

Bronchodilation test in patients with allergic rhinitis

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Abstract

Background: Allergic rhinitis (AR) may be considered a risk factor for the onset of asthma. Recently, it has been reported that forced expiratory flow between 25% and 75% of vital capacity (FEF₂₅₋₇₅) may predict a positive response to bronchodilation test in asthmatic children. The aim of this study was to evaluate a large group of adult AR patients to investigate the frequency of response to bronchodilation test and FEF₂₅₋₇₅ values.

Methods: One thousand four hundred and sixty-nine consecutive patients suffering from persistent AR were evaluated. Clinical examination, spirometry, and bronchodilation test were performed in all patients.

Results: In this study, 62.9% of patients had reversibility to bronchodilation test and 17.8% had impaired FEF₂₅₋₇₅ values ($\leq 65\%$ of predicted). Impaired FEF₂₅₋₇₅ values associated with longer rhinitis duration may predict reversibility to bronchodilation test (OR = 11.3; $P < 0.001$). In addition, a FEF₂₅₋₇₅ cutoff value $\leq 71\%$ of predicted may already discriminate patients with reversibility.

Conclusions: This study highlights that about two-thirds of patients with persistent AR may be considered at risk of becoming asthmatic. This finding should be adequately considered as a precocious spirometry may allow the early detection of patients prone to develop asthma and consequently to treat them.

Numerous studies have demonstrated a close association between allergic rhinitis (AR) and asthma (1–4). Allergic rhinitis may be also considered a relevant risk factor for both the onset and the worsening of asthma (5).

Asthma is characterized by a reversible airflow obstruction, bronchial inflammation, and hyperreactivity. Asthma diagnosis is based on clinical and functional evaluation. Spirometry is mandatory in patients with asthma, and Global Initiative for Asthma (GINA) guidelines state that the forced expiratory volume/1 s (FEV₁) is the gold standard lung function measurement to evaluate bronchial obstruction (<http://www.ginasthma.com>). Spirometric parameters are well standardized and their interpretation is commonly recognized (6, 7). In addition, reversibility of airflow obstruction is considered a main functional characteristic of asthma. This reversibility may be spontaneous or induced by drugs, such as bronchodilators, mainly β_2 -agonists. The bronchodilation test is prescribed to demonstrate the reversibility of bronchial obstruction, and a positive response allows a sure asthma diagnosis.

However, patients with asthma may often have normal FEV₁ values when they are clinically stable (8). Moreover, small airways are deeply involved in the pathogenesis of

asthma. Even though there is no direct marker for obstruction/inflammation of small airways, it has been proposed that the forced expiratory flow at the 25% and 75% of the pulmonary volume (FEF₂₅₋₇₅) might be a more sensitive parameter to determine a small airways obstruction rather than FEV₁ (9). It has been demonstrated that the value of FEF₂₅₋₇₅ is useful in predicting airway responsiveness, as it may also be a more sensitive indicator of chronic airflow obstruction than FEV₁, as well as a risk factor for the persistence of respiratory symptoms in patients with asthma. Also, it has to be considered that subjects with mild asthma and normal FEV₁ may show impaired FEF₂₅₋₇₅ only (10). In this regard, it has been demonstrated that both FEV₁ and mainly FEF₂₅₋₇₅ may be impaired in patients suffering from AR and perceiving nasal symptoms alone (11). Moreover, the American guidelines on rhinitis report that an impaired FEF₂₅₋₇₅ may be a marker of early bronchial pathology in patients with AR (12).

A very recent study evidenced that FEF₂₅₋₇₅ might predict the presence of reversible airflow obstruction in asthmatic children with normal FEV₁ (13). This study established a cutoff value of 65% of predicted for defining impaired FEF₂₅₋₇₅ values (13).

On the other hand, it has been previously reported that the duration of AR is related to the presence of a positive response to bronchodilation test (14). The presence of reversibility to bronchodilation test might allow to precociously detect patients with AR who could become asthmatic (14).

For this reason, the present study aimed at evaluating a large group of adult patients with persistent AR to investigate the frequency of response to bronchodilation test and FEF_{25–75} values.

Materials and methods

Patients

This cross-sectional study included 1469 patients with age ranging between 18 and 48 years (mean 23.8, SD 3.3, median 24 years), suffering from persistent AR. They were Navy aspirants or soldiers who referred to Navy Medical Service for a mandatory visit to obtain or to maintain health qualification certification. The visit included skin prick test, spirometry, and bronchodilation test, in order to be allowed to maintain the qualification certificate. The visits were performed during the spring immediately before the beginning of courses. The Navy Review Board approved the study procedure, and written informed consent was obtained from each subject. The new rule to exclude asthma diagnosis includes bronchodilation test since the 2007.

Study design and setting

A detailed clinical history was taken, and a complete physical examination was performed. The patients were enrolled in the study on the basis of a diagnosis of AR made by the concordance between positive skin prick test and presence of nasal symptoms after exposure to sensitizing allergen, according to validated criteria (12). Exclusion criteria were the following: any prior documented history of asthma or referred asthma symptoms, including cough, wheezing, dyspnoea, and shortness of breathing, impaired FEV₁ values (such as <80% of the predicted) and <0.75 FEV₁/Forced Vital Capacity (FVC) ratio, presence of acute or chronic upper respiratory infections, anatomical nasal disorders (i.e. nasal polyps, septum deviation, etc.), previous or current smoking (screened by expired-CO assessment: such as analyzing carboxyhemoglobin and carbon monoxide levels in a single breath by Bedfont Micro Smokerlyzer III, Bedfont Scientific Ltd & Decode, England), previous or current specific immunotherapy, and use of nasal or oral corticosteroids, nasal or oral vasoconstrictors, antileukotrienes, and antihistamines during the previous 4 weeks.

Age, gender, duration of rhinitis, FEF_{25–75} and FEV₁ at baseline and after bronchodilation were registered for all patients in the analysis.

Skin prick test

It was performed as stated by the European Academy of Allergy and Clinical Immunology (15). The panel consisted of house dust mites (*Dermatophagoides farinae* and *pteronysinus*),

cat, dog, grasses mix, *Compositae* mix, *Parietaria officinalis*, birch, hazel, olive tree, *Alternaria tenuis*, *Cladosporium*, *Aspergilli* mix (Stallergenes, Milan, Italy).

Spirometry

Spirometry was performed by using a computer-assisted spirometer (Pulmolab 435-spiro 235, Morgan, England – using the predictive values ECCS 1993), with optoelectronic whirl flow meter. It was performed as stated by the European Respiratory Society (6, 7).

Bronchodilation test

Test of bronchodilation was performed according to international guidelines and using a salbutamol metered dose of 400 µg. Reversibility was considered if an increase in at least 12% of FEV₁ from baseline was achieved, according to international guidelines (6, 7).

Statistical analysis

FEF_{25–75} at baseline was categorized as ≤65% (abnormal values) and >65% (normal values) (16). In addition, an increase in at least 12% concerning FEV₁ postbronchodilation with respect to baseline FEV₁ value was considered as positive test of bronchodilation.

Data were described as median and 25th–75th percentiles for age, duration of rhinitis, FEF_{25–75} and FEV₁ pre- and postbronchodilation and as counts and percentages for sex, categorized FEF_{25–75} and FEV₁, and for bronchodilation test. A chi-square test was used to evaluate relation between bronchodilation and FEF_{25–75}.

In addition, a multivariate logistic regression model was used with categorized FEF_{25–75} and duration of rhinitis as covariates and results of bronchodilation test as dependent variable. Age and gender, possible confounders, were added into the model. Subsequently, another logistic model was interpolated with interaction between FEF_{25–75} and duration of rhinitis as covariates. In interaction factor, patients with higher values of duration of rhinitis, defined as values over median, and with abnormal values of FEF_{25–75} were compared to patients with normal values of FEF_{25–75} and lower values of duration of rhinitis.

Finally, a receiver operating characteristic (ROC) curve to test validity of FEF_{25–75} as diagnostic test for bronchodilation was realized with lower values of FEF_{25–75} considered as 'positive' results of test. Area under curve (AUC) and 95% CI were assessed, and optimal cutoff was found. A value of $P < 0.05$ was considered statistically significant. SPSS (version 18.0; SPSS (IBM Corporation); New York, USA) was used for computation.

Results

Overall analysis

In Table 1, general characteristics of evaluated population were reported: 1157 patients (78.8%) were men, duration of

Table 1 Characteristics of evaluated population

Characteristic	Median (25th–75th) or N (%)
Age (years)	24 (22–25)
Gender	
Male	1157 (78.8)
Female	312 (21.2)
Duration of rhinitis (years)	3 (2–7)
Lower duration (years)	2 (2, 3)
Higher duration (years)	7 (5–9)
FEF _{25–75} (% predicted)	71 (66–73)
FEV ₁ (% predicted)	90 (86–95)
FEF _{25–75} post (% predicted)	94 (88–100)
FEV ₁ post (% predicted)	103 (96–106)

FEV₁, forced expiratory volume/1 s.

Table 2 Distribution of distinct outcomes

Outcome	n (%)
Bronchodilation test	
<12% (Negative)	545 (37.1)
≥12% (Positive)	924 (62.9)
FEF _{25–75}	
≤65% (Abnormal)	261 (17.8)
>65% (Normal)	1208 (82.2)

rhinitis was equal or lower than 3 years in 50% of patients, median FEV₁ value was 90.0% of predicted, and FEF_{25–75} was 71.0% of predicted.

Table 2 reported distribution of categorized bronchodilation test and FEF_{25–75}: 924 patients (62.9%) were classified as 'positive' for bronchodilation test, and 261 patients (17.8%) had abnormal FEF_{25–75} values at baseline.

Table 3 represented contingency table for FEF_{25–75} and results of bronchodilation test. Between patients who showed abnormal values of FEF_{25–75}, 91.9% resulted positive at bronchodilation test, and a statistically significant relation between FEF_{25–75} and positive bronchodilation response was revealed ($\chi^2 = 114.8$; $P < 0.001$).

Similar results were obtained from logistic regression (Table 4) controlling for age and gender. In fact, a higher probability of presenting a positive response to bronchodilation test (OR = 6.25; $P < 0.001$) was found in patients with abnormal values of FEF_{25–75} compared with patients with normal FEF_{25–75} values. Also for duration of rhinitis, a higher probability of bronchial reversibility resulted for 1-year increment in rhinitis duration (OR = 1.11; $P < 0.001$).

Interaction between FEF_{25–75} and duration of rhinitis resulted statistically significant: a higher risk to result positive at bronchodilation test in patients with abnormal values of FEF_{25–75} and higher duration of rhinitis (OR = 11.03; $P < 0.001$) if compared with patients with lower duration of rhinitis and normal values of FEF_{25–75} was found.

From ROC curve (Fig. 1), best cutoff of 71.0 of FEF_{25–75} was found: 61% of patients with a positive bronchodilation had a value of FEF_{25–75} under or equal to 71.0 of predicted

Table 3 Joint distribution of FEF_{25–75} and bronchodilation with row percentages

FEF _{25–75}	Bronchodilation		Total	P
	No	Yes		
>65	524 (43.4%)	684 (56.6%)	1208	<0.001
≤65	21 (8.1%)	240 (91.9%)	261	
Total	545	924	1469	

Table 4 Results of multivariate logistic regression for bronchodilation

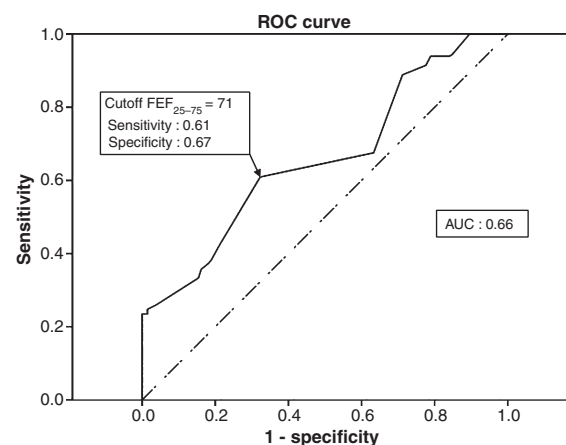
	OR	<i>P</i>	95% CI for OR	
			Lower	Upper
Model 1				
Age (1-year increment)	0.96	0.03	0.93	0.99
Male vs Female	0.89	0.40	0.68	1.17
Duration of rhinitis (1-year increment)	1.11	<0.001	1.06	1.15
FEF _{25–75} (Abnormal vs Normal)	6.25	<0.001	3.87	10.1
Model 2				
Abnormal FEF _{25–75} – Higher duration*	11.03	<0.001	6.58	18.5

*Controlled for age and sex.

(sensitivity), while 67% of patients with a negative bronchodilation had a value of FEF_{25–75} higher than 71.0 (specificity). AUC resulted 0.66 (95% CI: 0.63–0.69).

Discussion

Allergic rhinitis may precede asthma onset, indeed AR may be considered a relevant risk factor for it (17, 18). In this regard, it has been previously demonstrated that patients

**Figure 1** ROC Curve with FEF_{25–75} as diagnostic test and bronchodilation as true outcome.

with AR alone may frequently show impaired FEF_{25-75} values (16), even in patients with recent onset (19): in fact this parameter has been considered an early marker of bronchial impairment in AR (16). Therefore, impaired FEF_{25-75} values might be considered a reliable marker of precocious bronchial involvement in patients with AR as reported also by international guidelines on rhinitis (12).

The duration of AR may be also considered another relevant risk factor for a bronchial involvement: in fact, it has been reported that the duration of AR is associated with positive response to bronchodilation test (14). Particularly, reversibility to bronchodilation test might be a precocious marker of bronchial function deterioration in patients with AR. On the other hand, it has been reported that duration of rhinitis is related to a worsening of nasal function, such as a nasal airflow limitation (20). In this regard, there is a close association between nasal and bronchial airflow (21).

Moreover, a recent study evidenced that reduced FEF_{25-75} values may predict positive bronchodilation test in asthmatic children with normal FEV_1 values (13). In addition, this study defined a cutoff value $<65\%$ of predicted for impaired FEF_{25-75} values (13). Therefore, this cutoff has been used in the present study.

The current study investigated the possible presence of spirometric impairment, such as FEF_{25-75} and response to bronchodilation test in a large cohort of adult patients with persistent AR, perceiving nasal symptoms alone, and with normal FEV_1 values.

First, this study demonstrates that many subjects had impaired bronchial function: more than 60% of them had reversibility to bronchodilation (also with normal FEV_1 values and normal FEV_1/FVC ratio) and about 18% had impaired FEF_{25-75} values. These findings support and confirm the concept that patients with AR may frequently present functional impairment, also without perceiving overt bronchial symptoms.

Secondly, almost all patients with impaired FEF_{25-75} values had reversibility to bronchodilation test. Thus, impaired FEF_{25-75} values might be considered a marker of bronchial reversibility. However, more than half of patients with normal FEF_{25-75} values had reversibility to bronchodilation test. This fact might mean that most of patients with AR have latent bronchial airflow limitation, even though not sufficiently perceived.

Thirdly, two factors associated with the positive response to bronchodilation may be identified: impaired FEF_{25-75} values and duration of rhinitis. Both factors have been previously recognized by other studies (14). In particular, duration of rhinitis appeared to be a relevant risk factor for the development of impaired lung function. This finding might highlight the role of the minimal persistent inflammation that might allow the development of structural bronchial remodel-

ing. Indeed, continuous exposure to allergen induces the persistence of inflammatory phenomena that might consequently suggest the hypothesis of a worsening of respiratory function (22). Therefore, from a clinical point of view, it may be beneficial to consider in each patients with AR the duration of nasal symptoms.

Therefore, this study underlines the concept that AR may frequently precede the asthma onset. In this regard, this study showed that a FEF_{25-75} value $\leq 71\%$ of predicted could already define patients with bronchial reversibility, such as initial airflow limitation. This finding could thus reinforce the value of the FEF_{25-75} cutoff at 65% of predicted for defining the abnormal value. Another important issue is that all patients did not perceive past bronchial symptoms. However, it is well known that also patients with asthma have poor recognition of their symptoms and poor perception of symptoms severity, especially if their asthma is long-standing. Moreover, young people have relevant respiratory reserve, and thus, if there is no exercise-dependent dyspnoea, it is possible that patients do not recognize bronchial airflow limitation as they get used to breath with a bronchial sub-obstruction without perceiving it.

However, this study has some limitations: the subjects studied are not completely representative for the general population, there is a prevalence of male gender, and there is no follow-up of patients. On the other hand, the strength of the study is the large number of evaluated patients. Of course, further studies should be conducted to confirm these theories. Finally, it has to be noted that this cross-sectional study was not evaluating, as an outcome, the development of asthma. Thus, the presence of reversibility and/or abnormal FEF_{25-75} in bronchial asymptomatic patients, having AR, could help to detect candidates for asthma.

In conclusion, this study confirms previous studies and increases the strength of the role of impaired FEF_{25-75} (such as $\leq 65\%$ of predicted) as a marker of early bronchial involvement in patients suffering from persistent AR. From a clinical point of view, it is relevant to consider that about two-thirds of patients may be considered at risk of becoming asthmatic, and this risk might be more evident in patients with the presence of both spirometric impairment and longer rhinitis duration. Therefore, it should be desirable to precociously perform spirometry in patients presenting with persistent AR, mainly if its duration is long, to early treat them in order to prevent asthma onset.

Conflict of interest

All authors contributed to realize the paper. There is no conflict of interest for all of them.

References

1. Bugiani M, Carosso A, Migliore E, Piccioni P, Corsico A, Olivieri M et al. Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. *Allergy* 2005;**60**: 165–170.
2. Asher I. ISAAC International Study of Asthma and Allergies in Childhood. *Pediatr Pulmonol* 2007;**42**:100.
3. Braunstahl GJ, Kleinjan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000;**161**:2051–2057.

4. Braunstahl GJ, Overbeek SE, Fokkens WJ, Kleinjan A, McEuen AR, Walls AF et al. Segmental in allergic rhinitis patients affects mast cell and basophil numbers in nasal and bronchial mucosa. *Am J Respir Crit Care Med* 2001;**164**:858–865.
5. Plaschke PP, Janson C, Norrman E, Björnsson E, Ellbjär S, Järholm B. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. *Am J Respir Crit Care Med* 2000;**162**:920–924.
6. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;**26**:948–968.
7. Miller MR, Hankinson J, Brusasco V, Burgos R, Casaburi R, Coates R et al. Standardisation of spirometry. *Eur Respir J* 2005;**26**:319–338.
8. Bacharier LB, Mauger DT, Lemanske RF, Schend V, Sorkness C, Strunk RC. Classifying asthma severity in children: is measuring lung function helpful? *J Allergy Clin Immunol* 2002;**109**:S266.
9. Bjermer L. Past and future perspectives in the asthma treatment. *Resp Med* 2001;**95**:703–719.
10. Lipworth BJ, Clark DJ. Effects of airway calibre on lung delivery of nebulised salbutamol. *Thorax* 1997;**52**:1016–1021.
11. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca MA, Passalacqua G, Pallestrini E et al. Seasonal and perennial allergic rhinitis: is this classification adherent to real life? A population based study. *Allergy* 2005;**60**:882–887.
12. Wallace DV, Dykewicz MS. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008;**122**:S1–S84.
13. Simon MR, Chinchilli VM, Phillips BR, Sorkness CA, Lemanske RF, Szefer SJ et al. Forced expiratory flow between 25% and 75% of vital capacity and FEV₁/forced vital capacity ratio in relation to clinical and physiological parameters in asthmatic children with normal FEV₁ values. *J Allergy Clin Immunol* 2010;**126**:527–534.
14. Ciprandi G, Cirillo I, Pistorio A, La Grutta S, Tosca MA. Impact of allergic rhinitis on asthma: effects on bronchodilation test. *Ann Allergy Asthma Immunol* 2008;**101**:42–46.
15. Dreborg S (editor). EAACI Subcommittee on Skin Tests. Skin tests used in type I allergy testing. Position Paper. *Allergy* 1989;**44**:S22–S31.
16. Ciprandi G, Cirillo I, Klersy C, Marseglia GL, Vizzaccaro A, Pallestrini E et al. Role of FEF^{25–75} as an early marker of bronchial impairment in patients with seasonal allergic rhinitis. *Am J Rhinol* 2006;**20**:641–647.
17. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002;**109**:419–425.
18. Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J et al. Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet* 2008;**372**:1049–1057.
19. Ciprandi G, Cirillo I, Klersy C. Lower airways are affected also in asymptomatic patients with recent onset of allergic rhinitis. *Laryngoscope* 2010;**120**:1288–1291.
20. Ciprandi G, Cirillo I, Pistorio A. Relationship between rhinitis duration and worsening of nasal function. *Otolaryngology–Head and Neck Surgery* 2008;**138**:725–729.
21. Ciprandi G, Cirillo I. The lower airway pathology of Rhinitis. Update review. *J Allergy Clin Immunol* 2006;**118**:1105–1109.
22. Ciprandi G, Buscaglia S, Pesce GP, Pronzato C, Ricca V, Bagnasco M et al. Minimal persistent inflammation is present at mucosal level in asymptomatic rhinitic patients with allergy due to mites. *J Allergy Clin Immunol* 1995;**96**:971–978.