

Early bronchial involvement in children with allergic rhinitis

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ABSTRACT

Background: Allergic rhinitis (AR) may be frequently associated with asthma or precede it. Bronchial involvement in AR is usually detected by spirometry. Forced expiratory volume in 1 second (FEV₁) is considered a reliable parameter for asthma diagnosis. However, forced expiratory flow at 25–75% (FEF_{25–75}) could be considered a possible marker of early bronchial involvement in AR; indeed, it has been proposed that FEF_{25–75} values <70% of predicted may predict this evolution. The aim of this study was to evaluate a large cohort of children with AR to define an FEV₁ value corresponding to impaired FEF_{25–75} values.

Methods: Eight hundred fifty AR children (555 boys; median age, 10 years) were studied. Spirometry and skin-prick test were performed in all of them. Descriptive statistic and multivariate analysis were considered.

Results: Three-hundred (35.3%) patients had FEF_{25–75} values <70% of predicted. Still, normal FEV₁ values were associated with overt impaired FEF_{25–75} values and the cutoff value was 83%.

Conclusion: Spirometry should be adequately interpreted in AR patients; indeed, an FEV₁ cutoff value of 83% detects with good efficiency AR children with early bronchial impairment.

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Allergic rhinitis (AR) may be frequently associated with asthma or precede it. In this regard, AR is considered a relevant risk factor for asthma development as emphasized by the Allergic Rhinitis and Its Impact on Asthma (ARIA) document.¹

From a pathophysiological point of view, asthma is characterized by airflow obstruction. The bronchial airflow may be easily assessed by spirometry. Several spirometric parameters may be evaluated, but the most commonly considered measure of bronchial airflow is forced expiratory volume in 1 second (FEV₁) as stated by the Global Initiative for Asthma guidelines.² An FEV₁ value <80% of predicted is usually considered for persistent asthma diagnosis. Nevertheless, there is increasing interest in the role of small airways in the pathogenesis of asthma. Although there is no validated measure of airflow in small airways, it has been suggested that the forced expiratory flow at 25 and 75% (FEF_{25–75}) of the pulmonary volume might be more sensitive to detect small airways obstruction than FEV₁.³ In addition, it has been proposed that FEF_{25–75} may be considered a marker of early bronchial involvement in AR patients.⁴ This issue has been acknowledged both by the recently revised Joint Task Force Practice Parameter on Rhinitis and the updated ARIA document.^{1,5}

AR often predates asthma. It suggests the relevant need to precociously detect a bronchial involvement in AR patients. However, the screening spirometry might reveal still normal FEV₁ values, even in the presence of early bronchial involvement. In this regard, FEF_{25–75} values <80% of predicted was previously considered abnormal in AR patients and it was considered an early marker of bronchial impairment.⁴ More recently, it has been proposed that FEF_{25–75} values <70% of predicted may be a better threshold to predict this evolution in adult patients with recent onset of AR.⁶ Indeed, logistic models confirmed that FEF_{25–75} values <70% of predicted fit very well with several risk factors, such as polysensitization, bronchial hyperreactivity, and FEV₁ values <92%.⁶ Therefore, the aim of this study was to evaluate a large cohort of children with AR to define an FEV₁ value corresponding to impaired FEF_{25–75} values, such as <70% of predicted.

MATERIALS AND METHODS

Study Design

The study included children, aged between 8 and 13 years, with AR and only nasal symptoms. All of them were evaluated performing skin-prick test and spirometry. The Review Board approved the study and an informed consent was obtained from the parents of each patient.

Subjects

Eight hundred fifty children with AR were prospectively and consecutively evaluated during 2 years. Demographic and spirometric characteristics are reported in Table 1.

All of them were children who referred to “Ave Gratia Plena” Hospital for rhinitis. Detailed clinical history and complete physical examination were performed by an expert pediatrician (M.C.). The patients were included in the study based on a clinical history of AR and presence of nasal symptoms according to validated criteria.^{1,5}

We excluded all subjects who met the following exclusion criteria: any previously documented diagnosis of asthma or presence of asthma symptoms including dry cough, wheezing, dyspnea, and shortness of breathing in the 3 previous years; acute or chronic upper respiratory infections in the past 6 months; anatomic nasal disorders (*i.e.*, nasal polyps, severe septum deviation, *etc.*); previous or current specific immunotherapy; and use of inhaled, nasal, or oral corticosteroids, nasal or oral vasoconstrictors, antileukotrienes, and antihistamines during the previous 4 weeks. All patients were previously treated only on demand with drugs (*e.g.*, antihistamines) alone. The diagnosis of persistent AR was made based on a concordance between history of nasal symptoms and positive skin-prick test, according to ARIA international guidelines.⁵

Skin-Prick Test

Skin-prick test was performed as stated by the European Academy of Allergy and Clinical Immunology.⁷ The panel consisted of house-dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cat, dog, grasses mix, *Compositae* mix, *Parietaria officinalis*, birch, hazel, olive tree, *Alternaria tenuis*, *Cladosporium*, and *Aspergillus* mix (Stallergenes, Milan, Italy).

Spirometry

Spirometry was performed by using a computer-assisted spirometer (Pulmolab 435-spiro 235; Morgan, Kent, U.K.) with optoelectronic

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Table 1 Clinical and demographic characteristic of the 850 evaluated patients

Characteristic	Patients with Rhinitis <i>n</i> = 850
Gender, males, <i>n</i> (%)	555 (65.2)
Age (yr), (median)	10 (8–13)
FVC, (% of predicted median)	101 (92–119)
FEV ₁ , (% of predicted median)	93 (83–109)
FEF _{25–75} , (% of predicted median)	75 (66–86)

The percentage in parentheses is calculated over the total number of subjects reported at top of column. All numbers in brackets represent first to third quartiles.

FVC = forced vital capacity; FEV₁ = forced expiratory volume in the 1st second; FEF_{25–75} = forced expiratory flow at the 25 and 75% of the pulmonary volume.

whirl flow meter. Spirometry was performed as stated by European Respiratory Society and American Thoracic Society^{8,9} and interpreted as suggested by Collen *et al.*¹⁰

Statistical Analysis and Data Definitions

Descriptive statistics were firstly performed and quantitative parameters were reported as medians with quartiles. Qualitative data were reported as frequencies and percentages. Comparison of qualitative data among various groups of patients was made by the chi-square test.

To evaluate the role of different independent variables for FEF_{25–75} < 70%, a multiple logistic regression analysis was performed. Variables that were statistically significant in the bivariate analysis or that were considered *a priori* important were entered in the model. Before performing logistic regression, some continuous predictors were dichotomized based on the receiver operating characteristic (ROC) curve analysis, and sensitivity and specificity were calculated. The following predictors were evaluated in the logistic regression model: FEV₁ (≤83% versus ≥83% of predicted), forced vital capacity (FVC, <111% versus ≥111% of predicted), and type of sensibilization (perennial versus seasonal).

For the multivariate analysis, the step-down strategy was chosen; the effect was expressed in terms of adjusted odd ratio (OR_{Adj}) and 95% confidence interval and was tested by means of the likelihood ratio test. The area under ROC curve (AUC) of the model was used as an indicator of the model's predictive ability. All tests were two sided and a value of *p* < 0.05 was considered statistically significant. A statistical software program 3 (Statistica 2005; Statsoft Italia s.r.l., Vigonza, Italy) was used for all the analyses.

RESULTS

Eight hundred fifty patients, 555 boys (65.2%), were included in the study. The median age was 10 years. All of them were white. Patients presented a median (25th–75th) FVC value of 101% of predicted (92–119), a median FEV₁ value of 93% (83–109) of predicted, and a median FEF_{25–75} value of 75% (66–86) of predicted (Table 1). Three hundred (35.3%) patients had FEF_{25–75} values <70% of predicted. Four hundred sixty-one patients showed sensitization to seasonal allergens (54.2%; Table 2).

To evaluate possible risk factors for FEF_{25–75} < 70%, all patients were more deeply investigated. A significant relationship exists between FEF_{25–75} and FEF_{25–75} values as shown by Fig. 1. A ROC curve analysis was first performed to find the best cutoff value discriminating between patients with FEF_{25–75} < 70% and patients with FEF_{25–75} ≥ 70%. The results of this analysis are shown in Table 3 and in Fig. 2. As shown in this table, FEV₁ variable had a particularly interesting predictive ability (AUC ROC, >0.70). In Table 2, demographic and

Table 2 Sensitivity, specificity, area under curve (AUC), and best cutoff values for different predictors of FEF_{25–75} < 70%, obtained by receiver operating characteristic curve analysis (*n* = 850)

Predictors	Sensitivity	Specificity	AUC (95% CI)	Best Cutoff
Age (yr)	0.60	0.53	0.52 (0.44–0.79)	≥10
FVC % of predicted	0.81	0.41	0.59 (0.51–0.63)	<111
FEV ₁ % of predicted	0.79	0.81	0.79 (0.76–0.84)	≤83

CI = confidence interval; FVC = forced vital capacity; FEV₁ = forced expiratory volume in the 1st second; FEF_{25–75} = forced expiratory flow at the 25 and 75% of the pulmonary volume.

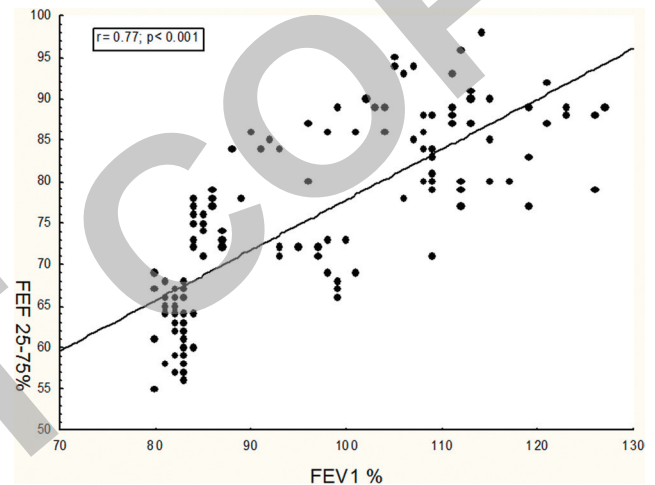


Figure 1. Relationship between forced expiratory flow at 25–75% (FEF_{25–75}) and forced expiratory volume in 1 second (FEV₁) values in the evaluated children.

Table 3 Demographic and clinical parameters in rhinitis patients with FEF_{25–75} < 70% of predicted and in patients with rhinitis with FEF_{25–75} ≥ 70% of predicted

	FEF _{25–75} < 70% of predicted <i>n</i> = 300	FEF _{25–75} ≥ 70% of predicted <i>n</i> = 550	<i>p</i> Value
Gender, male	230 (76.6)	325 (59)	0.7*
Age, ≥10 yr	201 (67)	285 (51)	0.6*
FVC < 111%	167 (56.6)	182 (33)	0.005*
FEV ₁ ≤ 83% of predicted	235 (78.3)	88 (16)	<0.0001*
Sensitivity to perennial allergens, <i>n</i> (%)	206 (68.6)	183 (33.2)	<0.0001*

Values denote *n* (%). All percentages in parentheses are calculated over total number of subjects at top of column.

*Chi-square test.

FVC = forced vital capacity; FEV₁ = forced expiratory volume in the 1st second; FEF_{25–75} = forced expiratory flow at the 25 and 75% of the pulmonary volume.

clinical parameters of the patients with FEF_{25–75} < 70% and with FEF_{25–75} ≥ 70% are presented. There was no difference between the two groups of patients in terms of gender and age distribution, but very significant differences were found with spirometric parameters (FVC and FEV₁) and with allergens sensibilization. Patients with FEF_{25–75} < 70% were more frequently positive to perennial sensitizations (*p* < 0.0001).

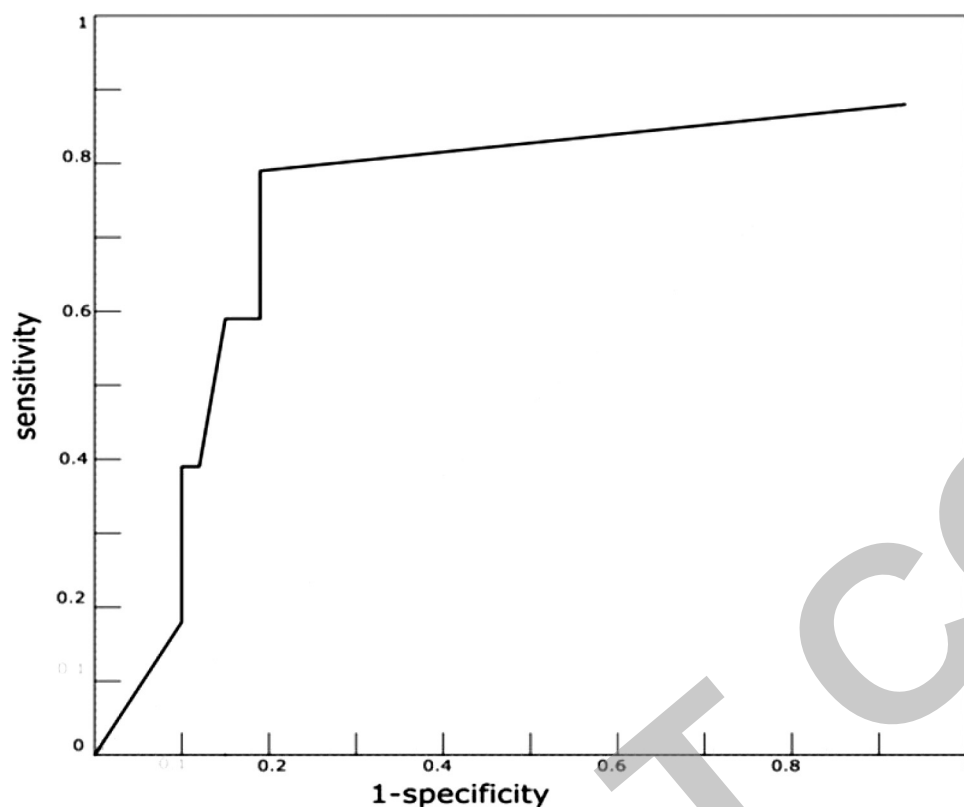


Figure 2. Receiver operating characteristics (ROCs) for forced expiratory volume in 1 second (FEV_1) as a predictor of forced expiratory flow at 25–75% (FEF_{25-75}) <70% of predicted.

Table 4 Best-fitting logistic regression models for independent predictors of the presence of $FEF_{25-75} < 70\%$ of predicted ($n = 850$)

Variables	OR _{Adj} [*]	95% CI	p Value
$FEV_1 \leq 83\%$ of predicted	4.9	(2.1–16.7)	0.0003
Sensitivity to perennial allergens	7.4	(2.2–18.8)	0.0002

Outcome variables: $FEF_{25-75} < 70\%$ of predicted.

^{*}Likelihood Ratio test.

CI = confidence interval; OR_{Adj} = adjusted odds ratio.

Multivariate Logistic Analysis

To evaluate the role of possible predictors for $FEF_{25-75} < 70$, a logistic regression model was performed (Table 4). Two predictors turned out to be significantly associated with $FEF_{25-75} < 70\%$: sensitization to perennial allergens (OR_{Adj} 7.4), and $FEV_1 \leq 83\%$ of predicted (OR_{Adj} 4.9). The model's discriminative ability is very satisfactory (AUC = 0.90).

DISCUSSION

AR and asthma are frequently associated in the same patient. Patients with AR may frequently present with asthma symptoms and/or spirometric impairment. Indeed, impaired spirometric values, mainly FEF_{25-75} , may be detected in some patients with AR and who perceive nasal symptoms alone.⁴ In addition, it has been reported that subjects with mild asthma and normal FEV_1 may have impaired FEF_{25-75} only.¹¹ Moreover, it has been pointed out that the majority of children with asthma will have FEV_1 values that are within the normal range.¹² If one considers the slowly progressive nature of lung function decline in asthma, it is not surprising that even children with severe asthma based on symptoms and health care use will show FEV_1 values in the mild-to-moderate persistent asthma range, according to the National Heart, Lung, and Blood Institute lung function criteria for asthma severity.¹²

This is important for all who care for children with asthma for a number of reasons: first, children with persistent asthma can have normal or nearly normal FEV_1 values (as a result, asthma may be undiagnosed if one solely relies on FEV_1 values when stable to make the diagnosis); second, in clinical research, FEV_1 criteria for inclusion/exclusion into pediatric asthma studies must be adjusted so as to include fully representative populations of children with asthma in efficacy studies.¹³ It has been shown that the value of FEF_{25-75} is useful in predicting airway responsiveness, because it might also be a more sensitive indicator of chronic airflow obstruction than FEV_1 , as well as a risk factor for the persistence of respiratory symptoms in children suffering from allergic asthma. Recently, it has been reported that about one-quarter of a large cohort of adult patients with recent onset of AR had $FEF_{25-75} < 70\%$ of predicted.⁶

Thus, these issues underline the link between upper and lower airways and reinforce the concept that AR may precede overt asthma. In this regard, to investigate a bronchial impairment in AR patients is clinically relevant.

This study confirms these concepts: indeed, 35% of children with AR and referring nasal symptoms alone had impaired FEF_{25-75} values. In other words, data provide evidence in support of bronchial airflow obstruction in the absence of overt bronchial symptoms.

This finding is, however, partially consistent with the previous study⁶ because that cohort included only AR patients with recent onset. In addition, this study may suggest a possible role of allergy to perennial allergens for inducing bronchial airflow obstruction. This finding highlights the role of the minimal persistent inflammation that might allow the development of structural bronchial remodeling. Indeed, continuous exposure to mite allergen induces the persistence of inflammatory phenomena.¹² Therefore, from a clinical point of view, it appears to be beneficial to evaluate in each patient with AR the type of sensitization.

This study provides evidence that also borderline FEV_1 values (e.g., $\leq 83\%$) should be carefully considered because they may be signifi-

cantly associated with overt impaired FEF_{25-75} values (e.g., <70%) of predicted. Therefore, care should be taken when interpreting the results of spirometric tests in adolescents with AR: an FEV_1 < 83% may be associated with impaired midflows, which might represent subclinical bronchial obstruction and patients should be further observed for future occurrence of overt clinical symptoms consistent with asthma.

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