

Histamine nasal provocation test

An evaluation of active anterior rhinomanometry and of threshold criteria of provocative dose

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This study is a methodological approach to histamine nasal provocation. The test uses active anterior rhinomanometry and a histamine titration method, challenging both nasal cavities with a metered dose pump. It has been confirmed that the histamine nasal provocation test can differentiate between controls and non-allergic rhinitis patients. This study shows, moreover, that the method is more sensitive in assessing response to histamine provocation when a 25 % increase of post-saline nasal airway resistance (PD₂₅) is considered than a PD₅₀ or PD₁₀₀ criterion. The histamine response, was found to be independent of the baseline nasal airway resistance value. Pronounced unilateral responsiveness was frequently noticed. Both nasal cavities should be challenged and the most reactive side considered.

Key words: active anterior rhinomanometry; histamine nasal provocation test; histamine threshold; non-allergic rhinitis.

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Standardization of nasal provocation tests is still controversial and there does not appear to be sufficient agreement about the recommendations for a standardized method of nasal provocation testing. One of the reasons is the paucity of methodological studies, although the need to standardize methods has been recently emphasized (14).

Several authors have demonstrated that nasal histamine provocation tests can differentiate controls from non-allergic rhinitis patients (2, 4), although others have been unable to confirm this (9, 12).

This study presents further efforts to standardize nasal provocation testing. Our aims were to establish whether unilateral or bilateral nasal cavity challenge was more appropriate, whether baseline nasal airways resistance

(NAR) influenced the subsequent response to challenge, and which method of assessing the dose response curves discriminated best between normals and subjects with non-allergic rhinitis.

Histamine was chosen as the provocation agent because of its direct, local effect on nasal capacitance vessels and the apparent lack of tachyphylaxis with respect to nasal congestion (8).

MATERIAL AND METHODS

Subjects

Eleven control subjects (6 men and 5 women) and 53 patients (28 men and 25 women) with

Table 1

Histamine provocation test
Effect of study design and unilateral responsiveness on overall achievability of thresholds at provocative dose

	Total <i>n</i>	No. $R_2 > R_1$	R_1 not reaching			R not reaching		
			PD ₂₅	PD ₅₀	PD ₁₀₀	PD ₂₅	PD ₅₀	PD ₁₀₀
Controls	11	3	1	3	7	0	2	6
Non-allergic rhinitis	53	13	7	9	20	3	9	20

non-allergic rhinitis were included. The controls had no rhinological complaints. The non-allergic rhinitis patients had typical perennial complaints of nasal obstruction, sneezing and aqueous rhinorrhoea.

Both groups had negative allergen skin tests for grass pollen, weed pollen, tree pollen, house dust, *Dermatophagoides pteronyssinus*, animal dander and moulds, and a negative RAST (specific IgE determination by the Phadebas RAST method provided by Pharmacia, Brussels, Belgium) score for these allergens.

They had no history of infectious rhinitis for at least 2 months prior to the study.

Methods

NAR was measured by active anterior rhinomanometry (AAR) at baseline and 10 min after delivery to each nostril of 100 μ l aerosol (a metered dose appliance (Société Technique de Pulvérisation, 10 rue Singer 75016 Paris, France) was used to deliver 100 μ l of aerosol, with a particle size of $\pm 150 \mu$.) containing isotonic saline, and 25, 50, 100, 200 and 400 μ g histamine (Haarlem Allergen Laboratories, Haarlem, The Netherlands) at 10 min intervals.

AAR was performed according to the recommendations of the committee report on rhinomanometry (3). The subjects were instructed to breathe quietly through the nose. A nose and mouth mask (Laerdal Silicon Masks), connected to a laminar flow meter (Pneumotachograph, A. Fleisch No. 1) and a differential pressure transducer (Siemens), was applied to the subject's face achieving an airtight seal.

The airflow was measured through the unobstructed and unchanged nostril while the posterior nasal pressure was obtained by measuring the pressure in the other nostril, which was obstructed by the pressure transducer. This manoeuvre was made on both sides. Flow-pressure curves were recorded during quiet nasal respiratory on a fast X-Y recorder (Hewlett-Packard 7045B).

The resistance in each nasal cavity was computed on the basis of the arithmetic mean of 5 inspiratory and expiratory curves at 150 Pa pressure difference.

Total NAR was computed assuming laminar flow and a parallel system.

The test was continued until the NAR of one nasal cavity had increased by 100 % or until the highest dose had been administered.

The symbol R denotes the total NAR: R_1 the resistance of the nasal cavity reacting least to histamine challenge, and R_2 the resistance of the nasal cavity reacting most.

The first dose of histamine producing at least a 25 %, 50 % and 100 % rise in post-saline baseline NAR was called provocative dose PD₂₅, PD₅₀ and PD₁₀₀.

Statistics

Whenever possible, parametric tests (analysis of variance, Student's *t* test) were carried out. This was applicable for comparing nasal resistance of patients and controls before nasal provocation.

As the histamine nasal provocative doses were not normally distributed, the non-parametric Mann-Whitney U-test was performed using original data (16).

RESULTS

The baseline total NAR (R) of controls (2.32 ± 0.5 kPa/l⁻¹/s) and non-allergic rhinitis patients (3.34 ± 1.3 kPa/l⁻¹/s) are significantly different ($P < 0.01$).

Due to the study design, the test was stopped when R_2 increased by 100 %. Inevitably in a number of cases R_1 and R did not reach the threshold value of 25 %, 50 % or 100 % increase.

Table 1 gives a survey of the impact of this study design, showing the number of persons in whom the total NAR R , or the NAR of the least reactive side (R_1) did not increase sufficiently to meet the criteria for PD₂₅, PD₅₀ or PD₁₀₀.

Moreover, Table 1 shows the number of patients and controls in whom the baseline R_2 was lower than the baseline R_1 , i.e. in whom the most patent nasal cavity reacted earlier to histamine challenge than the most obstructed nasal cavity. This occurred in one quarter of the tests.

In further statistical work the patient or control not obtaining a specific PD was not entered into the calculations. This considerably biased the value of an item, as for instance in the case of PD₁₀₀ and R_1 , the value was not obtained in 7 of 11 controls and 20 of 50 non-allergic rhinitis patients.

To know which index value of the increase from baseline NAR best differentiates the controls from the non-allergic rhinitis group, and to evaluate the impact of measuring one or both nasal cavities, nine Mann-Whitney U-tests

Table 2

Nasal provocation tests. Mann-Whitney U-test: controls vs non-allergic rhinitis patients

	PD ₂₅	PD ₅₀	PD ₁₀₀
R_1	ts = 3.21	ts = 3.17	ts = 3.01
R_2	ts = 4.09	ts = 2.71	ts = 1.33 NS
R	ts = 3.97	ts = 3.41	ts = 2.87

Test statistic (ts) must be compared to provide a two-tailed test ($P = 0.05$) with table-value 1.96 NS: non-significant

Table 3

Analysis of variance: provocative dose vs baseline R_1 and R_2

	VR	Table value F	Result
PD ₂₅	1.01	2.32	NS
PD ₅₀	1.83	2.47	NS
PD ₁₀₀	2.15	2.32	NS

VR: variance ratio; F: test statistic; NS: non-significant

were performed for the different situations. The results of these M-W U-tests are summarized in Table 2.

The calculated test statistics ts-values are an indirect measure of overlapping between groups: higher U-values give less overlapping, better separation and higher discrimination power. The highest ts-values are found for the PD₂₅ criterion analysing R and R_2 .

Table 3 represents the results of an analysis of variance evaluating the impact of the initial baseline R_1 and R_2 values on the ultimate provoking histamine dose. No statistical relationship was found, and it could be concluded that the initial baseline NAR did not influence the ultimate PD.

The calculated mean and standard deviations of histamine PD₂₅ for controls and non-allergic rhinitis patients are shown in Table 4.

DISCUSSION

AAR was the method chosen for assessing nasal obstruction as it is the most sensitive way of measuring the NAR of both nasal cavities sep-

Table 4

PD₂₅ in mg/ml solution (100 µl delivery)

	Controls Mean SE	Patients Mean SE
R_1	2.59 ± 0.39	0.56 ± 0.19
R_2	1.14 ± 0.12	0.35 ± 0.08
R	1.30 ± 0.14	0.42 ± 0.06

arately. Although the determination of total NAR by active posterior rhinomanometry appeared to be more correct (5), AAR is superior to other measuring systems such as passive anterior rhinomanometry (4, 13). Also the reproducibility of AAR appeared to be good (4). The sole index of NAR adapted is the NAR value calculated at the pressure difference of 150 Pa. Although other indices (e.g. Rohrer's constants) can be used, it was not the aim of the present study to evaluate their different values. The one chosen has been widely advocated and recommended by the committee reports on standardization of rhinomanometry (3). The authors wanted to propose threshold criteria that can be used in a routine clinical setting, without needing computing facilities.

In our material the controls had significantly lower total NAR than the non-allergic rhinitis patients ($P < 0.01$). This has also been reported by others (2, 4, 12).

Irrespective of the provocative threshold chosen, we have demonstrated that the initial NAR value did not influence the provocative dose (Table 3). From this finding it may be concluded that the difference in mean total NAR of the controls and patients does not diminish the diagnostic value of the histamine nasal provocation test. However, some authors reported an inverse relationship between the post-saline NAR and the PD (7).

It is noted that both nasal cavities do not respond equally to histamine challenge. These findings are in agreement with those of other authors (6). In 25% of the subjects tested, the most patent nasal airway reacted first.

From this observation it is concluded that we can not foresee which nasal side will react first. The corollary is that both nasal cavities have to be challenged and measured.

In many cases total NAR, R and R_1 (NAR of the least reactive side) did not attain the PD. This is not only due to the study design but also to the sometimes pronounced unilateral responsiveness of the nasal cavities. This finding considerably reduces the value of R_1 and hence of R. In some cases the clear advantage of measuring the most reactive side to the total NAR (R) was demonstrated (6).

Table 2 summarizes the Mann-Whitney U-values resulting from comparison of the PD_{25} , PD_{50} and PD_{100} and considering the R, R_1 and R_2 of controls and non-allergic rhinitis groups. Our approach for determining the best clinical test (PD_{25} , PD_{50} or PD_{100} of R_1 , R_2 or R) is based on the idea that the best clinical test will produce the most significant results in the statistical analysis.

The results of the Mann-Whitney U-test indicate that PD_{25} of R_2 is the most valuable clinical test. This means that PD_{25} produces the least overlap of groups and we can confirm that, using the PD_{25} criterion, the histamine nasal provocation test can differentiate between controls and non-allergic rhinitis patients.

The second best choice is the PD_{25} of R, but we have to take into account that the unilateral responsiveness of the nasal cavities influences this result and that in some patients PD_{25} may not be reached.

The probability of $P < 0.05$ for R_2 and PD_{100} found by Clement et al. (3) was not found by us. Our results confirm those of McClean et al. (4) and Guercio et al. (5), who could demonstrate no differentiation between controls and non-allergic rhinitis patients when using the PD_{100} criterion.

However, many authors used the PD_{100} criterion (7, 10). Others use such threshold criteria as PD_{30} (1), or PD_{40} (15) mainly for the evaluation of pharmacological studies.

No other studies evaluated the ability of various indices other than the 100% increase of resistance (PD_{100}) to separate controls and non-allergic rhinitis patients.

The phenomenon that a higher percentage increase in resistance (e.g. PD_{100}) was less discriminating than a lower resistance increase (e.g. PD_{25}) was formerly noted in the search for the ideal PD for histamine bronchial inhalation challenges (16).

CONCLUSION

We can conclude from the results of this study that both nasal cavities should be challenged and measured. Histamine nasal provocation testing using a metered dose pump delivery

system and assessing nasal blockage by active anterior rhinomanometry can differentiate between controls and non-allergic rhinitis patients.

The PD₂₅ of the most reactive side (R₂) discriminated better between controls and non-allergic rhinitis patients than the PD₅₀. The PD₁₀₀ criterion was unable to discriminate either group.

There was no effect of the initial baseline NAR on the provocative dose.

Further studies are needed to find the most suitable PD as the most widely used assessment index, i.e. doubling the nasal airway resistance, is not the most sensitive method (17).

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