

Correlation of nasal inflammation and nasal airflow with forced expiratory volume in 1 second in patients with perennial allergic rhinitis and asthma

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Background: Allergic rhinitis and asthma are frequently associated and are characterized by T_H2 -dependent inflammation. Nasal and bronchial obstruction largely depend on allergic inflammation.

Objective: To evaluate the relationships among nasal eosinophil counts, interleukin 4 (IL-4) and interferon- γ (IFN- γ) levels, nasal airflow, and forced expiratory volume in 1 second (FEV₁) in patients with perennial allergic rhinitis and asthma.

Methods: Eight men and 7 women (mean $\pm$ SD age, 24.8 $\pm$ 4.7 years) with perennial allergic rhinitis and asthma were evaluated. All 15 patients had a moderate-to-severe grade of nasal obstruction. Total symptom score, rhinomanometry, nasal lavage, nasal scraping, and spirometry were evaluated in all patients. Eosinophils were counted using conventional staining; IL-4 and IFN- γ levels were measured by immunoassay in fluids recovered from nasal lavage.

Results: Significant positive relationships were demonstrated between eosinophil infiltration and IL-4 levels, nasal airflow and IFN- γ levels, FEV₁ and IFN- γ levels, and nasal airflow and FEV₁ ($P < .001$ for all). Significant negative relationships were demonstrated between eosinophil infiltration and IFN- γ levels, IL-4 and IFN- γ levels, eosinophil infiltration and nasal airflow, IL-4 values and nasal airflow, nasal eosinophil counts and FEV₁, and IL-4 values and FEV₁ ($P < .001$ for all).

Conclusions: There is a close association between T_H2 cytokines and eosinophil infiltration in the nose. There is also clear evidence concerning the relationships among eosinophil infiltration, IL-4 and IFN- γ levels, and nasal airflow. Nasal eosinophil, IL-4, and IFN- γ levels correlate with FEV₁. Finally, nasal airflow is related to FEV₁. These findings constitute the first evidence of a relationship between T_H2 -related nasal inflammation and nasal and bronchial airflow in patients with perennial allergic rhinitis and asthma.

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INTRODUCTION

A clinical relationship between allergic rhinitis and asthma has been defined for a long time.¹ Patients commonly are seen with both disorders. Thus, an increasing body of evidence suggests the existence of a clear link between the upper and lower airways.^{2,3} In this regard, our group⁴ previously reported that 77% of patients with respiratory allergy had allergic rhinitis associated with asthma. Anatomic and physiologic connections between allergic rhinitis and asthma have been widely reported.⁵

Immunopathologically, allergic rhinitis and asthma are similar in that there is infiltration by inflammatory cells, including T cells, mast cells, and eosinophils, in both disorders.⁶ Mediators, such as histamine and leukotrienes, are demonstrated at the nasal and bronchial levels in patients with rhinitis and in patients with asthma.⁷ The cytokine pattern is typically characterized by T_H2 polarization in both disorders.⁸

T_H2 -derived cytokines are responsible for recruiting and activating eosinophils in airways. However, vascular tissue and smooth muscle characterize the final response: nasal congestion and bronchospasm, respectively. For these reasons, antihistamines, antileukotrienes, and topical corticosteroids can be prescribed in both diseases, although with different efficacy.⁹

Asthma is defined as chronic inflammation of the lower airways,¹⁰ and inflammatory infiltration has been well documented in allergic rhinitis.¹¹ Allergic airway inflammation causes airflow obstruction at the nasal and bronchial levels that may be objectively measured using rhinomanometry and spirometry, respectively.

For these reasons, we aimed to investigate the possible relationships among nasal eosinophils, cytokines recovered from nasal lavage, rhinomanometry, and spirometry in patients with perennial allergic rhinitis and asthma.

MATERIALS AND METHODS

Participants

Fifteen patients (8 men and 7 women; mean $\pm$ SD age, 24.8 $\pm$ 4.7 years) with perennial allergic rhinitis and asthma were consecutively evaluated. A detailed clinical history and

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a complete physical examination were performed for each patient. Asthma was diagnosed according to Global Initiative for Asthma guidelines¹⁰ by clinical and functional features. The diagnosis of perennial allergic rhinitis was made, according to international guidelines,¹² on the basis of history and skin prick test positivity for perennial allergens. In our geographic area, the most important perennial allergens include *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, cat, and dog.⁴ Ten nonatopic healthy individuals (9 men and 1 woman; mean $\pm$ SD age, 23.5 ± 2.6 years) were included as a control population in this study.

Study Design

The study was conducted when patients were symptomatic. Only patients who met all the following criteria were eligible for inclusion in the study: men and women older than 18 years; history of perennial allergic rhinitis and asthma due to perennial allergen exposure for the previous 2 years; rhinitis symptoms for the previous 2 weeks; a minimum total symptom score greater than 6 at baseline, particularly with moderate-to-severe nasal obstruction; forced expiratory volume in 1 second (FEV₁) values less than 80% of predicted; reversibility of airway obstruction of at least 12% of FEV₁ from baseline; and an informed consent form signed before study entry.

Exclusion criteria were as follows: pollen allergy; acute and chronic upper respiratory tract infections within 30 days of the study; anatomic nasal disorders (ie, septum deviation); nasal polyps; use of antibiotics; use of intranasal, inhaled, or oral corticosteroids in the previous 4 weeks; and use of antihistamines, antileukotrienes, and long-acting β_2 -agonists in the previous week.

Symptom evaluation, rhinomanometry, nasal scraping, nasal lavage, and spirometry were performed in all subjects. The study was approved by the Navy Hospital of La Spezia Review Board.

Skin Prick Test

Allergy was evaluated by the presence of sensitization to the most common classes of aeroallergens by performing skin prick testing, as stated by the Italian Society of Allergy and Clinical Immunology.¹³ The allergen panel consisted of house dust mites (*D farinae* and *D pteronyssinus*), cat, dog, grass 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 was used as negative control. Each patient was skin tested on the volar surface of the forearm using 1-mm prick lancets (Stallergenes). The skin reaction was recorded after 15 minutes by evaluating the skin response rate to the inoculation of each allergen extract compared with the wheal given by the positive and negative controls. A wheal diameter of 3 mm or

greater was considered a positive reaction. Antihistamine therapy was discontinued 1 week before skin prick testing.

Nasal Symptoms

The following symptoms were described by the patient when answering questions asked by the investigator: nasal obstruction, sneezing, rhinorrhea, and itchy nose. Each symptom was evaluated using the following 4-point 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, the sum of the individual symptom scores, was considered.

Rhinomanometry

Nasal airflow was measured using active anterior rhinomanometry. Patients wore a tight-fitting face mask and, with the mouth closed, breathed through 1 nostril. A sensor, placed in the contralateral nostril, recorded data on prenasal and postnasal pressures via airflow and pressure transducers. The instrument (ZAN 100 Rhino, ZAN; Messgeraete GmbH, Frankfurt, 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 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.

Spirometry

Spirometry was performed using a computer-assisted spirometer (COSMED Srl, Rome, Italy), with an optoelectronic whirl flowmeter. Spirometry is performed as stated by the European Respiratory Society¹⁴ using the European Community for Steel and Coal reference equations.

Because airway obstruction was present, as evidenced by FEV₁ values less than 80% of predicted, a test of bronchodilation was performed using a salbutamol metered dose of 200 μ g. Reversibility was considered if an increase of at least 12% in FEV₁ from baseline was achieved, according to international guidelines.¹⁰

Nasal Cytologic Examination

Nasal cytologic specimens were obtained by scraping the head of the inferior turbinate with a cotton swab, as described elsewhere.¹⁵ Briefly, after nasal scraping, the cotton tip of the swab was immersed in a plastic tray filled with phosphate-buffered saline solution and then transferred to a 10-mL polypropylene tube. The recovered fluids were centrifuged at 220g for 10 minutes, and each pellet was resuspended in phosphate-buffered saline solution (2 mL). Cell suspensions were filtered to reduce the quantity of mucus, and cytospin slides were prepared using standard techniques. Smears were

stained with Diff-Quik stain and were analyzed using an optic microscope (Olympus U-SPT; Olympus Italy, Rome, Italy). The number of inflammatory cells was expressed as the mean of 10 optical fields at $\times 100$ magnification. Samples were examined in a masked manner.

Nasal Lavage

Lavage of the nasal cavity was performed using 5 mL of physiologic saline, according to standard methods described elsewhere.¹⁶ In this procedure, 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°C .¹⁶

Cytokine Evaluation

Cytokine levels were measured by enzyme-linked immunosorbent assay (ELISA) (R&D Systems Inc, Minneapolis, MN). This assay used the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific to each cytokine was precoated onto a microplate. Study samples and standard dilutions of each specific cytokine were assayed separately in duplicate according to the ELISA kit manufacturer's instructions. Standards and samples were pipetted into the wells, and each cytokine was bound by the immobilized antibody. After removing unbound substances, enzyme-linked polyclonal antibodies specific to each cytokine were added to the wells. After removing unbound antibody-enzyme reagent, a substrate solution was added to the wells, and color developed in proportion to the amount of cytokine bound in the initial step. Then, color development was stopped, and the intensity of the color was measured. The color intensity was read at a wavelength of 490 nm using a spectrophotometer (Molecular Devices Corp, Sunnyvale, CA). The average net optical density of the standards was plotted, and the amount of each cytokine in each sample was evaluated by interpolation from the standard curve. Results were the means of duplicate samples. The interassay and intra-assay coefficients of reproducibility for each cytokine were as follows: interleukin 4 (IL-4), 2% to 5% and 3% to 6%; and interferon- γ (IFN- γ) 1% to 3% and 3% to 5%. The sensitivity of the commercially prepared ELISA was less than 1 pg/mL for IL-4 and IFN- γ .

Statistical Analysis

Analysis of correlation coefficients was calculated using the Pearson test. Nasal eosinophil counts, cytokine levels, and nasal and lung function measurements are given as mean $\pm$ SD. $P < .05$ was considered statistically significant.

RESULTS

Patients and Symptoms

Fifteen patients with perennial allergic rhinitis and asthma were studied. All of them were sensitized to perennial allergens only. General physical examination results were normal, apart from rhinitis and asthma symptoms, in all patients. All patients were symptomatic, with moderate (9 patients) or

severe (6 patients) nasal obstruction. The total symptom score was 6.8 ± 1.7 .

Rhinomanometry, Nasal Cytology, Cytokine Levels, and Spirometry

Rhinomanometry was performed in all patients. A clear decrease in nasal airflow was present in all patients vs controls (333.7 ± 77.1 vs 742.8 ± 128.4 mL/s). Eosinophils were present in nasal smears in all patients (15.5 ± 5). A clear T_H2 polarization was present in all patients: low levels of IFN- γ and high levels of IL-4. The mean value of IFN- γ was 0.93 ± 0.5 pg/mL (controls: 32.4 ± 4.6 pg/mL). The mean value of IL-4 was 11.8 ± 3.3 pg/mL (controls: 0.8 ± 0.4 pg/mL). All patients had reduced FEV₁ values ranging from 65% to 77% of predicted. The mean FEV₁ was $70.8\% \pm 4.0\%$ of predicted. All the patients had a positive response to bronchodilator therapy.

Correlations

Significant positive correlations were detected between IL-4 levels and eosinophil counts ($P < .001$; Fig 1). On the contrary, there was a significant negative relationship between IFN- γ values and nasal eosinophil counts ($P < .001$; Fig 1). As expected, a significant negative relationship was demonstrated between IL-4 and IFN- γ levels ($P < .001$; Fig 2). Significant negative correlations were detected between eosinophil counts and nasal airflow (Fig 3) and between IL-4 and nasal airflow (Fig 4), whereas there was a significant positive correlation between nasal airflow and IFN- γ levels ($P < .001$ for all; Fig 4). A negative relationship existed between nasal eosinophil counts and FEV₁ values ($P < .001$; Fig 5). There was a negative relationship between IL-4 level and FEV₁ and a positive relationship between IFN- γ level and FEV₁ ($P < .001$ for both; Fig 6). Finally, a positive correlation was shown between nasal airflow and FEV₁ values ($P < .001$; Fig 7).

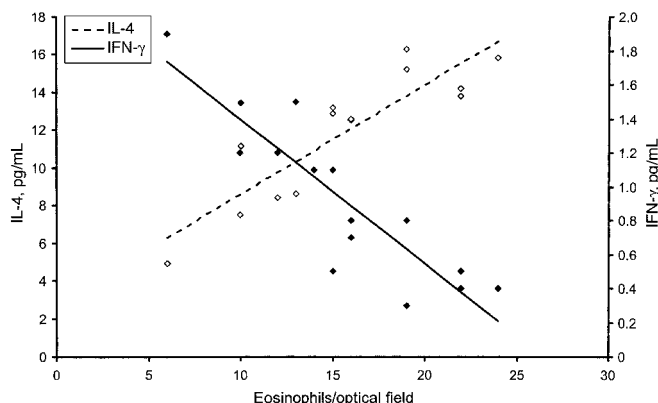


Figure 1. Relationship between eosinophil counts and interleukin 4 (IL-4; $r = 0.79$) and interferon- γ (IFN- γ ; $r = 0.88$) levels in nasal lavages ($P < .001$ for both).

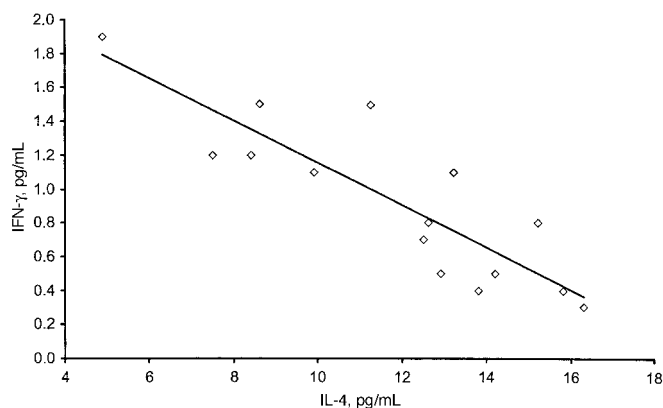


Figure 2. Relationship between interleukin 4 (IL-4) and interferon- γ (IFN- γ) concentrations ($r = 0.95$; $P < .001$).

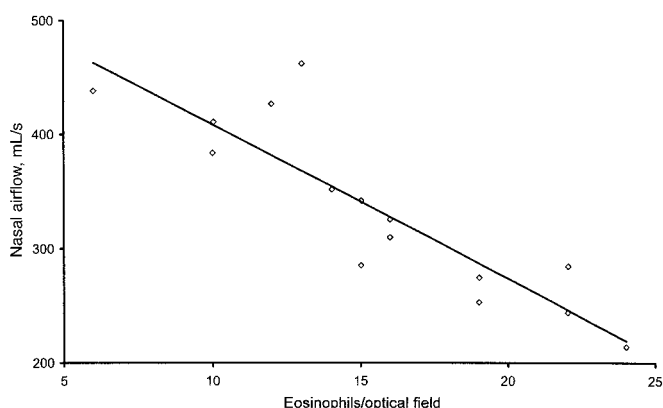


Figure 3. Relationship between eosinophil counts and nasal airflow ($r = 0.83$; $P < .001$).

DISCUSSION

The present study sought to investigate possible relationships among nasal eosinophils, IL-4, and IFN- γ collected from nasal lavage, nasal airflow, and FEV₁ in patients with perennial allergic rhinitis associated with asthma.

Allergic rhinitis and asthma are characterized by T_H2 polarization. T_H2-derived cytokines have been previously investigated in patients with allergic rhinitis and asthma, particularly concerning the role of IL-4.¹⁷ Interleukin 4 is a pivotal cytokine that orchestrates allergic inflammation because it is the most important signal to induce T_H2 polarization in allergic individuals.¹⁸ Interleukin 4 is produced by a variety of cells, including T_H2 lymphocytes, eosinophils, and mast cells; IL-4 promotes IgE synthesis, up-regulates adhesion molecules selective for eosinophil recruitment, and causes increased mucus production.¹⁸ Thus, there is agreement about the role exerted by IL-4 as a main pathogenetic factor in inducing, maintaining, and amplifying allergic inflammation.

On the other hand, there is accumulating evidence that T_H1-related cytokines, such as IFN- γ and IL-12, suppress and counteract this T_H2 response and vice versa because there is

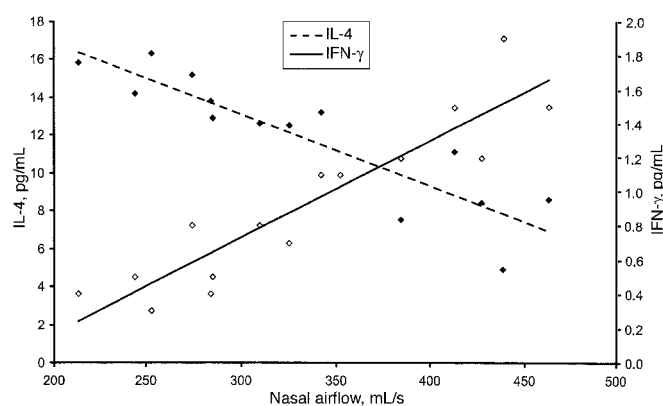


Figure 4. Relationship between interleukin 4 (IL-4; $r = 0.88$) and interferon- γ (IFN- γ ; $r = 0.91$) concentrations and nasal airflow ($P < .001$ for both).

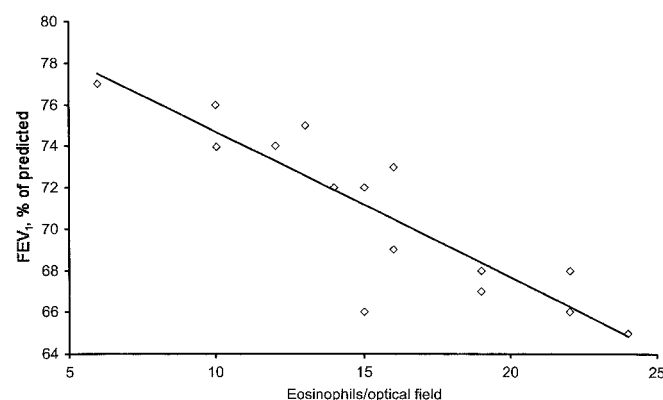


Figure 5. Relationship between eosinophil counts and forced expiratory volume in 1 second (FEV₁) values ($r = 0.882$; $P < .001$).

a clear dichotomy between T_H1 and T_H2 cells.¹⁹ The suppressive effects of IFN- γ are mediated by various mechanisms, such as inhibiting the production of T_H2-derived cytokines and skewing the differentiation of naive T cells toward T_H1 subtype preference.²⁰ In addition, exogenous IFN- γ protein could reverse the ongoing reactions.²¹ Thus, IFN- γ may play a regulatory role in the extent of airway responses to allergen. Some of the mechanisms that may be relevant include suppressing the release of T_H2-type cytokines from activated T cells,²⁰ facilitating apoptosis of T cells and eosinophils,¹⁶ and inhibiting local recruitment of eosinophils.²²

Therefore, T_H1- and T_H2-derived cytokines have an important role in regulating allergic inflammation, mainly concerning eosinophil recruitment and activation. In this regard, allergic inflammation accounts for occurring respiratory symptoms, especially regarding airflow obstruction.

The pathogenesis of nasal obstruction is complex and consists of 3 main events: inflammatory mucosal edema, vascular congestion, and mucus hypersecretion.²³ On the other hand, bronchial obstruction is sustained by the spasm of

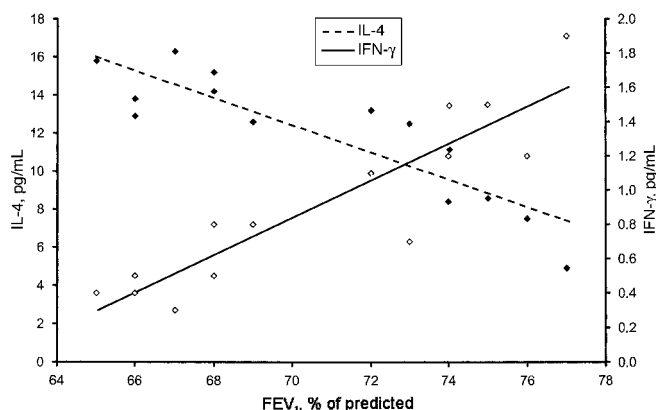


Figure 6. Relationship between interleukin 4 (IL-4; $r = 0.87$) and interferon- γ (IFN- γ ; $r = 0.90$) concentrations and forced expiratory volume in 1 second (FEV₁) values ($P < .001$).

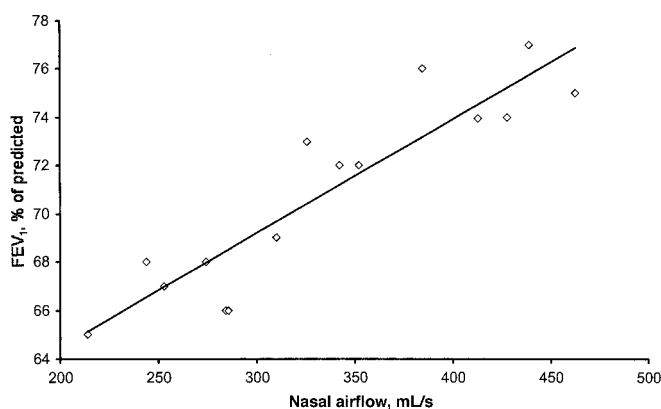


Figure 7. Relationship between nasal airflow and forced expiratory volume in 1 second (FEV₁) values ($r = 0.90$; $P < .001$).

smooth muscle, inflammatory edema, and mucus hyperproduction.⁸ All these pathogenic events are generated by mediators, including leukotrienes and histamine, and cytokines, mainly concerning IL-4, released by activated mast cells, eosinophils, and T cells.¹⁸ Similar pathophysiologic pathways occur at the nasal and bronchial levels, so airflow obstruction may appear. In this regard, airway obstruction constitutes the symptom more representative of allergic inflammation.

On the basis of these issues, the present study suggests some considerations concerning the link between the upper and lower airways. First, there is a significant positive relationship between nasal eosinophil infiltration and IL-4 levels, confirming previous findings.¹⁰ This aspect highlights the pathogenic role exerted by T_H2 cytokines in accumulating eosinophils. Second, a negative relationship between nasal eosinophils and IFN- γ levels has been demonstrated, indirectly confirming the "protective" role of T_H1-derived cytokines. As proof of this finding, a close relationship between IL-4 and IFN- γ levels is provided by our results, which confirms the close dichotomy existing between T_H1 and T_H2

subpopulations. Third, this study provides evidence concerning the linear correlation between eosinophil counts and nasal airflow obstruction because many eosinophils infiltrate the nasal mucosa as more airflow impairment occurs. This finding is supported by 2 other data: the positive correlation between IFN- γ levels and nasal airflow and the negative relationship between IL-4 levels and nasal airflow. These aspects, taken together, actually underline the close relationship between the structure and the function of the nose. In other words, nasal mucosa is more inflamed as nasal airflow is more impaired. In addition, these findings seal the strict T_H1-T_H2 counter-regulation.

Fourth, we provided evidence concerning the relationship between nasal allergic inflammation, sustained by eosinophil infiltration, and bronchial obstruction as determined by FEV₁ values. Like in the nasal compartment, this finding is supported by the positive correlation between IFN- γ levels and FEV₁ and the negative relationship between IL-4 levels and FEV₁. This issue probably represents the most important outcome of the present study because it documents the close association between allergic inflammation at the nasal level and bronchial obstruction. Furthermore, this finding indirectly confirms the previous finding observed in asthmatic children with rhinosinusitis. Our group²⁴ demonstrated a significant relationship between nasal IFN- γ levels and FEV₁ values. These issues underline the close association between T_H2-polarized immune responses at the nasal level and bronchial patency.

Finally, as further demonstration of this link between upper and lower airways, a significant relationship between nasal airflow obstruction and FEV₁ impairment is documented. This finding constitutes the formal and objective proof concerning the close link between nasal and bronchial function.

Furthermore, the present findings have to be added to our previous survey in patients with allergic rhinitis. Recently, our group²⁵ demonstrated in 100 patients with perennial allergic rhinitis alone that 5 patients had impaired FEV₁ values ($<80\%$ of predicted) without any perceived lower respiratory tract symptoms and that 48 patients had reduced forced expiratory flow between 25% and 75% values. Furthermore, 72 patients had positive methacholine challenge results, and there was a significant relationship between the degree of bronchial hyperresponsiveness and FEV₁ and forced expiratory flow between 25% and 75% values.²⁴

In conclusion, the present study provides evidence of the relationships among nasal eosinophil infiltration, T_H1- and T_H2-derived cytokines, nasal airflow impairment, and FEV₁ values in patients with perennial allergic rhinitis and asthma. Therefore, we believe that these data may be considered convincing proof of the close link between allergic rhinitis and asthma.

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