

Allergic rhinitis phenotypes based on bronchial hyperreactivity to methacholine

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ABSTRACT

Background: Allergic rhinitis (AR) and asthma may be associated, bronchial hyperreactivity (BHR) is quite common in AR patients. Methacholine (MCH) is a stimulus able to elicit BHR, as many other ones. Phenotyping AR is an up-to-date issue.

Objective: The aim of this study was to evaluate whether MCH bronchial challenge is able to differentiate patients with AR.

Methods: A total of 298 patients (277 males, mean age 28.9 years), suffering from AR were evaluated. Sensitization, rhinitis duration, values for bronchial function (forced vital capacity [FVC], forced expiratory volume [FEV]₁, forced expiratory flow [FEF]_{25–75}, and FEV₁/FVC ratio), MCH bronchial challenge, visual analog scale (VAS) for nasal and bronchial symptoms perception, and fractionated exhaled nitric oxide (FeNO) were evaluated.

Results: BHR-positive patients (22.8%) had significantly more frequent mite allergy ($p = 0.025$), longer AR duration ($p < 0.001$), lower FEV₁ ($p = 0.003$), FEV₁/FVC ($p < 0.001$), FEF_{25–75} ($p < 0.001$), higher ($p < 0.001$), and higher VAS values for both nasal and bronchial symptoms ($p < 0.001$ for both) in comparison with BHR-negative patients. FeNO can be considered a good predictor for BHR in AR patients (area under the curve, 0.90) with 27.0 ppb as cutoff.

Conclusions: The present study demonstrates that BHR to MCH could define two distinct phenotypes in AR patients. It could be clinically relevant as BHR-positive patients have initial impairment of lung function, impaired FeNO values, and worsening of respiratory symptoms perception.

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Allergic rhinitis (AR) is the most common atopic disorder and may be frequently associated with asthma, in effect, AR represents a main risk factor for asthma onset and worsening.¹ AR and asthma share some pathophysiological mechanisms.^{2–6} In this regard, some AR patients may have bronchial hyperreactivity (BHR). This condition may mean a bronchial involvement^{7,8} and may also suggest possible evolution in asthma, the so called “asthma march.”⁹ Therefore, BHR assessing may have a prognostic value in a patient with AR. BHR is usually assessed performing bronchial provocation testing, using a variety of stimuli, that may be direct (histamine or methacholine) and indirect (exercise, adenosine 5'-monophosphate, hypertonic solution, mannitol, or allergen).¹⁰ There are relevant differences among them, concerning pathophysiologic mechanisms (direct effect on receptors or release of mediators), dependence on smooth muscle functioning, airway caliber and inflammation, maximal dose, sensitivity and specificity, severity, and duration of clinical response. In particular, allergen challenge may induce more severe and prolonged reaction (both clinical and inflammatory) and, in some subjects, a biphasic response. However, methacholine (MCH) bronchial challenge is widely used as it is well defined and validated, allows for defining a severity grade as quantitative test, and rarely induces severe bronchospasm.¹⁰ MCH challenge has therefore become popular in the clinical practice and is routinely used by the Italian Navy Medical Service. In addition, AR patients may frequently present impaired lung function, mainly concerning the forced expiratory flow at 25%–75% of the vital capacity (forced expiratory flow [FEF]_{25–75}), suggesting a bronchial involvement, also subclinical, such as without overt respiratory symptoms.¹¹

On the other hand, airway inflammation is the hallmark of both AR and asthma.¹² A bidirectional link between upper and lower airways exists. In fact, it has been evidenced that local segmental bronchial allergen challenge may induce a nasal inflammatory response¹³ as

well as nasal allergen challenge can induce a bronchoconstriction and sometimes some of the inflammatory processes in the bronchial tree in allergic patients.¹⁴ In particular, eosinophil infiltration may be considered a reliable marker of allergic inflammation.¹⁵ Allergic bronchial inflammation may be easily measured and monitored using the fractional exhaled nitric oxide.¹⁶

Another aspect has to be carefully evaluated in the management of AR patients: the subjective perception of symptoms. Visual analog scale (VAS) could be considered a practical tool for assessing this issue.¹⁷

Because phenotyping AR could be clinically relevant, a hypothesis to be tested is whether a nonallergenic bronchial stimulus, such as MCH, may be also able to define two possible distinct AR phenotypes. Therefore, the aim of this study was to evaluate whether MCH bronchial challenge is able to differentiate patients with AR.

MATERIALS AND METHODS

Patients

This cross-sectional study included 298 patients (277 males, mean age 28.9 years), suffering from AR. They were Navy soldiers who were referred to the Navy Medical Service for mandatory certification of their physical suitability for specific military training.

The subjects were enrolled in the study based on a diagnosis of AR made by the consistency between positive skin-prick test and presence of nasal symptoms after exposure to sensitizing allergen, according to validated criteria.¹ Exclusion criteria were any previous documented history of asthma or referral for asthma symptoms (including cough, wheezing, breathlessness, chest tightness), impaired forced expiratory volume (FEV)₁ values (such as less than 80% of the predicted) and less than 0.7 FEV₁/forced vital capacity (FVC) ratio, presence of acute or chronic upper respiratory infections, nasal polyps, clinically relevant septal deviation, previous or current intensive smoking, such as more 20 cigarettes/day (screened by expired-CO assessment, such as analyzing carboxyhemoglobin and carbon monoxide levels in a single breath using the Bedfont Micro Smokerlyzer III, Bedfont Scientific Ltd & Decode, England), previous or current specific immunotherapy, and use of nasal or oral corticosteroids, nasal or oral vasoconstrictors, antileukotrienes, and antihistamines during the previous four weeks. Subjects with acute upper respiratory airway infection returned after four weeks.

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The Navy Review Board approved the study procedure and written informed consent was obtained from each subject.

Study Design

The visit included clinical examination, VAS assessment of nasal obstruction and breathlessness perception, skin-prick test, nasal endoscopy, lung function assessment (including FVC, FEV₁, FEF₂₅₋₇₅, and FEV₁/FVC ratio), fractionated exhaled nitric oxide (FeNO) measurement, and MCH bronchial challenge. The visits were performed during the first months of 2014.

VAS Assessment

VAS was used to assess the subjective perception of both nasal and bronchial respiration. The perception of nasal obstruction was measured by rhino-visual analogue scale (R-VAS): it ranges from 0 (complete nose patency) to 10 cm (complete nose obstruction). Bronchial-visual analogue scale (B-VAS) was used to measure the subjective perception of breathlessness: it ranges from 0 cm (completely normal breathing) to 10 cm (severe dyspnea). Patients were asked to position a cross on a line corresponding to their own perception of respiration as previously reported.¹⁸

Skin-Prick Test

It was performed as stated by the European Academy of Allergy and Clinical Immunology.¹⁹ The panel consisted of house dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), cat, dog, grasses mix (including *Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*, and *Anthoxanthum odoratum*), *Compositae* mix, *Parietaria officinalis*, birch, hazel, olive tree, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix, including positive (histamine) and negative (saline solution) control (Stallergenes, Milan, Italy).

Spirometry

Spirometry was performed by using a computer-assisted spirometer (HDPft-2000 - nSpire Health, Morgan, England, predictive values European Convention for Constructional Steelwork 1993), with optoelectronic whirl flow meter. It was performed as stated by the European Respiratory Society.^{20,21} The quality control was performed daily to achieve a grade A (two acceptable FEV₁ values matching within 0.1 L).

MCH Bronchial Challenge

Chloride MCH 1% (Lofarma, Milan, Italy) was used for bronchial challenge. The test was performed only if basal FEV₁ was equal or more than 80% of predicted and basal FEV₁/FVC ratio was equal or more than 0.7. The dilution schedule was based on American Thoracic Society guidelines for MCH challenge, using a progressive dilution from 100 mg in 6.25 mL (16 mg/mL) to 0.031 mg/mL.¹⁰ Aerosol was delivered using a dosimetric computerized supply (MEFAR MB3, Marcos, Italy) by DeVilbiss ampoules (model 646). The testing procedure was performed after the American Thoracic Society guidelines, using the two-minute tidal breathing method.¹⁰ The starting dose was 0.031 mg/mL diluted in 3 mL of saline isotonic (0.9%) solution. The next doses were progressively doubled. MCH administration time was 1.7 seconds. The threshold concentration causing a 20% fall of FEV₁ (provocative concentration for 20% fall of FEV₁) was calculated, stopping the testing. Subjects without response to the cumulative concentration of 16 mg/mL were considered having normal bronchial responsiveness, according to the Navy Medical Service rules.

Statistical Analysis

Demographic and disease characteristics at baseline were summarized as count and percentage, mean $\pm$ standard deviation, and median with range. The normality of continuous variables was checked by analysis of the histograms and confirmed by the Kolm-

ogorov-Smirnov test. Any statistically significant relationship between BHR-positive and BHR-negative patients and continuous variables was evaluated with an independent sample *t*-test or a nonparametric Mann-Whitney test. A χ^2 test (or a Fisher exact probability test) was performed to investigate whether distributions of categorical variables differed from the BHR groups of rhinitis patients. A logistic regression model was performed to ascertain the effects of statistically significant variables assessed at univariate analysis on the likelihood that rhinitis patients have BHR. Correlation assessments between continuous variables were carried out with a Spearman's ρ test. A receiving operator characteristic (ROC) curve was plotted to assess how accurate FeNO marker was at predicting BHR in rhinitis patients. Data were expressed as odds ratio or relative risk (RR) with 95% confidence interval (95%CI). Statistical analysis was computed using Statistical Package for Social Science (SPSS version 20; IBM). All statistical tests were two sided, and the significance level was set at 0.05.

RESULTS

Table 1 summarizes demographic, clinical, and disease characteristics of the study sample (298 rhinitis patients). Globally, 68 AR patients (22.8%) had BHR to MCH.

Univariate analysis showed a statistically significant difference between patients with BHR and patients without BHR regarding the next variables: mites allergy ($p = 0.025$), rhinitis duration ($p < 0.001$), FEV₁ ($p = 0.003$), FEV₁/FVC ($p < 0.001$), FEF₂₅₋₇₅ ($p < 0.001$), FeNO ($p < 0.001$), R-VAS ($p < 0.001$), and B-VAS ($p < 0.001$).

The logistic regression model (Table 2) was statistically significant ($p < 0.001$). The model explained 71.9% (Nagelkerke R²) of the variance in BHR and correctly classified 91.3% of cases.

If R-VAS and B-VAS increased by one unit, rhinitis patients were, respectively, approximately 1.3 and 1.7 more times likely to have BHR.

A one-unit increasing FeNO value was associated with an increased probability 11% (RR, 1.11; 95%CI: 1.08–1.15, $p < 0.001$) of having BHR. Inversely, a one-unit increasing FEF₂₅₋₇₅ value was associated with a reduction in the likelihood 3% (RR, 0.97; 95%CI, 0.95–0.99, $p = 0.001$) of having BHR (Fig. 1).

Statistically significant correlations between continuous variables are shown in Table 3. In particular, there was a moderate positive correlation between disease duration and R-VAS in negative BHR patients ($\rho = 0.539$, $p < 0.001$) and a moderate negative correlation between age and FEV₁/FVC ($\rho = -0.576$, $p < 0.001$) in BHR patients.

FeNO can be considered a good predictor for BHR in AR patients: the area under the ROC curve was 0.90 (95%CI, 0.846–0.945; $p < 0.001$); and at FeNO value of 27.00 ppb (cutoff), sensitivity in detecting BHR was approximately 86.8% and specificity was 80.6% (Fig. 2).

DISCUSSION

The nose and the bronchi are closely related from a pathophysiological point of view. In particular, it has been evidenced that AR frequently may precede asthma onset. In this regard, the duration of rhinitis and sensitization to perennial allergens were demonstrated to be relevant risk factors for impairment of FEV₁,²² positive response to bronchodilation test,²³ and positive response to MCH bronchial challenge.¹⁸ On the other hand, local segmental bronchial allergen challenge may induce nasal inflammatory response.¹⁴ Therefore, a bidirectional talking between the nose and the bronchi exists, and allergic inflammation may explain the trait-d'union. The nose may negatively impact the lung function through different pathophysiological mechanisms, including a vagal naso-bronchial reflex, a continuum progression of respiratory allergic inflammation (from the nose to the smallest bronchi), a release of mediators into the blood stream, the postnasal drip, and the oral respiration consequent to nasal obstruction. Therefore, there is convincing belief that nose may significantly affect lower airways. On the other hand, not all AR patients develop asthma. It seems that they may be "protected" by asthma. In this

Table 1. Demographic, clinical, and disease characteristics

	Total (N = 298)	Negative BHR (N = 230)	Positive BHR (N = 68)	p-value
Age	28.9 ± 6.0 28.0 (19.0–55.0)	28.5 ± 5.0 28.0 (20.0–45.0)	30.5 ± 8.4 28.0 (19.0–55.0)	0.35
Sex, males (%)	277 (93.0)	218 (94.8)	62 (87.3)	0.05
Smokers	62 (20.8)	47 (20.4)	15 (22.1)	0.91
Polysensitization, n (%)	227 (76.2)	174 (75.7)	53 (77.9)	0.82
Mites allergy, n (%)	206 (69.1)	151 (65.7)	55 (80.9)	0.025*
Pets allergy, n (%)	98 (32.9)	73 (31.7)	25 (36.8)	0.53
Moulds allergy, n (%)	36 (12.1)	24 (10.4)	12 (17.6)	0.16
Pollens allergy, n (%)	231 (77.5)	181 (78.7)	50 (73.5)	0.47
Rhinitis duration (years)	5.9 ± 5.7 4.0 (0.0–30.0)	5.1 ± 4.7 4.0 (0.0–22.0)	8.7 ± 7.6 6.0 (0.0–30.0)	<0.001*
FVC (% of predicted)	105.4 ± 10.4 105.5 (78.0–133.0)	105.6 ± 10.4 106.0 (78.0–131.0)	104.9 ± 10.7 104.0 (82.0–125.0)	0.63
FEV ₁ (% of predicted)	106.7 ± 11.5 107.0 (81.0–132.0)	108.0 ± 11.2 107.0 (81.0–132.0)	102.6 ± 11.9 104.0 (82.0–125.0)	0.003*
FEV ₁ /FVC	0.9 ± 0.1 0.9 (0.7–1.0)	0.9 ± 0.1 0.9 (0.7–1.0)	0.8 ± 0.1 0.8 (0.7–1.0)	<0.001*
FEF _{25–75} (% of predicted)	105.5 ± 26.8 103.0 (49.0–174.0)	110.8 ± 25.3 108.5 (56.0–174.0)	87.8 ± 24.0 82.5 (49.0–173.0)	<0.001*
FEF _{25–75}	≤65% >65%	7 (3.0) 223 (97.0)	12 (17.6) 56 (82.4)	<0.001*
FeNO (ppb)	26.5 ± 24.3 18.0 (1.0–220.0)	18.0 ± 12.0 15.0 (1.0–63.0)	55.3 ± 32.3 55.0 (10.0–220.0)	<0.001*
FeNO	≤25 >25	190 (63.8) 108 (36.2)	9 (13.2) 59 (86.8)	<0.001*
R-VAS	2.6 ± 1.7 2.0 (0.0–9.0)	2.2 ± 1.5 2.0 (1.0–8.0)	3.6 ± 2.0 3.0 (0.0–9.0)	<0.001*
B-VAS	0.5 ± 1.5 0.0 (0.0–8.0)	0.2 ± 0.7 0.0 (0.0–7.0)	1.7 ± 2.5 0.0 (0.0–8.0)	<0.001*

Difference between positive and negative BHR rhinitis patients. Data are expressed as mean (standard deviation), median (minimum–maximum), and count (percentage frequency).

* = statistically significant; BHR = bronchial hyperreactivity; FVC = forced vital capacity; FEV = forced expiratory volume; FEF = forced expiratory flow; FeNO = fractionated exhaled nitric oxide; R-VAS = rhino-visual analogue scale; B-VAS = bronchial-visual analogue scale.

Table 2. Independent predictors of positive BHR in rhinitis patients

	Logistic Regression Model		
	OR-RR	95%CI	p-value
FEF _{25–75} (% of predicted)	0.97	0.95–0.99	0.001
FeNO (ppb)	1.11	1.08–1.15	<0.001
R-VAS	1.30	1.03–1.65	0.026
B-VAS	1.68	1.19–2.36	0.003

Results are expressed as odds ratio (OR) or relative risk (RR) and 95% confidence interval (95%CI).

BHR = bronchial hyperreactivity; FEF = forced expiratory flow; FeNO = fractionated exhaled nitric oxide; R-VAS = rhino-visual analogue scale; B-VAS = bronchial-visual analogue scale; CI = confidence interval.

regard, BHR in AR patients might suggest a possible further development of asthma.

The primary outcome of the present study was to investigate whether MCH bronchial challenge could define two different AR phenotypes about possible bronchial involvement.

In fact, AR patients with BHR are different in comparison with BHR-negative AR patients. BHR-positive AR patients have several distinctive characteristics. BHR-positive patients are more frequently sensitized to house dust mites. This point might be interesting, because mite allergy is characterized by a persistent inflammation because mites are perennial allergens, which could promote some risk

factors for asthma, such as turbinate hypertrophy associated with nasal obstruction and consequently impaired nasal function. Closely related to this issue, duration of rhinitis is longer in BHR-positive patients. As longer AR lasts as more frequently asthma may develop in rhinitis patients, such as the concept of an asthma march.⁹ In addition, BHR-positive patients show lower values of lung function parameters, mainly concerning FEV₁, FEV₁/FVC ratio, and FEF_{25–75}, than BHR-negative ones. It is to note that mean values are anyhow within normal references in both BHR subgroups. This finding underlines the concept that BHR positivity in AR patients might permit to define two distinct phenotypes.

Another interesting topic is the evaluation of the subjective perception of respiratory symptoms both regarding nasal obstruction and breathlessness. BHR-positive patients perceive more severe nasal obstruction and dyspnea than BHR-negative subjects. This point may be clinically relevant, because it highlights the importance of carefully considering the patient's perception of symptom because it may be related to impaired parameters.

Finally, BHR-positive patients have increased FeNO. This aspect may be particularly intriguing as the cut-off (for predicting BHR to MCH) found in the present study (27 ppb) is close to the reference value able to define the presence of bronchial allergic inflammation, such as 25 ppb.²⁴ In other words, BHR in AR patients seems to be associated with impaired FeNO values. The present study is also consistent with previous experiences that evidenced a relationship between FeNO values and BHR severity.^{25–31}

This study partially confirms a previous study conducted on children that showed a relationship between nasal airflow and

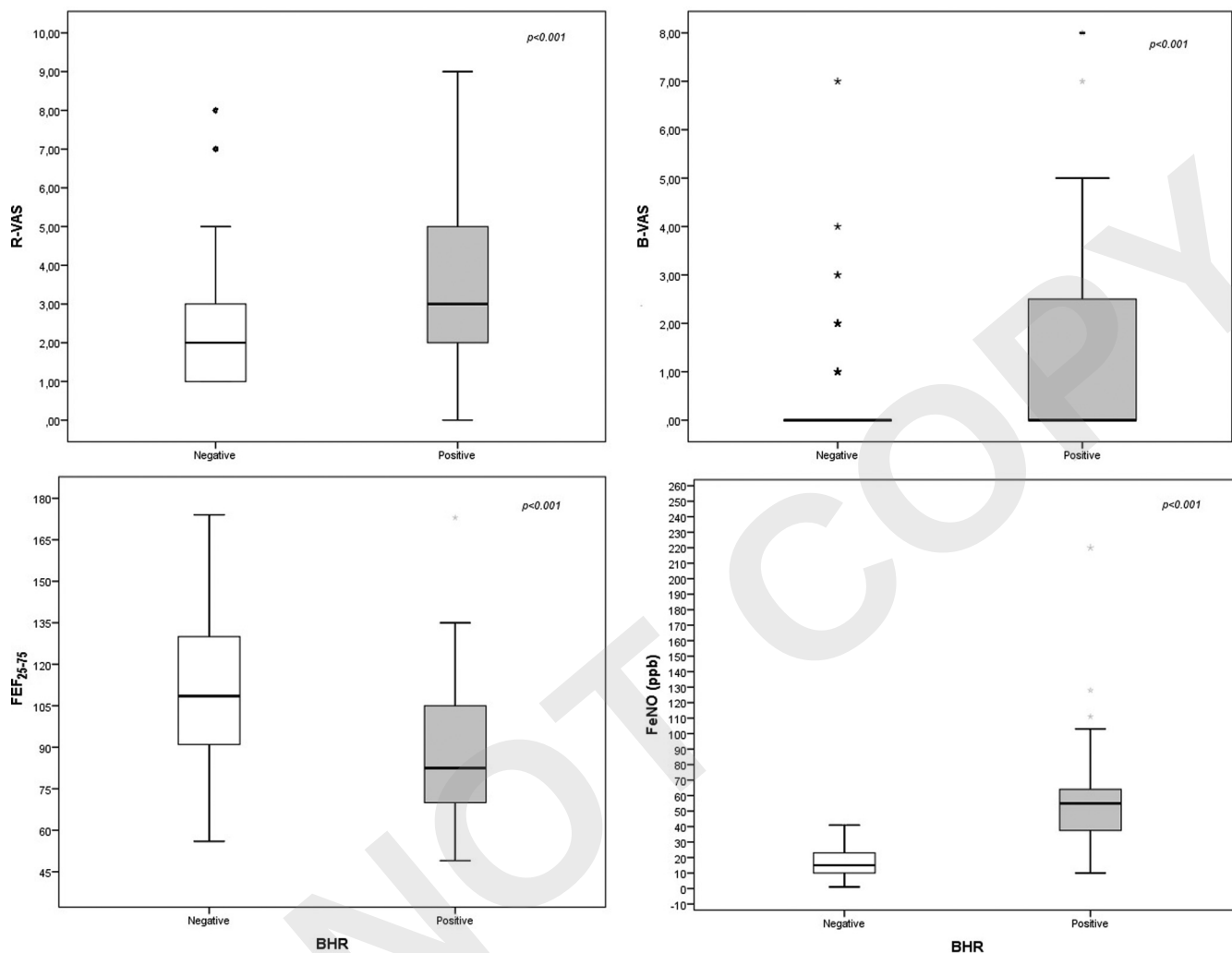


Figure 1. Statistically significant differences between BHR groups as regards to R-VAS, B-VAS, FeNO values, and FEF₂₅₋₇₅. BHR = bronchial hyperreactivity; R-VAS = rhino-visual analogue scale; B-VAS = bronchial-visual analogue scale; FEF = forced expiratory flow; FeNO = fractionated exhaled nitric oxide.

Table 3. Relationship between demographic and clinical variables both for negative and positive BHR rhinitis patients

		Negative BHR					Positive BHR				
		Age	Smoke	R-VAS	B-VAS	Duration	Age	Smoke	R-VAS	B-VAS	Duration
FVC	ρ	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	0.323	N.S.	N.S.
	(p-value)								(0.006)		
FEV ₁	ρ	N.S.	-0.202	N.S.	N.S.	-0.134	N.S.	N.S.	N.S.	-0.350	-0.297
	(p-value)		(0.002)			(0.042)				(0.003)	(0.012)
FEV ₁ /FVC	ρ	-0.252	-0.236	N.S.	N.S.	-0.160	-0.591	N.S.	N.S.	-0.237	N.S.
	(p-value)	(<0.001)	(<0.001)			(0.015)	(<0.001)			(0.046)	
FEF ₂₅₋₇₅	ρ	N.S.	-0.200	N.S.	-0.136	N.S.	N.S.	N.S.	N.S.	-0.360	-0.317
	(p-value)		(0.002)		(0.039)					(0.002)	(0.008)
FeNO (ppb)	ρ	N.S.	-0.309	N.S.	N.S.	N.S.	N.S.	-0.322	N.S.	N.S.	N.S.
	(p-value)		(<0.001)					(0.006)			
R-VAS	ρ	N.S.	N.S.			0.547	N.S.	N.S.			0.304
	(p-value)					(<0.001)					(0.010)
B-VAS	ρ	N.S.	0.132	0.314		0.236	0.275	N.S.	N.S.		0.334
	(p-value)		(0.045)	(<0.001)		(<0.001)	(0.021)				(0.005)

Results are expressed with Spearman's ρ (p-value).

N.S. = not significant; BHR = bronchial hyperreactivity; R-VAS = rhino-visual analogue scale; B-VAS = bronchial-visual analogue scale; FVC = forced vital capacity; FEV = forced expiratory volume; FEF = forced expiratory flow; FeNO = fractionated exhaled nitric oxide.

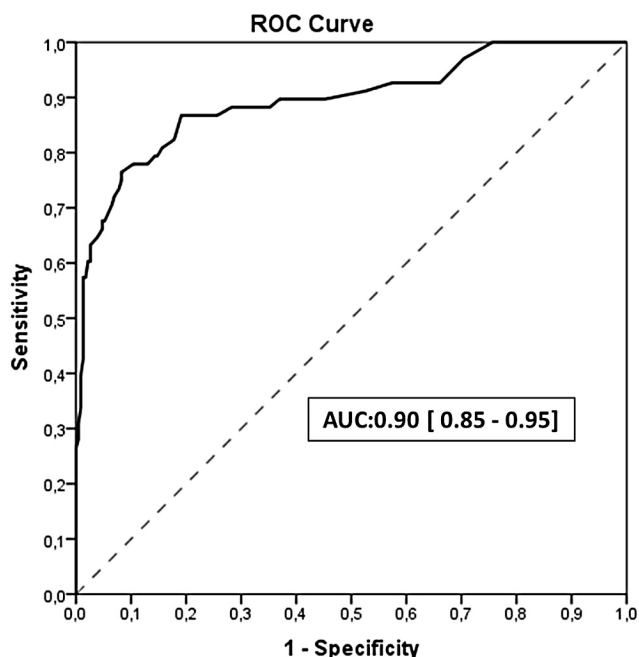


Figure 2. Evaluation of sensitivity and specificity of fractionated exhaled nitric oxide (FeNO) by a receiving operator characteristic (ROC) curve for a diagnosis of bronchial hyperreactivity (BHR).

BHR, even though the symptom perception was not evaluated.³² In addition, the present study is consistent with a recent population-based international study which reported that BHR predicted new-onset AR.³³

However, the present study has some limitations: 1) the high prevalence of males, 2) the relatively low number of patients, and 3) the lack of a follow-up to confirm these findings. In addition, data were presented on a continuum, including borderline subjects, but BHR may change over the time (for example after allergen exposure, respiratory infections, irritants, etc.). For this reason, further studies should be conducted to address these unanswered questions.

In conclusion, the present study demonstrates that BHR to MCH could define two distinct phenotypes in AR patients. It could be clinically relevant as BHR-positive patients have initial impairment of lung function, impaired FeNO values, and worsening of respiratory symptoms perception.

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