

Impact of allergic rhinitis on bronchi: An 8-year follow-up study

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ABSTRACT

Background: Allergic rhinitis is considered a strong risk factor for the onset of asthma. However, few studies addressed this issue from a functional point of view. The aim of this study was to follow up a group of patients with allergic rhinitis to investigate the onset of possible spirometric abnormalities and/or bronchial hyperreactivity (BHR).

Methods: Eighty-nine patients with moderate-severe persistent allergic rhinitis were prospectively and consecutively evaluated; 940 controls were also included in the study. Clinical examination, skin-prick test, spirometry, and methacholine challenge were performed in all patients every 2 years for 8 years.

Results: The number of patients with forced expiratory flow at 25 and 75% of pulmonary volume of <70% of predicted significantly increased during the observation time. At baseline, no subjects had BHR; whereas 34 patients had BHR after 8 years. Sensitization to mites, birch, and *Parietaria* as well as rhinitis duration are risk factors for these changes.

Conclusion: This study highlights the close link between upper and lower airways and suggests that spirometry should be performed in patients with allergic rhinitis.

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Allergic rhinitis is characterized by an IgE-mediated inflammatory response of the nose to allergen exposure.¹ Numerous studies have shown a close association between allergic rhinitis and asthma.^{2–5} Allergic rhinitis may be a risk factor for the onset of asthma.^{6–8}

Asthma is characterized by a reversible airflow obstruction. The gold standard to evaluate bronchial obstruction is forced expiratory volume/1 second (FEV₁).^{9,10} Small airways are deeply involved in the pathogenesis of asthma.¹¹ Although 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 (FEF_{25–75}) might be a more sensitive parameter to determine a small airways obstruction rather than FEV₁.^{12,13} It has been shown that the value of FEF_{25–75} is useful in predicting airway responsiveness, because 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 children suffering from allergic asthma. Also, it has to be considered that subjects with mild asthma and normal FEV₁ may show impaired FEF_{25–75} only.^{14,15}

In these regards, it has been shown that FEV₁ and mainly FEF_{25–75} may be impaired in patients suffering from allergic rhinitis with nasal symptoms alone.¹⁶ Therefore, allergic rhinitis may be considered as the first step of a progression of respiratory allergy toward asthma. Indeed, in the newest published version of the World Health Organization document, "Allergic Rhinitis and Its Impact on Asthma," the role of allergic rhinitis as a risk factor for asthma development is clearly emphasized.¹⁷ More recently, the new American guidelines on rhinitis reported that a reduced FEF_{25–75} (i.e., <70% of predicted) may be a marker of early bronchial pathology in patients with allergic rhinitis.¹⁸ In addition, a new concept has been recently established: the duration of allergic rhinitis is *per se* a risk factor for inducing spirometric impairment,¹⁹ bronchial hyperreactivity (BHR),²⁰ and positive response to a bronchodilation test.²¹ However, these studies were conducted considering the patients in retrospective manner. Therefore, we have conducted an 8-year follow-up in a cohort of patients with allergic rhinitis to investigate the possible occurrences

of spirometric abnormalities and/or BHR, also considering the possible risk factors.

MATERIALS AND METHODS

Study Design and Setting

This prospective longitudinal study included a group of patients with allergic rhinitis only. They were Navy military personnel (all of them combat divers) who were referred to the Navy Medical Service for a periodic fitness visit, including skin-prick test, spirometry, and methacholine bronchial challenge, to be allowed to maintain the qualification certificate. The visits were performed during the spring every 2 years. The Navy Review Board approved the study procedures and written informed consent was obtained from each subject.

Subjects

Eighty-nine patients (76 men) aged between 18 and 30 years (median, 24 years) affected by allergic rhinitis alone were consecutively evaluated and followed up for 8 years; 940 combat divers (857 men; median age, 25.1 years) without allergic rhinitis were included as control group in the study and underwent the same procedures at the same times. Clinical characteristics of allergic patients are reported in Table 1.

A detailed clinical history was taken and a complete physical examination was performed. The patients were included in the study based on a clinical history of allergic rhinitis and presence of nasal symptoms, according to validated criteria.¹⁷ Exclusion criteria were any history of asthma or presence of asthma symptoms including cough, wheezing, dyspnea, and shortness of breathing; acute or chronic upper respiratory infections; anatomic nasal disorders (i.e., nasal polyps, septum deviation, etc.); previous or current specific immunotherapy; and use of nasal or oral corticosteroids, nasal or oral vasoconstrictors, antileukotrienes, and/or 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 had symptoms of lower airway disease or asthma. The military service does not accept subjects who have asthma or other known lung diseases.

Skin-prick test was performed as stated by the European Academy of Allergy and Clinical Immunology.²² The panel consisted of house-dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cat, dog, grasses mix, *Compositae* mix, *Parietaria officinalis*, birch,

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Table 1 Characteristics of the evaluated population

Characteristic	Median (25th–75th) or n (%)
Age at baseline (yr)	24 (22–25)
Gender	
Male	76 (85.4)
Female	13 (14.6)
Smoking	
No	84 (94.4)
Yes	5 (5.6)
Duration of rhinitis at baseline (yr)	4 (2–8)
Sensitizations	
Only mites	8 (9)
Mites + birch	18 (20.2)
Birch + molds + <i>Parietaria</i>	13 (14.6)
Mites + birch + <i>Parietaria</i>	16 (18)
Mites + <i>Parietaria</i> + grass	11 (12.4)
Grass	9 (10.1)
Others (pets)	14 (15.7)

hazel, olive tree, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix (Stallergenes, Milan, Italy).

Spirometry

Spirometry was performed by using a computer-assisted spirometer (Pulmolab 435-spiro 235; Pulmolab, Morgan, England), with optoelectronic whirl flowmeter. It was performed as stated by the European Respiratory Society.^{9,10} FEF_{25–75} was considered impaired if <70% of predicted.²⁰

Methacholine Bronchial Challenge

Methacholine bronchial challenge was performed to evaluate BHR only if basal FEV₁ was ≥80% of predicted. Aerosol was delivered using a dosimetric computerized supply (MEFAR MB3; Marcos, Italy). The test was performed following the American Thoracic Society guidelines for methacholine challenge.²³ The threshold dose causing a 20% fall of FEV₁ (PC₂₀) was calculated.

Degree of BHR

Three categories of BHR were considered based on PC₂₀: severe PC₂₀ <1 mg/mL; mild PC₂₀ between 1 and 4 mg/mL; borderline PC₂₀, ranging from 4 to 16 mg/mL, according with the criteria of the American Thoracic Society guidelines for methacholine challenge.²³ Subjects responding to the cumulative dose of 16 mg/mL were considered having normal bronchial responsiveness.

Statistical Analysis

Development of FEF_{25–75} values <70% of predicted and PC₂₀ under 16 mg/mL were considered as distinct outcomes. Categorization for FEF (≤70) and BHR (<1; 1–4; >4 to <16 mg/mL) was realized. Data were described as median and 25th–75th percentiles for age and as counts and percentages for all other categorical variables. Initially, to determine the relationship between development of FEF <70% and BHR <16 mg/mL, for both classic and repeated measures, univariate logistic regression models were used to assess the connection between outcomes and age, sex, smoking habit, length of rhinitis, and sensitization. In classic logistic model, age and length of rhinitis were considered at baseline. A repeated measures one-way ANOVA was used to evaluate trend of FEF and BHR with respect to the visits. Finally, a random-effects regression model for longitudinal data (xtreg with Stata) was interpolate to assess relation between FEF and BHR with age and length of rhinitis at each visit, sex, smoke and sensitization added to the model. The association between FEF

and BHR was assessed also by means of Pearson's *r* coefficient, also measuring the 95% CI. The association between length of rhinitis and FEF and BHR was evaluated using the chi-square test. A value of *p* < 0.05 was considered statistically significant. Stata 10 (StataCorp, College Station, TX) was used for computation.

RESULTS

Baseline Characteristics

Table 1 reports the demographic characteristics at baseline. The majority of patients were nonsmokers (94.4%), and median duration of rhinitis at baseline from beginning was 4 years. In addition, 20.2% of patients were allergic to mites and birch; 18% were allergic to mites, birch, and *Parietaria*; 14.6% were allergic to birch, molds, and *Parietaria*; 12.4% were allergic to mites, *Parietaria*, and grass; 10.1% were allergic to grass; and 9% were allergic only to mites. Finally, 57 patients (64%) developed an FEF_{25–75} value <70% and 39 patients (43.8%) developed a PC₂₀ value <15.9 mg/mL in at least one visit.

FEF_{25–75} and BHR

Table 2 shows the distribution of FEF_{25–75} into two levels (< or ≥70% of predicted) and BHR into four levels (severe, mild, borderline, and negative) with respective years. Median of FEF_{25–75} decreased over time. The number of patients with impaired FEF_{25–75} value (<70% of predicted) increased from 27% at baseline to 54% after 8 years of follow-up. Regarding BHR, only after 8 years 3.6% of patients had a PC₂₀ of <1 (severe), while 9.5% of patients had a PC₂₀ value between 1 and 4 mg/mL (mild), and 27.4% had borderline BHR. Both FEF_{25–75} values and BHR severity were in relation with year (chi-square FEF = 22.7; *p* < 0.001; chi-square BHR = 122.04; *p* < 0.001). Trend of FEF_{25–75} for each subsequent visit was reported in Fig. 1 and changes of FEF_{25–75} were pointed out since the second visit. Trend with respect to year of visits was statistically significant both for FEF_{25–75} and BHR (*p* < 0.001). In particular, fourth visit versus third visit and fifth visit versus fourth visit for FEF_{25–75} and BHR were statistically significant. Correlation between FEF_{25–75} values and BHR severity were statistically significant (*r* = 0.30 with *p* < 0.001; results not reported). FEV₁ values remained normal in all subjects (>80% of predicted) through the study time. No control subject developed spirometric impairment or BHR.

Risk Factors

The first step was to assess association between risk factors of patients and development of FEF_{25–75} < 70% and BHR < 16 (Table 3). Results of classic logistic model were reported in the left columns and in the right columns mixed-effects logistic model results were reported. Gender (male subject versus female subject) and smoking were not statistically significant with respect to development of both impaired FEF_{25–75} and BHR, considered separately.

In the classic logistic model, duration of rhinitis at baseline was statistically significant with an increased risk to develop impaired FEF_{25–75} (<70% of predicted) of 55% (odds ratio [OR] = 1.55; 95% CI, 1.23–1.94; *p* < 0.001) and of 18% to develop BHR (OR = 1.18; 95% CI, 1.02–1.37; *p* = 0.03) for each year increment in rhinitis duration onset at baseline. In logistic model for repeated measures, duration of rhinitis at each visit was statistically significant with an increased risk for each patient to develop impaired FEF_{25–75} of about twofold (OR = 2.04; 95% CI, 1.56–2.67; *p* < 0.001) and an increased risk for each patient to develop BHR of about four- and one-half-fold (OR = 4.52; 95% CI, 1.68–12.2; *p* = 0.003) for 1-year increment in duration of rhinitis.

Age at baseline was assessed in classic logistic regression and was not statistically significant; however, when all visits were considered, age was statistically significant. For every 1-year increment in age, there was an increased risk for each patient to develop FEF_{25–75} of 55%

Table 2 Distribution of FEF₂₅₋₇₅ and bronchial hyperreactivity (BHR) with respect to year in subjects

Characteristic	2000	2002	2004	2006	2008	p Value
FEF ₂₅₋₇₅						<0.001
<70 (%)	24 (27)	28 (31.5)	42 (47.2)	47 (52.8)	48 (53.9)	
≥70 (%)	65 (73)	61 (68.5)	47 (52.8)	42 (47.2)	41 (46.1)	
Median (25th–75th)	72 (66–73)	70 (68–75)	70 (62–75)	69 (62–74)	68 (63–74)	
BHR (PC ₂₀)						<0.001
<1 (severe)	0	0	0	0	3 (3.6)	
1–4 (mild)	0	0	0	5 (5.6)	8 (9.5)	
4.01–15.90 (borderline)	0	0	0	5 (5.6)	23 (27.4)	
>15.90 (negative)	89 (100)	89 (100)	89 (100)	79 (88.8)	50 (59.5)	

Percentiles are equal to median.

FEF₂₅₋₇₅ = forced expiratory flow at 25 and 75% of pulmonary volume.

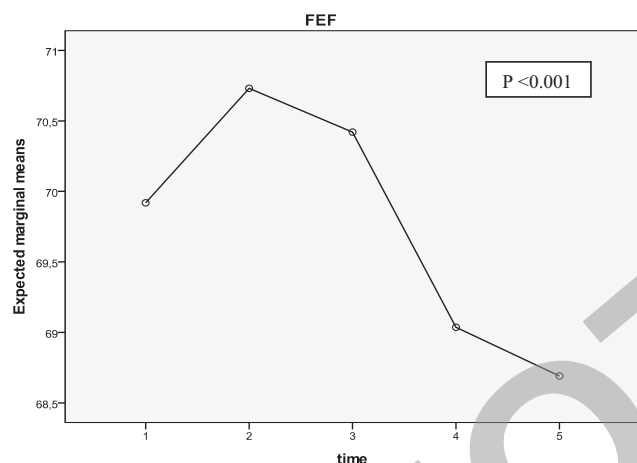


Figure 1. Trend over time for FEF₂₅₋₇₅ in subjects with allergic rhinitis and followed up for 8 years.

(OR = 1.55; 95% CI, 1.34–1.79; $p < 0.001$) and an increased risk for each patient of ~11-fold (OR = 11.2; $p < 0.001$) to develop BHR.

Sensitization patients with an allergy to only mites had more than two- and one-half-fold increased risk (OR = 2.61; 95% CI, 1–6.8; $p = 0.05$) to develop impaired FEF₂₅₋₇₅ and about threefold increased risk to develop BHR (OR = 3.13; 95% CI, 1.14–8.62; $p = 0.03$). Allergy to mites was a statistically significant risk factor for the development of impaired FEF₂₅₋₇₅ in the subject-specific model, whereas no significant increased risk was revealed for the development of BHR. Patients with allergy only to birch had a greater than threefold risk to develop impaired FEF₂₅₋₇₅ (OR = 3.54; 95% CI, 1.36–9.18; $p = 0.009$) and almost a threefold risk to develop BHR (OR = 2.71; 95% CI, 1.10–6.67; $p = 0.03$). Allergy to birch was also a statistically significant risk in the subject-specific model. All patients ($n = 16$) with an allergy to mites, birch, and *Parietaria* developed an FEF₂₅₋₇₅ value of <70% and they had a high risk to develop BHR; in the subject-specific model ORs were large and statistically significant. Most of the patients with this type of allergy developed FEF₂₅₋₇₅ values of <70% from the time of the first visit. Also, patients allergic to mites and *Parietaria* had an approximately four times higher risk factor to develop FEF₂₅₋₇₅ <70% and to develop PC₂₀ < 16 mg/mL, while in the other model they were statistically significant only to develop impaired FEF₂₅₋₇₅.

DISCUSSION

Allergic rhinitis and asthma are frequently associated; and allergic rhinitis may precede asthma onset. Indeed, allergic rhinitis has been considered a risk factor for the development of asthma.^{3,24–26} In this regard, it has been previously indicated that patients with allergic

rhinitis alone may frequently show impaired lung function by spirometry, such as FEF₂₅₋₇₅ values <70% of predicted.²⁷ The duration of allergic rhinitis may be considered a relevant risk factor for a bronchial involvement; in fact, it has been reported that the duration of allergic rhinitis is associated with impaired spirometry,¹⁹ BHR,²⁰ and positive response to bronchodilation test.²¹ Although the progression from rhinitis to asthma has been longitudinally studied,^{3,28,29} no studies have also longitudinally assessed BHR.

The present study prospectively investigated the possible presence of spirometric impairment and/or BHR in a cohort of patients with allergic rhinitis. The purpose was to show the relevance of bronchial impairment and to recognize possible risk factors. We assumed that a value of FEF₂₅₋₇₅ < 70% of predicted constitutes the proof of bronchial impairment, as previously validated.¹⁹ Moreover, we chose a study model composed by subjects well trained and followed because of their profession as military personnel.

First, this study demonstrated that a quarter of subjects with allergic rhinitis had impaired bronchial function at baseline, as marked by FEF₂₅₋₇₅ less than 70% of predicted; however no subjects at baseline manifested BHR. Secondly, the percentage of subjects with impaired FEF₂₅₋₇₅ significantly increased over the time, and BHR developed in some patients.

More interestingly, this study provides evidence of some risk factors for development of impaired FEF and BHR: allergy to mites, birch, *Parietaria*, and trees as well as duration of rhinitis. These findings highlight the role of minimal persistent inflammation, which contributes to the development of structural bronchial remodeling. Indeed, continuous exposure to mite allergen induces the persistence of inflammatory phenomena that induce a worsening of respiratory function.³⁰ Another possible mechanism to explain dust-mite allergy acting as a risk factor may be allergenic proteolytic enzymes that degrade tight junctions, as reported by a study that showed that peptidase allergens from house-dust mites compromise epithelial barrier function by degrading the extracellular domains of the tight junction proteins, such as occludin and claudin, thus facilitating allergen delivery across epithelial layers, which is an event considered to have a role in disrupting tight junctions.³¹ Other work has indicated bronchial responsiveness to be increased in patients sensitized to cat, *D. pteronyssinus*, timothy grass, and *Cladosporium*, but decreased in subjects also positive to birch; thus, it is important to take into account that the exposure to indoor molds depends on the climate, which may be very different from that of the Mediterranean.³²

From a clinical perspective, based on the aforementioned information, it appears beneficial to evaluate the type of sensitization and the duration of nasal symptoms in patients with moderate–severe persistent allergic rhinitis. In addition, the present study emphasizes the concept that allergic rhinitis frequently precedes the onset of asthma. This progression of the allergic inflammation from nose to bronchi may be referred to as the “asthma march.” In this regard, the present

Table 3 Odds ratio (OR) with 95% CI, scored with two different logistic models, associated with potential risk factors for developing impaired FEF₂₅₋₇₅ and BHR

Risk factors	At Least One Visit Under Cutoff				All Visits Considered			
	FEF ₂₅₋₇₅		BHR		FEF ₂₅₋₇₅		BHR	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95%CI)	p Value	OR (95%CI)	p Value
Age (yr)	1.14 (0.94–1.39)§	0.18	0.99 (0.83–1.18)§	0.92	1.55 (1.34–1.79)	<0.001	11.2 (3.2–39)	<0.001
Male vs Female	1.13 (0.34–3.81)	0.84	0.90 (0.28–2.92)	0.85	1.56 (0.19–12.54)	0.68	1.03 (0.44–2.40)	0.95
Smoking vs nonsmoking	0.77 (0.12–4.95)*	0.79	2.00 (0.32–12.7)*	0.46	0.79 (0.01–55.5)*	0.91	2.42 (0.01–>1000)*	0.88
Rhinitis duration (yr)	1.55 (1.23–1.94)§	<0.001	1.18 (1.02–1.37)§	0.03	2.04 (1.56–2.67)*	<0.001	4.52 (1.68–12.2)*	0.003
Sensitizations								
Only mites	1.10 (0.23–5.1)*	0.91	1.29 (0.30–5.66)*	0.73	0.18 (0.01–4.72)*	0.30	14.9 (0.02–>1000)*	0.41
Mites + other	2.61 (1–6.82)*	0.05	3.13 (1.14–8.62)*	0.03	17.2 (2.04–144)*	0.009	16.03 (1.14–8.62)*	0.14
Birch + other	3.54 (1.36–9.18)*	0.009	2.71 (1.10–6.67)*	0.03	33.4 (4.66–239)*	<0.001	994 (6.28–>1000)*	0.008
Mites + birch	0.86 (0.29–2.54)*	0.79	0.76 (0.26–2.21)*	0.62	0.20 (0.02–2.08)*	0.18	0.23 (0.01–48.7)*	0.59
Birch + molds + Parietaria	1.29 (0.33–5.08)*	0.72	0.26 (0.06–1.15)*	0.08	0.46 (0.03–6.89)*	0.57	37.6 (0.37–>1000)*	0.13
Mites + birch + Parietaria	#		34.7 (4.24–284)*	0.001	4678 (150–>10000)*	<0.001	1998 (6.08–>1000)*	0.01
Mites + Parietaria + grass	0.86 (0.22–3.26)*	0.82	0.70 (0.19–2.62)*	0.60	0.18 (0.01–3.04)*	0.23	0.01 (0–9.39)*	0.19
Mites + Parietaria	3.91 (1.29–11.9)*	0.02	3.75 (1.44–9.79)*	0.007	59.3 (7.77–451.9)*	<0.001	11.56 (0.43–314)*	0.15
Grass	0.99 (0.27–3.69)*	0.99	0.60 (0.16–2.19)*	0.44	0.26 (0.02–4.13)*	0.34	0.01 (0–2.47)*	0.10

*Adjusted for sex and age.

#All 16 cases with FEF₂₅₋₇₅ < 70%.

§At baseline.

BHR = bronchial hyperreactivity; FEF₂₅₋₇₅ = forced expiratory flow at 25 and 75% of pulmonary volume.

study shows some similarities and differences with the Settupane study.³ Both studies evaluated young adults with respiratory allergy; however, Settupane enrolled a larger cohort of patients, including asthmatic patients, and the 23-year follow-up was longer.³ Another significant difference was in the use of objective measures of lung function. Settupane did not consider functional assessment of bronchial airways by performing spirometry and methacholine challenge as was done in the current study. Similarly, both studies evidenced that both duration of allergy and sensitization were relevant risk factors for inducing worsening of respiratory allergy.³

Limitations of the current study include the following: the subjects studied were not representative of the general population, there is a prevalence of male gender, and the subjects were combat divers. In addition, this study leaves some open questions: (1) how to manage patients differently if their FEF₂₅₋₇₅ decreases over time but they have no symptoms, (2) is there a possible relationship between the fall in FEF₂₅₋₇₅ and/or the development of BHR and asthma symptoms over the time, and (3) is a similar pattern of progression seen in patients with intermittent allergic rhinitis? Future studies should be conducted to answers to these issues.

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 allergic rhinitis. Therefore, it is a reasonable consideration to perform spirometry in patients presenting with allergic rhinitis.

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