The relationship between FEF25-75 and skin test sensitization, nasal inflammation, and bronchial hyperreactivity in young subjects without asthma

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Citation

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Abstract

Background: A close link exists between allergic rhinitis and asthma. Small airway disease (SAD), defined by a reduction in FEF_{25-75} and normal spirometry (normal FEV_1, FVC, and FEV_1/FVC ratio), may be a marker for early allergic or inflammatory involvement of the small airways in subjects with allergic diseases and no asthma.

Objectives: The aim of the present study was to determine if there is a relationship with SAD, the outcome variable, and several allergic predictors in patients without asthma but with allergic disease.

Study Design: Cross-sectional.

Methods: Two-hundred eleven midshipmen attending the third and fifth course of Navy Academy of Livorno were screened. Fifty-eight showed slight spirometric anomalies. Thus, they were referred to Navy Hospital of La Spezia for standardized tests: skin prick test, nasal cytology, spirometry, and methacholine bronchial challenge. A reduced FEF_{25-75} was defined as less than 80% of predicted.

Results: All 58 subjects had a normal FEV_1, FVC, and FEV_1/FVC ratio. Twenty subjects had a reduced FEF_{25-75} consistent with the definition of SAD. A mean value of FEF_{25-75} of 70.3 (SD 8.5) was measured in patients with a reduced FEF, while it was 108.0 (SD 14.3) in those with preserved FEF_{25-75}. All the candidate allergic predictors appeared to be strongly associated with a reduced FEF_{25-75}. The proportion of subjects with reduced FEF_{25-75} appeared to increase with increasing severity of the allergic predictors, and correspondingly the mean value of FEF_{25-75} appeared to decrease.

Conclusions: The FEF_{25-75} value may be envisioned as a possible marker of SAD in atopic subjects. Moreover, this study supports the link between upper and lower airways in sensitized subjects.

INTRODUCTION

Despite the fact that asthma prevalence is increasing worldwide ([1]), asthma is still underdiagnosed, especially in children and young adults ([2,3]).

A close association between allergic rhinitis and asthma has been reported ([4]). Moreover, allergic rhinitis has been demonstrated to be a strong risk factor for the onset of asthma in adults ([5]).

Asthma is characterized by a reversible airflow obstruction and small airways are involved in the pathogenesis of asthma ([6]). The forced expiratory flow at the 25 and 75% of the pulmonary volume (FEF_{25-75}) might be considered as a measure of the caliber concerning distal airways, particularly in subjects with normal FEV_1 ([7]). Thus, FEF_{25-75} may be envisioned as a possible marker of early bronchial impairment, as recently described by ourselves in patients with allergic rhinitis alone ([8,9,10]). Therefore, small airways disease (SAD) as defined by a reduction in FEF_{25-75} and normal spirometry (normal FEV_1 and FVC) may be a marker

for early allergic or inflammatory involvement of the small airways in subjects with allergic disease and no asthma. On the other hand, bronchial hyperreactivity (BHR) is a paramount feature of asthma and may be observed in a high proportion of rhinitics, sensitized to perennial allergens ([9]), pollens ([10]), or both ([8]). In addition, Th2-dependent cytokines and eosinophilic inflammation are related to nasal and bronchial airflow impairment in rhinitics ([11,12]).

The aim of the present study was determine if there was a relationship between SAD, the outcome variable, and allergic predictors in healthy as Naval conscripts without asthma but with allergic disease.

MATERIALS AND METHODS

Study design: The study included all the midshipmen attending the third and fifth course of Navy Academy of Livorno. All of them were, of course, healthy subjects, continuously trained and checked. All of them had to carry out specialistic examinations, including spirometry, to obtain the fitness for attending specific courses (e.g. for pilot, frogman, diver, submariner, etc.).

The Review Board approved the study and an informed consent was obtained from each subject.

Subjects: Fifty eight midshipmen (out of 211) with slight spirometric abnormalities were referred to the Navy Hospital of La Spezia for standardized testing. These tests included the skin prick test, nasal symptoms, nasal cytology, spirometry, and methacholine bronchial challenge. These 58 patients form the basis of this study.

The diagnosis of allergic rhinitis was made on the basis of a history of nasal symptoms and a positive skin prick test according to validated criteria ([4]).

The most important perennial allergens in our geographic area are: house dust mites (i.e. Dermatophagoides farinae and pteronyssinus), cat, and dog ([9]). The most relevant pollen allergens in our geographic area are: Parietaria judaica, grasses, olive tree, birch, and hazel ([10]).

It should be noted that all 58 subjects included in this study had no symptoms of lower airway disease or asthma. Military service is not allowed for those with asthma or those with other known lung diseases.

Nobody had assumed nasal or oral corticosteroids, and antihistamines within the previous 4 weeks.

Skin prick test: Atopy was assessed by the presence of sensitization to the most common classes of aeroallergens by performing skin prick test. It was performed as stated by the European Academy of Allergy and Clinical Immunology ([13]). The allergen panel consisted of the following: house dust mites (Dermatophagoides farinae and pteronyssinus), cat, dog, grasses mix, Compositae mix, Parietaria judaica, birch, hazel tree, olive tree, Alternaria tenuis, Cladosporium, and Aspergilli mix; the concentration of allergen extracts was 100 I.R./mL (Stallergenes, Milan, Italy). A histamine solution in distilled water (10 mg/mL) was used as positive control and the glycerol-buffer diluent of the allergen preparations as negative control. Each patient was skin tested on the volar surface of the forearm using 1 mm prick lancets (Stallergenes, Milan, Italy). The skin reaction was recorded after 15 minutes by evaluating the skin response rate to the inoculation of each allergen extract in comparison with the wheal given by the positive and the negative control. A wheal diameter equal or greater than 3 mm was considered a positive reaction.

Nasal symptoms: The following symptoms were assessed by the subject, answering the questions made by the investigator: nasal obstruction, sneezing, rhinorrhea, and itchy nose. Each symptom was evaluated on the following scale: 0= absent, 1= mild (symptom was present but was not annoying or troublesome), 2= moderate (symptom was frequently troublesome but did not interfere with either normal daily activity or sleep), and 3= severe (symptom was sufficiently troublesome to have interfered with normal daily activity or sleep). Total symptom score (TSS) being the sum of each individual symptom was considered.

Rhinitis was considered according with TSS grade as mild (TSS=<6), moderate (TSS=6-8), and severe (TSS=>9). Subjects with no symptom were considered as normal.

Nasal cytology: Nasal cytologic specimens were obtained by scraping the head of the inferior turbinate with a cotton swab, as described in previous reports ([11,12]). Briefly, after the nasal scraping, the cotton tip of the swab was immersed in a plastic tray with phosphate-buffered saline (PBS) and transferred to a 10 mL polypropylene tube. The recovered fluids were centrifuged at 220 g per minute for 10 minutes, and each pellet was re-suspended in PBS (2 mL). Cell suspensions were filtered to reduce the quantity of mucus, and cytospin slides were prepared by using standard techniques.

Smears were stained with Diff Quik stain and were analysed by optic microscope (Olympus U-SPT). The number of inflammatory cells was expressed as a mean of 10 optical fields at 100x magnification. Samples were examined in a blinded fashion.

Spirometry: It was performed by using a computer-assisted spirometer (Pulmolab 435-spiro 235, Morgan, England), with optoelectronic whirl flow meter. Spirometry was performed as stated by European Respiratory Society ($_{14}$). About FEF_{25-75}, reversibility was considered when there was an increase of at least 15% from baseline values ($_{15}$).

SAD was defined as a normal FEV_1, FVC and FEV_1/FVC ratio with a reduction of the FEF_{25-75} below 80%.

Methacholine bronchial challenge: It was performed to evaluate BHR only if basal FEV_1 was equal or more than 80% of predicted. Aerosol is delivered using a dosimetric computerized supply (MEFAR MB3, Marcos, Italy). Subjects inhaled increasing doses of methacholine, starting from 30 µg/mL. The scheduled doses consisted of the following: 30, 30, 30, 60, 90, 150, 150, 300, 300, 300, 150 g/mL as previously reported ($_{8,9,10}$).

The test was interrupted and considered positive when FEV_1 value was reduced by more or equal than 20% of control or a maximal cumulative dose of 1,590 µg/ml was achieved. The threshold dose causing a 20% fall of FEV_1 (PD20) was calculated.

Degree of BHR: Three arbitrary classes of BHR were considered: mild = PD20/FEV_1 >400 g/mL, moderate = PD20/FEV_1 ranging from 400 to 101 g/mL, and severe = PD20/FEV_1 <100 g/mL as previously reported ($_{8,9,10}$). Subjects without response to cumulative dose of 1,590 g/ml were considered no BHR.

Statistical analysis: Descriptive statistics were computed as mean and standard deviation (SD) for continuous variables, or median and 25 th -75 th percentiles in case of skewed distribution, and as absolute frequency and percent for categorical variables.

To assess the role of allergic characteristics for predicting reduced FEF_{25-75}, logistic models were fitted; odds ratios (OR) and their 95% confidence intervals (95%CI) were calculated. A multivariate was fitted, not including eosinophils due to multicollinearity.

Stata 8 (StataCorp, College Station, TX) was used for computation. A 2-sided p-value<0.05 was considered statistically significant.

RESULTS

GENERAL CHARACTERISTICS

Patients characteristics are summarized in Table 1. Age ranged from 21 to 24; only a 3 recruits were female. None of them smoked. Most subjects did not elicit symptoms. Among those with symptoms, 2 had score 2, 3 had score 4 and 5 had score 5. Slightly more than 50% had moderate eosinophil infiltration. The BHR challenge was positive in half of the case series, at a median dose of 170 µg/ml (25 th -75 th 90-420). Fifteen percent of patients showed mono and 50% poly-sensitivity at skin prick test. FEV_1 and FVC were normal (>80%) in all cases, while 34% of patients had a reduced FEF_{25-75} (all of them showed reversibility).

It is of note that subjects without a positive skin prick test (ie nonatopic) do not have any of the other manifestations of allergic disease. In other words, only those with a positive skin prick test are positive for nasal eosinophils, nasal symptoms, have a positive BHR test, or a reduced FEF_{25-75}.

Figure 1

Table 1: summary of allergic findings and lung function studies in 58 military recruits

Characteristic		Description
Age (years)		21.9 (1.0)[1]
Gender (male)		55 (94.8%)[2]
Smoking habits		0 (0%)[2]
Symptoms score	2-9	9 (15.5%)[2]
Eosinophils	0	24 (41.4%)[2]
	1-2	18 (31.0%)[2]
	≥3	16 (27.6%)[2]
BHR	Negative	29 (50.0%)[2]
	Very mild	8 (13.8%)[2]
	Mild	5 (8.6%)[2]
	Moderate	6 (10.3%)[2]
	Severe	10 (17.3%)[2]
Prick test	Negative	19 (32.8%)[2]
	Monosensitivity	9 (15.5%)[2]
	Polysensitivity	30 (51.7%)[2]
FEV1		101.5 (7.4)[1]
FVC		102.8 (6.4)[1]
FEF25-75		94.4 (22.1)[1]
Reduced FEF25-75 (<80%)		20 (34.5)[2]

[1] mean (SD); [2] number (%)

PREDICTORS OF DEPRESSED FEF

A mean value of FEF_{25-75} of 70.3 (SD 8.5) was measured in patients with a reduced FEF, while it was 108.0 (SD 14.3) in those with preserved FEF_{25-75}. All the candidate allergic predictors appeared to be strongly associated with a reduced FEF_{25-75}, as shown in Table 2. The proportion of subjects with reduced FEF_{25-75} appeared to increase with increasing severity of the allergic predictors, and correspondingly the mean value of FEF_{25-75} appeared to decrease.

Figure 2

Table 2: Allergic predictors of reduced FEF

(Multivariate Logistic Model Chi2=44.2, p<0.001)

Variable		Number of pts with reduced FEF (%)	Mean FEF (SD)	OR (95%CI) (univariate)	p-value (univariate)	OR (95%CI) (multivariate)	p-value (multivariate)
Symptoms score	0	12 (24.5%)	98.4 (21.0)		<0.001		
	2-9	8 (88.9%)	72.7 (14.7)	24.7 (2.8-217.9)		1.75 (0.08-36.67)	0.719
Eosinophils	0-2	5 (11.9%)	103.4 (17.8)		<0.001		
	≥3	15 (93.7%)	70.6 (12.8)	111 (11.9-1031)		-	-
BHR	Negative to Mild	5 (11.9%)	103.8 (17.1)				
	Moderate to Severe	15 (93.7%)	69.6 (12.5)	111 (11.9-1031)	<0.001	74.21 (4.59-1200)	0.002
Prick test	Negative/Mono-sens	2 (7%)	108.8 (16.2)		<0.001		
	Poly-sensitivity	18 (60%)	80.9 (18.1)	19.5 (3.9-97.8)		15.28 (1.46-160)	0.023

Moderate to severe BHR and poly-sensitivity appeared to be independent predictors of a reduced FEF_{25-75} at multivariate analysis.The independent role of eosinophil infiltration could not be evaluated due to multicollinearity with the remaining predictors.

DISCUSSION

Evaluating substantially healthy subjects with slight spirometric anomalies, we showed that all the candidate allergic predictors, such as nasal symptoms, nasal eosinophils, sensitizations, and bronchial hyperreactivity, appeared to be strongly associated with a reduced FEF_{25-75}. Moreover, the proportion of subjects with reduced FEF_{25-75} appeared to increase with increasing severity of the allergic predictors, and correspondingly the mean value of FEF_{25-75} appeared to decrease.

It is well known that eosinophilic infiltration is the hallmark of allergic inflammation, as Th2-derived cytokines account for recruiting and activating eosinophils in airways.

The presence of nasal eosinophils in sensitized subjects here reported was in agreement with the observation that these cells and their mediators were found in nasal secretions of subjects allergic to mites, even in symptom-free periods ([16,17]).

In this study, nasal eosinophils were recovered from sensitized subjects only. Consistent with previous studies, eosinophil number was related to nasal symptom severity ([10,11]).

We also found a significant association between nasal involvement and BHR. The relationship between allergic inflammation and airway hyperreactivity or airflow obstruction is still controversial ([18]). However, significant correlations have been reported between total serum IgE or

blood eosinophils and BHR to methacholine ([19]), and between the decrease in circulating eosinophils following allergen inhalation challenge, and the degree of late asthmatic response and changes in BHR to histamine ([20]) in allergic patients.

Our findings are in agreement with those observed in allergic children ([17]) and furthermore support the concept of a link between allergic inflammation and increased bronchial reactivity in sensitized subjects.

Moreover, it is noteworthy that the lowest FEF_{25-75} values were present in those subjects with nasal symptoms, severe BHR and more intense eosinophilic infiltration. In addition, FEF_{25-75} impairment and BHR were demonstrated in sensitized subjects only. This finding was even more evident in polysensitized subjects. Therefore, in sensitized subjects, mainly rhinitics, with normal FVC and FEV_1 values, impaired FEF_{25-75} values (i.e. <80% of predicted) suggest the presence of SAD. Therefore, SAD may be a marker for early allergic or inflammatory involvement of the small airways in subjects with allergic disease and no asthma. This idea is consistent with the associations seen but needs to be validated with longitudinal studies comparing those with nonasthmatic allergic disease and SAD with those with allergic disease without asthma and no SAD to determine if progression to frank asthma actually occurs, relative to those without SAD.

Thus, the present study provides evidence, relevant to clinical care, that spirometry should be performed in all rhinitics who will perform strenuous physical exercises or risky works.

In conclusion, we retain that these data may be considered convincing proof of the close link existing between atopy and airway disorders.

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