
Association between response to decongestion testing and sensitizations and allergic inflammation

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Background: Rhinomanometry is used to measure nasal airflow, which is frequently impaired in allergic rhinitis (AR). Decongestion testing consists of spraying an intranasal vasoconstrictor drug to evaluate recovery of nasal airflow.

Objective: To evaluate the relationships among type and number of sensitizations, nasal airflow recovery after topical vasoconstrictor drug use, and allergic inflammation.

Methods: A total of 123 patients (112 men and 11 women; mean $\pm$ SD age, 22.9 ± 5.7 years) were studied: 40 with perennial AR (PAR), 43 with mixed AR (MAR), and 40 with seasonal AR (SAR). Patients with anatomic nasal defects were excluded. Total symptom scores (including nasal itching, sneezing, rhinorrhea, and nasal obstruction), sensitizations, nasal eosinophils, and cytokines (including interleukin 4 [IL-4], IL-5, and interferon- γ) were evaluated. Electronic rhinomanometry and decongestion testing were performed in all the patients.

Results: After administration of a topical nasal vasoconstrictor agent, mean nasal airflow significantly increased from 471 to 580 mL/s ($P < .001$). In 12 patients (3 with PAR, 3 with MAR, and 6 with SAR), no increase was shown. Changes from baseline were different in the PAR, MAR, and SAR populations (PAR vs MAR, $P < .001$; PAR vs SAR, $P < .001$; and MAR vs SAR, $P = .25$). Type of sensitization (MAR, PAR, or SAR), concentration of eosinophils, and levels of IL-4, IL-5, and interferon- γ were associated with nasal airflow recovery of at least 120 mL/s.

Conclusions: This study provides the first evidence of a different response to decongestion testing taking into consideration the type of AR.

Ann Allergy Asthma Immunol. 2006;96:431–436.

INTRODUCTION

Allergic rhinitis (AR) is the most frequent IgE-mediated disease. Its prevalence is high in the general population and is still progressively increasing.^{1–3} Allergic rhinitis is classically subdivided into seasonal (SAR) and perennial (PAR), according to the type of allergen and the occurrence of symptoms year round.⁴ Seasonal AR is mainly caused by outdoor allergens, such as pollens, whereas PAR is sustained by indoor allergens, including house dust mites, pets, and cockroaches. This classification has recently been revised by the ARIA (Allergic Rhinitis and its Impact on Asthma) Workshop.⁵ The new classification of “intermittent” and “persistent” does not consider the type of allergen but rather the duration of symptoms (days per week and consecutive weeks). On the basis of these considerations, this group⁶ studied a large population of patients perceiving only nasal symptoms to evaluate the clinical and functional aspects in relation to the type of AR and the causal allergen(s). The most important finding of this study is, however, that most patients (80%) exhibited a mixed

AR (MAR) because they were sensitized to seasonal and perennial allergens. Furthermore, seasonal variability in the symptom score was detectable for patients with SAR and PAR (patients with SAR have more symptoms during spring-summer, and those with PAR worsen during autumn-winter), whereas patients with MAR did not show seasonal variations.

Allergen exposure induces a cascade of inflammatory events that lead to the onset of symptoms. Experimental evidence⁷ supports a direct relationship between the IgE-mediated reaction and the resulting inflammatory process in AR. Allergen exposure activates mast cells, with the consequent release of preformed mediators, mainly histamine and leukotrienes, and cytokines capable of inducing the recruitment and activation of inflammatory cells, including eosinophils, neutrophils, and T_H2 lymphocytes.⁷

Typical nasal symptoms include itching, sneezing, rhinorrhea, and obstruction. The first 3 symptoms are considered “irritative” phenomena, mainly due to histamine, whereas nasal obstruction is mainly related to mucosal inflammation. Allergic inflammation, mucosal congestion, and increased production of mucus contribute to cause nasal obstruction as allergic inflammation induces a swollen mucosa, vasodilation causes engorgement of sinusoidal capacitance vessels, and excess mucus impairs nasal airflow.⁸ Recently, the relationships among nasal obstruction, T_H2-dependent inflammation, and airflow limitation have been seen in adults and children

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Received for publication June 8, 2005.

Accepted for publication in revised form July 26, 2005.

with AR.^{9,10} Actually, nasal obstruction may be objectively measured by using rhinomanometry.¹¹

Because bronchodilation testing using β_2 -agonists is considered to be a mainstay in asthma diagnosis, decongestion testing has been proposed as a prognostic test in AR.¹² The decongestion test consists of evaluating the percentage of recovery of nasal airflow after administering an intranasal vasoconstrictor drug (such as α -adrenoreceptor stimulants).¹² Nevertheless, to our knowledge, no study has investigated its role in AR considering the different etiology and inflammatory events. The purpose of the study was to evaluate the association between sensitization type (PAR, MAR, or SAR) and nasal airflow recovery after topical vasoconstrictor drug treatment. Second, we evaluated the relationship among nasal airflow recovery and nasal symptoms, number of sensitivities, and inflammation (eosinophils and cytokines).

METHODS

Study Design and Patients

The study was conducted during the pollen season, ie, during spring.^{6,9,11} We included 123 consecutive patients with AR (112 men and 11 women; mean $\pm$ SD age, 22.9 ± 5.7 years). All the patients were Navy soldiers who were referred to the Navy Hospital of La Spezia in Italy for periodic fitness examinations. In this observational study, we enrolled only patients reporting symptoms of rhinitis with skin sensitization to pollens ($n = 40$), perennial allergens ($n = 40$), or both ($n = 43$). Patients who reported present or past asthma symptoms, such as persistent cough, wheezing, dyspnea, and shortness of breathing, either diurnal or nocturnal, were excluded. Also, patients with acute upper respiratory tract infections, anatomic nasal defects (ie, septum deviation), and nasal polyps and those using nasal or oral corticosteroids, nasal or oral decongestants, and antihistamines during the previous 4 weeks were excluded.

The diagnosis of AR was made on the basis of a history of nasal symptoms and positive skin prick test results according to validated criteria.¹³ Based on the sensitizing allergen, we subdivided the patients into 3 groups, as previously reported⁶: sensitized to pollens only (the SAR group), sensitized to perennial allergens only (the PAR group), and sensitized to both pollens and perennial allergens (the MAR group). In our geographic area, the most relevant pollens are *Parietaria judaica*, grasses, olive, birch, and hazel, whereas the most important perennial allergens are house dust mites, cat, and dog.^{3,6,9–11} Skin prick tests, symptom evaluation, anterior rhinoscopy, rhinomanometry, and decongestion testing were performed in all the patients. The study was approved by the Navy Hospital institutional review board, and informed consent was obtained from all the patients.

Diagnostic Tests

Skin prick tests. Allergy was evaluated by the presence of sensitization to the most common classes of aeroallergens by performing skin prick tests as stated by the European Society

of Allergy and Clinical Immunology. Sensitization was considered when the wheal diameter was greater than or equal to 3 mm.¹⁴ The allergen panel consisted of house dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cat, dog, grasses mix, Compositae mix, *P judaica*, birch, hazel tree, olive tree, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix; the concentration of allergen extracts was 100 IR/mL (Stallergenes, Milan, Italy).

Nasal symptoms. The following symptoms were evaluated by the patient before and after treatment: nasal obstruction, sneezing, rhinorrhea, and itchy nose. Each symptom was evaluated according to the following scale: 0 = absent, 1 = mild (symptom was present but was not annoying or troublesome), 2 = moderate (symptom was frequently troublesome but did not interfere with either usual daily activity or sleep), and 3 = severe (symptom was sufficiently troublesome to have interfered with usual daily activity or sleep). Total symptom score, that is, the sum of each individual symptom score, was considered too.

Nasal cytologic examination. Nasal cytologic specimens were obtained by scraping the head of the inferior turbinate with a cotton swab, as described in previous articles.^{9,10} Smears were stained with hematoxylin-eosin and were analyzed using an optic microscope (Olympus U-SPT, Olympus Italy, Rome). The number of inflammatory cells (ie, neutrophils and eosinophils) was expressed as a mean of 10 optical fields at $\times 100$ magnification. Samples were examined in a blinded manner.

Nasal lavage. Nasal cavity lavage was performed using 5 mL of physiologic saline according to standard methods described elsewhere.^{9,10} The patient's head was bent backwards during closure of the soft palate. The recovered fluid was comparable in all groups; it was collected to evaluate cytokine levels and was stored at -20° .^{14,15}

Cytokine evaluation. The following panel of cytokines was evaluated: interleukin 4 (IL-4), IL-5, IL-8, and interferon- γ (IFN- γ). The cytokines were measured using the enzyme-linked immunosorbent assay method (R&D Systems, Minneapolis, MN). This assay used the quantitative sandwich enzyme immunoassay technique. Study samples and standard dilutions of each specific cytokine were assayed according to the enzyme-linked immunosorbent assay kit manufacturer's instructions.

Rhinomanometry. Nasal airflow was measured by using active anterior electronic rhinomanometry. Patients wore a tight-fitting face mask and breathed through 1 nostril with their mouth closed. A sensor, placed in the contralateral nostril, recorded data on prenasal and postnasal pressures via airflow and pressure transducers. The instrument (ZAN 100 Rhino Flow Handy II; ZAN Messgeraete GmbH, Germany) was connected to a personal computer. The signals of transnasal airflow and pressure were amplified, digitized, and saved for statistical analysis. Nasal airflow was reported as the sum of recorded airflow through the right and left nostrils in milliliters per second at a pressure difference of 150

Table 1. Baseline Characteristics According to Type of Sensitization

Characteristic	PAR (n = 40)	MAR (n = 43)	SAR (n = 40)	P value*
Age, mean (SD), y	23.3 (6.7)	22.1 (4.5)	23.3 (5.7)	.41
TSS, median (25th-75th percentile)	8 (7-9)	9 (8-10)	8 (7.5-9)	.01
				MAR vs SAR: .02
				PAR vs MAR: .01
Sneezing score 0/1/2/3, No.	2/8/27/3	2/22/19	7/15/18	.001
				PAR vs SAR: .003
				PAR vs MAR: .002
Itchy nose score 0/1/2/3, No.	0/17/21/2	0/10/27/6	1/9/22/8	.12
Rhinorrhea score 1/2/3, No.	10/15/15	7/23/13	8/27/5	.18
Nasal obstruction score 1/2/3, No.	0/14/26	0/15/28	8/17/15	.001
				MAR vs SAR: .001
				PAR vs SAR: .002
Polysensitization, No. (%)	40 (100)	43 (100)	28 (70)	<.001
				MAR vs SAR: <.001
				PAR vs SAR: <.001
No. of sensitivities, No. (%)				<.001
1-2	0	0	12 (30)	MAR vs SAR: <.001
3-4	40 (100)	12 (28)	18 (45)	PAR vs SAR: <.001
>4	0	31 (72)	10 (25)	PAR vs MAR: <.001
No. of sensitivities, median (25th-75th percentile)	2 (2-3)	6 (4-7)	2.5 (1-4.5)	<.001
				MAR vs SAR: <.001
				PAR vs MAR: <.001
Baseline nasal airflow, mean (SD)	471.6 (123.4)	493.5 (182.0)	445.3 (194.4)	.13
Eosinophils, median (25th-75th percentile)	5.5 (4.5-7.5)	9 (7-11)	14.5 (11.5-17)	<.001
				MAR vs SAR: <.001
				PAR vs SAR: <.001
				PAR vs MAR: <.001
IL-4, median (25th-75th percentile)	5.7 (4.5-7.0)	5.9 (5.2-6.7)	5.9 (5.1-6.5)	.78
IL-5, median (25th-75th percentile)	5.6 (4.2-6.7)	7.3 (6-7.9)	7.7 (6.8-8.5)	<.001
				PAR vs SAR: <.001
				PAR vs MAR: <.001
IFN- γ , median (25th-75th percentile)	1.2 (1.0-1.4)	1.0 (0.8-1.2)	0.9 (0.8-1.1)	<.001
				PAR vs SAR: <.001
				PAR vs MAR: <.001

Abbreviations: IL, interleukin; IFN- γ , interferon- γ ; MAR, mixed allergic rhinitis; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis; TSS, total symptom score.

* For post hoc comparisons, $P < .02$ is significant after Bonferroni correction.

pascals across the nasal passage. Four or more airflow measurements were performed for each patient, and the mean was recorded when reproducible values were achieved.

Decongestion testing. Decongestion testing was performed as previously described.¹³ In brief, after baseline rhinomanometry, 2 sprays of naphazoline (0.1%) were applied per nostril. This drug is a potent α -adrenostimulator that induces quick vasoconstriction. Rhinomanometry was performed 5 and 10 minutes later. The best result was considered. Total nasal airflow volume and percentage of recovery were evaluated.

Statistical Analysis

Descriptive statistics are reported as mean (SD) or median (25th-75th percentile) for continuous variables and as number (percentage) for categorical variables. Kruskal-Wallis and

Fisher exact tests were used for comparisons among patients with PAR, MAR, and SAR. Comparison of nasal airflow before and after topical nasal vasoconstrictor drug application by means of paired t tests. Nasal airflow recovery was arbitrarily defined as clinically relevant with a 120-mL increase from baseline (corresponding to a 25% increase in the overall mean baseline flow). Logistic regression was used to evaluate the association of patient characteristics with this outcome. Odds ratios and their 95% confidence intervals were computed. A multivariate model was fitted that included clinically relevant factors after checking for multicollinearity. For this analysis, eosinophils and cytokines were dichotomized according to their median value. A software program (Stata 8, StataCorp, College Station, TX) was used for all computations. A 2-sided $P < .05$ was considered statistically significant.

RESULTS

Baseline Characteristics

Baseline characteristics according to type of sensitization are detailed in Table 1. The 3 groups of patients did not differ in family and clinical history, whereas symptoms, as measured by the total symptom score, seemed to have a larger impact in the MAR group (median, 8, 9, and 8 for PAR, MAR, and SAR, respectively) (Table 1). Particularly, severe sneezing was more frequent in the MAR (44%) and SAR (45%) groups (MAR vs PAR $P = .002$ and PAR vs SAR $P = .003$), and severe obstruction was more frequent in the PAR and MAR groups (65% for both), with a significant difference between PAR and SAR ($P = .002$) and between MAR and SAR ($P = .001$). Similarly, the number of sensitivities was higher in the MAR group. Eosinophil counts and IL-5 levels seemed to be highest and IFN- γ levels lowest in the SAR group. Baseline nasal airflow was comparable in the PAR, MAR, and SAR groups (472, 493, and 445 mL/s, respectively; $P = .13$).

Nasal Airflow Recovery

After administration of a topical nasal vasoconstrictor agent, mean (SD) nasal airflow significantly increased from 470.9 (169.6) to 579.7 (160.2) mL/s ($P < .001$). In 12 patients (3 with PAR, 3 with MAR, and 6 with SAR), no increase was shown. Fifty patients (41%) had an increase of at least 120 mL/s, with a mean (SD) of 229.3 (62.9) mL/s. The mean (SD) change from baseline was 187.3 (113.2), 83.8 (118.9), and

52.2 (114.9) mL/s in the PAR, MAR, and SAR populations, respectively (Kruskal-Wallis test $P < .001$; PAR vs MAR: $P < .001$; PAR vs SAR: $P < .001$; and MAR vs SAR: $P = .25$). Type of sensitization (MAR, PAR, or SAR), concentration of eosinophils, and levels of IL-4, IL-5, and IFN- γ all seemed to be associated with nasal airflow recovery of at least 120 mL/s in the univariate analysis (Table 2 and Figs 1 and 2). This was not the case for total symptom score and number of sensitivities. However, none of the 12 patients with 1 sensitivity had only nasal airflow recovery after the test (Fisher exact test $P = .001$). In the multivariate analysis, group and IFN- γ level seemed to independently predict the outcome (Table 3). The MAR and SAR groups had a lower probability of nasal airflow recovery than the PAR group, whereas increasing concentrations of IFN- γ were associated with higher probability. Neither the severity of symptoms, as evaluated by the total symptom score, nor the number of sensitivities seemed to be associated with changes in nasal airflow in the multivariate analysis (Table 3).

DISCUSSION

Allergic rhinitis is characterized by T_H2-dependent inflammation associated with nasal symptoms, mainly concerning nasal obstruction.^{9,10} Decongestion testing provides evidence about the recovery of nasal airflow after vasoconstrictor drug use. Managing rhinitis, the percentage of recovery accounts for medical or surgical options, as absent or poor response

Table 2. Association of Patient Characteristics and Nasal Airflow Recovery: Univariate Logistic Regression*

Characteristic	Nasal airflow recovery	OR (95% CI)	P value
Type of sensitization			<.001
PAR	31 (78)	1 (referent)	
MAR	13 (30)	0.13 (0.04–0.34)	<.001
SAR	6 (15)	0.05 (0.02–0.16)	<.001
Age, mean (SD), y†	23.5 (5.9)/22.0 (5.3)	0.95 (0.89–1.02)	.15
TSS, mean (SD)†	8.7 (1.3)/8.5 (1.6)	0.92 (0.71–1.19)	.51
No. of sensitivities			.35
1–2	22 (45)	1 (referent)	
3–4	15 (45)	1.02 (0.42–2.48)	
>4	13 (32)	0.57 (0.24–1.35)	
Eosinophils			<.001
<10	45 (65)	1 (referent)	
≥10	5 (9)	0.05 (0.02–0.15)	
IL-4			.02
<6	33 (50)	1 (referent)	
≥6	17 (30)	0.42 (0.20–0.89)	
IL-5			<.001
≤7	43 (69)	1 (referent)	
>7	7 (12)	0.06 (0.02–0.15)	
IFN- γ			<.001
≤1	5 (8)	1 (referent)	
>1	45 (79)	45.7 (15.0–139.1)	

Abbreviations: CI, confidence interval; IL, interleukin; IFN- γ , interferon- γ ; MAR, mixed allergic rhinitis; OR, odds ratio; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis; TSS, total symptom score.

* Data are given as number (percentage) except where indicated otherwise.

† No nasal airflow recovery/nasal airflow recovery.

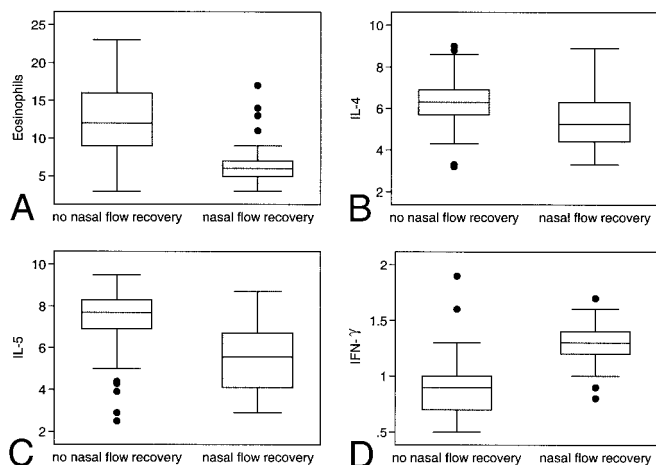


Figure 1. Distribution of eosinophils (A), interleukin 4 (IL-4) (B), IL-5 (C), and interferon- γ (IFN- γ) (D) according to nasal airflow recovery after decongestion testing. Horizontal bars and boxes indicate median and 25th to 75th percentile; and black circles, dispersed values. Error bars represent SD.

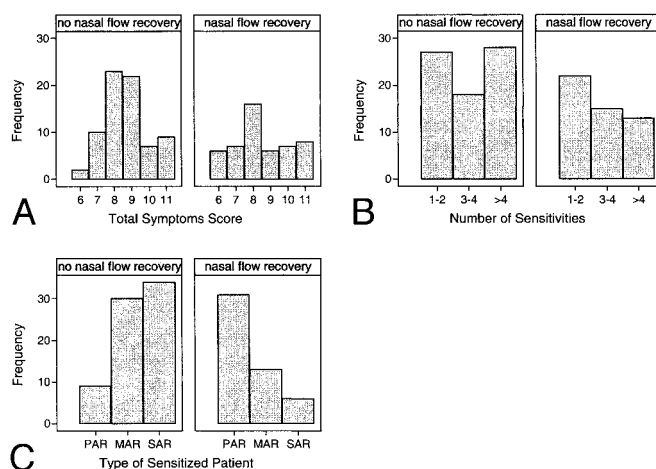


Figure 2. Distribution of total symptom scores (A), number of sensitivities (B), and type of sensitization (C) according to nasal airflow recovery. PAR indicates perennial allergic rhinitis; MAR, mixed allergic rhinitis; and SAR, seasonal allergic rhinitis.

has previously been proposed as an indication for a surgical approach.¹² However, this statement is based on empirical evidence alone, and no study investigated the response to decongestion testing considering underlying inflammation.

This study demonstrates a different pattern concerning the type of symptoms among the groups: patients with SAR showed more severe sneezing, and those with PAR had more severe obstruction, confirming previous results.⁶ On the other hand, there were no differences concerning baseline nasal airflow values. This finding might depend on the generally moderate severity of clinical sensitization detectable in the studied cohort.

Table 3. Association of Patient Characteristics and Nasal Airflow Recovery: Multivariate Logistic Model*

Characteristic	OR (95% CI)	P value
Type of sensitization		.003
PAR	1 (referent)	
MAR	0.04 (0.00–0.45)	.008
SAR	0.02 (0.00–0.20)	.001
Age	1.04 (0.92–1.17)	.53
TSS	1.04 (0.68–1.60)	.85
No. of sensitivities		.27
1–2	1 (referent)	
3–4	5.28 (0.70–40.12)	
>4	3.67 (0.38–35.54)	
IFN- γ		<.001
≤1	1 (referent)	
>1	62.8 (13.05–302)	

Abbreviations: CI, confidence interval; IFN- γ , interferon- γ ; MAR, mixed allergic rhinitis; OR, odds ratio; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis; TSS, total symptom score.

* Model $\chi^2 = 84.86$; $P < .001$. Eosinophils, interleukin 4, and interleukin 5 were also highly correlated within each other and with the type of sensitization to be included in the model.

Second, patients with MAR showed, as expected, the highest number of sensitizations: a median of 6 positivities compared with 2 and 2.5 for PAR and SAR, respectively. Furthermore, allergic inflammation, characterized by eosinophilic infiltrate and T_H2 -dependent cytokines, was more evident in patients with SAR and MAR compared with the PAR group. In addition, IFN- γ levels were low in all the patients, confirming a T_H2 polarization, but they were higher in patients with PAR. These findings demonstrate that pollen allergy is characterized by a more evident inflammation.

The results of this study also demonstrate that nasal airflow recovery may not occur or may not be relevant. Furthermore, multivariate analysis found that symptom severity and number of sensitizations are not associated with nasal airflow recovery. A possible explanation for the absent response might derive from the hypertrophy of turbinates consequent to inflammation and poorly responsive to pharmacologic stimuli, as recently pointed out.¹⁵

In addition, patients with SAR showed the smallest increase in airflow after decongestion, whereas the PAR group alone showed relevant recovery. As previously discussed, this study did not consider the degree of severity of clinical sensitization. This issue may be evaluated by performing the allergen-specific nasal challenge measuring the allergen threshold dose as previously reported.¹⁶ This aspect deserves the attention of further studies. The present findings suggest that more aggressive therapeutic options may be necessary in individuals with pollen allergy.

Furthermore, not only the type but also the number of sensitizations was associated with nasal airflow recovery: patients with SAR and those with more than 4 sensitizations showed the lowest grade of recovery. Finally, allergic inflammation is inversely associated with nasal airflow recovery:

the more a rhinitic individual is inflamed, the less the nasal airflow is reversible. This issue may be the most important finding of this study because it demonstrates that decongestion testing may provide data concerning the inflammatory grade of nasal tissues. Thus, the response to decongestion testing might mean different levels of allergic inflammation. Therefore, further studies should investigate the role of severity of clinical sensitization and the effects of treatments on reversibility to demonstrate decongestant activity.¹³ Furthermore, from a practical point of view, reduced reversibility may account for the prescribing of anti-inflammatory drugs, such as intranasal corticosteroids. In conclusion, this study provides the first evidence of the different response to decongestion testing taking into consideration inflammation and skin sensitization in AR.

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