

Persistent Allergic Rhinitis Includes Different Pathophysiologic Types

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Background: Allergy rhinitis is typically classified as seasonal allergy rhinitis (SAR) and perennial allergy rhinitis (PAR). More recently, the Allergic Rhinitis and its Impact on Asthma document proposed the intermittent (ITR) and persistent forms (PER). However, it has been previously reported that each single allergen may induce different clinical and pathophysiologic features.

Objective: The aim of the study was to test the hypothesis that the type of causal allergen might characterize pathophysiologic differences in a cohort of patients with PER.

Methods: Three hundred nineteen patients, sailors of the Italian Navy, with moderate-severe PER were prospectively and consecutively evaluated with clinical evaluation, skin prick test, rhinomanometry, and nasal decongestion test.

Results: Patients with pollen allergy showed significantly more severe symptoms, lower nasal airflow, and higher response to decongestion test than patients with allergy to perennial allergens ($P < .0001$).

Conclusion: This study provides evidence that patients with PER may show different pathophysiologic patterns depending on the type of causal allergen.

Key Words: Allergic rhinitis, seasonal, perennial, intermittent, persistent, pollens, perennial allergens.

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INTRODUCTION

Allergic rhinitis is the most frequently encountered immunoglobulin E-mediated disease. Its prevalence is high in the general population and is still progressively increasing.^{1–3}

Allergic rhinitis is classically subdivided into seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR), according to the type of allergen and the occurrence of symptoms during the year.⁴ SAR is mainly caused by

outdoor allergens, such as pollens, whereas PAR is caused by indoor allergens, including house dust mites (HDM), pets, and cockroaches. This classification has been recently revised by the Allergic Rhinitis and its Impact on Asthma (ARIA) workshop.⁵ The new classifications of “intermittent” (ITR) and “persistent” (PER) allergic rhinitis does not consider the type of allergen but rather the duration of symptoms (days/wk and consecutive wk) and the impact on quality of life.

Moreover, we have previously performed a study on a large population of subjects perceiving only nasal symptoms to evaluate the clinical and functional aspects in relation to the type of allergic rhinitis and the causal allergen(s).⁶ This study confirmed a seasonal variability in the symptom score for both SAR and PAR patients (SAR patients had more symptoms during spring–summer, PAR patients worsen during autumn–winter) and thus determined the validity of the ARIA classification.⁶

It is well known that allergen exposure activates mast cells, with consequent release of both preformed mediators, mainly histamine and leukotrienes, and cytokines capable of inducing the recruitment and activation of inflammatory cells, including eosinophils, neutrophils, and Th2 lymphocytes.⁷ These inflammatory events lead to the onset of typical nasal symptoms, including itching, sneezing, rhinorrhea, and obstruction. Recently, the relationship between nasal obstruction, Th2-dependent inflammation, and nasal airflow limitation has been evidenced in both adults and children suffering from allergic rhinitis.⁸ In addition, it has been very recently shown that reversibility of the nasal decongestion test is dependent on allergic inflammation degree and type of causal allergen.⁹

On the other hand, it has been reported that ITR is not synonymous with SAR, as PER is not with PAR.^{10,11} Indeed, PER, PAR, ITR, and SAR should be considered different types of allergic rhinitis. Therefore, the purpose of this cross-sectional study was to test the hypothesis that the type of causal allergen might characterize pathophysiologic differences in a cohort of patients with PER.

MATERIALS AND METHODS

Study Design

This study included patients with moderate-severe PER. All were evaluated by clinical visit, skin prick test, rhinomanometry,

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and nasal decongestion test. Patients were tested during the pollen season (i.e., spring). The Navy Hospital Review Board approved the study, and informed consent was obtained from each patient.

Subjects

Three hundred nineteen patients with moderate-severe PER were prospectively and consecutively evaluated. Demographic characteristics, including sex, age, and duration of rhinitis (expressed in years), are reported in Table I. All were Navy sailors who were referred to the Navy Medical Service for a periodic fitness visit. A detailed clinical history was taken, and a complete physical examination was performed. The patients were included in the study on the basis of a clinical history of PER and presence of moderate-severe nasal symptoms according to validated criteria.⁵ We excluded all subjects who met the following exclusion criteria: any prior history of asthma or presence of asthma symptoms, including cough, wheezing, breathlessness, and shortness of breathing, acute or chronic upper respiratory infections, anatomic nasal disorders (i.e., nasal polyps, septum deviation, etc.), previous or current smoking, previous or current specific immunotherapy, and use of nasal or oral corticosteroids, nasal or oral vasoconstrictors, or antileukotrienes during the previous 4 weeks or antihistamines during the previous week.

The diagnosis of PER was made on the basis of a history of nasal symptoms and positive skin prick test according to validated criteria.⁵ Patients were subdivided in two groups on the basis of the causal allergen(s): 1) allergy to pollens, b) allergy to perennial allergens, such as HDM or pets.

Skin Prick Test

Skin prick test was performed as delineated by the European Academy of Allergy and Clinical Immunology.¹² The panel consisted of HDM (*Dermatophagoides farinae* and *pteronyssinus*), cat, dog, and grasses mix, *Compositae* mix, *Parietaria officinalis* and *judaica*, birch, hazel, and olive trees, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix (Stallergenes, Milan, Italy). This panel is most representative of causal allergens found in Italy, as previously reported.⁶

Symptoms

The following nasal symptoms were assessed through questions asked by the investigator: nasal obstruction, sneezing, rhinorrhea, and itchy nose. Each symptom was evaluated on 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 normal daily activity or sleep), and 3 = severe (symptom was sufficiently troublesome to have interfered with normal daily activity or

sleep). Total symptom score (TSS), being the sum of each individual nasal symptom, was considered.

Rhinomanometry

Nasal airflow was measured by active anterior rhinomanometry (ZAN 100 Rhino Flow Handy II, ZAN, Messgeraete GmbH, Nürnberg, Germany), as previously described.^{8,9} 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 Pa 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 Test

Decongestion test was performed following validated criteria.⁹ After baseline rhinomanometry, two sprays of naphazoline (1 mg/mL) were applied per nostril. This drug is a potent α -adrenostimulator that induces rapid vasoconstriction. Rhinomanometry was performed 5 and 10 minutes later. The higher response was considered analogous with a bronchodilation test. Total nasal airflow volume and percentage of reversibility were evaluated.

Statistical Analysis and Data Definitions

Descriptive statistics were performed, and quantitative parameters were reported as means and standard deviations (SD) or as medians with quartiles. Qualitative data were reported as frequencies and percentages. Comparison of quantitative variables between two groups of patients (patients with allergy to pollens vs. allergy to perennial allergens) was made by means of the nonparametric Mann-Whitney *U* test because the parameters were not normally distributed. Comparison of paired data (pre-test vs. post-test values of nasal airflow) was made by means of the nonparametric Wilcoxon test. Correlation between TSS and nasal flow data was evaluated by means of the nonparametric Spearman's correlation coefficient (r_s).

All tests were two sided, and a *P* value less than .05 was considered statistically significant. The Statistica package, release 6 (StatSoft Corp., Tulsa, OK), was used for all analyses.

RESULTS

Three-hundred nineteen patients, 240 (75.2%) males and 79 (24.8%) females, were included in the study. The mean age was 23.6 (SD 1.9) years, with a minimum age of 19 and a maximum of 30 years. Two hundred ten (65.8%) patients had a diagnosis of rhinitis, and 109 (34.2%) had a diagnosis of rhinoconjunctivitis. Patients' mean disease

TABLE I.
Demographic and Clinical Parameters of Patients Divided Into Two Groups According to Causal Allergens (Pollens or Perennial Allergens).

	All Patients, n = 319	Patients Allergic to	
		Pollens, n = 82	Perennial Allergens, n = 237
Sex, males, n (%)	240 (75.2)	65 (79.3)	175 (73.8)
Age (yr), median	24 [22–25]	23 [21–25]	24 [23–25]
Rhinitis duration (yr), median	7 [4–9]	5 [3–8]	8 [5–9]
Total symptoms score, median	5 [4–8]	7 [7–8]	5 [4–7]

All percentages in parentheses are calculated over total number of subjects as reported at top of column. All numbers in brackets represent first to third quartiles.

duration was 6.7 (SD 3.2) years, and the mean TSS was 5.7 (SD 2.0).

Eighty-two (25.7%) patients were allergic to pollens, and 237 (74.3%) were allergic to perennial allergens. Demographic and clinical parameters of the two groups of patients are reported in Table I. Patients with pollen allergy showed a significantly higher TSS with respect to patients with allergy to perennial allergens ($P < .0001$) and a significantly lower nasal airflow both before ($P < .0001$) and after ($P < .0001$) nasal decongestion test (Fig. 1A). Post-test values of nasal airflow were significantly higher with respect to pretest values in either patients with pollen allergy or with perennial allergy ($P < .0001$), but the percentage of change was significantly higher in patients with pollen allergy ($P = .002$) (Fig. 1B).

Pretest nasal airflow values were inversely correlated with TSS either in patients with pollen allergy ($r_s = -0.61$) or in patients with perennial allergy ($r_s = -0.66$) (Fig. 2A). Moreover, the percentage of change of nasal airflow was positively correlated with TSS in both groups of patients ($r_s = 0.55$ and $r_s = 0.44$, respectively) (Fig. 2B).

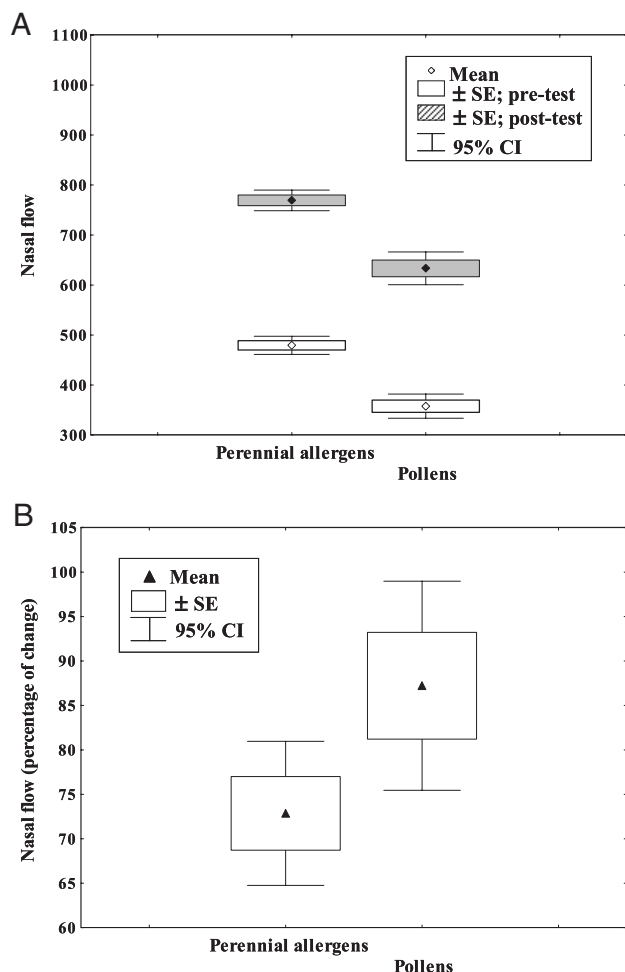


Fig. 1. (A) Pre- and post-test nasal airflow in patients with pollen allergy and with allergy to perennial allergens. (B) Percentage of change of nasal airflow in patients with pollen allergy and with allergy to perennial allergens.

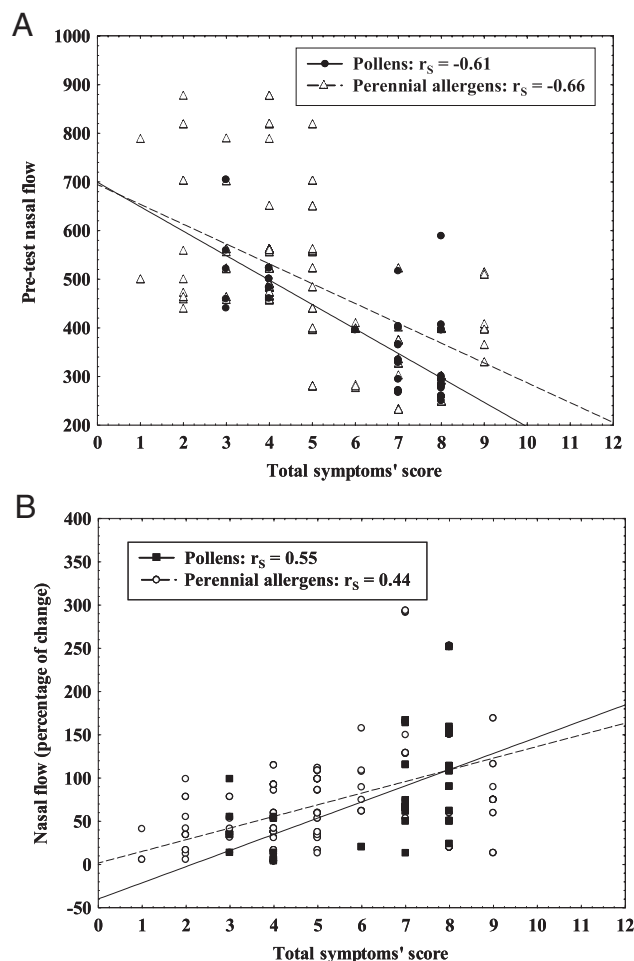


Fig. 2. (A) Correlation between pretest nasal airflow and total symptom score in patients with pollen allergy and with allergy to perennial allergens. (B) Correlation between percentage of change of nasal airflow and total symptom score in patients with pollen allergy and with allergy to perennial allergens.

DISCUSSION

Allergic rhinitis is characterized by an inflammatory response that causes symptom occurrence. Nasal obstruction in particular is the symptom that best denotes allergic inflammation.^{8,9} Indeed, it has been reported that nasal obstruction may be considered the key symptom in allergic rhinitis.¹³ Nasal obstruction may be evaluated both subjectively by symptom score and objectively by airflow assessment. The limitations of nasal airflow evaluation are its reversibility and the degree of recovery that is associated with inflammatory grade; severe inflammation is characterized by poor response to the test.⁹ The decongestion test provides evidence about the amount of recovery of nasal airflow after use of a vasoconstrictor drug. It has also been reported that patients allergic to pollen show a more severe inflammation than do patients with allergy to perennial allergens.¹⁴ This finding underlines the concept that each allergen may induce a different biological response.

In this study, we made some interesting findings, although it should be noted that there is an age bias

because this is a military setting. First, there is a different pattern of baseline nasal airflow between groups: patients with pollen allergy showed lower values of nasal airflow than patients with allergy to perennial allergens show. This finding confirms results of previous studies that demonstrated a more intense and severe rhinitis in patients with pollen allergy during the peak season.^{9,14}

Second, patients with pollen allergy show a higher response to the decongestion test in comparison with patients allergic to perennial allergens. As previously shown, patients with pollen allergy have a more intense inflammation than patients allergic to perennial allergens.^{9,14} On the other hand, patients with allergy to perennial allergens have less inflammation, but the reversibility of the decongestion test is lower. This might account for the nasal remodeling seen similarly in the bronchial model.¹⁵ Indeed, patients with allergy to perennial allergens have a longer duration of disease. This might suggest that more aggressive therapeutic options, such as the use of local corticosteroids, may be necessary in subjects with pollen allergy.

Finally, nasal symptoms correlate well with both baseline nasal airflow and response to decongestion. This finding confirms previous results and underlines the relevance of clinical assessment in patients with PER.

It has to be noted that the living conditions of this cohort of patients are similar to the general population because Italian Navy ships do not sail for several reasons. Indeed, the effective time of sailing is restricted to a few weeks per year. As such, the crew mainly lives on land in barracks or at private homes where allergen exposure may be considered similar to the general population. Thus, the present study confirms and is consistent with previous studies and points out the relevance of causal allergen(s). Indeed, pollens induce a more intense inflammation that accounts for the more intense symptoms and airflow limitations and the better response to decongestion. On the contrary, perennial allergens cause less intense symptoms, airflow limitations, and reduced responses to decongestion, which may depend on chronic remodeling. In conclusion, this study provides the first evidence that patients with PER may show different pathophysiologic patterns depending on the type of causal allergen.

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