



CASE REPORT

Early bronchial airflow impairment in patients with persistent allergic rhinitis and bronchial hyperreactivity

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Received 28 July 2004

KEYWORDS

Persistent allergic rhinitis;
Bronchial hyperreactivity;
Methacholine challenge;
Nasal and bronchial obstruction

Summary

Background: Allergic rhinitis and its impact on asthma (ARIA) document underlines the link between upper and lower airways. Patients suffering from allergic rhinitis frequently (up to 80%) show bronchial hyperreactivity (BHR).

Objectives: This study aimed at evaluating a group of subjects suffering from persistent allergic rhinitis, with BHR but with nasal symptoms only, to investigate the type and intensity of nasal symptoms, nasal and bronchial airflow, and BHR grade during the pollen season.

Methods: One hundred and twenty one polysensitized rhinitics were investigated. Total symptom score (TSS) was assessed in all patients. Rhinomanometry, spirometry and methacholine bronchial challenge were performed in all patients.

Results: 65 (53.7%) patients had impaired FEF 25–75 values. TSS correlated with nasal airflow ($P < 0.001$) and BHR grade ($P < 0.001$). Nasal airflow correlated with FEF 25–75 values ($P < 0.05$) and BHR ($P < 0.001$). FEF 25–75 values correlated with FEV₁ levels ($P < 0.003$), BHR grade ($P < 0.001$), and nasal obstruction symptom ($P < 0.05$). Severe BHR correlated with FEV₁ ($P < 0.05$) and FEF 25–75 ($P < 0.03$) values, nasal airflow ($P < 0.05$) and nasal symptoms ($P < 0.001$).

Conclusions: This study evidences that early bronchial impairment is frequently detectable in patients with persistent allergic rhinitis and BHR. Moreover, nasal function is strictly related with bronchial calibre and BHR grade. Therefore, careful evaluation of lower airways should be investigated in all rhinitics as suggested by the ARIA document.

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Introduction

Allergic rhinitis is characterized by a cascade of inflammatory events that cause symptom appearance.

Close association between allergic rhinitis and asthma has been reported.^{1,2} Moreover, allergic rhinitis has been demonstrated to be a strong risk factor for the onset of asthma in adults.³ Allergic rhinitis and its Impact on Asthma (ARIA) document underlines this strong link between upper and lower airways.⁴ Moreover, ARIA document classifies allergic rhinitis as persistent or intermittent. We recently confirmed that this classification is adherent to real life.⁵

Asthma is characterized by a reversible airflow obstruction and forced expiratory volume/1s (FEV₁) is considered the main parameter to evaluate bronchial obstruction.⁶ Moreover, small airways are involved in the pathogenesis of asthma.⁷ The forced expiratory flow at the 25% and 75% of the pulmonary volume (FEF 25–75) might be considered as a measure of the caliber concerning distal airways, particularly in subjects with normal FEV₁.⁸ Thus, FEF 25–75 may be envisaged as a marker of initial bronchial impairment, as recently described by ourselves in patients with allergic rhinitis alone.^{5,9}

On the other hand, bronchial hyperreactivity (BHR) is a paramount feature of asthma. Moreover, BHR may be observed in a high proportion of rhinitics, more than 80% in patients sensitized to perennial allergens.^{5,9} In addition, Th2-dependent inflammation is related with nasal symptoms and airflow.¹⁰

On the basis of these considerations, we evaluated a group of patients suffering from persistent allergic rhinitis and with BHR but perceiving nasal symptoms alone, sensitized both to pollens and perennial allergens. Thus, we aimed at investigating the type and intensity of nasal symptoms, nasal and bronchial airflow, and BHR grade in these patients during the pollen season.

Materials and methods

Study design

The study included patients with pure allergic rhinitis such as with perceived symptoms only to upper airways level and with BHR. They were sensitized both to pollens and perennial allergens. We excluded all the subjects who referred presence of asthma symptoms, including cough, wheezing,

dyspnoea, and shortness of breathing, acute upper respiratory infections and use of intranasal or oral corticosteroids, and antihistamines within the previous 4 weeks.

The study was approved by the Navy Hospital Review Board and an informed consent was obtained from patients.

Subjects

One hundred and twenty-one subjects, 114 males and 7 females, aged 21.5 ± 3.1 years, were consecutively visited. We chose this type of patients as it is the most representative in the common clinical practice. As recently reported, about 70% of patients with allergic rhinitis are polysensitized and more than 70% of them have BHR during the pollen season.⁵ All of them were Navy soldiers who referred to Navy Hospital for nasal complaints during the pollen season of 2003. A detailed clinical history and a complete physical examination, including allergy evaluation, were performed. All of them were evaluated performing rhinomanometry, spirometry and methacholine bronchial challenge.

The diagnosis of allergic rhinitis was made on the basis of a history of nasal symptoms and positive skin prick test according with validated criteria.⁴

The most important perennial allergens are in our geographic area: house dust mites (i.e. *Dermatophagoides farinae* and *pteronyssinus*), cat, and dog.⁹ The most relevant pollen allergens are in our geographic area: *Parietaria judaica*, grasses, olive tree, birch, and hazel.⁵

Skin prick test

Allergy was assessed by the presence of sensitization to the most common classes of aeroallergens by performing skin prick test. It was performed as stated by the Italian Society of Allergy and Clinical Immunology.¹¹ The allergen panel consisted of the following: house dust mites (*D. farinae* and *pteronyssinus*), cat, dog, grasses mix, *Compositae* mix, *Parietaria officinalis*, birch, hazel tree, olive tree, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix; the concentration of allergen extracts was 100 IR/mL (Stallergenes, Milan, Italy). A histamine solution in distilled water (10 mg/mL) was used as positive control and the glycerol-buffer diluent of the allergen preparations as negative control. Each patient was skin tested on the volar surface of the forearm using 1 mm prick lancets (Stallergenes, Milan, Italy). The skin reaction was recorded after 15 min by evaluating the skin

response rate to the inoculation of each allergen extract in comparison with the wheal given by the positive and the negative control. A wheal diameter equal or greater than 3 mm was considered a positive reaction. Antihistamines were stopped 1 week before skin prick test.

Nasal symptoms

The following symptoms were assessed by the patient, answering the questions made 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 symptom was considered.

Patients were subdivided according with TSS grade as mild ($TSS \leq 6$), moderate ($TSS = 6-8$), and severe ($TSS \geq 9$).

Rhinomanometry

Nasal airflow was measured by active anterior rhinomanometry. Patients wore a tight-fitting facemask, and with the mouth closed, breathed through one nostril. A sensor, placed in the contralateral nostril, recorded data on pre- and post-nasal 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 right and left nostrils in milliliter 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. Patients were subdivided according with nasal airflow values as mild (>720 mL/s), moderate (451–720 mL/s), and severe impairment (<450 mL/s).

Decongestion test

After baseline rhinomanometry, two sprays of naphazoline (100 mg/puff) were then applied per

nostril. This drug is a potent α -adrenostimulator inducing quick vasoconstriction. Rhinomanometry was performed 5 and 10 min after. The best result was considered. Total nasal airflow volume and percentage of reversibility were evaluated.

Spirometry

It was performed by using a computer-assisted spirometer (Pulmolab 435-spiro 235, Morgan, England), with optoelectronic whirl flow meter. Spirometry is performed as stated by ERS,¹² using the European Community for Steel and Coal (ECSC) reference equations. If an airway obstruction was present as detected by FEV_1 values less than 80% of the predicted, a test of bronchodilatation was performed using a salbutamol metered dose of 200 mcg. Reversibility was considered if an increase of at least 12% of FEV_1 from baseline was achieved, according to international guidelines.¹³ About FEF 25–75, reversibility was considered when there was an increase of at least 15% from baseline values.¹⁴

Patients were subdivided according with FEF 25–75 values as having normal ($>80\%$ of predicted), mild (70–80% of predicted), or moderate involvement of bronchial airflow ($<70\%$ of predicted).

Methacholine bronchial challenge

It was performed to evaluate BHR only if basal FEV_1 was equal or more than 80% of predicted. Aerosol was delivered using a dosimetric computerized supply (MEFAR MB3, Marcos, Italy). Subjects inhaled increasing doses of methacholine, starting from 30 μ g/mL. The scheduled doses consisted of the following: 30, 30, 30, 60, 90, 150, 150, 300, 300, 300, 150 μ g/mL as previously reported.^{5,9}

The test was interrupted and considered positive when FEV_1 value was reduced by more or equal than 20% of control or a maximal cumulative dose of 1590 μ g/mL was achieved. The threshold dose causing a 20% fall of FEV_1 (PD20) was calculated.

Degree of BHR

Four arbitrary classes of BHR were considered: very mild = $PD20/FEV_1 > 800$ μ g/mL, mild = $PD20/FEV_1$ ranging from 401 to 800 μ g/mL, moderate = $PD20/FEV_1$ ranging from 400 to 101 μ g/mL, and severe = $PD20/FEV_1 < 100$ μ g/mL as previously reported.⁹

Statistical analysis

Statistical analysis was performed using χ^2 test, calculating confidential limits of the relative risk at 95%. Differences were considered significant if P values were <0.05 . Data are presented as mean $\pm$ standard deviation.

Results

All rhinitics were consecutive subjects and no adverse event was reported during the study.

Total symptom score (Table 1): Twenty-two patients had mild TSS, 79 moderate TSS, and 20 severe TSS.

Nasal airflow (Table 2): Seventeen patients had mild nasal airflow impairment, 62 moderate, and 42 severe.

FEF 25–75 values (Table 3): Fifty six patients had normal values, 30 mild impairment, and 35 moderate one.

BHR grade (Table 4): Five patients had very mild BHR, 15 mild, 62 moderate, and 39 severe.

We then compared each parameter with others.

Total symptom score (Table 1): There was significant association between TSS level and nasal airflow ($P<0.001$). The percentage of nasal decongestion correlated with TSS grade ($P<0.05$). Moreover, there was significant correlation between TSS grade and BHR severity ($P<0.001$).

Nasal airflow (Table 2): There was significant correlation between nasal airflow and FEF 25–75 values ($P<0.05$). In addition, nasal airflow values correlated with BHR grade ($P<0.001$) and TSS ($P<0.03$).

FEF 25–75 values (Table 3): There was significant correlation between the lowest values of FEF 25–75 and FEV₁ values, even though the FEV₁ value was always normal in all subjects ($P<0.003$). FEF 25–75 values correlated with BHR grade ($P<0.001$) and nasal obstruction symptom ($P = 0.043$).

It is noteworthy to highlight that all subjects perceived nasal symptoms only as confirmed by normal FEV₁ values.

BHR grade (Table 4): Severe BHR correlated with the lowest FEV₁ values ($P<0.05$) and FEF 25–75 values ($P<0.003$). Severe BHR correlated with the lowest nasal airflow levels ($P<0.05$). Moreover, patients with the more severe BHR perceived more intense TSS ($P<0.001$), mainly concerning obstruction ($P<0.03$). In addition, there was association with the grade of nasal decongestion ($P<0.05$).

Discussion

We performed a study on a cohort of patients suffering from persistent allergic rhinitis with “perceived” nasal symptoms only and showing BHR. It is to note that about a half of the patients referring allergic nasal symptoms are polysensitized and have BHR as recently reported.⁵ Thus, this clinical profile is very common in the daily medical setting. We therefore aimed to evaluate the impact of persistent allergic rhinitis due to polysensitization on nasal airflow, bronchial airflow, and BHR grade.

First of all, more than half of patients showed reduced FEF 25–75 values suggesting an early bronchial impairment.

Secondly, nasal symptoms well correlated with objective assessment of nasal airflow, thus confirming that subjective perception well reflects objective nasal function as previously reported.¹⁰ In addition, clear relationship between symptom severity and BHR grade was demonstrated.

Thirdly, nasal airflow well correlated with FEF 25–75 values and BHR: it means that reduced nasal patency predisposes to bronchial impairment. All these findings underline the importance of nasal conditioning in assuring physiological ventilation. In fact, if nasal respiration is impaired dry and cold air penetrates into the bronchi, thus BHR and bronchial airflow limitation may occur.

Fourthly, FEF 25–75 may be envisaged as an early marker of bronchial involvement in patients with allergic rhinitis as it correlates with FEV₁ values. In fact, even though these patients had normal FEV₁ values, a linear trend to a sub-obstructive state of

Table 1 Relationships between TSS and other parameters.

TSS	Pts	%	FVC	FEV ₁	FEF	BHR	Pre-NAF	Post-NAF (mL/s)
<6	22	16.5	96.8 $\pm$ 8.1	95.6 $\pm$ 11	85 $\pm$ 24	340 $\pm$ 277	618 mL/s $\pm$ 168.2	735 mL/s $\pm$ 110.9(+19%)
6–8	79	65.3	96.9 $\pm$ 10.3	98 $\pm$ 10.4	84.8 $\pm$ 21.4	214 $\pm$ 200	554 mL/s $\pm$ 127.6	631 mL/s $\pm$ 128.9(+14%)
9–12	20	18.2	93.3 $\pm$ 11.2	93.1 $\pm$ 11.2	82.6 $\pm$ 29.3	196 $\pm$ 107	374 mL/s $\pm$ 124	493 mL/s $\pm$ 112 (+32%)

Pre-NAF, basal nasal airflow; Post-NAF, nasal airflow after decongestion.

Significant associations between TSS level and nasal airflow ($P<0.001$), and percentage of nasal decongestion ($P<0.05$), and BHR severity ($P<0.001$).

Table 2 Relationships between nasal airflow and other parameters.

Nasal airflow (%)	Pts	%	FVC	FEV ₁	FEF	BHR	TSS	S	I	R	O
> 720 mL/s (> 80%)	17	14.1	98.3 ± 6.5	99.2 ± 11.9	88.8 ± 31	450 ± 380	5.70 ± 1.86	1.70 ± 0.9	1.23 ± 0.8	1.17 ± 0.8	1.58 ± 0.7
451–720 mL/s (50–80%)	62	51.2	101.3 ± 11.7	102.4 ± 11.2	87.4 ± 21.4	212 ± 199	6.95 ± 1.51	1.64 ± 0.6	1.61 ± 0.6	1.61 ± 0.6	2.08 ± 0.7
< 450 mL/s (< 50%)	42	34.7	93.2 ± 7.9	92.6 ± 8.5	78 ± 22.5	199 ± 175	7.95 ± 1.95	1.97 ± 0.8	1.88 ± 0.9	1.88 ± 0.6	2.21 ± 0.7

Nasal airflow % is compared with theoretic normal flow corresponding to 900 mL/s; S = sneezing, I = itching, R = rhinorrhea, O = obstruction. Significant correlations between nasal airflow and FEF 25–75 values ($P < 0.05$), and BHR grade ($P < 0.001$), and TSS ($P < 0.03$).

Table 3 Relationships between FEF 25–75 and other parameters.

FEF _{25–75%}	Pts	%	FVC	FEV ₁	BHR	Pre-NAF	Post-NAF	TSS	S	I	R	O
> 80%	56	46.3	98.1 ± 11.7	103.6 ± 9.5	324 ± 300	571 mL/s ± 154.7	647 mL/s ± 140.6 (+13.4%)	7.10 ± 1.75	1.69 ± 0.7	1.78 ± 0.6	1.67 ± 0.6	1.94 ± 0.7
70–80%	30	24.8	95.5 ± 8.4	94.7 ± 7	211 ± 184	508 mL/s ± 163.4	636 mL/s ± 128 (+25.2%)	6.70 ± 2.03	1.60 ± 0.8	1.50 ± 0.9	1.43 ± 0.8	2.16 ± 0.6
< 70%	35	28.9	94 ± 8.2	87.3 ± 6.8	110 ± 96	504 mL/s ± 136.9	601 mL/s ± 149.2 (+19.4%)	7.20 ± 1.93	1.94 ± 0.8	1.48 ± 0.9	1.71 ± 0.7	2.40 ± 0.8

Pre-NAF, basal nasal airflow; Post-NAF, nasal airflow after decongestion (%), S = sneezing, I = itching, R = rhinorrhea, O = obstruction. Significant correlations between FEF 25–75 and FEV₁ ($P < 0.003$), and BHR grade ($P < 0.001$), and nasal obstruction symptom ($P = 0.043$).

Table 4 Relationships between BHR (PD_{20}/FEV_1 in μg) and other parameters.

PD_{20}/FEV_1 (μg)	Pts	%	FVC	FEV_1	FEF	Pre-NAF	Post-NAF	TSS	S	I	R	O
≤ 100	39	32.2	95.5 ± 13.1	92.4 ± 12	69.6 ± 20.7	$513 \text{ mL/s} \pm 136.4$	$613 \text{ mL/s} \pm 130.9(+19.6\%)$	7.20 ± 1.93	1.79 ± 0.9	1.66 ± 0.7	1.66 ± 0.7	2.07 ± 0.7
101–400	62	51.2	96.1 ± 8.5	97 ± 9.2	84.5 ± 20	$525 \text{ mL/s} \pm 148.9$	$621 \text{ mL/s} \pm 140.6(+18.3\%)$	7.10 ± 1.72	1.72 ± 0.7	1.69 ± 0.8	1.69 ± 0.7	2.04 ± 0.7
401–800	15	12.4	97.1 ± 8.4	100.8 ± 9.4	83.8 ± 24.6	$592 \text{ mL/s} \pm 181.2$	$687 \text{ mL/s} \pm 147.9(+16.1\%)$	7.10 ± 1.45	1.86 ± 0.7	1.66 ± 0.6	1.60 ± 0.6	2.00 ± 0.7
> 800	5	4.2	102.1 ± 6.3	102.8 ± 4.5	84.2 ± 5.3	$686 \text{ mL/s} \pm 193.4$	$744 \text{ mL/s} \pm 140.4(+8.6\%)$	3.80 ± 1.78	1.20 ± 1.1	0.40 ± 0.4	0.60 ± 0.5	1.60 ± 0.9

Pre-NAF, basal nasal airflow; Post-NAF, nasal airflow after decongestion (%), S = sneezing, I = itching, R = rhinorrhea, O = obstruction.

Significant correlations between severe BHR and FEV_1 ($P < 0.05$), and FEF 25–75 ($P < 0.003$), and nasal airflow ($P < 0.001$), and TSS ($P < 0.001$), and nasal obstruction ($P < 0.03$), and nasal decongestion ($P < 0.05$).

proximal airways may be appreciated. Moreover, early bronchial impairment correlates with BHR grade. It means that the persistence of nasal inflammation may affect lower airways inducing both initial reduction of smaller airway calibre and BHR.

Thus, all these findings underline the close association regarding the relationship between the functions of the nose and bronchial calibre and reactivity. In other words, as nasal patency is more compromised as bronchial airflow becomes more impaired.

These issues confirm the very important concept provided by ARIA document: the link between upper and lower airways.⁴ Allergic rhinitis and asthma should be considered as a single syndrome involving two parts of the respiratory tract.¹⁵ Moreover, it is evident that these two disorders affect each other. The pathophysiology of allergic rhinitis is similar to that of asthma and their responses to pharmacological and specific immunological interventions are comparable.¹⁶

Thus, this study highlights the link between upper and lower airways in patients with allergic rhinitis and BHR. Therefore, our data strengthen the suggestion provided by ARIA document that a new diagnostic approach should be carried out in the patients with pure allergic rhinitis.

All rhinitics, even in absence of history suggesting for asthmatic symptoms, must be evaluated performing spirometry. If early bronchial impairment is demonstrated, bronchial methacholine challenge may be considered as supplemental exam to achieve a more exhaustive evaluation in rhinitics. Moreover, rhinitics should be carefully followed up to evaluate the possible onset of asthma.

In conclusion, our study underlines the frequent early bronchial impairment in patients with allergic rhinitis alone and supports the strong link between upper and lower airways.

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