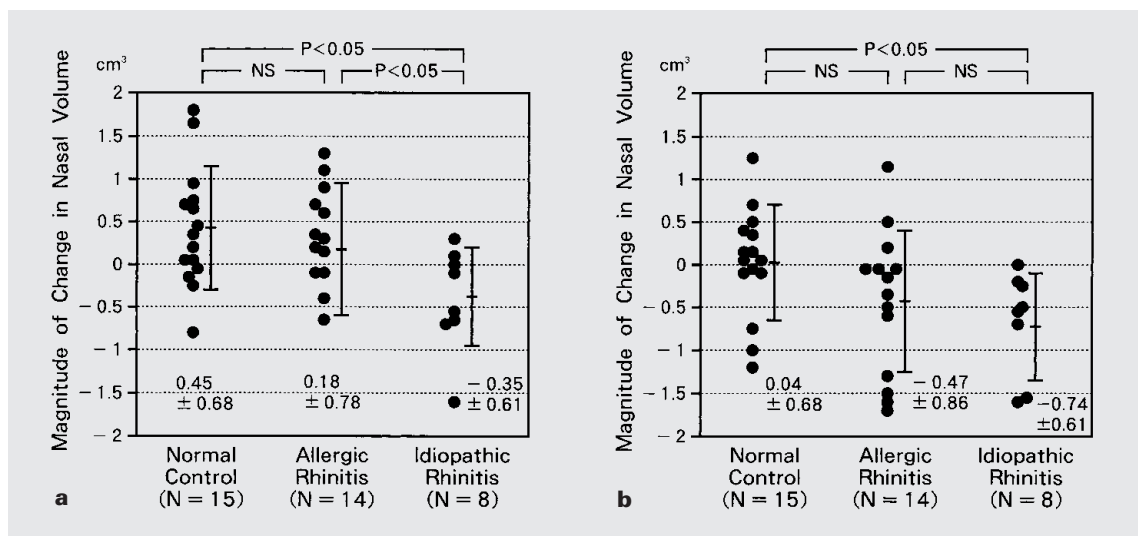


Fig. 2. Distribution of magnitudes of changes in nasal volume 1 min after starting stimulation (**a**) and maximum decrease in nasal volume during and after cold stimulation of the feet (**b**) in patients with allergic rhinitis and idiopathic rhinitis compared to normal controls.

Table 5. Distribution of patterns of time-course changes in nasal volume induced by cold stimulation of the feet and by dry cool air stimulation of the nasal mucosa

	Cold stimulation of the feet							Dry cool air stimulation of the nasal mucosa						
	I	II	III	IV	V	VI	VII	I	II	III	IV	V	VI	VII
Normal controls, n = 15	8	4	2	0	0	0	1	0	2	1	2	3	2	5
Allergic rhinitis, n = 14	2	2	4	0	4	0	2	0	2	2	1	7	1	1
Idiopathic rhinitis, n = 8	0	0	2	2	1	3	0	0	1	2	1	3	1	0

See Results for characterization of type I–VII.

and in normal controls, although differences were not statistically significant due to a large diversity of values obtained in both patients with idiopathic rhinitis and those with allergic rhinitis. The incidence of decreases in nasal volume 5 min after cold stimulation was higher in patients with idiopathic rhinitis (6/8) and those with allergic rhinitis (9/14) than in normal controls (3/15). Decreases in nasal volume were still greater, but not significantly, in patients with idiopathic rhinitis than in normal controls 15 min after termination of cold stimulation (data not shown).

Changes in the nasal volume observed during the maximum nasal mucosal swelling in response to cold stimulation of the feet were -0.74 ± 0.61 and -0.47 ± 0.86 cm³, respectively, in patients with idiopathic rhinitis and those with allergic rhinitis compared to 0.04 ± 0.68 cm³ in normal controls (fig. 2). The differences between patients with idio-

pathic rhinitis and normal controls were significant ($p < 0.05$).

Weight of Nasal Secretion. Nasal Secretion weight during 5 min of cold stimulation was the largest for patients with idiopathic rhinitis (59 ± 23 mg), followed by those with allergic rhinitis (31 ± 11 mg) and normal controls (17 ± 9 mg), and differences were statistically significant between patients with idiopathic rhinitis and normal controls ($p < 0.05$).

Nasal secretion weight during 15 min after cold stimulation was the largest for patients with allergic rhinitis (78 ± 104 mg), followed by those with idiopathic rhinitis (50 ± 59 mg) and normal controls (22 ± 25 mg). However, there were no significant differences among the 3 groups (table 6).

Table 6. Magnitudes of changes in nasal volume and amount of nasal secretion induced by cold water stimulation of the feet and by dry cool air stimulation of the nasal mucosa

	Cold stimulation of the feet				Dry cool air stimulation of the nasal mucosa			
	magnitudes of change in nasal volume cm ³		amount of nasal secretion mg		magnitudes of change in nasal volume cm ³		amount of nasal secretion mg	
	after 1 min of stimulation	after 5 min of stimulation	during 5 min of stimulation	15 min after stimulation	after 5 min of stimulation	15 min after stimulation	during 5 min of stimulation	15 min after stimulation
Normal controls n = 15	0.45±0.68	0.31±0.66	17±9	22±25	0.08±0.49	-0.12±0.89	32±29	26±28
Allergic rhinitis n = 14	0.18±0.78	0.03±1.48	31±11	78±104	0.04±0.69	-0.24±0.73	107±93*	464±529*
Idiopathic rhinitis n = 8	-0.35±0.61*, **	-0.04±0.78	59±23*	50±59	-0.17±0.95	-0.09±1.04	175±127*	305±378*

*p<0.05 compared to controls; **p<0.05 compared to allergic rhinitis.

Sneezing. No subject sneezed during cold stimulation.

Blood Pressure. Systolic blood pressure increased compared to that determined at rest in all subjects except 1 with idiopathic rhinitis measured 1 min after onset of cold stimulation of the feet. Increases were comparable in the 3 groups: 9.1±3.4 mm Hg in normal controls, 12.7±3.7 mm Hg in patients with allergic rhinitis, and 9.7±4.0 mm Hg in those with idiopathic rhinitis.

Stimulation of Nasal Mucosa by Dry Cool Air

Changes in Nasal Volume. The incidence of each pattern of time course changes in nasal volume observed after stimulation of the nasal mucosa with dry cool air is shown in table 5. Normal controls showed no consistent pattern, while type V was seen in a large number of patients with allergic rhinitis (7/14). The majority of patients with idiopathic rhinitis showed type V (3/8) or III (2/8), types associated with nasal mucosal swelling after stimulation.

The nasal volume decreased in patients with idiopathic rhinitis (-0.17±0.95 cm³), while it increased in those with allergic rhinitis (0.04±0.69 cm³) and in normal controls (0.08±0.49 cm³) 5 min after direct exposure of the nasal mucosa to dry cool air. However, differences among the 3 groups were not significant due to the great diversity of values obtained. The nasal volume decreased in all 3 groups 15 min after completion of stimulation to -0.09±1.04, -0.24±0.73 and -0.12±0.89 cm³, respectively, in patients with idiopathic rhinitis, with allergic rhinitis and in normal controls. No significant differences were observed among the 3 groups (table 6).

Weight of Nasal Secretion. The weight of nasal secretion determined immediately after dry cool air stimulation of the nasal mucosa increased significantly (p<0.05) in patients with idiopathic rhinitis (175±127 mg) compared to those with allergic rhinitis (107±93 mg) and to normal controls (32±29 mg).

The weight of nasal secretion determined 15 min after completion of dry cool air stimulation of the nasal mucosa increased significantly (p<0.05) in patients with idiopathic rhinitis (305±378 mg) and those with allergic rhinitis (464±529 mg) compared to normal controls (26±28 mg) (table 6).

Sneezing

One attack of sneezing was provoked in 1 patient with idiopathic rhinitis.

Blood Pressure

There were no significant differences in the changes in systolic blood pressure among the 3 groups.

Discussion

The objective of the present study was to evaluate pathological and pathophysiological features of the nasal mucosa in patients with idiopathic rhinitis and with allergic rhinitis compared to normal controls, and to determine if aberrant vasomotor response of the nasal mucosa to cold stimulation are observed in patients with idiopathic rhinitis. The term idiopathic rhinitis was used as a synonym for vasomotor

rhinitis defined in the guideline for the treatment of allergic diseases established by the Japanese Society of Allergology [1].

As expected from the diagnostic criteria shown in table 1, there were no significant differences between patients with idiopathic rhinitis and normal controls in the number of eosinophils, the percentage of EG2-positive cells, and the eosinophil/neutrophil ratio in nasal lavage or the eosinophil/epithelial cell ratio or percentage of EG2-positive cells in scraped inferior turbinate epithelium. This is consistent with previous reports [10, 11], although there remains some controversy [12] which is considered to be due to differences in diagnostic criteria of this disease. In the present study, all these markers of eosinophilic inflammation showed significant increases in patients with allergic rhinitis and those with NARES compared to normal controls and patients with idiopathic rhinitis. No significant differences were observed between patients with allergic rhinitis and those with NARES. Inflammatory cells, in particular eosinophils, are involved in the pathogenesis of allergic rhinitis and NARES, but not in that of idiopathic rhinitis.

The pathogenesis of NARES is thought to differ completely from that of idiopathic rhinitis, i.e. in the former, a type I allergic reaction due to undetermined antigen or nasal mucosal reactions induced by chemical mediators released from mast cells via non-IgE-mediated mechanisms [13–15] may be involved. Reactivity of the nasal mucosa to histamine was significantly increased in patients with idiopathic rhinitis compared to normal controls, but it was significantly lower compared to those with allergic rhinitis.

In normal controls, cold stimulation of the feet caused a contraction of the nasal mucosa and increases in the nasal volume due to excitation of the sympathetic center. This sympathetic vascular response of the nasal mucosa induced by cold stimulation in normal subjects is consistent with previous reports [4–6]. However, the literature is conflicting in regard to vasomotor response of the nasal mucosa to cold stimulation of the skin in patients with hyperreactive nasal symptoms [4–6]. Speisman and Arnold [4] reported that cold air stimulation of the skin of the back caused a rapidly established transient fall in nasal mucosal temperature in subjects with hyperreactive nasal symptoms and that the vascular reaction of the nasal mucosa was directly opposite to that of the normal controls. This finding was disputed by Ralston and Kerr [5] and Drettner [6]. However, none of these previous investigators separated the patients with idiopathic rhinitis from those with allergic rhinitis; they were combined for comparison with normal subjects. Moreover, in most studies, the change of surface tempera-

ture of the nasal mucosa was monitored to evaluate vasomotor response of the nasal mucosa to cold stimulation of the skin, while Ralston and Kerr [5] monitored pressure changes in a balloon inserted in to the nasal cavity. Drettner [6] used posterior rhinomanometry. Now we can use acoustic rhinometry, a very sensitive and noninvasive method, by which vasomotor responses of the nasal mucosa can be evaluated within a minute without imposing much psychophysiological disturbance on the subjects [7–9].

The present study showed that sympathetic vasomotor responses of the nasal mucosa to cold stimulation of the feet were significantly inhibited in patients with idiopathic rhinitis, and that the stimulation caused relaxation, rather than contraction, of the nasal vascular smooth muscle. Because nasal secretion was significantly enhanced during cold stimulation of the feet in patients with idiopathic rhinitis compared to normal controls and patients with allergic rhinitis, the relaxation of vascular smooth muscle observed was thought to be due to reflexive excitation of the parasympathetic center which controls the nasal mucosa. Cold stimulation of the feet caused increases in systolic blood pressure of 5–15 mm Hg in all subjects except in 1 with idiopathic rhinitis. As there were no significant differences in the magnitude of increase of blood pressure among patients with idiopathic rhinitis, nasal allergy and normal controls, inhibition of the nasal sympathetic reflex associated with idiopathic rhinitis is considered to take place at the peripheral level, probably in the nasal mucosa.

Dry cool air stimulation of the nasal mucosa caused the largest reduction in nasal volume in patients with idiopathic rhinitis, followed by patients with nasal allergy and normal controls, but intergroup differences were not statistically significant due to the large diversity of values obtained. Nasal vascular reactions caused by direct dry cool air stimulation of the nasal mucosa are difficult to interpret because besides centrally mediated sympathetic and parasympathetic reflexes, also axonal and ganglionic reflexes, as well as direct reactions of the nasal vasculature to cool air, contribute to their development.

Recently, Wilde et al. [16, 17] reported suppressed sympathetic vasomotor response of the nasal mucosa to exercise and axillary pressure evaluated by anterior rhinomanometry in patients with idiopathic rhinitis compared to normal controls, while Casano et al. [18] reported significantly greater variations in the vasomotor responses of the nasal mucosa to exercise in patients with idiopathic rhinitis compared to patients with allergic rhinitis. Togias et al. [14, 19–21] studied changes in chemical mediators and inflammatory cells in nasal lavage obtained after dry cold air stimulation of the nasal mucosa in patients with nonallergic noninfectious

rhinitis who showed hyperreactive nasal symptoms. Because both hyperreactive nasal symptoms and the release of chemical mediators from mast cells induced by dry cold air stimulation of the nasal mucosa were significantly inhibited by surface sensory anesthesia of the nasal mucosa, enhanced sensory reactivity of the nasal mucosa was thought to have been induced by stimulation of the sensory nerve terminals and mast cell degranulation secondary to changes in osmotic pressure of nasal secretions. However, because substance P does not cause significant degranulation of mast cells to induce sneezing and nasal hypersecretion in human nasal mucosa [22–26], those mechanisms remain unknown.

In some patients, cold stimulation may directly cause degranulation of mast cells in the nasal mucosa, as in the case

of cold urticaria [15]. Degranulation of mast cells induces allergic inflammatory changes in the nasal mucosa mediated by chemical mediators, such as platelet activating factor, leukotriene B₄ and various cytokines, such as IL-5 and IL-4. However, the pathogenesis of idiopathic rhinitis cannot be explained by mast cell degranulation because the possible participation of allergic inflammation is ruled out in its diagnosis.

Although pathophysiological mechanisms which cause exaggerated nasal responses to daily stimuli, such as cold air, are not well understood, aberrant neurological responses to these stimuli are certainly involved in the pathogenesis of idiopathic rhinitis. Further studies are necessary to determine the mechanisms by which sensory hyperreactivity [3, 27] is initiated in idiopathic rhinitis.

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