

Could routine spirometry suggest sensitisation in the military medicine setting?

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ABSTRACT

Introduction Providing evidence of sensitisation is the formal requirement for allergy diagnosis. The aim of this study was to evaluate whether spirometry may be able to predict sensitisation in a representative cohort of Italian Navy military personnel.

Methods 2043 (1875 men, 168 women, mean age 28.35±11.6 years) Italian Navy military personnel were enrolled into this study. Spirometry and skin prick testing were performed to predict sensitisation.

Results Sensitisation, assessed by skin prick test, was documented in 658 (32.2%) subjects. Impaired forced expiratory flow at the 25% and 75% of the pulmonary volume (FEF₂₅₋₇₅) as demonstrated on spirometry was detected in 82 subjects, of whom 69 were sensitised (P<0.0001). Impaired FEF₂₅₋₇₅ was significantly associated with sensitisation (OR 7.43; 95% CI 4.04 to 14.66; P<0.0001).

Discussion The findings of this study suggest that impaired FEF₂₅₋₇₅ may predict sensitisation in this cohort of Italian Navy personnel. This outcome is relevant in the military medical setting, as it could allow early identification of subjects with subclinical asthma.

INTRODUCTION

Allergic rhinitis and asthma are closely associated and are both characterised by airway inflammation.^{1,2} This results in airflow obstruction in asthma and nasal obstruction in patients with allergic rhinitis. In asthma, functional evaluation of bronchial airflow is primarily evaluated by lung function testing. Airflow obstruction is defined by a low forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) ratio, and FEV₁ is considered a gold standard in asthma management.^{3,4} However, the forced expiratory flow at the 25% and 75% of the pulmonary volume (FEF₂₅₋₇₅) might be useful in clinical practice, predicting airway responsiveness, bronchial reversibility and early bronchial obstruction in patients with allergic rhinitis or asthma.⁵⁻⁸ On the other hand, allergen-specific IgE production (ie, sensitisation) is the most important biomarker for documenting allergic reaction. The diagnosis of allergic disease is based on the association between sensitisation and symptom occurrence following the exposure to the sensitising allergen.

Within the Italian Navy, certain occupational groups (such as frogmen or combat divers) must undergo spirometry. If the results of spirometry are impaired, subjects require further evaluation through skin prick testing and a methacholine challenge, within a specialised service at the Navy Hospital in La Spezia. Italian Navy military service

Key messages

- ▶ Spirometry and skin prick testing can be used to predict sensitisation.
- ▶ Impaired airflow forced expiratory flow at the 25% and 75% of the pulmonary volume predicted sensitisation in this cohort of Italian Navy personnel.
- ▶ This may enable early identification of subjects with subclinical asthma in the military medical setting.

does not accept subjects who have asthma or other known lung diseases, and therefore if a diagnosis of asthma is made subjects are discharged. On the contrary, allergic rhinitis does not preclude military service. A previous study of 778 Italian naval academy cadets reported that impaired spirometry, namely considering FEF₂₅₋₇₅ value <65% of predicted, may suggest sensitisation.⁹ The aim of this study was to confirm whether sensitisation could be predicted through spirometry.

MATERIALS AND METHODS

This study analysed the findings of a session of certificate visits of all Italian Navy military personnel, who performed spirometry for periodic fitness visit in order to be allowed to maintain the qualification certificate of the personal military profile during 2016. All subjects included in this study had never had symptoms of lower airway disease or asthma. Written informed consent was obtained from each subject.

Spirometry was performed using a computer-assisted spirometer (Pulmolab 435-Spiro 235, Morgan, England), as recommended by the European Respiratory Society.³ At least four complete forced blows had to be completed by each subject. Skin prick testing was performed on all subjects as stated by the European Academy of Allergy and Clinical Immunology.¹⁰ Allergic rhinitis was diagnosed when there was consistency between documented sensitisation and occurrence of nasal symptoms after exposure to the sensitising allergen.

Continuous variables were provided as means with SD, and categorical variables as number of subjects and percentage values. The FEF₂₅₋₇₅ was determined as <65% of the predicted value (abnormal values) and ≥65% (normal values). The univariate logistic regression models were performed to screen the effect of the clinical and demographic variables on sensitisation. The ORs associated with sensitisation were calculated with



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Table 1 Demographic and clinical characteristics of study participants (n=2043)

Characteristics	Overall
Sensitisation	
No	1385 (67.79%)
Yes	658 (32.21%)
Age	28.35 (6.05%)
Gender	
Male	1875 (91.78%)
Female	168 (8.22%)
FVC % of predicted	106.11 (11.2)
FEV ₁ % of predicted	106.49 (11.42)
FEV ₁ /FVC	83.81 (5.71)
FEF ₂₅₋₇₅ % predicted	106.8 (25.56)
FEF ₂₅₋₇₅	
Normal ($\geq 65\%$ of predicted)	1961 (95.99%)
Abnormal ($< 65\%$ of predicted)	82 (4.01%)

The results are expressed as mean with SD or as number of subjects with percentage. FEF₂₅₋₇₅, forced expiratory flow at the 25% and 75% of the pulmonary volume; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

their 95% CI for each factor from the logistic model. The likelihood ratio test was used as a test of statistical significance, and the estimated P values were adjusted for multiple comparisons by the Bonferroni correction method. The bivariate relationship between FEF₂₅₋₇₅ and sensitisation was adjusted for those variables with a univariate P value < 0.05 , using again the logistic regression model. The model selection was performed using the Akaike information criterion. Differences with a P value < 0.05 were selected as significant, and data were acquired and analysed in the R V.3.4.1 software environment (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During this period the records of 2043 individuals were analysed; 1875 were male and 168 were female, with a mean age of 28.4 ± 11.6 years (Table 1). Descriptive statistics of age, gender, FVC, FEV₁, FEV₁/FVC and FEF₂₅₋₇₅, in the levels of sensitisation, are reported in Table 2. Categorising FEF₂₅₋₇₅, it was observed that 1961 subjects (95.99%) had normal FEF₂₅₋₇₅ ($\geq 65\%$ of predicted), while 82 subjects (4.01%) had abnormal FEF₂₅₋₇₅ values ($< 65\%$ of predicted). The mean of predicted values of

Table 3 Multivariate analysis, the predictor effects on the sensitisation in sensitised subjects (n=2043)

Characteristics	OR (95% CI)	P value
(Intercept)	15.06 (2.93 to 78.13)	0.0012
FEF ₂₅₋₇₅		< 0.0001
Normal	1	
Abnormal	7.43 (4.04 to 14.66)	
FEV ₁	0.98 (0.97 to 0.99)	0.0093
FEV ₁ /FVC	0.97 (0.96 to 0.99)	0.0052

Results are expressed as OR with 95% CI.

P value: likelihood ratio P value.

FEF₂₅₋₇₅, forced expiratory flow at the 25% and 75% of the pulmonary volume; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

FVC, FEV₁ and FEV₁/FVC was 106.11% (SD=11.2), 106.49% (SD=11.42) and 83.81 (SD=5.71), respectively. There were 1385 (67.79%) subjects who did not show sensitisation, while 658 ones were sensitised. Most of the subjects were polysensitised (533 subjects; 81%): the most frequent cause of sensitisation was house dust mites (62%), followed by *Parietaria officinalis* (41%), birch (35%) and pets (26%). In terms of polysensitisation on lung function, no significant difference was found between polysensitised and monosensitised subjects (P=NS). The frequency of allergic rhinitis symptoms was $> 90\%$, that is, 593 subjects reported allergic nasal complaints. When lung function was analysed, subjects with rhinitis showed slightly lower FEV₁ and FEV₁/FVC than subjects without reported nasal symptoms but without significant difference (P=NS), while FEF₂₅₋₇₅ was significantly lower in comparison with the normal group (95%, SD=13.5; and 109.3%, SD=14.7, respectively; $P < 0.05$).

The mean values of FEV₁ and FEV₁/FVC were lower in subjects demonstrating sensitisation than in non-sensitised subjects. The mean FVC values were similar among subjects with and without sensitisation. In subjects with a normal FEF₂₅₋₇₅, the majority did not demonstrate sensitisation (69.96%). In the cohort with abnormal FEF₂₅₋₇₅, 84.15% had demonstrated sensitisation. Univariate logistic regression analysis (Table 2), using the complete set of data, demonstrated a significant association among age, FEF₂₅₋₇₅, FEV₁, FEV₁/FVC and sensitisation (P values < 0.05). The categorical FEF₂₅₋₇₅ and univariate variables with a P value < 0.05 were then considered in the multivariate analysis (Table 3), which showed a significant association between FEF₂₅₋₇₅ and sensitisation, adjusted

Table 2 Contingency tables and output of the univariate analysis

Characteristics	Descriptive statistics		Univariate analysis	
	Sensitisation		OR (95% CI)	P value
	No	Yes		
Gender				0.5545
Male	1281 (68.32%)	594 (31.68%)	1	
Female	104 (61.9%)	64 (38.1%)	1.33 (0.95 to 1.83)	
Age*	28.02 (5.7%)	29.05 (6.68%)	1.03 (1.01 to 1.04)	0.0023
FVC % of predicted	106.19 (11.01)	105.95 (11.61)	1.00 (0.99 to 1.01)	0.9999
FEV ₁ % of predicted	107.63 (10.75)	104.09 (12.37)	0.97 (0.96 to 0.98)	< 0.0001
FEV ₁ /FVC*	84.43 (5.18)	82.5 (6.51)	0.94 (0.93 to 0.96)	< 0.0001
FEF ₂₅₋₇₅ *				< 0.0001
Normal	1372 (69.96%)	589 (30.04%)	1	
Abnormal	13 (15.85%)	69 (84.15%)	12.36 (7.02 to 23.56)	

Characteristics: variable taken into account. P value: likelihood ratio P value adjusted by using Bonferroni method.

*Variables entering the multivariate analysis (see the text for abbreviations and further details).

for FEV_1 and FEV_1/FVC values (P value <0.0001), and an OR of 7.43 (95% CI 4.04 to 14.66; $P<0.0001$).

DISCUSSION

The aim of this study was to confirm whether FEF_{25-75} could potentially be able to predict sensitisation in a cohort of Italian Navy military personnel. This may have clinical and practical relevance in the military medical setting, as the concomitant presence of initial airflow limitation (low FEF_{25-75} and sensitisation) could suggest the presence of subclinical asthma requiring further investigation. This study demonstrated that 32% of subjects were sensitised. Sensitised subjects had significantly lower FEV_1 , FEV_1/FVC and FEF_{25-75} values than not sensitised subjects. However, it has to be noted that the lung function parameters, but FEF_{25-75} were always in the normal range in all subjects.

The main outcome of the study was that 84% of subjects with abnormal FEF_{25-75} (such as $\leq 65\%$ of predicted) were sensitised, and approximately 90% had allergic rhinitis diagnosis, whereas only 15.8% of subjects with impaired FEF_{25-75} were non-sensitised. This study provides evidence that there is a significant association between impaired FEF_{25-75} values and the presence of sensitisation. In other words, to find impaired FEF_{25-75} constitutes a relevant risk factor for being sensitised. Moreover, there was also a significant association between sensitisation and reported allergic rhinitis symptoms, as well as between sensitisation and reduced FEV_1 and FEV_1/FVC , even though these differences were slight and not clinically meaningful. This is in contrast with FEF_{25-75} , which was markedly reduced and below a recognised threshold in some subjects. This issue highlights the role of FEF_{25-75} as potential biomarker of early bronchial involvement in allergic rhinitis, as previously demonstrated.⁵ In addition, this finding is consistent with the outcomes reported in the previous study on cadets of the Italian Navy Academy.⁹

Another interesting perspective is the possibility of suspecting that atopic personnel may have undiagnosed and asymptomatic small airways disease as suggested by impaired FEF_{25-75} values. In other words, this could represent a cohort of undiagnosed asthmatics. These issues may be noteworthy in the military medical setting as an early identification of allergic disorders and asthma is desirable. In particular, asthma should be screened out in the presence of allergic rhinitis and impaired spirometry. This study did not identify a role for polysensitisation or specific sensitisation in defining greater risk of having impaired lung function. This most likely represented the high frequency of polysensitised subjects and also the presence of allergic rhinitis diagnosis in the sensitised group.

The authors acknowledge that this study has potential limitations. The study was performed on a specific cohort of patients

of whom the vast majority were male. However this cohort was representative of the wider Italian Navy, which are also predominantly male (approximately 90%) and with a similar mean age (approximately 39 years old). Patients with diagnosed asthma were excluded, and the study design was cross-sectional in nature. For example, a previous longitudinal study on Navy personnel with allergic rhinitis¹¹ demonstrated that approximately 40% of subjects with allergic rhinitis developed bronchial hyper-responsiveness during the 8-year follow-up. However the authors believe that this study has demonstrated that impaired FEF_{25-75} when performing spirometry may be a predictor of sensitisation and potentially subclinical asthma. Clinicians should be encouraged to perform spirometry routinely and follow up abnormal results carefully to potentially exclude a diagnosis of asthma.

Contributors IC collected clinical data and discussed the findings. FG analysed the data. GC designed the study and wrote the paper.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The Italian Navy Review Board approved the study procedures.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- 1 Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA2LEN and AllerGen). *Allergy* 2008;63:S8–160.
- 2 Frieri M. Inflammatory issues in allergic rhinitis and asthma. *Allergy Asthma Proc* 2005;26:220–6.
- 3 Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
- 4 Global Initiative for Asthma. GINA guidelines. global strategy for asthma management and prevention. <http://www.ginasthma.org/> (accessed Jul 2017).
- 5 Ciprandi G, Cirillo I. FEF_{25-75} may be a marker of bronchial impairment in allergic rhinitis. *J Allergy Clin Immunol* 2011;127:549–51.
- 6 Lipworth B. Targeting the small airways asthma phenotype: if we can reach it, should we treat it? *Ann Allergy Asthma Immunol* 2013;110:233–9.
- 7 Siroux V, Boudier A, Dolgoploff M, et al. Forced midexpiratory flow between 25% and 75% of forced vital capacity is associated with long-term persistence of asthma and poor asthma outcomes. *J Allergy Clin Immunol* 2016;137:1709–16.
- 8 Malerba M, Radaeli A, Olivini A, et al. Association of FEF_{25-75} impairment with bronchial hyperresponsiveness and airway inflammation in subjects with asthma-like symptoms. *Respiration* 2016;91:206–14.
- 9 Ciprandi G, Salpietro A, Leonardi S, et al. Impaired spirometry may suggest sensitization. *J Biol Regul Homeost Agents* 2012;26:S15–S17.
- 10 Anon. Skin tests used in type I allergy testing Position paper. Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology. *Allergy* 1989;44(Suppl 10):1–59.
- 11 Ciprandi G, Signori A, Tosca MA, et al. Spirometric abnormalities in patients with allergic rhinitis: Indicator of an "asthma march"? *Am J Rhinol Allergy* 2011;25:181–5.

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