

Bronchial responsiveness and airway inflammation in patients with nonallergic rhinitis with eosinophilia syndrome

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Background: Nonallergic rhinitis with eosinophilia syndrome (NARES) is characterized by persistent nasal symptoms without allergy and by a marked eosinophil recruitment in the nasal cavities.

Objective: We studied whether patients with NARES had bronchial responsiveness to methacholine and airway inflammation and examined the relationship between these factors. **Methods:** We selected a group of 39 patients referred to our allergy clinic for symptoms of perennial rhinitis. Atopic status was excluded by skin prick tests and RASTs. None of the patients had a history of respiratory symptoms. We preliminarily performed nasal lavage in all patients, and the diagnosis of NARES was made on the basis of the presence of at least 10% eosinophils in nasal lavage fluid. A methacholine challenge and sputum induction were also done on two different days.

Results: Eosinophils in nasal lavage fluid ranged between 10% and 86%. Serum IgE levels were within normal range. Total circulating eosinophils ranged between 40 and 890/mm³. Methacholine PD₂₀ values were measurable in only 18 patients (range, 0.32 to 22.56 μ mol; group 1). In the remaining 21 patients, methacholine PD₂₀ values were greater than 24 μ mol (group 2). We found that differential cell counts in nasal lavage fluid in group 1 were not different from those in group 2. Methacholine PD₂₀ values were not significantly related to any cell count in the nasal lavage fluid. Induced sputum was accomplished only in 22 patients. Eosinophils in induced sputum ranged between 0% and 56.5%. Numbers of total cells, macrophages, lymphocytes, neutrophils, and epithelial cells in the two subgroups were not different. The number of metachromatic cells tended to be higher in group 1 compared with group 2 (0.31% vs 0.05%), but the difference was not significant. The eosinophil count in the induced sputum was significantly higher in group 1 compared with group 2 (16.8% vs 3.1%; $p < 0.05$). In the entire population, methacholine PD₂₀ values were significantly correlated with the number of eosinophils in sputum ($r = -0.63$; $p < 0.001$).

Conclusion: We showed that 46% of patients with NARES but without histories of respiratory symptoms had a measurable bronchial responsiveness. The presence of bronchial responsiveness was associated with an increased number of

eosinophils in induced sputum but not with the inflammatory process in the nose. (*J Allergy Clin Immunol* 1997;100:775-80.)

Key words: Nonallergic rhinitis with eosinophilia syndrome, bronchial responsiveness, nasal lavage, induced sputum

Nonallergic rhinitis with eosinophilia syndrome (NARES) was first described in 1980.¹⁻³ This condition is characterized by perennial symptoms of rhinorrhea, nasal obstruction, and sneezing. It has been suggested that NARES is a precursor of the aspirin triad (characterized by intrinsic asthma, nasal polyposis, and aspirin intolerance).^{4,5} The presence of NARES is determined by the appearance of a high percentage of eosinophils in nasal secretions.^{3,4,6,7} The diagnosis of NARES has been made on the basis of the cytologic analysis of nasal secretions recovered by the washing-blowing technique^{6,8} and tissue specimens from nasal biopsy.⁴

Nasal lavage is a noninvasive and reproducible standardized technique that allows for the assessment of nasal inflammation.^{9,10} However, to date this method has not been applied to define differential counts of inflammatory cells in the nasal cavities of patients with NARES.

Bronchial responsiveness is often measurable in patients with seasonal and perennial rhinitis.¹¹⁻¹³ Thus allergic rhinitis has been recognized as an important risk factor for the development of asthma.¹⁴ Jacobs et al.² have found that bronchial responsiveness to methacholine was not in the asthmatic range in all the selected patients with NARES. However, Moneret-Vautrin et al.⁵ later reported the presence of bronchial hyperresponsiveness in two of three patients with NARES. Thus the degree of bronchial responsiveness to methacholine over a wide range of inhaled doses has not yet been examined, and its prevalence has not been fully established.

The use of bronchoalveolar lavage,¹⁵ bronchial biopsy,¹⁶ and, more recently, induced sputum¹³ has greatly increased our knowledge about inflammation of the bronchial airways in subjects with allergic rhinitis. These studies demonstrated the presence of inflammatory cells such as eosinophils and metachromatic cells in the bronchoalveolar lavage fluid¹⁵ and biopsy specimens¹⁶ in the lower airways of subjects with seasonal allergic rhinitis. More recently, we have shown that inflammatory cells are present in induced sputum from patients

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Abbreviation used

NARES: Nonallergic rhinitis with eosinophilia syndrome

with seasonal allergic rhinitis even outside the pollen season.¹³ The association between airway inflammation and bronchial hyperresponsiveness in asthma is a widely accepted concept,^{13, 16, 17} whereas the pathogenesis of bronchial responsiveness in allergic rhinitis is still debated.^{14, 15} In a previous study we demonstrated that bronchial responsiveness to methacholine is associated with the presence of eosinophils in induced sputum in patients with allergic rhinitis.¹³ Whether eosinophilic inflammation is also present in patients with NARES and whether it is related to bronchial responsiveness still need to be established.

In this study we performed nasal lavage in select patients with NARES and studied the presence and degree of bronchial responsiveness to methacholine in these patients. Moreover, we examined the differential cell count of induced sputum to assess the relationship between airway inflammation and bronchial responsiveness.

METHODS

Population

We studied 39 patients between November 1993 and April 1995 referred to our outpatient clinic on the basis of a history of perennial rhinitis. All patients lived in a highly polluted area (Milan, northern Italy). Patients were selected if they matched the following criteria: negative responses to skin prick tests with extracts of 16 common airborne allergens; negative RAST results; levels of total serum IgE within the normal range; absence of any history of respiratory symptoms, including recurrent cough, wheezing, chest tightness, or asthma attacks; and nasal eosinophilia. Thus we excluded patients with an established history of bronchial asthma. Patients who had undergone nasal surgery within 6 months before the study were also excluded. None of the patients had been treated with topical steroids or chromones for at least 3 months before the study. No patient was exposed to occupational sensitizers known to be a risk factor for asthma.

The diagnosis of NARES was made on the basis of the presence of at least 10% eosinophils in nasal lavage fluid. To establish the "threshold" value for percentage of eosinophils, we examined 55 consecutive patients referred to our laboratory on the basis of persistent nasal symptoms (13 patient with vasomotor rhinitis, 22 patients with quiescent sinusitis without allergy, and 20 patients with perennial rhinitis caused by *Dermatophagoides* spp.). In these patients the mean value ($\pm$ SD) for eosinophil count in nasal lavage fluid was 1.81% ($\pm$ 3.26%). Thus a value equal to or greater than 10% was assumed to be the threshold percentage for eosinophils (mean plus 2 SD).

An accurate record of personal history was also obtained by means of a questionnaire. Questionnaire data revealed that only three patients were active smokers; one patient had a history of urticaria; three patients had food intolerance; two patients had intolerance to aspirin; two patients had intolerance

to sulphamides; seven patients had intolerance to nickel; and one patient had persistent anosmia. Patients also underwent an accurate otorhinolaryngologic examination and standard roentgenography for the sinus cavities. Only three patients showed the presence of nasal polyposis, which was confirmed by roentgenographic analysis. Roentgenographic analysis also revealed the presence of maxillary sinusitis in 13 patients, marked septal deviation in 17 patients, and hypertrophy of turbinates in 31 patients. Only six patients reported previous nasal surgery.

The study was conducted after informed consent had been obtained from the participants and was performed according to the Helsinki declaration.

Study design

Each patient attended the laboratory on 4 different days, between 9 AM and 10:30 AM. On the first day, questionnaire data were recorded and skin prick tests were performed according to a standardized procedure. Blood samples were taken for the assessment of specific and total IgE and for the counting of total circulating eosinophils. On a second day, nasal lavage was performed. Patients were asked to attend the clinic on a third day, at least 3 days later, to undergo a methacholine challenge. On a separate occasion, sputum induction was performed again after a 3-day interval.

Nasal lavage

Nasal lavage was performed as previously described.^{9, 18} Briefly, each nostril was washed with 5 ml of saline solution warmed to 37° C. After 4 minutes, lavage fluid was recovered and pooled in a plastic tube. Then it was filtered and centrifuged at 300 g for 10 minutes. The cell pellet was resuspended in saline solution, and a total cell count was done with a Neubauer hemocytometer. When total cells recovered in lavage fluid exceeded 5×10^4 cells/ml, we accepted the sample as adequate. The cell suspension was cytocentrifuged (Cytospin 3; Shandon, Inc., Pittsburgh, Pa.) at 700 rpm for 5 minutes, and the slides were air-dried for 6 hours. Differential cell counts (on the basis of 300 cells) were obtained by staining one slide with Diff-Quik (Baxter Scientific Products, Fla.). Counts were done by an expert observer, in blinded fashion.

Serum IgE and blood eosinophil count

Total IgE levels were assessed by the paper disk radioimmunoassay technique (Pharmacia, Uppsala, Sweden) and expressed as international units per milliliter. Normal values ranged between 0 and 200 IU/ml. Specific IgE levels were assessed by RAST. Blood eosinophil counts were expressed as cells per cubic millimeter. Normal values were lower than 400 cells/mm³.

Methacholine challenge

Bronchial challenge with methacholine was always performed between 8 and 10 am according to a standard procedure.¹⁹ After three reproducible FEV₁ measurements were performed, doubling concentrations of methacholine from 0.1 mg/ml were inhaled at 5-minute intervals. Solutions were delivered by a De Vilbiss 646 nebulizer attached to a dosimeter (Mefar MB3, Brescia, Italy). Inhalations were continued until FEV₁ decreased by 20% or more from postsaline measurements or when a dose of methacholine equal to 24 μ mol was administered. Bronchial responsiveness was expressed as methacholine PD₂₀ and given in micromoles. When methacholine PD₂₀ values were not measurable, a PD₂₀ value equal to 24 μ mol was assigned to the patient.

TABLE I. Physiologic and clinical characteristics of patients

	Entire population (N = 39)	Group 1 (N = 18)	Group 2 (N = 21)
Sex (M/F)	13/26	4/14	9/12
Age (yr)	35.7 ± 2.1 (17-67)	36.4 ± 3.6 (19-67)	35.2 ± 2.5 (17-58)
Length of clinical history (yr)	3.3 ± 0.7 (0.3-20)	1.8 ± 0.4 (0.3-6)	4.5 ± 1.3* (0.3-20)
FEV ₁ (percent predicted)	98.1 ± 2.0 (60-121)	91.3 ± 1.8 (75-102)	104.0 ± 2.9† (60-121)
Blood eosinophils (cells/mm ³)	350.6 ± 40.2 (40-890)	363.3 ± 66.7 (40-890)	336.1 ± 42.2 (133-735)
Total IgE (IU/ml)	3.6-200	7.3-200	3.6-111
Methacholine PD ₂₀ range (μmol)	0.32->24	0.32-22.56	>24

Values are mean ± SEM with range in parentheses. Group 1 had a measurable methacholine PD₂₀ value; and group 2 had methacholine PD₂₀ value that was not measurable (>24 μmol).

*p < 0.05 compared with Group 1.

†p < 0.001 compared with Group 1.

Sputum induction and processing

Twenty-six of 39 patients agreed to undergo sputum induction. Sputum induction was successful in only 22 patients (85%). Sputum induction was performed as previously described,¹³ according to the method proposed by Fahy et al.,²⁰ slightly modified. Briefly, before sputum induction, all patients inhaled two puffs of salbutamol (200 μg) and underwent spirometry 10 minutes later. Then they inhaled nebulized sterile 3% saline solution for 20 minutes from an ultrasonic nebulizer (Mistogen EN143; mean output: 2 ml/min). Patients coughed throughout the procedure and expectorated into a glass container. The sputum sample so obtained was homogenized with 5% N-acetyl-L-cysteine added in equal volume. The sample was placed in a shaking bath at 37°C for 30 minutes to ensure complete homogenization. Ten microliters of homogenized sputum was used to determine the total cell count using a Neubauer's hemocytometer. Then sputum was washed three times in saline solution with a centrifuge at 300 g for 10 minutes. The suspension was cytocentrifuged at 700 rpm for 5 minutes, and the slides were air-dried for 6 hours. Differential cell counts (on the basis of 300 cells) were obtained by staining two slides with Diff-Quik. Counts of metachromatic cells were made by fixing cells in Carnoy's fluid for 1 hour and staining them with 0.5% toluidine blue (HCl, 0.7 mol/L; pH 0.5). Metachromatic cell counts were based on 1000 cells. Differential cell counts were always expressed as percentage of total nucleated cells, excluding squamous cells. The cell count was performed by an expert observer, without knowledge of the clinical characteristics of the patients.

Statistical analysis

Data were reported as mean ± SEM. Methacholine PD₂₀ values were logarithmically transformed before the analysis. Results were tested for normality by the Kolmogorov-Smirnov test. Differences between groups were analyzed by the Mann-Whitney U test or Student's *t* test. The correlations were assessed either by Spearman's rank method or Pearson's method. Probability values of less than 0.05 were accepted as significant.

RESULTS

The clinical and functional characteristics of the entire population are shown in Table I. None of these patients had measurable levels of specific IgE in serum. Total IgE levels ranged from 3.6 to 200 IU/ml. Total circulating eosinophils ranged from 40 to 890 cells/mm³. Nasal symptoms lasted for more than 4 months (range, 4

months to 20 years). In the entire population, methacholine PD₂₀ values ranged between 0.32 and greater than 24 μmol. Methacholine PD₂₀ values were measurable in 18 subjects (range, 0.32 to 22.56 μmol; group 1), whereas 21 patients had a methacholine PD₂₀ value that was not measurable (>24 μmol; group 2). Characteristics of patients according to presence (group 1) or absence (group 2) of a measurable methacholine PD₂₀ value are also reported separately in Table I. The two groups were not different with regard to sex, age, serum eosinophil count, and total IgE level. Baseline FEV₁ values, as percent of predicted values, were higher in group 2 compared with group 1 (*p* < 0.001). Moreover, the duration of nasal symptoms was slightly longer in group 2 than in group 1 (*p* < 0.05). However, the number of patients reporting nasal symptoms for less than 1 year, between 1 and 3 years, and for more than 3 years in each group showed the same distribution (4, 10, and 4 patients from group 1 and 5, 7, and 9 patients from group 2, respectively, as determined by chi-square test).

Nasal lavage

Differential cell counts in the entire population and the two subgroups are reported in Table II. The mean value of total cells recovered in the nasal lavage fluid was 122.3 × 10³ cells/ml. In all patients percentage of eosinophils in the nasal lavage fluid ranged between 10% and 86%. There was no statistically significant difference between groups in the number of total cells, eosinophils, neutrophils, lymphocytes, monocytes, and epithelial cells. When the relationship between cell counts in nasal lavage fluid and the clinical characteristics of patients was examined, there was a significant correlation only between neutrophil count and total cell counts (*n* = 39; *r*² = 0.51; *p* < 0.001). Analysis of the two subgroups showed that only eosinophils in group 1 correlated with length of nasal symptoms (*n* = 18; *r* = 0.48; *p* < 0.05). We did not find any correlation between blood eosinophil counts and nasal eosinophil counts.

Induced sputum

Differential cell counts in the entire population and the two subgroups are reported in Table III and Fig. 1.

TABLE II. Differential cell counts in nasal lavage fluid

	Entire population (N = 39)	Group 1 (N = 18)	Group 2 (N = 21)
Total cell count ($\times 10^3$)	122.3 $\pm$ 21.9	129.2 $\pm$ 39.9	116.5 $\pm$ 23.1
Eosinophils (%)	32.6 $\pm$ 3.3	29.3 $\pm$ 5.1	35.5 $\pm$ 4.2
Neutrophils (%)	24.1 $\pm$ 2.9	19.8 $\pm$ 5.0	27.7 $\pm$ 3.2
Lymphocytes (%)	0.65 $\pm$ 0.23	0.74 $\pm$ 0.49	0.58 $\pm$ 0.19
Monocytes (%)	0.35 $\pm$ 0.12	0.39 $\pm$ 0.22	0.31 $\pm$ 0.11
Epithelial cells (%)	42.2 $\pm$ 3.9	49.7 $\pm$ 6.5	35.8 $\pm$ 4.4

Values are mean $\pm$ SEM.

TABLE III. Differential cell counts in induced sputum

	Entire population (N = 22)	Group 1 (N = 10)	Group 2 (N = 12)
Total cell count ($\times 10^6$ cells/ml)	2.39 $\pm$ 0.4	2.47 $\pm$ 0.5	2.33 $\pm$ 0.5
Eosinophils (%)	9.3 $\pm$ 2.9	16.8 $\pm$ 5.6	3.1 $\pm$ 1.3*
Neutrophils (%)	54.9 $\pm$ 4.8	46.5 $\pm$ 6.3	61.9 $\pm$ 6.7
Metachromatic cells (%)	0.17 $\pm$ 0.06	0.31 $\pm$ 0.12	0.05 $\pm$ 0.04
Lymphocytes (%)	1.11 $\pm$ 0.22	1.02 $\pm$ 0.24	1.18 $\pm$ 0.37
Macrophages (%)	30.4 $\pm$ 3.8	31.0 $\pm$ 4.4	29.8 $\pm$ 6.1
Epithelial cells (%)	4.1 $\pm$ 0.5	4.3 $\pm$ 0.6	3.9 $\pm$ 0.8

Values are mean $\pm$ SEM.

* $p < 0.05$.

The mean value of the total cell count in the sputum was 2.39×10^6 cells/ml. In all patients percentage of eosinophils in induced sputum ranged between 0% and 56.5%. Percentage of eosinophils in group 1 was significantly higher compared with that found in group 2 ($p < 0.04$). Percentage of metachromatic cells was slightly higher in group 1 than in group 2, but the difference was not significant ($p = 0.08$). Eosinophil counts were positively correlated with metachromatic cell counts ($n = 22$; $r = 0.57$; $p < 0.01$).

There was no significant correlation between eosinophil counts in blood and eosinophil counts in sputum. Moreover, eosinophils in sputum were not significantly correlated with those in nasal lavage fluid. There was, however, a correlation between neutrophils in nasal lavage fluid and the epithelial cell count observed in the induced sputum ($r^2 = 0.44$; $p < 0.05$).

In the entire population, methacholine PD₂₀ values were inversely correlated with percentage of eosinophils ($n = 22$; $r = -0.63$; $p < 0.002$) and metachromatic cells in induced sputum ($n = 22$; $r = -0.57$; $p < 0.01$). However, there was no significant correlation between methacholine PD₂₀ values and differential sputum cell counts when only patients with measurable methacholine PD₂₀ values were considered (group 1).

DISCUSSION

This study demonstrated that bronchial responsiveness is measurable in approximately 46% of patients with NARES and that there is clear evidence for the presence of bronchial inflammation in patients with NARES. We observed that the mean percentage of eosinophils in induced sputum is significantly higher in patients with measurable methacholine PD₂₀ values

compared with that found in patients without bronchial responsiveness.

NARES has been defined on the basis of the presence of persistent nasal symptoms without allergy and nasal eosinophilia.^{1,3,4} In the past, nasal inflammation in patients with NARES has been assessed by analysis of nasal secretions obtained by nasal smears,² by nasal swabbing,^{7,21} or by the washing-blowing technique.^{6,8} In these studies the "threshold" value for eosinophil percentage was arbitrarily set as greater than 20% of total leukocytes. On the basis of differential cell counts in nasal lavages from a large group of subjects, we established that 10% eosinophils is a significant threshold value for the presence of NARES. We suggest that besides clinical characteristics and laboratory data, nasal lavage, when performed according to a standardized procedure, is a valuable tool for the diagnosis of NARES.

This is the first time that the prevalence of bronchial responsiveness has been assessed in a large group of patients with NARES. The range of methacholine PD₂₀ values was rather wide, with only three patients having values within the asthmatic range ($< 2 \mu\text{mol}$).²² In a previous report, Jacobs et al.² found that methacholine challenge was not measurable in patients with NARES. They did, however, administer a relatively low dose of methacholine. This technical factor may explain this discrepancy. Moreover, our results are in line with other studies in which the prevalence of bronchial responsiveness has been studied in patients with perennial allergic rhinitis^{11,12} or chronic rhinitis related to sinusitis.²³ Bronchial responsiveness was found in 66.6%¹¹ and 64.9%¹² of patients with perennial rhinitis and in 43.4% of patients with chronic sinusitis.²³ Thus the prevalence of bronchial responsiveness in NARES is similar to that

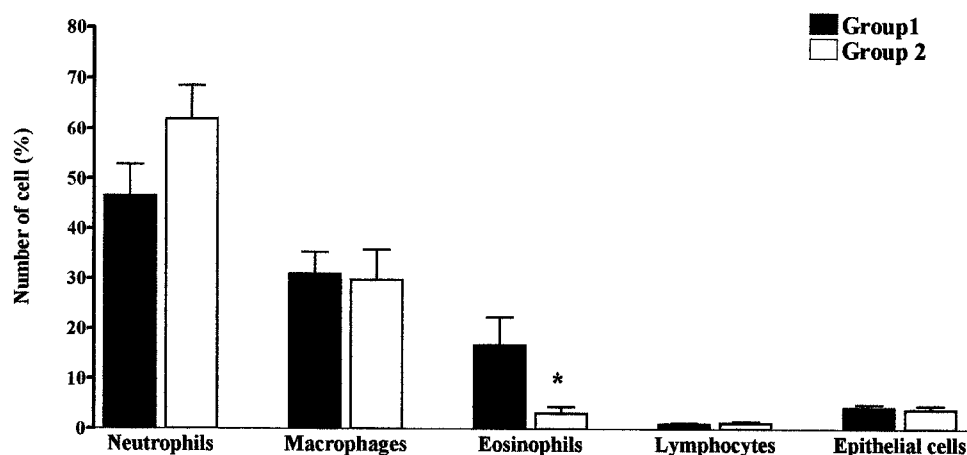


FIG. 1. Mean values and standard errors of each cell count in induced sputum from 22 patients with NARES. Patients in group 1 ($n = 10$) had a methacholine PD_{20} value less than $24 \mu\text{mol}$ and patients in group 2 ($n = 12$) had a methacholine PD_{20} value that was not measurable ($>24 \mu\text{mol}$). * $p < 0.05$.

found in other chronic inflammatory diseases of the nose. This finding is particularly important because bronchial responsiveness is regarded as an important predisposing condition for the subsequent development of asthma.^{14, 24, 25}

Some patients with NARES showed evidence of the presence of airway inflammation in induced sputum. This is the first study that examined the cytologic pattern of induced sputum in patients with NARES. The number of eosinophils in sputum was higher in patients with a measurable bronchial responsiveness. Moreover, there was a tendency toward a significant increase in the number of metachromatic cells. In these patients it appears that the percentage of eosinophils and metachromatic cells was similar to that reported by us¹³ and others²⁰ in patients with mild asthma during clinical remission. On the other hand, the number of eosinophils and metachromatic cells in the group without bronchial responsiveness was similar to that found in patients with seasonal rhinitis, not exposed to the sensitizing allergen.¹³

Presence of airway inflammation is a well-established concept in asthma,^{17, 26} although it is still debated in rhinitis. However, recent studies in patients with seasonal allergic rhinitis demonstrated that inflammation is present in bronchoalveolar lavage fluid¹⁵ and bronchial biopsy specimens.^{16, 27} The characteristics of mucosal inflammation in patients with perennial rhinitis have not yet been examined.

A significant correlation between eosinophil cell counts and methacholine PD_{20} values was found only when all patients with NARES ($n = 39$) were considered. It should be noted that correlation was no longer significant when patients that did not respond to methacholine were excluded from the analysis. However, it is noteworthy that eosinophil counts were significantly higher in patients that responded to methacholine compared with those that did not. In patients with asthma,

eosinophil counts in induced sputum,¹³ in bronchoalveolar lavage fluid,²⁶ and in bronchial biopsy specimens¹⁶ are significantly related to methacholine responsiveness. Moreover, we recently found that in patients with seasonal allergic rhinitis to grass pollens, the presence of measurable methacholine PD_{20} is associated with a significantly higher eosinophil count in induced sputum, even outside natural exposure.¹³ The results of this study suggest that eosinophilic inflammation plays a role in determining bronchial responsiveness in patients with NARES. However, other factors, such as genetic predisposition, are also likely involved.²⁸

The absence of any correlations between bronchial responsiveness to methacholine and nasal inflammation suggests that in patients with NARES, nasal inflammation per se is not a sufficient condition to induce bronchial inflammation. Patients affected by chronic rhinitis and severe nasal obstruction are likely to develop preferential mouth breathing. This may expose patients to inhaled environmental pollutants that could lead to the development of bronchial responsiveness in a genetically predisposed individual.²⁸ However, the clinical relevance of this mechanism has not yet been examined. Several other mechanisms have been suggested, such as postnasal drip of mediators or activation of nasopharyngeal-bronchial reflexes.²⁹ The importance of these mechanisms is indirectly supported by the finding of a modulation of bronchial responsiveness by topical nasal steroids in seasonal rhinitis,¹⁰ perennial rhinitis,³⁰ and chronic sinusitis.²³

In conclusion, the results of this study demonstrate that approximately half the patients with NARES but without a history of respiratory symptoms exhibit bronchial responsiveness to methacholine. We did not find a relationship between inflammatory cells in nasal lavage fluid and bronchial responsiveness, although it appears that eosinophil recruitment in sputum is associated with the presence of bronchial responsiveness. Although air-

way inflammation certainly contributes to bronchial responsiveness in patients with NARES, it is likely that other factors are also involved. Whether the presence of bronchial responsiveness in these patients is also an important and not fully appreciated predisposing condition for the development of asthma should be firmly proved.

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