

Spirometric abnormalities in patients with allergic rhinitis: Indicator of an “asthma march”?

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ABSTRACT

Background: Allergic rhinitis (AR) may precede and promote the onset of asthma. However, few studies addressed this issue mainly concerning bronchial physiological parameters. The aim of this study was to assess forced expiratory flow at 25–75% (FEF_{25–75}), forced expiratory volume at 1 second (FEV₁), and response to bronchodilation test in a large group of AR patients.

Methods: Sixteen hundred five adult AR patients were evaluated. Clinical examination, assessment of nasal obstruction perception by visual analog scale, spirometry, and bronchodilation test were performed in all patients.

Results: There were 8.4% of patients with abnormal FEV₁ values, 24.7% had impaired FEF_{25–75}, and 66.1% had reversibility with bronchodilation. A trend of spirometric impairment seems to exist in these patients. Age, gender, and duration of rhinitis may be risk factors for these findings. Different grades of bronchial impairment seem to exist.

Conclusion: This study highlights the close link between upper and lower airways and suggests the possible existence of a progression from AR toward asthma, such as an “asthma march.” Therefore, asthma should be suspected and carefully investigated in AR patients.

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Allergic rhinitis (AR) is a common disorder sustained by an IgE-dependent inflammation.¹ There is evidence of a close link between AR and asthma.^{2–5} AR frequently precedes asthma.⁶

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 asthmatic patients and Global Initiative for Asthma guidelines propose the forced expiratory volume/1 second (FEV₁) as the gold standard lung function measurement to evaluate bronchial obstruction (www.ginasthma.com). Spirometric parameters have been recently well standardized and their interpretation is commonly recognized.^{7,8} In addition, reversibility of airflow obstruction is considered a main physiological characteristic of asthma. This reversibility may be spontaneous or induced by drugs, such as bronchodilators. The bronchodilation test is usually prescribed to show the reversibility of bronchial obstruction and so its positivity allows a sure asthma diagnosis.

On the other hand, there is evidence that FEV₁ values may be frequently normal in stable asthmatic patients.⁹ Nevertheless, the forced expiratory flow at 25 and 75% (FEF_{25–75}) of the pulmonary volume might be a more sensitive parameter to detect slight airways obstruction rather than FEV₁.¹⁰ In fact, it has been reported that subjects with mild asthma and normal FEV₁ may show impaired FEF_{25–75} only.¹¹ In addition, it has been shown that FEF_{25–75} may be frequently impaired in patients suffering from AR and perceiving nasal symptoms alone.¹² Therefore, AR may be considered as the first step of a possible progression of AR toward asthma. Indeed, in the revised version of the World Health Organization document on “Allergic Rhinitis and Its Impact on Asthma,” it is clearly emphasized that the role of AR is a risk factor for development and/or worsening of asthma.¹³ Moreover, the last American guidelines on rhinitis reported that a reduced FEF_{25–75} value may be a marker of early bronchial pathology in patients with AR.¹⁴ Moreover, a new concept has been recently emphasized: the duration of AR is *per se* a risk factor for inducing spirometric impairment,¹⁵ bronchial hyperreactivity,¹⁶ and positive response to bronchodilation test.¹⁷ On the other hand, it

has been recently reported that an initial bronchial airflow limitation may be even documented in patients with recent onset of AR.¹⁸

However, the possible definition of a progression from AR to asthma has not been deeply investigated from a functional point of view. For this reason, the present study aimed at identifying possible spirometric steps of the progression from rhinitis to asthma in a large group of patients with AR.

MATERIALS AND METHODS

Patients

This cross-sectional study included 1603 patients, aged between 18 and 49 years (mean, 24.5 years; SD, 5.6 year; median, 24 years), suffering from AR. They were Navy aspirants or military personnel who referred to the Navy Medical Service for a fitness visit, including skin-prick test, visual analog scale (VAS) assessment of nasal obstruction, spirometry, and bronchodilation test, to obtain the qualification certificate. The visits were performed during the spring before summer courses. The Navy Review Board approved the study procedures and written informed consent was obtained from each subject.

Study Design and Setting

A detailed clinical history was taken and a complete physical examination was performed. The patients were enrolled in the study based on 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.¹³ Exclusion criteria were any prior documented history of asthma or presence of asthma symptoms including cough, wheezing, breathlessness, and chest tightness; impaired FEV₁ values (such as <80% of the predicted) and <0.75 FEV₁/FVC ratio; presence of acute or chronic upper respiratory infections; anatomic nasal disorders (*i.e.*, nasal polyps, septum deviation, *etc.*); previous or current smoking (screened by expired-CO assessment); previous or current specific immunotherapy; and use of nasal or oral corticosteroids, nasal or oral vasoconstrictors, antileukotriene, and antihistamines during the previous 4 weeks. All patients assumed second-generation antihistamines only on demand for controlling nasal symptoms. It should be noted that all subjects included in this study never referred symptoms of lower airway disease or asthma. In fact, the military service does not accept subjects who have asthma or other known lung diseases.

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

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analysis. FEF₂₅₋₇₅ at baseline was categorized as ≤65% (abnormal values) and >65% (normal values)¹⁸; FEV₁ was categorized as <80% (abnormal values) and ≥80% (normal values).

Skin-Prick Test

Skin-prick test was performed as stated by the European Academy of Allergy and Clinical Immunology.¹⁹ The panel consisted of: house-dust mites (*Dermatophagoides farinae* and *D. pteronyssinus*), cat, dog, grasses mix, *Compositae* mix, *Parietaria officinalis*, birch, hazel, olive tree, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix (Stallergenes, Milan, Italy).

VAS Assessment. VAS was used to assess the subjective feeling of respiration; it ranges from 0 (complete nose obstruction) to 10 cm (nose completely patent). Patients were asked to position a cross on a line corresponding to their own perception of respiration as previously reported.²⁰

Spirometry

Spirometry was performed by using a computer-assisted spirometer (Pulmolab 435-spiro; Morgan Scientific, Haverhill, MA) with optoelectronic whirl flowmeter. It was performed as stated by the European Respiratory Society, using the predictive values ECCS (European Community Coal Steel) 1993.^{7,8}

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 of at least 12% of FEV₁ from baseline was achieved, according to international guidelines.^{8,9}

Subgroups

Subsequently, based on values of FEF₂₅₋₇₅ and FEV₁ and response to the bronchodilation test, patients were classified in five distinct classes representing different spirometric impairment: (i) patients with normal values for FEF₂₅₋₇₅ and FEV₁ and with negative results of bronchodilation test (first class), (ii) patients with only positive reversibility to bronchodilation test (second class), (iii) patients with abnormal values of FEF₂₅₋₇₅ alone (third class), (iv) patients with abnormal values of FEF₂₅₋₇₅ and positive response to bronchodilation but normal values for FEV₁ (fourth class), and (v) patients with abnormal values of FEF₂₅₋₇₅ and FEV₁ and positive response to bronchodilation test (fifth class).

Statistical Analysis

Data were described as median and 25th–75th percentiles for the following variables: age, duration of rhinitis, VAS, pre- and postbronchodilation change for FEF₂₅₋₇₅ and FEV₁, whereas data were expressed as counts and percentages for the following variables: sex, categorized FEF₂₅₋₇₅ and FEV₁, and bronchodilation response. Pre- and postbronchodilation change of FEV₁ and FEF₂₅₋₇₅ was defined as percentage of increment (or decrement) in comparison to baseline value.

Multinomial logistic regression model was interpolated to evaluate effect of VAS and duration of rhinitis on the risk to be classified in a determined class in comparison with the first class, used as reference class. Age and sex were considered as possible confounders and were added to the model. A value of $p < 0.05$ was considered statistically significant. SPSS was used for computation (SPSS, Inc., Chicago, IL).

RESULTS

Table 1 reports the general characteristics of the evaluated population: the median rhinitis duration was 4 years, the median FEF₂₅₋₇₅ value was 71% of predicted, the median FEV₁ value was 90% of

Table 1 Characteristics of evaluated population

Characteristic	Median (25th - 75th) or n (%)
Age (yr)	24 (22–25)
Gender	
Male	1285 (80.2)
Female	318 (19.8)
Duration of rhinitis (yr)	4 (2–8)
VAS	4.2 (3.3–6.7)
FEF ₂₅₋₇₅	71 (66–73)
FEV ₁	90 (83–9)
Positive bronchodilation	1058 (66)

FEF₂₅₋₇₅ = forced expiratory flow at 25–75%; FEV₁ = forced expiratory volume at 1 s; VAS = visual analog scale.

predicted, and 66% of patients had positive bronchodilation test results. Table 2 shows the characteristics of patients subdivided in five classes with different spirometric impairment. The most relevant result was represented by a decreasing trend of median values for FEF₂₅₋₇₅ and FEV₁ prei (Figs. 1 and 2) and postbronchodilation with the increasing severity of spirometric impairment. In particular, 24.7% of patients had abnormal FEF₂₅₋₇₅ values, 8.4% of patients had abnormal FEV₁ values, and 66.1% of patients had reversibility to bronchodilation test. Into fifth class median for baseline FEF₂₅₋₇₅ values were progressively decreasing from the first class to the fifth class (Table 2).

Table 3 reports the results of multinomial logistic regression. A statistically significant increased risk of falling into classes with increased severity of spirometric impairment versus reference category resulted from a 1-year increase in duration of rhinitis (OR ranged from 1.10 in second class to 1.97 in last class; $p < 0.001$). Regarding VAS, a statistically significant increased risk of falling into fourth (OR = 1.44; $p < 0.001$) or fifth class (OR = 1.15; $p = 0.013$) with increased severity of spirometric impairment versus reference category resulted from a 1-unit decrease on VAS scale.

DISCUSSION

AR may precede asthma; indeed, AR may be considered a relevant risk factor for asthma onset.²¹ In this regard, it has been previously shown that patients with AR alone may frequently show impaired FEF₂₅₋₇₅ values²² as well as in patients with recent onset.¹⁸ The duration of AR may be considered another relevant risk factor for bronchial involvement; in fact, it has been reported that the duration of AR is associated with impaired spirometry,¹⁵ bronchial hyperreactivity,¹⁶ and positive response to bronchodilation test.¹⁷

However, there are some studies and reviews that evaluated the progression from rhinitis to asthma,^{23–31} but there is lack (to our knowledge) of studies that have evaluated the possible progression of rhinitis toward asthma from a functional point of view. The present study investigated the possible presence of spirometric impairment, such as FEF₂₅₋₇₅ and FEV₁, and response to bronchodilation test in a large cohort of patients with AR. Moreover, some recent studies proposed FEF₂₅₋₇₅ of <65% of predicted as the cutoff for defining the abnormal value.^{32–34}

This study was designed to show the possible presence of a progression of spirometric impairment and to recognize possible risk factors. First, this study indicated that many subjects had impaired bronchial function: ~25% of patients had impaired FEF₂₅₋₇₅ values, ~8% had impaired FEV₁ values, and >60% of patients had reversibility with bronchodilation (also with normal FEV₁ values). These findings confirm that patients with AR may often present functional impairment, also without perceiving overt bronchial symptoms.

Second, some risk factors for these abnormal values may be identified: male gender, age, perception of nasal obstruction, and dura-

Table 2 Characteristics of patients in different spirometric impairment

Characteristic	Median (25th–75th) or <i>n</i> (%)				
	FEF _{25–75} >65%; FEV ₁ >80%; Bronchodilation <12%	FEF _{25–75} >65%; FEV ₁ >80%; Bronchodilation >12%	FEF _{25–75} ≤65%; FEV ₁ >80%; Bronchodilation <12%	FEF _{25–75} <65%; FEV ₁ >80%; Bronchodilation >12%	FEF _{25–75} <65%; FEV ₁ <80%; Bronchodilation >12%
No.	524 (32.7)	684 (42.7)	21 (1.3)	240 (15)	134 (8.4)
Age (yr)	24 (22–25)	23 (22–25)	26 (23–26)	24 (24–24)	25 (20–49)
Gender					
Male	419 (80)	525 (76.8)	12 (57.1)	201 (83.8)	128 (95.5)
Female	105 (20)	159 (23.2)	9 (42.9)	39 (16.3)	6 (4.5)
Duration of rhinitis (yr)	3 (2–4)	3 (2–5)	8 (4–8)	9 (7–9)	10 (10–11)
VAS	5 (3.3–6.7)	5.8 (4.2–6.7)	4.2 (3.3–4.2)	3.3 (3.3–3.3)	3.3 (2.5–4.2)
FEF _{25–75}	72 (71–74)	72 (71–73)	65 (60–65)	57 (57–57)	46 (45–46)
FEV ₁	95 (91–98)	90 (89–92)	80 (80–92)	83 (83–83)	66 (64–68)
FEF _{25–75} post	95 (90–97)	99 (94–103)	71 (71–83)	80 (78–88)	74 (68–78)
FEV ₁ post	102 (97–105)	104 (102–106)	88 (88–103)	93 (93–95)	78 (78–87)
Pre-post FEF _{25–75} (%)	30.6 (25.8–33.8)	39.4 (30.9–44)	9.2 (9.2–38.3)	36.8 (36.8–54.4)	65.2 (54.4–69.6)
Pre-post FEV ₁ (%)	7.3 (5.1–11)	15.7 (13.7–16.9)	10 (10–12)	13.4 (12.1–14.5)	20.3 (18.2–29)

FEF_{25–75} = forced expiratory flow at 25–75%; FEV₁ = forced expiratory volume at 1 s; VAS = visual analog scale.

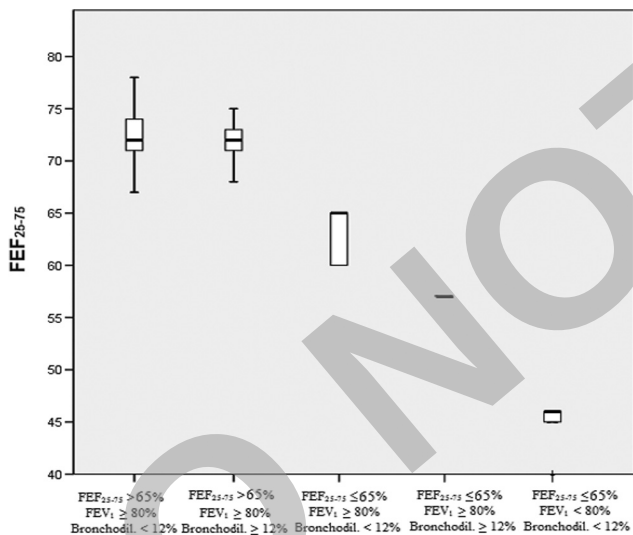


Figure 1. Box plot for baseline forced expiratory flow at 25–75% (FEF_{25–75}) values for each class of spirometric impairment.

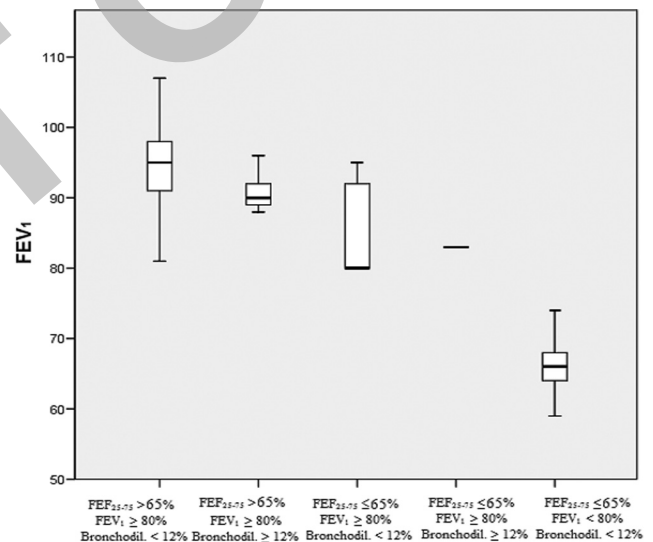


Figure 2. Box plot for baseline forced expiratory volume at 1 second (FEV₁) values for each class of spirometric impairment.

tion of rhinitis. All of them have been previously recognized by other studies.^{16,18,22} In particular, duration of rhinitis appeared to be an interesting risk factor for development of impaired lung function. This finding might highlight the role of minimal persistent inflammation that might allow the development of structural bronchial remodeling. Indeed, continuous exposure to allergens induces the persistence of inflammatory phenomena that might consequently suggest the hypothesis of a worsening of respiratory function.²⁴ Therefore, from a clinical point of view it appears beneficial to consider the duration of nasal symptoms in each patient. Another risk factor is nasal obstruction; it is quite obvious that this symptom corresponds to an impaired nasal function, such as filtering and conditioning the inspired air.

Third, a possible progression of spirometric impairment might be considered analyzing the results. Five possible classes of impaired spirometry could be identified, considering each parameter. In particular, we might hypothesize a possible correspondence between functional classes and clinical prognostic outcomes. In

other words, the first class (such as all parameters are normal) might identify patients with pure AR without bronchial involvement. The second class (such as patients with positive bronchodilation test) might characterize patients who are potentially candidates to become asthmatic. The third class (such as patients with only impaired FEF_{25–75} values) might define patients with initial broncho-obstruction. The fourth class (such as patients with impaired FEF_{25–75} values and positive response to bronchodilation) might single out patients with “preasthma.” Finally, the fifth class (such as patients with all parameters that are abnormal) defines asthmatic patients. In addition, there seems to exist a progression of the previously considered risk factors concerning the different classes. Therefore, this study underlines the concept that AR frequently precedes the asthma onset in a gradual way. Therefore, we could interpret this phenomenon as an “asthmatic march,” such as a progression of the allergic inflammation from nose to bronchi.

Table 3 Results of multinomial logistic regression

Classes	Characteristics	OR	p	95% CI of OR	
				Lower	Upper
FEF ₂₅₋₇₅ >65%	Age (yr)	0.97	0.038	0.95	0.99
FEV ₁ >80%	Duration of rhinitis	1.10	<0.001	1.06	1.15
Bronchodilation >12%	VAS	0.94	0.057	0.97	1.00
	Male vs female	0.75	0.045	0.56	0.99
FEF ₂₅₋₇₅ ≤65%	Age (yr)	1.01	0.89	0.91	1.12
FEV ₁ >80%	Duration of rhinitis	1.45	<0.001	1.27	1.65
Bronchodilation <12%	VAS	1.18	0.10	0.96	1.35
	Male vs female	0.27	.005	0.11	0.67
FEF ₂₅₋₇₅ <65%	Age (yr)	0.98	0.30	0.93	1.02
FEV ₁ >80%	Duration of rhinitis	1.63	<0.001	1.53	1.73
Bronchodilation >12%	VAS	1.44	<0.001	1.37	1.50
	Male vs female	1.00	0.99	0.62	1.61
FEF ₂₅₋₇₅ <65%	Age (yr)	1.13	<0.001	1.08	1.17
FEV ₁ <80%	Duration of rhinitis	1.97	<0.001	1.78	2.18
Bronchodilation >12%	VAS	1.15	0.013	1.03	1.25
	Male vs female	2.61	0.044	1.03	6.63

Reference class: FEF₂₅₋₇₅ of >65%; FEV₁ of >80%; Bronchodilation of <12%.

FEF₂₅₋₇₅ = forced expiratory flow at 25–75%; FEV₁ = forced expiratory volume at 1 s; VAS = visual analog scale.

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 additional studies should be conducted to confirm these theories. In conclusion, this study confirms previous studies and increases the strength of the role of FEF₂₅₋₇₅ as a marker of early bronchial involvement in patients suffering from AR.

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