

Impaired spirometry may predict bronchial hyperresponsiveness

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Clinical Implications

- Spirometry is routinely performed in wide samples of subjects for many reasons. In clinical practice, abnormal forced expiratory flow at 25% to 75% of forced vital capacity and/or forced vital capacity value might reasonably suggest the presence of bronchial hyperresponsiveness in smokers with allergic sensitization.

TO THE EDITOR:

Bronchial hyperresponsiveness (BHR) is a characteristic of asthma useful to its diagnosis.¹ Impaired forced expiratory flow at 25% to 75% of forced vital capacity (FVC) (FEF₂₅₋₇₅), namely, less than 65% of predicted, has been reported to be useful in predicting airway responsiveness, bronchial reversibility, and early bronchial involvement in patients with allergic rhinitis.^{2,3} Moreover, impaired FEF₂₅₋₇₅ values may be associated with long-term persistence of asthma and poor asthma outcomes⁴ and with BHR and airway inflammation in subjects with asthma-like symptoms.⁵

A study of 778 cadets showed that an FEF₂₅₋₇₅ value of less than 74% of predicted could suggest the presence of allergic sensitization (sensitivity, 100%), whereas a value of more than 79% could exclude allergic sensitization (area under of curve = 0.99).⁶ So, we tested the hypothesis that routine spirometry, if impaired, could be able to predict BHR. The aim of the current study was to investigate the effect of clinical and demographics factors, including sex, age, smoking, allergic sensitization, FVC, FEV₁, FEV₁/FVC, and FEF₂₅₋₇₅, on BHR presence in a wide cohort (2043 subjects; 1875 males; mean age, 28.3 years) of Italian Navy military personnel.

The demographic and clinical characteristics of the study participants are summarized in Table I. Very few subjects had abnormal spirometry and without clinical relevance because no subjects reported bronchial symptoms.

Sensitization was defined if skin prick test result was positive. All sensitized subjects reported nasal symptoms, and 5.9% of them were smokers. One hundred eighty-four subjects (9%) had BHR (Table II). Among subjects with normal FEF₂₅₋₇₅, 6.9% had BHR, whereas 64.9% of subjects with abnormal FEF₂₅₋₇₅ had BHR ($P < .0001$). Four out of 13 patients with abnormal FVC showed BHR. The mean age of BHR+ and BHR- patients was quite similar (28.1 and 30.7 years, respectively). The mean FEF₂₅₋₇₅, FEV₁, and FEV₁/FVC values were significantly lower in BHR+ patients than in BHR- patients without BHR (Table III; $P < .0001$); in contrast, the mean FVC values were quite similar between the 2 groups. There was a moderate

TABLE I. Demographic and clinical characteristics of study participants (N = 2043)

Characteristic	Overall
BHR	
Absent	1859 (91.0)
Present	184 (9.0)
Age (y)	28.35 ± 6.0
Sex	
Male	1875 (91.8)
Female	168 (8.2)
Smoking	
Not current	1913 (93.6)
Current	130 (6.5)
Allergic sensitization	
No	1385 (67.8)
Yes	658 (32.2)
FEF ₂₅₋₇₅ (% of predicted)	106.8 ± 25.6
FEF ₂₅₋₇₅	
Normal	1969 (96.4)
Abnormal	74 (3.6)
FVC	106.11 ± 11.2
FVC	
Normal	2030 (99.4)
Abnormal	13 (0.6)
FEV ₁ (% of predicted)	106.49 ± 11.4
FEV ₁	
Normal	2029 (99.3)
Abnormal	14 (0.7)
FEV ₁ /FVC	83.81 ± 5.7
FEV ₁ /FVC	
Normal	1650 (80.8)
Abnormal	393 (19.2)
PD ₂₀ (mg/mL)	6.86 ± 5.2

The results are expressed as mean with SD or as number of subjects with percentage. Normal: FEF₂₅₋₇₅ = ≥65% of predicted; FVC = ≥80% of predicted; FEV₁ = ≥80% of predicted; FEV₁/FVC = ≥0.8.

agreement between abnormal FEF₂₅₋₇₅ and abnormal FEV₁/FVC (Cohen κ = 0.41; 95% CI, 0.32-0.49).

The univariate logistic regression analysis demonstrated a significant association among BHR and age, smoking, allergic sensitization, FEF₂₅₋₇₅, FVC, FEV₁, and FEV₁/FVC (Table II; unadjusted odds ratio [OR]). The univariate variables with a P value of less than .05 were then considered in the multivariate analysis (Table II; adjusted OR), which showed a significant effect of age, smoking, FEF₂₅₋₇₅, and FVC on BHR (P values, .0238, <.0001, <.0001, and .0351, respectively). In particular, BHR was about 6 times more likely in smokers than in non-smokers keeping constant age, FEF₂₅₋₇₅, and FVC (OR = 5.74). BHR was almost 20 times and 5 times more likely in subjects with abnormal FEF₂₅₋₇₅ and FVC than in subjects with normal FEF₂₅₋₇₅ and FVC (OR = 19.9 and 5.0, respectively). Moreover, a 5-year increase in age was associated with an increased

TABLE II. Univariate and multivariate ORs (unadjusted and adjusted, respectively, with their 95% CIs) measuring the relation between BHR (positive/negative) and subject age (y) (continuous), and demographic and clinical characteristics (dichotomous) for 2043 subjects

Characteristic	BHR+, N (% total subjects)	Subjects, N	BHR (Present, Absent)	
			Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (y)	30.7 ± 8.2	2043	1.1 (1.0-1.1)	1.03 (1-1.06)
Sex				
Male	167 (8.9)	1875	1	
Female	17 (10.1)	168	1.2 (0.6-1.9)	
Smoking				
Not current	141 (7.4)	1913	1	1
Current	43 (33.1)	130	6.2 (4.1-9.3)	5.74 (3.64-8.93)
Allergic sensitization				
No	0 (0)	1385	1	
Yes	184 (27.9)	659	1077.4 (266.4- 4357.6)	
FEF ₂₅₋₇₅				
Normal (≥65% of predicted)	136 (6.9)	1969	1	1
Abnormal (<65% of predicted)	48 (64.9)	74	24.9 (15.1-41.9)	19.94 (11.64-34.71)
FVC				
Normal (≥80% of predicted)	180 (8.9)	2030	1	1
Abnormal (<80% of predicted)	4 (30.8)	13	4.6 (1.2-14.2)	5.03 (1.13-17.64)
FEV ₁				
Normal (≥80% of predicted)	177 (8.7)	2029	1	
Abnormal (<80% of predicted)	7 (50.0)	14	10.5 (3.5-30.9)	
FEV ₁ /FVC				
Normal (≥80% of predicted)	88 (5.3)	1650	1	
Abnormal (<80% of predicted)	96 (24.4)	393	5.7 (4.2-7.9)	

TABLE III. The mean values of spirometric parameters for BHR groups with Student *t* test *P* value

Characteristic	Mean ± SD		<i>P</i> value
	BHR–	BHR+	
FEF ₂₅₋₇₅	109.5 ± 24.1	79.1 ± 22.9	<.0001
FVC	106.1 ± 11.1	106.05 ± 11.9	.9415
FEV ₁	107.2 ± 11.1	99.2 ± 12.3	<.0001
FEV ₁ /FVC	84.3 ± 5.3	79.2 ± 7.2	<.0001

chance of about 5 times (OR = 5.2 *per* 5 years) of having BHR, maintaining constant the other variables.

The multivariate logistic regression equation was as follows:

$$\text{Logit}(P) = \text{Ln}\left(\frac{P}{1-P}\right) = -3.68 + 0.03 \times \text{age} \\ + 1.75 \times \text{smoking} + 2.99 \times \text{FEF}_{25-75} \\ + 1.62 \times \text{FVC}$$

where *P* is the probability of having BHR.

Moreover, the smoking effect on BHR was different in the allergic sensitization group (Table IV; likelihood ratio *P* value < .0001). Particularly, in subjects without allergic sensitization, BHR was about 2771 times more likely in smokers than in nonsmokers (OR = 2771; 95% CI, 22.8-337139.5). In subjects with allergic sensitization, BHR was about 1.4 times more likely in smokers than in nonsmokers (OR = 1.35; 95% CI, 0.9-2.0).

The receiver-operating characteristic curve analysis for FEF₂₅₋₇₅ (cutoff 65% of predicted) showed 98% specificity and

TABLE IV. Contingency tables of the FEF₂₅₋₇₅ and smoking vs BHR in allergic sensitization groups*

Characteristic	BHR+, N	Subjects, N	BHR (Present, Absent), OR (95% CI)	<i>P</i> value for interaction
FEF ₂₅₋₇₅				.99
Normal	136	596	1	
Abnormal	48	62	11.6 (6.2-21.7)	
Smoking				<.0001
Not current	141	528	1	
Current	43	130	1.4 (0.9-2.0)	

OR (95% CI): ORs with 95% likelihood ratio CIs; *P* value for interaction: Likelihood ratio *P* value.

*Subjects with allergic sensitization (N = 658).

28% sensitivity (area under the curve [AUC] = 0.18) for predicting the difference between BHR+ and BHR– subjects. In addition, 98% specificity and 0% sensitivity were estimated for FVC cutoff of 80% of predicted (AUC = 0.50). No satisfying cutoff was obtained for FEV₁/FVC in discriminating BHR+ and BHR– subjects (AUC = 0.29).

Descriptive statistics of the demographic and clinical factors in association with PD₂₀ in BHR+ subjects are reported in Table E1 in this article's Online Repository at www.jaci-inpractice.org. The median PD₂₀ values were quite similar between smokers and nonsmokers, whereas the median PD₂₀ values in males and in subjects with normal FEV₁ were greater than those in females and in subjects with abnormal FEV₁ (5.5 *vs* 1.9 and 5.4 *vs* 1.1, respectively). The PD₂₀ data were not

normally distributed (Shapiro-Wilk P value $< .001$). Low Spearman correlation was observed among PD_{20} and age (Spearman $\rho = 0.08$). Finally, significant effects of sex and FEV_1 on the PD_{20} were observed (Table E1; $P = .0081$ and $.0252$, respectively).

The current study demonstrated that 9% of enrolled subjects had BHR, but only 82 had abnormal FEF_{25-75} . Noteworthy, subjects with abnormal FEF_{25-75} and FVC values had more likely BHR than subjects with normal FEF_{25-75} and FVC values (OR = 19.9 and 13, respectively). Moreover, smokers had more likely BHR than did nonsmokers. Very interestingly, no subject without allergic sensitization had BHR.

The main outcomes of the study showed that impaired FEF_{25-75} values ($<65\%$ of predicted), as well as impaired FVC ($<80\%$ of predicted), and smoking, constitute a risk factor for having BHR (OR = 19.9 and 5.0, respectively). In clinical practice, a routine spirometry detecting impaired FEF_{25-75} and/or FVC in smokers with allergic sensitization could instill the suspicion of underlying BHR. So, to observe these findings in young symptom-free and active subjects deserves a thorough workup to investigate BHR.

On the other hand, the current study has some limitations: the study was performed on a selected cohort mainly represented by males, patients with asthma were excluded, and it was cross-sectional. In addition, FEF_{25-75} predictability is lessened by low sensitivity (even if the specificity is very high).

In conclusion, this study could suggest that an impaired spirometry in smokers with allergic sensitization might reasonably suggest the presence of BHR.

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TABLE E1. Descriptive statistics with univariate analysis in BHR+ group

Characteristic	Overall, Median (Range)	BHR+ (PD ₂₀ mg/mL)	P value
Age (y)	29 (19-55)	$\rho = 0.1$	.30
Sex			.01
Male	167 (90.8)	5.5 (0.4-15.9)	
Female	17 (9.2)	1.9 (1.0-14.4)	
Smoking			.74
Not current	141 (76.6)	4.4 (1.0-15.9)	
Current	43 (23.4)	5.1 (1.0-15.9)	
FEF ₂₅₋₇₅			.55
Normal	136 (73.9)	5.2 (10-1590)	
Abnormal	48 (26.1)	4.4 (1.0-15.7)	
FVC			.86
Normal	180 (97.8)	5.10 (1.0-15.9)	
Abnormal	4 (2.2)	7.3 (1.10-12.2)	
FEV ₁			.03
Normal	177 (96.2)	5.4 (1.0-15.9)	
Abnormal	7 (3.8)	1.1 (4.0-14.4)	
FEV ₁ /FVC			.19
Normal	88 (47.8)	5.5 (10-1590)	
Abnormal	96 (52.2)	4.4 (10-1590)	

Characteristic: Variable taken into account. Overall: median with range or number of subjects and percentage values are reported for continuous and categorical variables, respectively; BHR+: PD₂₀ median with range in the level of the covariates or Spearman rho coefficient is reported for categorical or continuous covariate, respectively; P values: P values of the Mann-Whitney test or the P values of the Spearman correlation test are reported for categorical or continuous covariate, respectively.

METHODS

The visits included spirometry, methacoline challenge, skin prick test, and clinical examination; they were performed during the spring. The Navy Review Board approved the study procedures, and written informed consent was obtained from each subject. It should be noted that all subjects included in this study had never had symptoms of lower airway disease or asthma: in fact, the military service does not accept subjects who have asthma or other known lung diseases.

FEF₂₅₋₇₅ was considered abnormal if less than 65% of the predicted value as previously demonstrated^{E1}; FEV₁ and FVC values of less than 80% of the predicted and FEV₁/FVC ratio of less than 0.8 were considered abnormal as stated by International guidelines.^{E2,E3} BHR was categorized as present (PD₂₀ <15.9 mg/mL) or absent (PD₂₀ >15.9 mg/mL), according to the rules of Italian Navy and the challenge procedure was standardized.^{E4} The univariate logistic regression models were used to test the effect of the clinical and demographic variables on BHR. The variables with a P value of less than .05 entered in the multivariate analysis, where the BHR was the dependent variable. The ORs associated with BHR were calculated with their 95% CI for each factor from the logistic model and the likelihood ratio test was used as a

test of statistical significance. In case of 0 observations in the corresponding 2 × 2 table that could be the cause of problems with computation of the OR or its standard error, we applied the amended estimator of the OR and its standard error by adding 0.5 to each cell as suggested by Gart and Zweife.^{E5} Multivariate analysis was performed, using, again, the logistic regression model and the model selection was performed by the Akaike information criterion. To assay whether the FEF₂₅₋₇₅ and smoking effect on BHR was different in allergic sensitization groups, the logistic regression model was used and then, the statistical significance was assayed by the likelihood ratio test. The mean values of spirometric parameters for BHR groups were studied using Student *t* test.

The receiver-operating characteristic curves were used to determine the best cutoff values of FEF₂₅₋₇₅ and FEV₁/FVC to differentiate between the presence and absence of BHR. The PD₂₀ data normality in BHR+ patients was evaluated using the Shapiro-Wilk test. Moreover, the Mann-Whitney *U* test and the Spearman correlation test were performed to evaluate the effects of the clinical and demographic variables on the PD₂₀ in BHR+ patients. The estimated P values of less than .05 were selected as significant in all the comparisons. Data were acquired and analyzed in R v3.4.3 software environment.

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