



Bronchial hyperreactivity and spirometric impairment in patients with seasonal allergic rhinitis

Giorgio Ciprandi^{a,*}, Ignazio Cirillo^b, Maria Angela Tosca^a,
Andrea Vizzaccaro^b

^aDipartimento Regionale Testa-Collo, Padiglione Specialità (piano terzo), Ospedale San Martino, Largo R. Benzi 10, Genoa 16132, Italy

^bMedicine Dept., Navy Hospital, La Spezia, Istituto Giannina Gaslini, Genoa, Italy

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KEYWORDS

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Summary We previously demonstrated in a group of patients with perennial allergic rhinitis alone, impairment of spirometric parameters and high percentage of bronchial hyperreactivity (BHR). Thus, the present study aimed at evaluating a group of subjects suffering from seasonal allergic rhinitis alone to investigate the presence of spirometric impairment and BHR both during and outside the pollen season.

Methods: One-hundred rhinitics sensitized to pollen allergens only were evaluated during and outside the pollen season. Spirometry and methacholine bronchial challenge were performed.

Results: Four rhinitics showed impaired values of FEV₁ without referred symptoms of asthma during the pollen season. FEF 25–75 values were impaired in 17 rhinitics during the pollen season and in 11 rhinitics outside the pollen season ($P < 0.05$). Fifty-four patients showed positive methacholine bronchial challenge both during and outside the pollen season. PD20/FEV₁ methacholine was lower during the pollen season than outside ($P < 0.05$). In BHR positive patients, reduced values of FVC ($P < 0.05$), FEV₁ ($P < 0.05$), and FEF 25–75 ($P < 0.01$) were significantly demonstrated in comparison with BHR negative rhinitics. There was a relationship between BHR degree and FEF 25–75 values only during the pollen season ($P < 0.001$).

Conclusions: This study evidences that an impairment of spirometric parameters may be observed also in patients with seasonal allergic rhinitis alone during the pollen season. A high percentage of these patients had BHR. A close relationship between upper and lower airways is confirmed also in the model of pollen allergy. Thus, a careful evaluation of lower airways should be performed also in those patients with seasonal allergic rhinitis alone.

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Introduction

Allergic rhinitis is characterized by an inflammatory response of the nose induced by an IgE-mediated reaction following allergen exposure.¹

Several studies demonstrated a close association between allergic rhinitis and asthma.^{2–5} In addition,

*Corresponding author. Tel.: +39-10-555-2124; fax: +39-10-555-6682.

E-mail address: gio.cip@libero.it (G. Ciprandi).

we reported that 77% of conscripts with respiratory allergy suffered from asthma associated with allergic rhinitis.⁶

Allergic rhinitis has been demonstrated to be a strong risk factor for the onset of asthma in adults.⁷

Asthma is characterized by a reversible airflow obstruction and forced expiratory volume/1s (FEV₁) is considered the main parameter to evaluate bronchial obstruction.⁸ Nevertheless, there is increasing interest to consider the involvement of small airways in the pathogenesis of asthma.⁹ Even though, there is no direct parameter able of assessing small airways, it has been assumed that 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.¹⁰ Particularly, subjects with mild asthma and normal FEV₁ may show impaired FEF 25–75 only.¹¹

On the other hand, bronchial hyperreactivity (BHR) is a paramount feature of asthma. Moreover, BHR may be observed in a proportion of rhinitics.¹² In this regard, it has been hypothesized that a positive bronchial challenge to methacholine could be considered as predictive for those rhinitics would progress to develop asthma.¹³ BHR was reported both in patients with perennial allergic rhinitis and in subjects with seasonal allergic rhinitis.¹⁴ In addition, a seasonal variability in BHR was described in subjects sensitized to pollens.¹⁵ Very recently, we demonstrated that 48% of patients with perennial allergic rhinitis alone showed reduced FEF 25–75 values.¹⁶ Moreover, 72% of patients showed positive methacholine challenge, and there was a significant relationship between BHR degree and FEV₁ ($P < 0.05$) and FEF 25–75 ($P < 0.01$) values.¹⁶

On the basis of these considerations, we aimed at evaluating a group of patients with seasonal allergic rhinitis alone to investigate the presence of BHR and spirometric abnormalities both during and outside the pollen season.

Materials and methods

Study design

The study was performed during (when patients were symptomatic) and outside the pollen season (when patients were symptomless). To evaluate spirometric abnormalities and the presence of BHR in patients with pure seasonal rhinitis, we included subjects with allergic rhinitis due to pollen allergens only. We excluded all the subjects who met

the following exclusion criteria: asthma symptoms, including cough, wheezing, dyspnoea, and shortness of breathing, allergy to perennial allergens, acute upper respiratory infections and use of nasal or oral corticosteroids, and antihistamines within the previous 4 weeks.

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

Subjects

One-hundred rhinitic patients were prospectively and consecutively evaluated, all males, age 23.7 ± 4.9 years. All of them were Navy soldiers who referred to Navy Hospital for periodic fitness visit. All of them were evaluated performing both spirometry and methacholine bronchial challenge during the pollen season, i.e. in the spring. Successively, all of them were re-evaluated outside the pollen season, i.e. in the winter, season without pollens in our geographic area.⁶

A detailed clinical history and a complete physical examination, including allergy evaluation, were performed. The patients were included in the study on the basis of a clinical history of seasonal allergic rhinitis. All patients were sensitized to pollens only (i.e. *Parietaria officinalis*, grasses, olive tree, birch, and hazel). The diagnosis of seasonal allergic rhinitis was made on the basis of a history of nasal symptoms and positive skin prick test for pollens as described elsewhere.⁶ None of the patients was a previous or a current smoker.

Skin prick test

It was performed, as stated by the Italian Society of Allergy and Clinical Immunology.¹⁷ The panel consisted of: house dust mites (*Dermatophagoides farinae* and *pteronyssinus*), cat, dog, grasses mix, *Compositae* mix, *Parietaria officinalis*, birch, hazel, olive tree, *Alternaria Tenuis*, *Cladosporium*, *Aspergilli* mix (Stallergenes, Milan, Italy).

Spirometry

It was performed by using a computer-assisted spirometer (COSMED, Eurasem, Italy), with optoelectronic whirl flow meter. Spirometry is performed as stated by ERS¹⁸, using the European Community for Steel and coal (ECSC) reference equations and C.E.C.A.

If an airway obstruction was present as detected by FEV₁ 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 FEV₁ from baseline was achieved, according to international guidelines¹⁹.

Methacholine bronchial challenge

It was performed to evaluate BHR only if basal FEV₁ was equal or more than 80% of predicted. Aerosol is delivered using a dosimetric computerized supply (MEFAR MB3, Marcos, Italy). Subjects inhaled increasing doses of methacholine, starting from 34 µg/ml. The scheduled doses consisted of the following: 34, 68, 68, 170, 170, 340, 170, 340, 170 µg/ml as previously reported.^{6,16}

The test was interrupted when FEV₁ value was reduced by more or equal than 20% or a maximal cumulative dose of 1590 µg/ml was achieved. The threshold dose causing a 20% fall of FEV₁ (PD20) was calculated.

Degree of BHR

Four arbitrary classes of BHR were considered: very mild = PD20 > 400 µg/ml, mild = PD20 ranging from 201 to 400 µg/ml, moderate = PD20 ranging from 200 to 101 µg/ml, and severe = PD20 < 100 µg/ml as previously reported.^{6,16}

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 means.

Results

All rhinitics were consecutive subjects meeting the inclusion and exclusion criteria and agreeing to join the study.

No adverse event was reported during the study.

During pollen season findings

Spirometry: Four patients showed a FEV₁ value less than 80% of the predicted (Fig. 1A). It has to be mentioned that all of them were completely symptomless for complaints concerning lower airways. A bronchial reversibility was achieved in all subjects.

Then, we evaluated the distribution of the patients considering FVC values (Fig. 1B), and FEF 25–75 values (Fig. 1C). Eight patients showed

impaired FVC values. Seventeen patients showed reduced FEF 25–75 values.

Methacholine bronchial challenge: It was performed in 96 rhinitics. Fifty-four rhinitics showed a positive methacholine challenge. On the basis of BHR degree, we subdivided the methacholine positive patients in 4 groups: very mild, mild, moderate, and severe. Fourteen patients had a very mild degree of BHR, 16 had a mild degree, 16 had a moderate degree, and 8 a severe degree (Fig. 1D).

Then, we analyzed subjects subdividing them in two groups: patients with BHR (BHR positive group) and patients without BHR (BHR negative group). FEF 25–75 values were reduced in 10 subjects of BHR positive group and in seven subjects of BHR negative group.

We considered the three spirometric parameters related with BHR degree (Fig. 2A). A significant difference was observed for FEF 25–75 only (*P* < 0.01) considering BHR severity.

Outside pollen season findings

Spirometry: All subject showed normal FEV₁ values (Fig. 1A). Five subjects showed reduced FVC values (Fig. 1B) and 11 subjects showed impaired FEF 25–75 values (Fig. 1C).

Methacholine bronchial challenge: It was performed in all rhinitics (100). Fifty-four rhinitics showed a positive methacholine challenge. Nineteen patients had a very mild degree of BHR, 11 had a mild degree, 13 had a moderate degree, and 11 a severe degree (Fig. 1D).

FEF 25–75 values were reduced in seven subjects of BHR positive group and in four subjects of BHR negative group.

No significant differences were observed for the 3 spirometric parameters considering BHR severity (Fig. 2B).

During versus outside pollen season findings

Spirometry: There was a significant difference concerning the number of rhinitics with abnormal FEV₁ values: 4 versus 0 (*P* < 0.001).

Concerning FEF 25–75 values, there was a significant difference between the two time of observation: 17 patients with FEF 25–75 < 80% of predicted during the pollen season in comparison with 11 patients evaluated outside the pollen season (*P* < 0.05).

Methacholine bronchial challenge: The mean methacholine PD20/FEV₁ was 352 ± 331 µg/ml during

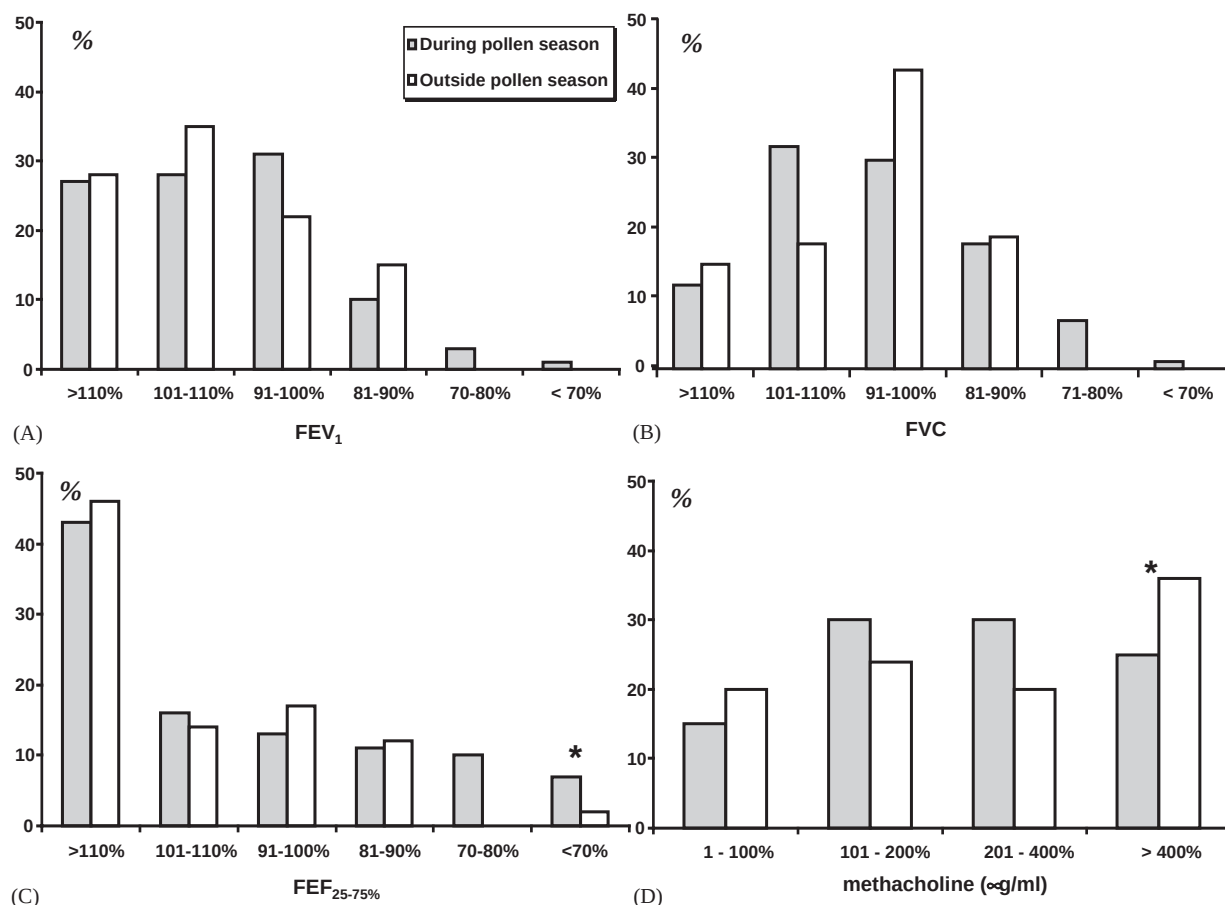


Figure 1 *Quadrant A* percentage distribution of FEV₁ values (as % of predicted) during and outside the pollen season; *quadrant B* percentage distribution of FVC values (as % of predicted) during and outside the pollen season; *quadrant C* percentage distribution of FEF 25–75 values (as % of predicted) during and outside the pollen season; *quadrant D* percentage distribution of BHR grade during and outside the pollen season.

the pollen season, whereas it was $448 \pm 427 \mu\text{g/ml}$ outside the pollen season ($P < 0.05$).

Concerning the BHR positive patients, there is a different impairment of FEF 25–75 values comparing during and outside pollen season findings ($P < 0.05$). Equally for BHR negative patients, a different impairment of FEF 25–75 values is detectable between the two period of observation ($P < 0.05$).

A significant relationship between BHR grade and FEF 25–75 values is detectable in BHR positive patients during the pollen season only (Fig. 2A).

Discussion

Allergic rhinitis and asthma should be considered as a single syndrome involving two parts of the respiratory tract.²⁰ 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.²¹ Epidemiological evidence supports the close link between allergic rhinitis and asthma and cross-sectional population surveys suggest that allergic rhinitis is a major risk factor for asthma development.²¹

Allergic rhinitis may contribute to worsen asthma through different pathophysiologic mechanisms: post-nasal drip, nasal-bronchial reflex, oral breathing, and systemic allergic inflammation.¹⁹

Allergic rhinitis frequently present a non-specific BHR even in absence of asthmatic symptoms. In these subjects with normal FEV₁ values, BHR may be envisaged as a marker of susceptibility to develop asthma.

On the other hand, in mild asthmatics during intercritical periods lung function may be normal concerning FEV₁ values.²² Moreover, asthma is a chronic inflammatory disease of airways and using other parameters it has been demonstrated a persistence of inflammation, also in absence of

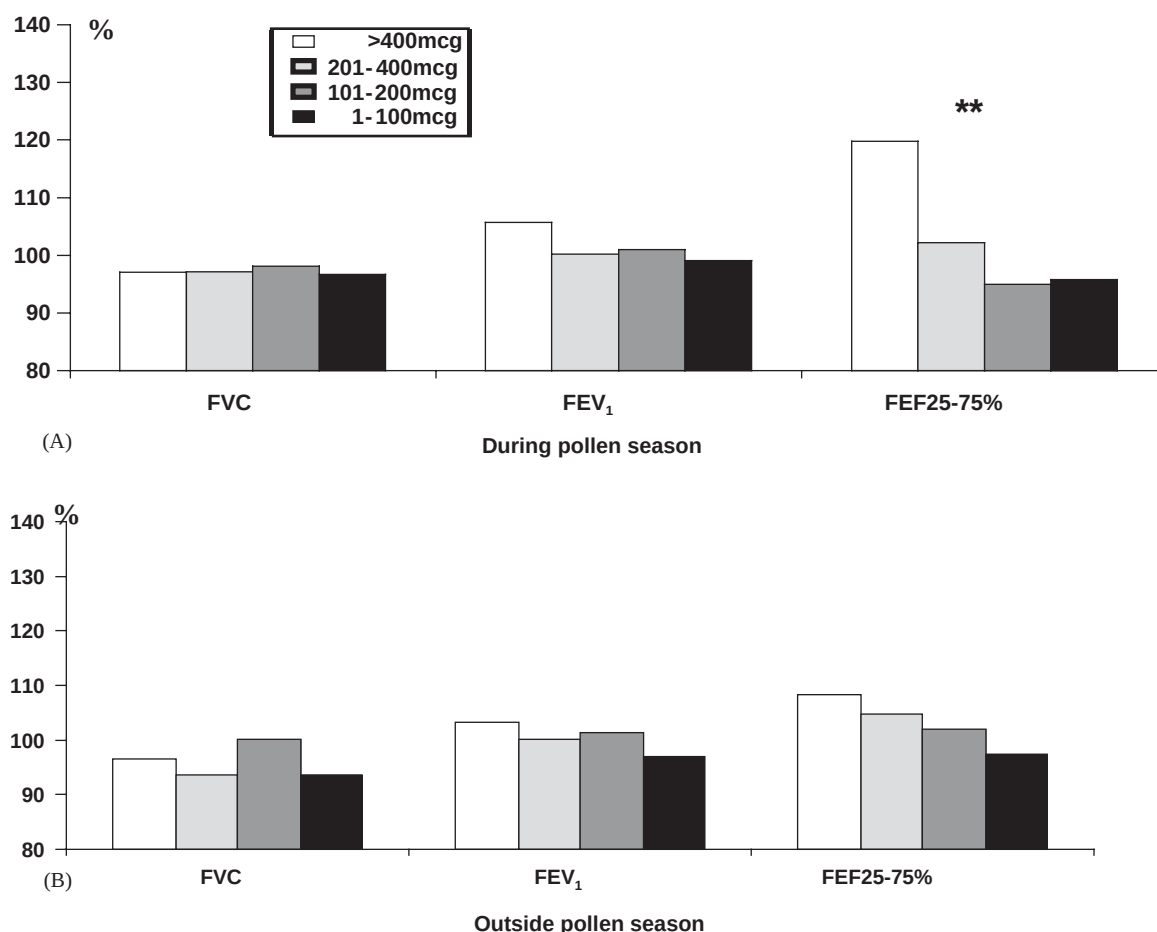


Figure 2 *Quadrant A* percentage distribution of mean values of FVC, FEV₁, and FEF 25–75 in comparison with BHR grade during the pollen season; *quadrant B* percentage distribution of mean values of FVC, FEV₁, and FEF 25–75 in comparison with BHR grade outside the pollen season.

symptoms, mainly involving smaller airways.²³ In these cases, abnormal FEF 25–75 values may be observed: it has been reported that FEF 25–75 may be reduced in asthmatics with normal FEV₁ and FVC values.¹¹ It has been suggested that FEF 25–75 might be considered a marker of small airways impairment in mild asthmatics with normal FVC values.¹⁰

Very recently, we demonstrated some interesting findings in a group of 100 patients with perennial allergic rhinitis alone.¹⁶ Five patients showed impaired FEV₁ values (<80% of predicted), without any perceived lower respiratory symptoms and 48 patients showed reduced FEF 25–75 values.¹⁶ Moreover, 72 patients showed positive methacholine challenge, and there was a significant relationship between BHR degree and FEV₁ and FEF 25–75 values.¹⁶ Thus, we aimed at investigating a large group of patients with seasonal allergic rhinitis both during and outside the pollen season to evaluate the influence of the natural allergen exposure on spirometry and BHR.

The present findings suggest some considerations concerning the link between upper and lower airways and the variations of respiratory parameters consequent on allergen exposure.

Firstly, evaluating a large cohort of subjects with seasonal allergic rhinitis alone, it is possible to single out some subjects with overt bronchial obstruction, as documented by impaired FEV₁ values, during the pollen season. These patients may be considered as “poor perceiver” of their lower respiratory symptoms. In fact, all of them had a normal life playing different sports without trouble. In addition, they never felt lower respiratory symptoms nor diagnosis of asthma has been made. In addition, it has to be highlighted that no subject showed overt bronchial obstruction outside the pollen season. This issue confirms the close relationship between pollen exposure and asthma appearance in those patients.

Secondly, most of our rhinitics (54%) showed BHR. This finding is not surprising if compared with literature analysis. The exposure to allergens is

characterized by nasal inflammation as previously described by ourselves.²⁴ This concept may be consistent with a consequent bronchial inflammation.²⁵ It is noteworthy that BHR was asymptomatic in all our rhinitics. Even though the number of BHR positive patients remains unchanged outside season, the PD20/FEV₁ methacholine significantly increased outside the pollen season. This point further on remarks the close connection between BHR and allergen exposure.

Thirdly, considering the evaluation of FEF 25–75 parameter we demonstrated that some rhinitics¹⁷ show an initial level of bronchial obstruction during the pollen season. It is noteworthy that this percentage diminishes outside the pollen season, but does not disappear: 11 patients continue to present this impairment. This issue is consistent with the concept that chronic bronchial inflammation as well as BHR may persist also in absence of allergen exposure.

Fourthly, there is a relationship between degree of BHR and FEF 25–75 impairment, mainly during the pollen season and in BHR positive patients. That finding underlines the relationship between BHR and airway caliber in patients with airway inflammation.

These data, taken together, partially confirm previous results observed in those patients with perennial allergic rhinitis.¹⁶ Patients with perennial allergic rhinitis, compared with patients with seasonal allergic rhinitis, more obviously show an association with asthma, the impairment of FEF 25–75, the BHR, and the relationship between BHR grade and spirometric abnormalities.

Anyway, our data suggest that a new diagnostic approach should be carried out also in those patients with seasonal allergic rhinitis.

Thus, rhinitics should be carefully followed up to evaluate the possible onset of asthma.

In conclusion, our study highlights the frequent coexistence of bronchial impairment in those patients with seasonal allergic rhinitis alone and supports the strong link between upper and lower airways.

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