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Methacholine bronchial challenge effects on nasal symptoms and function in patients with allergic rhinitis

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Key words

Allergic rhinitis, bronchial hyperreactivity, methacholine challenge, VAS, symptom perception, rhinomanometry

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Summary

Background *Allergic rhinitis and asthma may be associated, bronchial hyperreactivity (BHR) is quite common in AR patients. It has been reported that allergen bronchial challenge induces nasal inflammation. Methacholine (MCH) is a stimulus able to elicit BHR. There is no study that investigated the effect of MCH bronchial challenge on the nose.* ***Objective*** *The aim of this study was to evaluate whether MCH bronchial challenge is able to induce changes in nasal symptom perception and nasal function in patients with AR.* ***Methods*** *122 patients (117 males, median age 28 years) suffering from AR were evaluated. Values for bronchial function (FVC, FEV1, FEF25-75, and FEV1/FVC ratio), MCH bronchial challenge, VAS for nasal and bronchial symptoms, and nasal airflow and resistance were assessed.* ***Results*** *23 patients (18.9%) had BHR. MCH bronchial challenge induced a significant reduction of nasal obstruction perception ($p<0.001$), but did not affect the nasal function. Most of patients (91) did not perceive impairment of respiration. The perception of nasal obstruction was strongly related to the AR duration ($r = 0.65$). The highest values of both baseline rhinoVAS and Δ bronchial VAS predicted BHR (OR 1.7 and 2.9 respectively).* ***Conclusions*** *The present study demonstrates that in AR patients MCH bronchial challenge does not substantially affect nasal symptoms and function, also in subjects with an acute bronchospasm, such as in BHR patients. However, severity of nasal obstruction perception might predict BHR.*

Introduction

Allergic rhinitis (AR) may be frequently associated with asthma, and it represents a main risk factor for asthma onset (1,2). It is well known that AR and asthma are closely related both from a pathophysiological and a clinical point of view. In this regard, many AR patients may have bronchial hyperreactivity (BHR): this condition may mean a bronchial involvement and may also suggest possible evolution in asthma: the so called "asthma march" (3). Therefore, the assessment of BHR in a patient with AR may have a relevant prognostic role and also a legal relevance in some context. BHR is usually assessed performing bronchial provocation testing, using a variety of stimuli, such as exercise, methacholine (MCH), histamine, or adenosine 5'-monophosphate (4). MCH bronchial challenge is the most used as it is well defined and validated, and rarely induces severe bronchospasm (4). MCH challenge has therefore become popular in the clinical practice.

On the other hand, it has been evidenced that local segmental bronchial allergen challenge may induce a bronchial inflammatory response as well as nasal allergen challenge may induce bronchial inflammation in allergic patients (5,6). A hypothesis to be tested is whether a non-allergenic bronchial stimulus, such as MCH, may be also

able to induce clinical and functional changes on the nose. However, there is no study (at our best knowledge) that investigated this issue in AR patients. Therefore, the aim of this study was to evaluate whether MCH bronchial challenge may induce changes on nasal symptom perception assessed by the visual analogue scale and on nasal function measured by rhinomanometry in patients with AR.

Materials and Methods

Patients

This cross-sectional study included 122 patients (117 males, mean age 28 years), suffering from allergic rhinitis. They were Navy soldiers who were referred to the Navy Medical Service for mandatory certification of their health status. The patients were enrolled in the study on the basis of a diagnosis of AR made by the concordance between positive skin prick test and presence of nasal symptoms after exposure to sensitizing allergen, according to validated criteria (1). Exclusion criteria were: any prior documented history of asthma or referral for asthma symptoms, including cough, wheezing, dyspnea, and shortness of breathing, impaired FEV_1 values (such as < 80% of the predicted) and <0.7 FEV_1/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 analysing carboxyhaemoglobin 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 4 weeks. Subjects under drug treatment or with acute upper respiratory airway infection returned after adequate time.
The Navy Review Board approved the study procedure and written informed consent was obtained from each subject.

Study Design

The visit included: clinical examination, visual analogue scale (VAS) assessment, skin prick test, nasal endoscopy, rhinomanometry, spirometry, and methacholine bronchial challenge. The visits were performed during the late winter. A detailed clinical history was taken and a complete physical examination was performed. Age, gender, smoking, duration of rhinitis, FVC, FEV_1, FEF_{25-75}, and FEV_1/FVC ratio, MCH PC_{20}, RhinoVAS and bronchial VAS, nasal airflow and resistance were registered for all patients in the analysis.
Nasal and bronchial symptom assessment by VAS as well as nasal airflow and resistance were measured both immediately before and after MCH bronchial challenge.

VAS assessment

VAS was used to assess the subjective perception of both nasal and bronchial respiration. RhinoVAS was used to measure the subjective perception of nasal respiration: it ranges from 0 (complete nose patency) to 10 cm (complete nose obstruction). Bronchial VAS was used to measure the subjective perception of breathlessness: it ranges from 0 (completely normal breathing) to 10 cm (severe dyspnoea). Patients were asked to position a cross on a line corresponding to their own perception of respiration as previously reported (7).

Skin prick test

It was performed as stated by the European Academy of Allergy and Clinical Immunology (8). The panel consisted of: house dust mites (*Dermatophagoides farinae* and *pteronyssinus*), cat, dog, grasses mix, *Compositae* mix, *Parietaria officinalis*, birch, hazel, olive tree, *Alternaria tenuis*, *Cladosporium*, *Aspergilli* mix (Stallergenes, Milan, Italy).

Spirometry

Spirometry was performed by using a computer-assisted spirometer (Pulmolab 435-spiro 235, Morgan, England–predictive values ECCS 1993), with optoelectronic whirl flow meter. It was performed as stated by the European Respiratory Society (9,10).

Methacholine bronchial challenge

Methacholine bronchial challenge was performed in order to evaluate BHR only if basal FEV_1 was equal or more than 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

(6). The threshold concentration causing a 20% fall of FEV_1 (PC_{20}) was calculated. Subjects without response to the cumulative dose of 16 mg/ml were considered having normal bronchial responsiveness.

Rhinomanometry

Nasal airflow and resistance were measured by active anterior rhinomanometry (ZAN 100 Rhino Flow Handy II, ZAN, Messgeraete Gmbh, Germany) according to International Guidelines to avoid bias due to individual variability (11). Nasal airflow was reported as the sum of recorded airflow through right and left nostrils in milliliter per second at a pressure difference of 150 Pa across the nasal passage. Four or more airflow measurements were performed for each patient and the mean was recorded when reproducible values were achieved.

Statistical analysis

Mean and standard deviation (SD) or median and interquartile range (IQR) were reported for continuous features. Bronchial hyperreactivity (BHR) was categorized as "negative" (threshold of 1590) or "positive" (values under 1590) response. Changes after methacholine administration compared to baseline on rhinoVAS and bronchial VAS were assessed by mean of non-parametric Wilcoxon paired samples test, while changes on nasal airflow and resistance were assessed by mean of Student's t-test for paired samples. For nasal airflow and resistance analysis was performed both on overall sample and in the subgroups with positive or negative BHR. Differences between groups of BHR (positive/negative), deviation of nasal septum (yes/no) and hypertrophy of nasal septum (yes/no) on change after methacholine were assessed by means of Student's t-test for independent samples for nasal airflow and resistance and non-parametric Mann-Whitney test for rhinoVAS and bronchial VAS. Pearson's correlation coefficient was used to assess correlation between spirometric and rhinomanometric characteristics at baseline and change after MCH for nasal airflow and resistance. Spearman's rank coefficient was preferred for rhinoVAS. For the purpose of this analysis, correlation coefficients were considered as follows: ≥0.8 = very strong; 0.6 to 0.79 = strong; 0.4 to 0.59 = moderate; 0.2 to 0.39 = weak; and <0.2 = very weak (12).

Then, different multivariate linear models, with change after MCH challenge used as dependent variable, were performed to valuate which clinical and/or spirometric characteristics had an impact on both nasal airflow and resistance after MCH challenge. Only characteristics, which resulted significant at a univariate analysis, were considered, and final selection was performed by mean of stepwise selection.

Finally, a logistic regression model with BHR status (positive/negative) as binary dependent variable was performed to assess if some nasal characteristics could predict positive BHR. Odds-ratio (OR) and 95% CI were calculated.

A p-value of 0.05 was considered statistically significant and SPSS version 18 (IBM Corp.; New York, USA) was used for analysis.

Results

Clinical and functional characteristics

Table 1 shows the characteristics of patients: mean age was 28 years, and 117 were males. The median duration of rhinitis was 3 years. One hundred (82%) patients were not smokers. The median RhinoVAS was 2 before MCH bronchial challenge; most of patients (92.6%) reported a

Table 1 - Demographic, clinical, and functional characteristics of patients

Characteristics	Mean (SD) / Median (IQR) / N(%)
Age	28 (5)
Gender	
Females	5 (4.1)
Males	117 (95.9)
Rhinitis duration (years)	3 (1 – 7)
Smokers	22 (18)
RhinoVAS	2 (1 – 3)
Nasal airflow	643 (600 – 770)
Nasal resistance	0.24 (0.07)
FVC (% predicted)	107 (10)
FEV1 (% predicted)	110 (11)
FEF25-75 (% predicted)	110 (26)
FEV1/FVC ratio	87 (5)
BHR	
Negative	99 (81.1)
Positive	23 (18.9)

IQR: Interquartile range; SD: Standard Deviation

bronchial VAS corresponding to 0 before MCH challenge, only 9 patients reported a value between 1 and 2. The median nasal airflow value was 643 and the mean nasal resistance value was 0.24. Regarding lung function, all spirometric parameters were within the normal reference values: the mean FVC was 107% of predicted, the mean FEV_1 was 110% of predicted, the mean FEF_{25-75} was 110, and the mean FEV_1/FVC ratio was 87. About BHR, only 23 patients (18.9%) resulted positive to MCH challenge.

At endoscopic assessment, a light hypertrophy of inferior turbinate was found in 65 patients (53.3%), while only 20 patients (16.4%) showed a deviation of nasal septum.

Effect of MCH bronchial challenge on the nose

RhinoVAS significantly decreased after MCH bronchial challenge ($p<0.001$): with a median value of 1 (IQR: 1 – 3) compared to a median value of 2 (IQR : 1 – 3) at baseline. On the contrary, no significant changes were found for both nasal airflow ($p = 0.95$) and nasal resistance ($p = 0.82$) after MCH challenge (Table 2). No significant differences after MCH were also found for bronchial VAS ($p = 0.49$): 107 patients (87.7%) showed 0 at baseline and maintained this value after MCH challenge. Vice-versa, within the remaining patients: 7 decreased bronchial VAS value after MCH, while 8 increased their values.

Further, the patients were subdivided in two sub-groups according to the response (positive or negative) to MCH bronchial challenge: BHR positive and BHR negative.

The intragroup analysis showed that in BHR positive patients nasal airflow and resistance did not modified after MCH challenge, while rhinoVAS significantly diminished ($p = 0.005$). Also in BHR negative patients, a difference was significant for rhinoVAS after MCH ($p < 0.001$), while MCH challenge did not induce any significant change of the nasal function parameters (Table 2).

The intergroup analysis showed that there were no significant differences between positive and negative BHR patients concerning all nasal parameters after MCH (Table 2). Only regarding change on bronchial VAS, a difference, also if not completely significant ($p = 0.062$), was observed between positive and negative patients to BHR. In fact, on a total of 8 patients for which bronchial VAS increased, 3 patients were in positive-BHR subgroup, while all 7 patients who decreased bronchial VAS values were negative-BHR.

Table 2 – Clinical characteristics after methacholine challenge and differences compared to baseline

	Overall (n = 122)		BHR-positive (n = 23)		BHR-negative (n = 99)		p for difference between BHR groups on change
	Mean(SD)/ Median(IQR)/ N(%)	p*	Mean(SD)/ Median(IQR)/ N(%)	p*	Mean(SD)/ Median(IQR)/ N(%)	p*	
RhinoVAS baseline	2 (1 – 3)	< 0.001	3 (2 – 4)	0.005	2 (1 – 3)	< 0.001	0.69
RhinoVAS after MCH	1 (1 – 3)		2 (1 – 3)		1 (1 – 3)		
Bronchial VAS baseline							
0	113 (92.6)		22 (95.7)		91 (91.9)		
1	6 (4.9)	0.49	1 (4.3)	0.10	5 (5.1)	0.80	0.062
2	3 (2.5)		0		3 (3)		
Bronchial VAS after MCH							
0	111 (91)		19 (82.6)		92 (92.9)		
1	9 (7.4)		3 (13)		6 (6.1)		
3-4	2 (1.6)		1 (4.3)		1 (1)		
Nasal airflow at baseline	643 (600 – 770)	0.95	623 (607 – 707)	0.58	645 (592 – 776)	0.70	0.48
Nasal airflow after MCH	644 (602 – 744)		633 (605 – 680)		650 (601 – 755)		
Nasal resist. at baseline	0.24 (0.07)	0.82	0.24 (0.06)	0.69	0.24 (0.08)	0.72	0.70
Nasal resist. after MCH	0.25 (0.09)		0.24 (0.03)		0.25 (0.1)		

*SD: Standard deviation; IQR: Interquartile range; *p–value for difference after methacholine compared to baseline*

Moreover, no difference on change after MCH both for nasal airflow and resistance was observed considering the presence or absence of hypertrophy of inferior turbinate ($p = 0.52$ for nasal airflow; $p = 0.34$ for nasal resistance) or of nasal septum deviation ($p = 0.50$ for nasal airflow; $p = 0.26$ for nasal resistance). Similar results were found considering difference on rhinoVAS and bronchial VAS after MCH. In fact, no difference was found considering the presence of hypertrophy of inferior turbinate ($p = 0.75$ rhinoVAS, $p = 0.20$ bronchial VAS) or of nasal septum deviation ($p = 0.93$ rhinoVAS, $p = 0.55$ bronchial VAS).
Table 3 shows correlations between changes after MCH challenge for rhinomanometric values, demographic, and spirometric continuous characteristics. Particularly, the difference of nasal airflow after MCH compared to baseline (Δ) was significantly and directly, even though weakly, correlated with FEV1 ($r = 0.18$; $p = 0.043$), FEF_{25-75} ($r = 0.20$; $p = 0.025$), FEV1/FVC ($r = 0.18$; $p = 0.049$), while a negative weak correlation was observed with baseline nasal airflow ($r = -0.30$; $p = 0.001$), duration of rhinitis ($r = -0.31$; $p < 0.001$), and baseline rhinoVAS ($r = -0.20$; $p = 0.025$). Further, a significant negative weak correlation was found between Δ rhinoVAS and Δ nasal airflow after MCH challenge ($r = -0.25$; $p = 0.006$). Finally, there was a strong significant direct relationship between rhinoVAS at baseline and rhinitis duration ($r = 0.65$; $p < 0.001$).
In addition, after multivariate linear models for nasal airflow, the most important characteristics, impacting on its Δ, resulted: i) rhinitis duration ($p = 0.006$), ii) baseline nasal airflow ($p < 0.001$), iii) FEF_{25-75} ($p = 0.015$,) and iv) Δ of rhinoVAS ($p < 0.001$), with the same direction of association found from correlation coefficient.
From multivariate logistic regression, one-unit increase of baseline rhinoVAS (OR = 1.70; 95% CI: 1.24 – 2.32; $p = 0.001$) and Δ of bronchial VAS (OR = 2.91; 95% CI: 1.13 – 7.50; $p = 0.027$) were associated with an increased probability of positive BHR.

Discussion

The nose and the bronchi are closely related from a pathophysiologic point of view. In particular, it has been evidenced that AR frequently precedes asthma onset. In this regard, the duration of rhinitis and sensitization to perennial allergens were demonstrated to be relevant risk factors for: impairment of FEV_1 (13), positive response to bronchodilation test (14), and positive response to MCH bronchial challenge (15). On the other hand, it has been evidenced that a local segmental bronchial allergen challenge was able to induce also a nasal inflammation (6). Therefore, it seems to exist a bi-directional talking between the nose and the bronchi about the allergic inflammation. In this regard, the nasal disorders may affect lung function on the basis of some pathophysiological mechanisms, including a vagal naso-bronchial reflex, a *continuum* progression of respiratory allergic inflammation (from the nose to the smallest bronchi), the release of mediators

Table 3 - Correlation between basal spirometric and rhinomanometric characteristic and difference of rhinomanometric characteristics after methacholine challenge

		Age	Rhinitis duration	Basal FVC	Basal FEV1	Basal FEV1\FVC	Basal FEF25-75	PC20	Basal nasal airflow	Δ nasal airflow after MCH	
PC20^	r	-0.029	-0.062	0.148	0.094	-0.144	-0.054	-			
	P-value	0.89	0.78	0.50	0.67	0.51	0.81				
Basal nasal airflow	r	-0.035	0.029	0.130	0.191*	0.167	0.177*	0.028	-		
	P-value	0.70	0.748	0.154	0.035	0.066	0.05	0.90			
Δ nasal airflow	r	0.057	-0.313***	0.075	0.184*	0.179*	0.203*	-0.043	-0.303**	-	
after MCH	P-value	0.54	<0.001	0.415	0.043	0.049	0.025	0.85	0.001		
Basal	r	0.043	0.647***	-0.027	-0.032	-0.007	-0.088	0.17	0.044	-0.203*	
rhinoVAS	P-value	0.64	<0.001	0.77	0.73	0.94	0.33	0.43	0.63	0.025	
Δ rhinoVAS	r	0.029	0.25	-0.11	-0.17	-0.15	-0.14	0.33	-0.15	-0.25	
after MCH	P-value	0.75	0.006	0.24	0.06	0.09	0.12	0.13	0.10	0.006	

**p < 0.05; **p < 0.01; ***:p < 0.001 ; ^: considering only BHR-positive patients*

into the blood stream, the post-nasal drip, and the oral respiration consequent to nasal obstruction. This last mechanism is probably the most important as the oral respiration inhibits the nasal function, such as wetting, warming, and filtering the inspired aria. In other words, nasal obstruction causes the inhalation of air relatively dry and cold so stimulating a bronchial hyperreactivity. However, there was no study that has investigated the possible effect of a pharmacologic bronchial stimulus on the nose, concerning nasal function and symptom perception. Therefore, the present study was designed to test this hypothesis. The primary outcome was to investigate whether MCH bronchial challenge could affect nasal function, both concerning nasal airflow and resistance, and/or the perception of nasal obstruction. Secondary outcomes were: i) to assess whether MCH bronchial challenge could induce change in the perception of breathing, ii) to detect whether there is a difference between BHR positive and negative patients, and iii) to identify a possible predictive factor at nasal level for BHR.

Firstly, about the primary outcome, this study demonstrated that MCH bronchial did not affect both the nasal airflow and resistance, also considering the presence of BHR. This fact may fairly sound as MCH nasal challenge mainly induces increased mucous secretion, but does not affect the nasal air passage (16). Moreover, anticholinergic agents are able of reducing rhinorrhea alone (17), without modifying other nasal symptoms. Another important issue may be speculated: the different responses induced by an allergen challenge or by a pharmacologic stimulus. Allergen challenge causes an inflammatory response that occurs in a systemic way, whereas MCH bronchial challenge acts eminently at local level. In fact, allergic inflammation and BHR constitute two separate and dissociated pathophysiological events (18). Moreover, these findings outline the substantial difference between inflammatory phenomena and BHR: the first systemic and common to all allergic patients, the second limited to the target organ and present in a restricted percentage of patients. On the other hand, the perception of nasal obstruction was significantly affected by MCH bronchial challenge, even patients referred a reduction of perceived nasal obstruction. However, this significant result could be not clinically relevant as the baseline values were particularly low such as corresponding to mild rhinitis (19). In fact, patients were evaluated in the late winter when the global allergen pressure is rather low and so allergic inflammation and consequently symptoms. Therefore, the reported reduction of perceived nasal symptom could be attributable to psychological factors that deserve further in depth studies.

Secondly, MCH bronchial challenge did not significantly affect the breathing perception, also in all BHR positive patients, but one. This finding could be explained by two main reasons: the presence of poor perceivers and the negative history for bronchial symptoms as the patients suffered from AR alone. On the other hand, BHR positive patients had worst perception of nasal obstruction than BHR negative ones, even though there was no difference about the nasal function in the two sub-groups. In addition, even if the relationships were weak, there was a strong relationship between the duration of AR and the level of perceived nasal obstruction before MCH challenge.

Thirdly, this study identified a possible nasal predictive factor for BHR: the severity of nasal obstruction perception. It was previously reported that there was a positive relationship between VAS assessment of nasal obstruction and nasal airflow (20) as well as a study evidenced that nasal airflow was positively related to bronchial airflow and BHR is frequently related with lung function (21). Thus, the perception of stuffy nose could suggest the possible existence of BHR in AR patients.

This study partially confirms a previous study conducted on children that showed a relationship between nasal airflow and BHR, even though the symptom perception was not evaluated (22).

The present study has some limitations: i) the high prevalence of males, ii) the mild severity of AR, iii) the lack of measuring mediators of inflammation, and iv) the relatively low number of patients. For this reason, further studies should be conducted to address these answered questions.

In conclusion, the present study demonstrates that in AR patients MCH bronchial challenge, does not substantially affect nasal symptoms and function, also in subjects with an acute bronchospasm, such as in BHR patients. However, severity of nasal obstruction perception might predict BHR.

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