

Bronchial Hyperreactivity and Spirometric Impairment in Patients with Perennial Allergic Rhinitis

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Key Words

Bronchial hyperreactivity · Airways, smaller · Allergic rhinitis, perennial

Abstract

Background: Allergic disorders are characterized by a systemic involvement of the immune response. There is a clear link between allergic rhinitis and asthma. Bronchial hyperreactivity (BHR) may be present in rhinitics. Smaller airways may also be impaired in mild asthma. This study aimed at evaluating a group of subjects suffering from perennial allergic rhinitis alone to investigate the presence of BHR and spirometric impairment. **Methods:** One hundred rhinitics sensitized only to perennial allergens were evaluated. Spirometry and methacholine bronchial challenge were performed. **Results:** Five rhinitics showed reduced values of forced expiratory volume/1 s (FEV₁) without symptoms of asthma. Forty-eight rhinitics had reduced forced expiratory flow at 25 and 75% of pulmonary volume (FEF_{25–75}) values. Seventy-two patients showed a positive methacholine challenge. In this group, reduced values of FVC ($p < 0.05$), FEV₁ ($p < 0.05$), and FEF_{25–75} ($p < 0.01$) were demonstrated in comparison with BHR-negative rhinitics. There was a relationship between the degree of BHR and FEV₁ values ($p <$

0.05) and FEF_{25–75} values ($p < 0.01$). **Conclusions:** This study evidences that an impairment of spirometric parameters may be observed in patients with perennial allergic rhinitis alone. A high percentage of these patients have BHR. Thus, new management strategies should be employed in rhinitics.

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Introduction

Allergic rhinitis represents a worldwide health problem as it affects up to 40% of the population and its prevalence is still increasing [1]. It is characterized by an inflammatory response of the nose induced by an IgE-mediated reaction following allergen exposure. Moreover, there is a clear link between allergic rhinitis and asthma: patients very frequently present with both disorders even though they may focus on one or the other [2].

Several studies demonstrated a close association between allergic rhinitis and asthma. Allergic rhinitis has been demonstrated to be a strong risk factor for the onset of asthma in adults [3]. Pederson and Weeke [4] reported that between 58 and 78% of adult asthmatics had an associated allergic rhinitis. Settipane [5] found that 38% of rhinitics had coexistent asthma. The International Study

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of Asthma and Allergies in Childhood study reported that 5% of the general population had asthma associated with allergic rhinitis [6]. We reported that 77% of subjects with respiratory allergy suffered from asthma associated with allergic rhinitis [7].

Asthma is characterized by a reversible airflow obstruction and forced expiratory volume/1 s (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 capable of assessing small airways, it has been assumed that the forced expiratory flow at 25 and 75% of the pulmonary volume (FEF₂₅₋₇₅) may be considered as a measure of the caliber concerning distal airways [10]. Particularly, subjects with mild asthma and normal FEV₁ may show impaired FEF₂₅₋₇₅ [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]. The first observation that BHR exists in some subjects with allergic rhinitis in the absence of clinical asthma was made in 1947. Further, it has been hypothesized that a positive bronchial challenge to methacholine could be considered as predictive for those rhinitics who 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].

On the basis of these considerations, we aimed at evaluating a group of patients with perennial allergic rhinitis alone to investigate the presence of BHR and spirometric abnormalities.

Materials and Methods

Study Design

To evaluate the presence of BHR and spirometric abnormalities in patients with pure rhinitis, we included subjects with allergic rhinitis due to perennial allergens to avoid seasonal interferences of allergen exposure. We excluded all the subjects who met the following exclusion criteria: asthma symptoms, including cough, wheezing, dyspnea, and shortness of breathing, allergy to pollens, 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 oral consent was obtained from patients.

Subjects

One hundred rhinitic patients were prospectively and consecutively evaluated, all males, age 24 ± 4 years. All of them were navy soldiers who attended the navy hospital for regular health checks.

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 perennial rhinitis. All patients were sensitized to perennial allergens only (i.e. house dust mites, cat, or dog). The diagnosis of perennial allergic rhinitis was made on the basis of a history of nasal symptoms and positive skin prick test for perennial allergens as described elsewhere [7]. None of the patients was a previous or a current smoker.

Skin Prick Test

Skin prick test was performed as stated by the Italian Society of Allergy and Clinical Immunology [16]. The panel consisted of house dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cat, dog, grass mix, Compositae mix, *Parietaria officinalis*, birch, hazel tree, olive tree, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix (Stallergenes, Milan, Italy).

Spirometry

Spirometry was performed by using a computer-assisted spirometer (Cosmed, Eurasem, Italy) with an optoelectronic whirl flow meter. It was done as stated by ERS [17], using the European Community for Steel and Coal (ECSC) reference equations and CECA. If an airway obstruction was present as detected by FEV₁ values <80% of those predicted, a test of bronchodilatation was performed using a salbutamol metered dose of 200 µg. Reversibility was considered if an increase of at least 12% of FEV₁ from baseline was achieved according to international guidelines [18].

Methacholine Bronchial Challenge

Methacholine bronchial challenge was performed to evaluate BHR only if basal FEV₁ was $\geq 80\%$ of that predicted. Aerosol was 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, 68, 68, 170, 170, 340, 170, 340 and 170 µg/ml as previously reported [7]. The test was interrupted if FEV₁ was reduced by $\geq 20\%$ of control or a maximal cumulative dose of 1,590 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 [7].

Statistical Analysis

Statistical analysis was performed using χ^2 test, calculating confidence 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 evaluated performing both spirometry and methacholine bronchial challenge. All of them were consecutive subjects meeting the inclusion and ex-

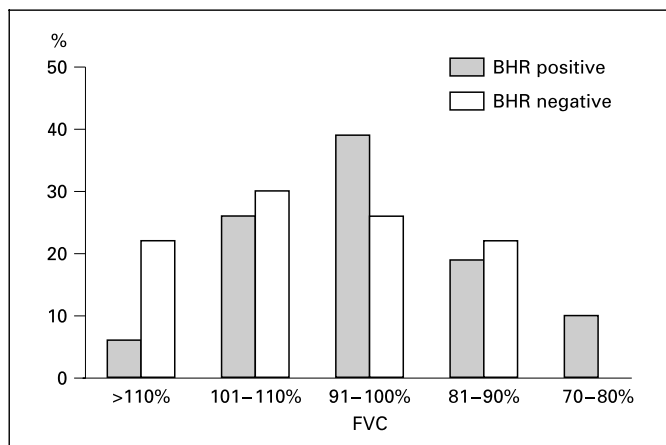


Fig. 1. Percentage distribution of FVC values (as % of predicted) in BHR-positive and BHR-negative groups.

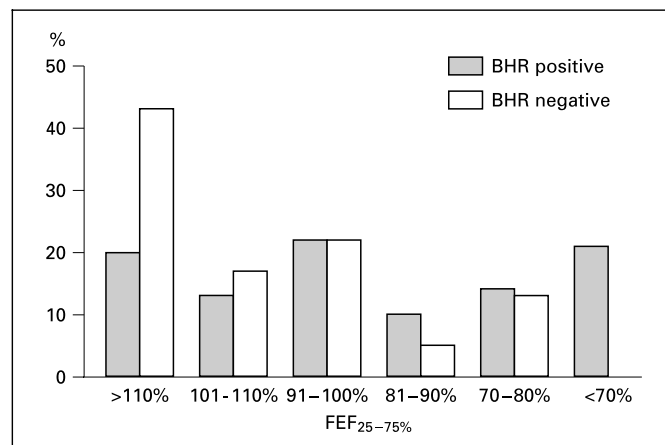


Fig. 3. Percentage distribution of FEF₂₅₋₇₅ values (as % of predicted) in BHR-positive and BHR-negative groups.

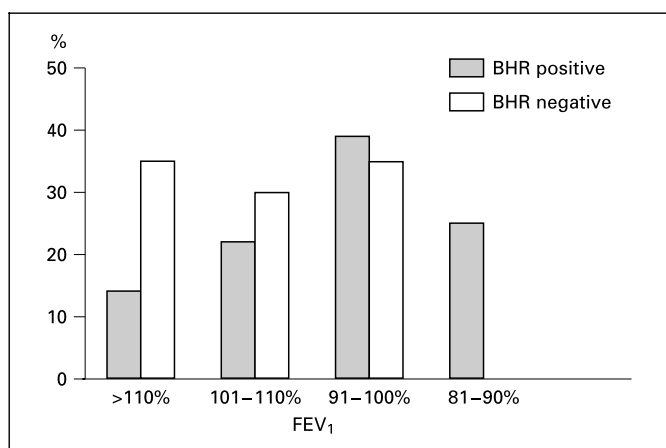


Fig. 2. Percentage distribution of FEV₁ values (as % of predicted) in BHR-positive and BHR-negative groups.

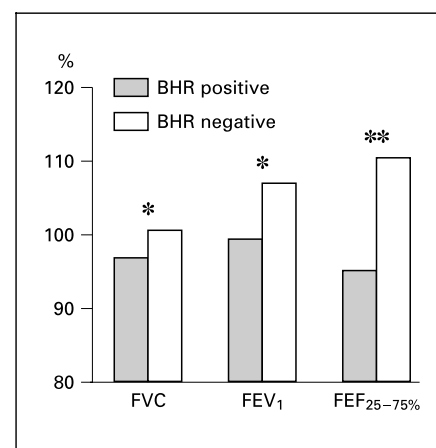


Fig. 4. Comparison of mean values of FVC, FEV₁, and FEF₂₅₋₇₅ in the two groups. * $p < 0.05$; ** $p < 0.01$.

clusion criteria and agreeing to join the study. No adverse event was reported during the study.

Spirometry

Five patients showed a FEV₁ value $<80\%$ of the predicted one. It has to be mentioned that all of them were completely asymptomatic for complaints concerning lower airways. A bronchial reversibility was achieved in all subjects.

Methacholine Bronchial Challenge

Methacholine bronchial challenge was performed in 95 rhinitics. 72 rhinitics showed a positive methacholine challenge. 13 patients had a very mild degree of BHR, 13

had a mild degree, 26 had a moderate degree, and 20 a severe degree.

We analyzed subjects subdividing them into two groups: patients without BHR and patients with BHR. Thus, we evaluated the distribution of the patients considering FVC values (fig. 1), FEV₁ values (fig. 2), and FEF₂₅₋₇₅ values (fig. 3). Ten subjects had reduced values of FVC only in the BHR-positive group. FEV₁ values were normal in both groups. FEF₂₅₋₇₅ values were reduced in 35 subjects of the BHR-positive group and in 13 subjects of the BHR-negative group. There was a significant difference between the two groups concerning FVC values ($p < 0.05$), FEV₁ values ($p < 0.05$), and FEF₂₅₋₇₅ values ($p < 0.01$) as reported in figure 4.

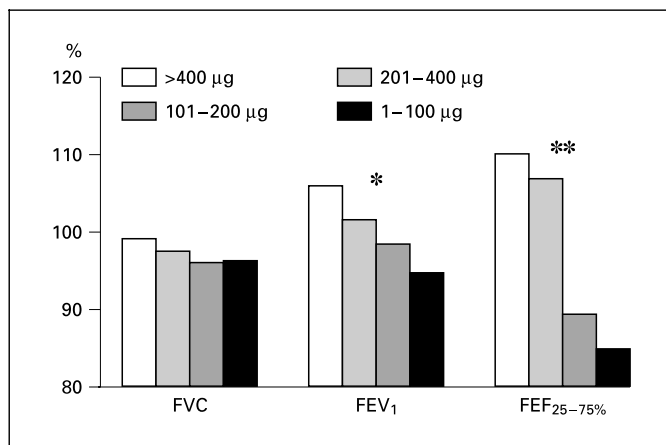


Fig. 5. Comparison of mean values of FVC, FEV₁, and FEF₂₅₋₇₅ considering the degree of BHR. * $p < 0.05$; ** $p < 0.01$.

On the basis of BHR degree, we subdivided the methacholine-positive patients into four groups: very mild, mild, moderate, and severe. We considered the three spirometric parameters related with BHR degree (fig. 5). A significant difference was observed for both FEV₁ ($p < 0.05$) and FEF₂₅₋₇₅ ($p < 0.01$) considering BHR severity.

Discussion

Allergic rhinitis and asthma should be considered as manifestations of one syndrome in two parts of the respiratory tract [19]. Moreover, it is evident that these 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 [19]. 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 [20].

Allergic rhinitis may contribute to worsening asthma through different pathophysiological mechanisms: post-nasal drip, nasal-bronchial reflex, oral breathing, and systemic allergic inflammation [19]. The last mechanism may be considered the most important. Very recently, we demonstrated that in asthmatic children there is a Th2 polarization in sinus nasal lavage both in allergic and non-allergic subjects [21]. This concept reinforces the pathophysiological link between upper and lower airways.

Allergic rhinitis frequently present a nonspecific BHR even in the absence of asthmatic symptoms. In these subjects, BHR may be envisaged as a marker of susceptibility to develop asthma. In these rhinitics FEV₁ values are typically normal.

On the other hand, in mild asthmatics during inter-critical periods lung function may be normal concerning FEV₁ values [22]. Moreover, asthma is a chronic inflammatory disease of the airways and using other parameters a persistence of inflammation has been demonstrated, also in the absence of symptoms, mainly involving smaller airways [23]. In these cases, abnormal FEF₂₅₋₇₅ values may be observed: it has been reported that FEF₂₅₋₇₅ may be reduced in asthmatics with normal FEV₁ and FVC values [11]. It has been suggested that FEF₂₅₋₇₅ may be considered a marker of small airways impairment in mild asthmatics with normal FVC values [10].

Considering these data together, our findings suggest some considerations concerning the link between upper and lower airways.

First, evaluating a large cohort of subjects with rhinitis alone, it is possible to single out some subjects with overt bronchial obstruction as documented by reduced FEV₁ values. These patients may be considered as 'poor perceivers' of their lower respiratory symptoms. In fact, all of them had a normal life doing different sports without problems. In addition, they never suffered from lower respiratory symptoms nor was a diagnosis of asthma made.

Second, most of our rhinitics (72%) showed BHR. This finding is not surprising if compared with the literature. We have to bear in mind that we chose the model of perennial allergy. The exposure to perennial allergen is characterized by a persistent nasal inflammation as previously described by ourselves [24]. This concept is consistent with a consequent bronchial inflammation [25]. It is noteworthy that all our rhinitics were asymptomatic for BHR.

Third, considering the evaluation of FEF₂₅₋₇₅ parameters we demonstrated that a considerable percentage of rhinitics (48%) shows an initial level of bronchial obstruction.

Fourth, there is a relationship between the degree of BHR and FEF₂₅₋₇₅ impairment. This finding underlines the relationship between BHR and airway caliber in patients with persistent airway inflammation. Thus, our data suggest that new management strategies should be carried out in patients with allergic rhinitis.

All rhinitics, even in the absence of a history suggesting asthmatic symptoms, must be evaluated performing spi-

rometry. Bronchial methacholine challenge may be considered as a supplemental exam to achieve a more exhaustive evaluation in allergic rhinitis.

In addition, an adequate treatment of allergic rhinitis must be prescribed both concerning pharmacological treatment and specific immunotherapy. Particularly, the last procedure is the only treatment that may modify the natural history of the allergic reaction. It has been demonstrated that specific immunotherapy may prevent the onset of asthma in patients with allergic rhinitis [26].

Moreover, some drugs may be used both in asthma and in allergic rhinitis such as corticosteroids, antileukotrienes, and antihistamines; thus an appropriate evalua-

tion of the individual patient makes a correct therapy possible [27]. Moreover, there is still no evidence that antihistaminic or antileukotrienic treatment has any impact on the development of asthma with the exception of the ETAC study [28]. This issue should be the object of future research. In addition, it is important to note that antileukotrienes have been approved in the US only for seasonal allergic rhinitis. Finally, rhinitis should be carefully followed up to evaluate the possible onset of asthma.

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

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