

The lower airway pathology of rhinitis

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There is a close link between allergic rhinitis (AR) and lower airways disorders, and this concept has been clarified and confirmed in several studies. AR constitutes a main risk factor for new-onset asthma. Furthermore, numerous epidemiologic surveys indicate that AR is very frequently associated with asthma. Bronchial hyperreactivity, a component of asthma, has often been reported to be present in patients with AR. Bronchial hyperreactivity in AR might represent a prognostic factor for further progress to asthma. In this regard forced expiratory flow at 25% and 75% of pulmonary volume has been proposed as an early marker of bronchial involvement in patients with AR who perceive only nasal symptoms. A close structural and functional relationship between the upper and lower airways has been recently demonstrated. Finally, adequate treatment of AR might positively affect the course of asthma. Taking these facts into consideration, a new diagnostic approach should be considered in managing patients with AR: a possible bronchial involvement must be sought in each patient. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Allergic rhinitis, airflow, bronchial obstruction, eosinophils, bronchial hyperreactivity

Allergic rhinitis (AR) is the most common immunologic disorder and is characterized by an IgE-mediated inflammation induced by allergen exposure. Infiltrating cells, including T cells, eosinophils, mast cells, and basophils, release several mediators that cause the symptoms and cytokines that promote and amplify the inflammatory cascade. Therefore AR triggers both a local and a systemic inflammatory process. In this regard a bidirectional relationship between the nose and the bronchi has been recently demonstrated in elegant experimental models: the nasal allergen challenge induces a bronchial response, and bronchial stimulation results in a nasal reaction.¹ Therefore the respiratory airways constitute a single anatomic-functional unit. This concept is based on the presence of numerous similarities existing between the upper and lower airways in regard to the following:

Abbreviations used

AR: Allergic rhinitis
BHR: Bronchial hyperreactivity
FEF₂₅₋₇₅: Forced expiratory flow at 25% and 75% of pulmonary volume
MAR: Mixed allergic rhinitis
PAR: Perennial allergic rhinitis
SAR: Seasonal allergic rhinitis

1. epidemiology—several surveys report the association between AR and asthma;
2. anatomy—the respiratory epithelium is substantially the same from the nasal cavities to the bronchioles;
3. physiology—the nose and bronchi share the same adrenergic and vagal innervation;
4. immunopathology—mast cells, T lymphocytes, and eosinophils might infiltrate both upper and lower airways;
5. pathophysiology—airflow limitation is the main functional consequence of both AR and asthma; and
6. therapy—antihistamines, antileukotrienes, corticosteroids, and specific immunotherapy can be prescribed both for AR and asthma.

Moreover, AR might promote, trigger, maintain, and worsen asthma through several pathophysiologic mechanisms:

1. the vagal reflex, the so-called rhinobronchial reflex;
2. the per continuum passage of allergic inflammation from the nose to bronchi;
3. the systemic release of mediators and cytokines;
4. the irritant mechanism sustained by the postnasal drip; and
5. the oral respiration caused by nasal obstruction, which promotes bronchial hyperreactivity (BHR) as dry and cold air penetrates into the bronchi.

Consequently, these immunologic and functional events weigh up and highlight the close nose-bronchi connection. In this review a series of issues will be considered to underline the pathophysiologic significance and the clinical relevance of the lower airway pathology of rhinitis.

AR AS A RISK FACTOR FOR ASTHMA

There is an abundance of evidence that supports this concept. Two studies provide convincing confirmation

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that AR is an independent risk factor for onset of asthma. Setticone et al² reported that patients with AR are at 3 times the risk of asthma compared with those without AR. In addition, a cross-sectional study of representative samples of young adults who completed a detailed questionnaire and underwent lung function tests, bronchoprovocation challenges, IgE measurements, and skin prick tests was performed in Europe.³ The results demonstrate and confirm that AR constitutes a main risk factor for asthma onset.

EPIDEMIOLOGIC LINK BETWEEN AR AND ASTHMA

Several cross-sectional studies have reported that there is a frequent association between AR and asthma. Among them, a recent European multicenter cross-sectional survey evaluated respiratory symptoms in a young adult population.⁴ About 60% of asthmatic patients had AR; on the other hand, patients with AR presented an 8-fold risk of having asthma compared with patients without AR. Furthermore, Downie et al⁵ found that the most severe nasal symptoms were associated with bronchial symptoms in patients with persistent AR.

Therefore published studies confirm the close epidemiologic association between AR and asthma. This has been acknowledged in several official position papers and international guidelines. On the other hand, these epidemiologic surveys evaluated the presence of bronchial symptoms by using specific questionnaires, but no study evaluated patients with AR perceiving nasal symptoms only.

ASYMPTOMATIC BRONCHIAL INVOLVEMENT IN AR

For the above reasons, 2 studies were performed in patients with pure AR (ie, reporting only nasal symptoms) to evaluate the possible effect of AR on the lower airways.

The first study evaluated a group of 100 patients with perennial allergic rhinitis (PAR) who only perceived nasal symptoms. All of them underwent spirometry and methacholine bronchial challenge.⁶ Five patients showed reduced values of FEV₁, and 25 patients had reduced forced expiratory flow at 25% and 75% of pulmonary volume (FEF₂₅₋₇₅) values. In addition, 72 patients had positive methacholine challenge results. Patients with BHR showed significantly lower values of forced vital capacity, FEV₁, and FEF₂₅₋₇₅ than patients without BHR. There was, moreover, a significant relationship between the degree of BHR and both FEV₁ and FEF₂₅₋₇₅ values.

A similar study was performed in patients with pure seasonal allergic rhinitis (SAR) conducted both during and outside the pollen season.⁷ In the pollen season 4 patients had pathologic FEV₁ values, and 54 had BHR. Outside the pollen season, no patient showed spirometric defects, but BHR persisted in the same patients.

These studies provided evidence that a clinically relevant percentage of patients with pure rhinitis might have a bronchial involvement without perception of it. Moreover, the degree of BHR might be related to this bronchial impairment.

BHR IN AR

Because BHR is a paramount component of asthma, BHR might be also observed in a high proportion of patients with rhinitis. In this regard it has been hypothesized that a positive bronchial challenge result to methacholine could be considered predictive of those patients with rhinitis who would progress to asthma.⁸ Moreover, BHR was reported to be an important risk factor for asthma development in patients with both PAR and SAR.⁹ On the basis of these considerations, it was hypothesized that patients with rhinitis might present different spirometric and BHR patterns relating to both cause and allergen exposure. A large group of patients with AR needed to be analyzed to confirm this theory. Thus 2347 patients were enrolled, subdividing them into 3 groups: patients with PAR, SAR, or mixed allergic rhinitis (MAR; eg, polysensitized patients).¹⁰ Most of the patients with AR were polysensitized (up to 80%), and BHR affected 82.2% of the patients with PAR, 73.6% of the patients with MAR, and 53.5% of the patients with SAR, confirming previous reports (Fig 1). Therefore these different patterns are related to specific sensitizations. In addition, a significant seasonal variability of the degree of BHR was present in patients with SAR and patients with MAR. Thus this study showed that BHR is very common in AR, even though it is independent of allergen exposure, as previously reported.⁷

EARLY BRONCHIAL IMPAIRMENT IN AR

Spirometric defects and BHR can be frequently associated with AR, even though bronchial symptoms are not perceived. As a consequence, it should be clinically relevant to have some parameter for early detection of bronchial involvement in patients with AR symptoms only.

Therefore a study was designed to evaluate a large group of patients (121) with persistent AR who had BHR but were without bronchial symptoms.¹¹ Sixty-five (53.7%) patients had impaired FEF₂₅₋₇₅ values. FEF₂₅₋₇₅ values significantly correlated with the degree of BHR and nasal obstruction symptoms. Thus this study provided evidence that an early bronchial impairment might be detectable by considering the FEF₂₅₋₇₅ parameter.

FEF₂₅₋₇₅ originally was considered to be more sensitive to obstruction in the small airways than FEV₁. Moreover, it has been demonstrated that FEF₂₅₋₇₅ is useful in predicting the presence of airway responsiveness, might be a more sensitive indicator of chronic airflow obstruction than FEV₁, and might be considered a risk factor for the

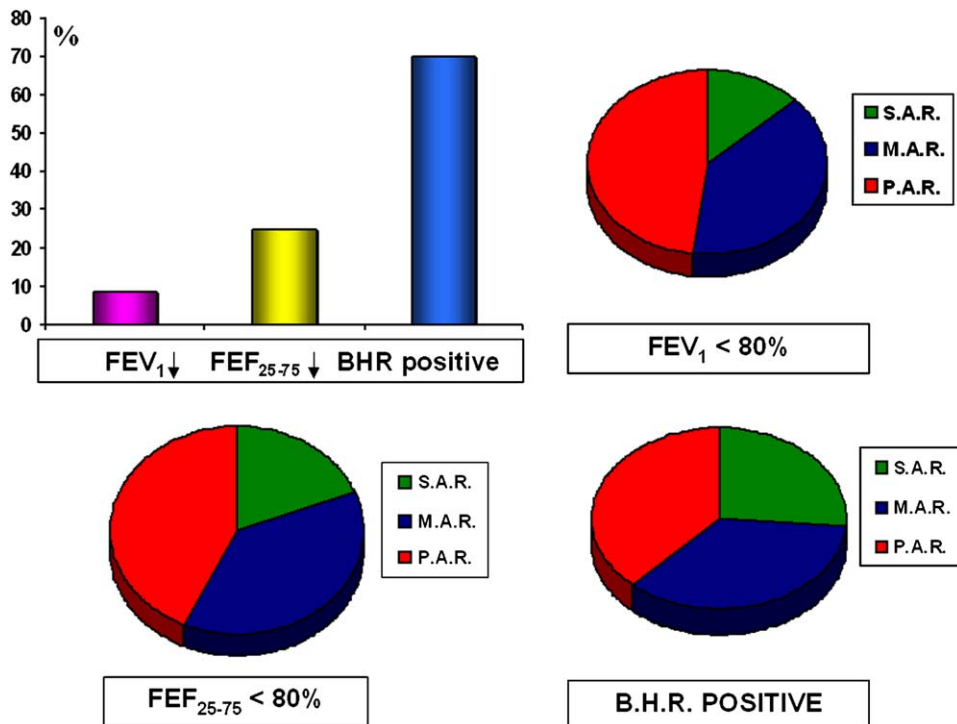


FIG 1. Bronchial involvement in patients with AR perceiving nasal symptoms only. *Upper left quadrant*, Percentages of 2347 subjects with PAR, SAR, and MAR with values of less than 80% of the predicted value for FEV_1 , FEF_{25-75} , and BHR. *Upper right quadrant*, Distribution of patients with FEV_1 of less than 80% of predicted value in accordance with the diagnosis of SAR, MAR, or PAR, respectively. *Lower left quadrant*, Distribution of patients with FEF_{25-75} values of less than 80% of predicted value in accordance with the diagnosis of SAR, MAR, or PAR, respectively. *Lower right quadrant*, Distribution of patients with BHR in accordance with the diagnosis of SAR, MAR, or PAR, respectively. Partially modified with permission from Ciprandi et al¹⁰ and Cirillo I, Vizzaccaro A, Tosca MA, et al. Monaldi Arch Chest Dis 2005;63:79-83.

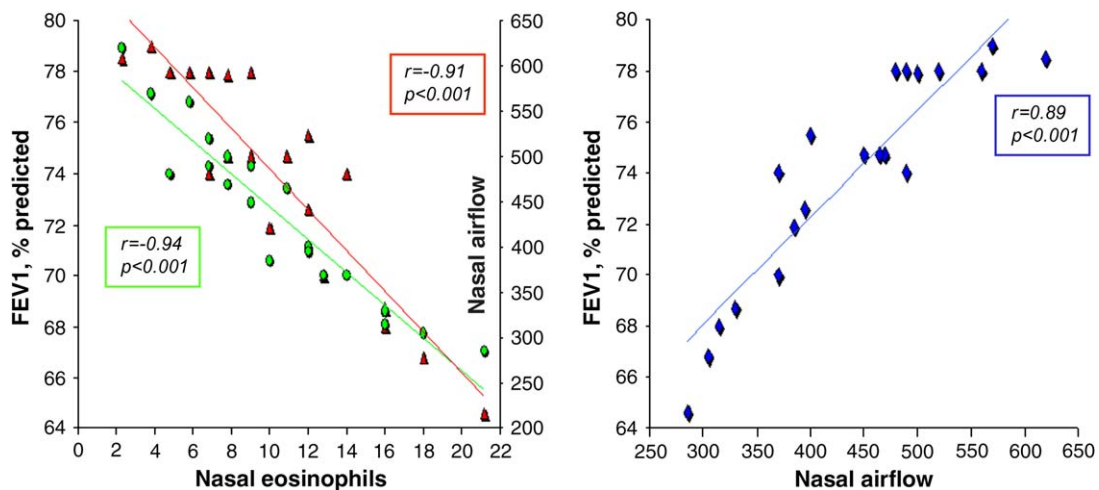


FIG 2. Nose-bronchi structure-function relationship. *Left quadrant*, Relationship between the number of nasal eosinophils and FEV_1 values (green) and nasal airflow (red). *Right quadrant*, Relationship between FEV_1 values and nasal airflow. Partially modified from Ciprandi et al.^{13,14}

persistence of respiratory symptoms in allergic asthmatic children.

On the basis of these considerations, another study was performed to confirm the role of FEF_{25-75} as an early

marker of bronchial impairment in AR.¹² Fifty patients with SAR were evaluated both during and outside the pollen season. All of them had a moderate-severe grade of nasal obstruction. FEF_{25-75} was significantly associated

with all evaluated parameters, including nasal symptoms, T_H1 - and T_H2 -dependent cytokine levels, nasal eosinophil counts, FEV_1 , degree of BHR, and especially nasal airflow. Thus this study confirmed and highlighted the role of FEF_{25-75} as a possible early marker of bronchial impairment in patients with pure SAR.

NOSE-BRONCHI STRUCTURE-FUNCTION RELATIONSHIP

Allergic inflammation is characterized by mucosal infiltration by several cell types, but eosinophils have been demonstrated to be the best marker of the allergic reaction.¹³ The number of eosinophils infiltrating the nasal mucosa correlates well with the most important clinical, functional (eg, nasal airflow), and immunologic parameters (Fig 2). Mainly, there is a significant relationship between nasal eosinophil counts and spirometric findings, including FEF_{25-75} and FEV_1 , and BHR. In other words, the more intense the nasal inflammation, the more evident is bronchial involvement (Fig 2). This evidence strengthens the concept that nasal inflammation significantly affects bronchial function because there is a direct relationship between eosinophil numbers and spirometric performance. Therefore 2 studies were performed to analyze the structure-function relationship between the nose and the bronchi. The first study was performed in a group of patients with SAR and asthma.¹⁴ Nasal airflow and FEV_1 were significantly correlated with nasal eosinophil counts, and nasal airflow was significantly correlated with FEV_1 (Fig 2).

The second study investigated a group of patients with PAR and asthma.¹⁵ Significant positive relationships were demonstrated among nasal eosinophil infiltration, nasal airflow, and FEV_1 , thus confirming the previous study.

Therefore both studies constituted the first evidence of a relationship between T_H2 -related nasal inflammation and nasal and bronchial airflow in patients with AR associated with asthma. These findings constitute the formal and objective proof concerning the close link between nasal and bronchial function. Moreover, these data are consistent with the concept of the so-called rhinobronchial cross-talk, such that there is a bidirectional relationship between structural (ie, inflammatory phenomena) and functional (ie, airflow) events. In other words, the nasal obstruction through different pathophysiologic mechanisms, including oral respiration, systemic absorption of mediators and cytokines, postnasal drip, and nervous reflex, significantly affects bronchial airflow.

EFFECT OF RHINITIS TREATMENT ON ASTHMA

Numerous trials have investigated the effect of nasal treatment on the course of asthma. There is evidence that both nasal corticosteroids and antihistamines might reduce admissions to emergency departments for asthma attacks, improve respiratory symptoms and spirometry, and reduce

the use of bronchodilators. Even though intranasal corticosteroids provide more efficacy in controlling symptoms than antihistamines and antileukotrienes, as demonstrated by meta-analysis, a recent large comparative study reported that desloratadine and montelukast were equally effective in reducing asthma symptoms and bronchodilator use in patients with seasonal AR and concomitant asthma.¹⁶

It is commonly believed that AR precedes asthma and that it is a risk factor for its development, especially in children. In this regard it has been shown that specific immunotherapy is able to prevent the onset of asthma in children with AR alone.¹⁷

All these reports support the concept that treating the nose represents a main step in managing patients with AR and asthma.

CONCLUSIONS

There are consistent observations supporting the effect of AR on the lower airways. Bronchial involvement, including spirometric defects, BHR, or both, might be frequently found. Moreover, these bronchial impairments depend on the specific allergen sensitization. However, an early bronchial involvement can be easily detected by performing spirometry. Because lower airways pathology can be adequately prevented or cured, a new diagnostic approach should be considered. Each patient with AR must be evaluated to detect a possible bronchial involvement as soon as possible. On the other hand, the AR-asthma link suggests that the therapeutic strategy is changing in favor of the integrated treatment of the 2 diseases.

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