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Evaluation of acoustic rhinometry in a nasal provocation test with allergen

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Key words: acoustic rhinometry; allergen provocation; allergic rhinitis; clinical score; congestion; nasal challenge; obstruction; peak nasal inspiratory flow.

Background: The objective was to validate acoustic rhinometry (AR) in a nasal challenge with allergen.

Methods: Nasal response to allergen provocation was based on clinical and symptom scores, cross-sectional changes of the nasal mucosa as measured by AR with the Rhinolack[®] system, and peak nasal inspiratory flow (PNIF), in atopic and nonatopic volunteers.

Results: After allergen challenge, mean variation in minimal cross-sectional area (Δ MCA), as measured by AR, or in peak nasal inspiratory flow (Δ PNIF) in nonatopic volunteers, was $-0.4 \pm 14.3\%$ and $5.2 \pm 15.7\%$, respectively, compared to baseline. This allowed the determination of a reaction threshold of -29% for Δ MCA and of -26% for Δ PNIF. All but one of the 30 atopic patients reached the AR reaction threshold, whereas all patients reached the PNIF reaction threshold. AR and PNIF closely correlated with clinical and symptom scores for nasal congestion, since there was no significant difference at reaction threshold between both methods.

Conclusions: In an allergen provocation test, AR appears to be as specific and sensitive as peak nasal inspiratory flow, with the advantage of being independent of the patient's active cooperation. Discrepancies between both methods emphasize the role of nasal cavity anatomy in measuring nasal congestion by AR.

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Apart from their relevance to clinical research trials, nasal challenges with allergen are often decisive in the diagnosis of allergic rhinitis when clinical history, skin prick tests (SPT), and specific IgE may not completely establish the

atopic nature of rhinitis. Peak nasal inspiratory flow (PNIF) and anterior rhinomanometry are long-established methods to evaluate nasal provocation tests with allergen (1–3). However, PNIF is limited by the need for the patient's active cooperation in the tests and its dependence on lung capacity. Rhinomanometry, which measures nasal resistance, is particularly difficult to perform in patients with allergic rhinitis who suffer mainly from nasal obstruction, as described by Scadding et al. (4). Furthermore, rhinomanometry does not closely correlate with the nasal mucosa reaction to allergen challenge because the mucosal reaction to allergen can be only circumscribed, without changes in the nasal resistance (5). Acoustic rhinometry (AR) is based on sound-reflection analysis and provides an estimate of the cross-sectional area of the nasal cavities as a function of the distance from the nostril. In contrast to PNIF, AR does not require the patient's active cooperation (6). AR has mainly been used in the pre- and postoperative evaluation of patients with impaired nasal patency due to septal deviation or turbinate abnormality (7), and to monitor therapeutic trials for seasonal rhinitis and nasal polyps (8–10). So far, there has been only limited evaluation of AR in nasal provocation tests with allergen (11–14). We here compare AR and PNIF in atopic patients with perennial or seasonal symptoms, and demonstrate that AR is as sensitive and specific as PNIF. AR should be considered a useful method to evaluate not only nasal anatomy, but also allergic response in provocation tests.

Material and methods

Patients

Fifty subjects were included in the study:

- 1) atopic patients with allergic rhinitis ($n=30$: 18 men, 12 women; mean age 30 ± 8 years, range 18–50), based on a clinical history of seasonal or perennial rhinitis, positive SPT (SmithKline Beecham, Bencard Allergy Research Unit, Epsom, Surrey, UK), and/or specific serum IgE (Pharmacia CAP System, Uppsala, Sweden) for the allergens used in the provocation test
- 2) nonatopic volunteers (control group) ($n=20$: 11 men, nine women; mean age 32 ± 8 years, range 23–58), including 12 healthy volunteers (no history of allergic rhinoconjunctivitis, negative SPT, and no specific IgE for the allergen chosen in the nasal provocation test), and another eight subjects with a history of chronic nonatopic perennial rhinitis and negative SPT.

All the patients with seasonal rhinitis were studied out of the season. Patients with active upper airway infection and asthma were excluded. Topical nasal vasoconstrictors, cromoglycate, or steroids had to be withdrawn at least 1 month before the provocation test. A wash-out period of 2 weeks for antihistamines (6 weeks for astemizole), and of 4 weeks for systemic steroids was required before skin testing and provocation test. The clinical protocol was approved by the hospital review board. Informed consent was obtained from all subjects before the provocation test.

AR and peak nasal inspiratory flow

AR is described in detail elsewhere (6, 8, 14, 15) (RHINOKLACK® RK1000, Stimotron Medizinische Geräte, Wendelstein, Germany). A wave tube was introduced into nostrils with an angle of 45° and fit tightly with a nose piece. An audible sound pulse was propagated into nasal cavities. Local changes in acoustic impedance after challenge were expressed as changes in cross-sectional area (cm^2). In this study, minimal cross-sectional area (MCA) measured at the head of the inferior turbinate was used as end point (16). Three measurements in each nasal cavity were performed during quiet oral respiration within about 1 s at each allergen concentration and automatically integrated by computer. PNIF (l/min) was measured by a Youtlen peak nasal inspiratory flow meter (Airmed, Clement Clarke International Ltd, London, UK). Three consecutive measurements were performed. Only the maximal value was used for calculation.

Nasal provocation test

The nasal provocation test was performed as described by Terrien et al. (14). Briefly, a volume of 0.2 ml of diluent (NaCl 5 mg/ml, NaHCO_3 2.5 mg/ml, phenol 5 mg/ml) (ALK, Hørsholm, Denmark) was administered in each nostril on the anterior part of the inferior turbinate with a De Vilbiss pulverizer. After 10 min, anterior rhinoscopy was repeated to establish the initial clinical score, and baseline measurements for MCA and PNIF were performed. Rhinoscopy, and MCA and PNIF measurements were repeated at 10-min intervals after challenge with 0.2 ml allergen extract per nostril, reconstituted in albumin/phenol (successively 30, 300, 1000, 3000, 10 000, 30 000, and 100 000 BU/ml) (Fig. 1).

Determination of nasal reaction threshold

With either AR or PNIF, the arithmetic difference between each individual value obtained at any allergen concentration and the baseline value obtained with the diluent in nonatopic volunteers was expressed as a percentage of baseline value (Δ MCA or Δ PNIF in %). All results at each allergen concentration were pooled for calculation of Δ mean. Cutoff value (reaction threshold) for a significant decrease in AR or PNIF was defined as the mean of all Δ MCA or Δ PNIF in control group plus 2 SD (95% CI).

Clinical and symptom scores

A clinical score was established on the basis of anterior rhinoscopy (Karl Zeiss microscope, Germany) to evaluate

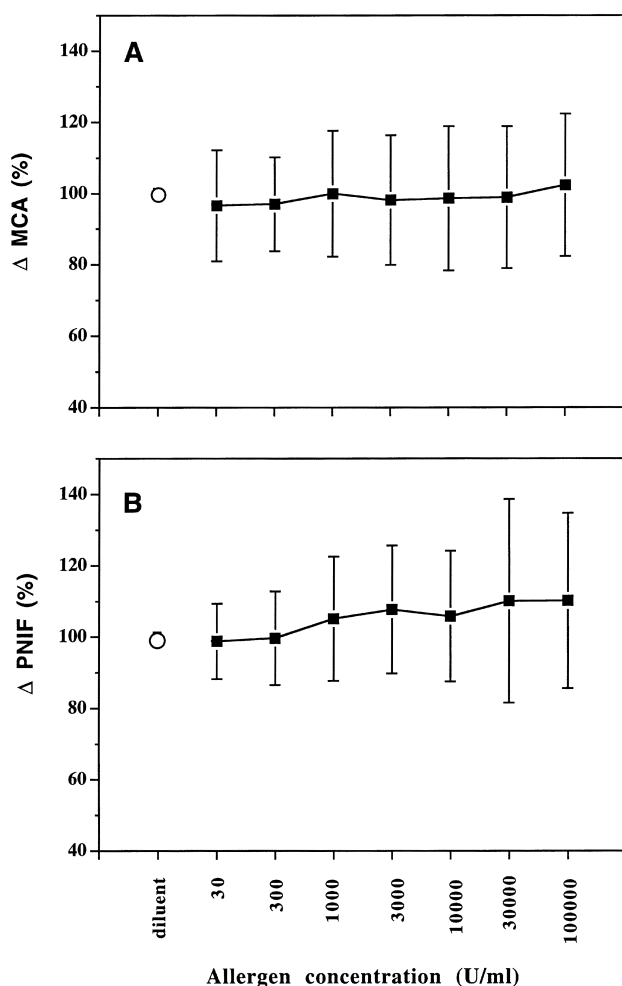


Figure 1. Variability of minimal cross-sectional area (MCA) (panel A) and PNIF (panel B) at each allergen concentration in control group (n=20). Results are expressed as mean variation in PNIF (Δ PNIF) or mean variation in minimal cross-sectional area (Δ MCA), compared to baseline (diluent O) in percentage $\pm$ SD.

nasal mucosa reaction to challenge, based on: 1) congestion, 2) hyperemia, 3) secretions. Each item was attributed a score of 0–3 points (maximal total score=9 points). In addition, the symptom score for nasal congestion was determined in an independent group of 25 grass-pollen-hypersensitive patients recruited on the above defined inclusion criteria, and expressed on an analog scale from 0 (no obstruction) to 10 (severe obstruction) at each allergen concentration.

Results

Establishment of AR and PNIF reaction threshold

Among the 20 volunteers from the control group, six were challenged with grass pollen, two with birch pollen, nine with house-dust mite (Der p [n=8], Der f [n=1]), and three with cat-dander extracts. Mean Δ MCA and Δ PNIF were $-4.2 \pm 11.2\%$ and $3.0 \pm 17.8\%$ (mean $\pm$ 2 SD), respectively, in nonatopic volunteers, and $5.2 \pm 16.7\%$ and $8.6 \pm 12.3\%$ respectively, in the subgroup of eight patients with nonallergic chronic rhinitis. Since the nasal response to allergen, as assessed by AR or PNIF, did not significantly differ in patients with nonatopic chronic rhinitis from healthy nonatopic controls ($P > 0.05$), the two subgroups were merged into a single control group, with mean MCA $-0.4 \pm 14.3\%$ and mean PNIF $5.2 \pm 15.7\%$ (Fig. 1). This allowed the determination of a reaction threshold of -29% and -26% drop from baseline for AR and PNIF, respectively. Maximal total clinical nasal score (at maximal allergen concentration, for AR and PNIF) in this control group was 1.6 ± 1.0 points, with 0.65 ± 0.6 for nasal congestion, 0.7 ± 0.6 for hyperemia, and 0.25 ± 0.4 for secretions (Fig. 3A). No sneezes were observed in any nonatopic volunteer.

Nasal challenge in atopic patients

Among the 30 atopic patients, seven were challenged with extracts of grass pollen, 10 with birch pollen, 10 with house-dust mite (seven with Der p, three with Der f), and three with cat dander according to their individual hypersensitivities. All had positive SPT, whereas specific IgE was negative in six of them. Comparison of reaction threshold between right and left nasal cavities as measured by AR showed that they were similar in 12 patients (40%), different by one shift in allergen concentration in eight (27%), and different by three shifts in two (7%). Reaction threshold for AR was never reached on one side in seven patients (23%). Only one

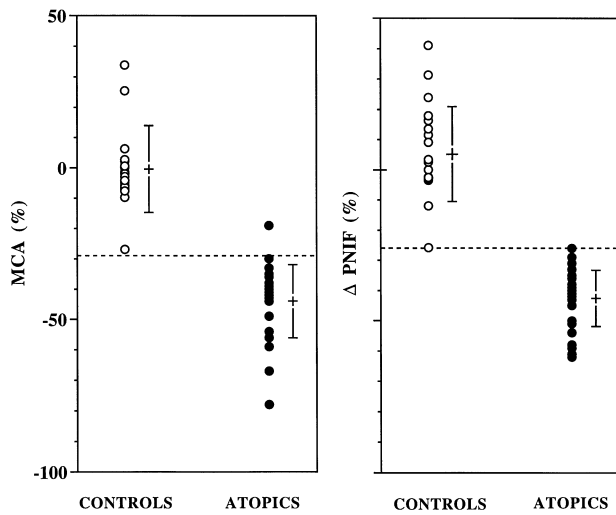


Figure 2. Determination of nasal reaction to allergen challenge by AR and PNIF in atopic patients (●, $n=30$) and in controls (○, $n=20$). Results are expressed as ΔMCA in percentage or $\Delta PNIF$ in percentage at threshold for AR and PNIF. All patients reached reaction threshold for PNIF and AR, except one for AR, despite maximal challenge with 100 000 U/ml allergen. Dashed line indicates reaction threshold as calculated from Fig. 1.

patient had a clearly positive provocation test on the basis of total clinical score (6 points) and reached reaction threshold for PNIF, but failed to reach reaction threshold for AR on either nostril (1/30 false negative). Therefore, only one representative nasal cavity was selected for MCA calculation, corresponding to the nasal cavity which first reached reaction threshold for AR. All patients reached reaction

threshold for PNIF, a method which, by definition, integrated airflow rates in right and left nasal cavities (Fig. 2). By either method, scores for hyperemia, congestion, and secretions at threshold were significantly higher in the atopic than in the nonatopic group ($P<0.05$, Mann-Whitney test) (Fig. 3A). The mean total clinical score was 5.7 ± 2.0 points for AR and for PNIF ($P>0.05$), but it significantly differed from the control group's mean total clinical score (1.6 ± 1.0 , $P<0.0001$). At threshold, the median allergen concentration was 1000 BU/ml (range 30–100 000 BU/ml) for AR and PNIF ($P>0.05$). Twenty-six of 30 allergic patients (87%) sneezed during the test but none in the control group. In complement, a symptom score for nasal congestion was performed in an independent group of 25 grass-pollen-hypersensitive patients selected on the same inclusion criteria. There was no significant difference in allergen concentration at threshold for AR and PNIF (300 BU/ml, range 100–1000 BU/ml, $P>0.05$), or in symptom score (4.2 ± 1.9 vs 4.5 ± 2.0 , $P>0.05$, Student's t -test).

For comparison of results obtained by both methods, the allergen concentration at reaction threshold for AR was correlated to the allergen concentration at reaction threshold for PNIF for each patient (Fig. 3B). Eleven out of 30 patients (35%) reached reaction threshold for AR and for PNIF at the same allergen concentration. In nine subjects, the reaction threshold for AR was reached before threshold for PNIF; i.e., at a threefold lower allergen concentration in six subjects (one shift in allergen concentration), a 10-fold

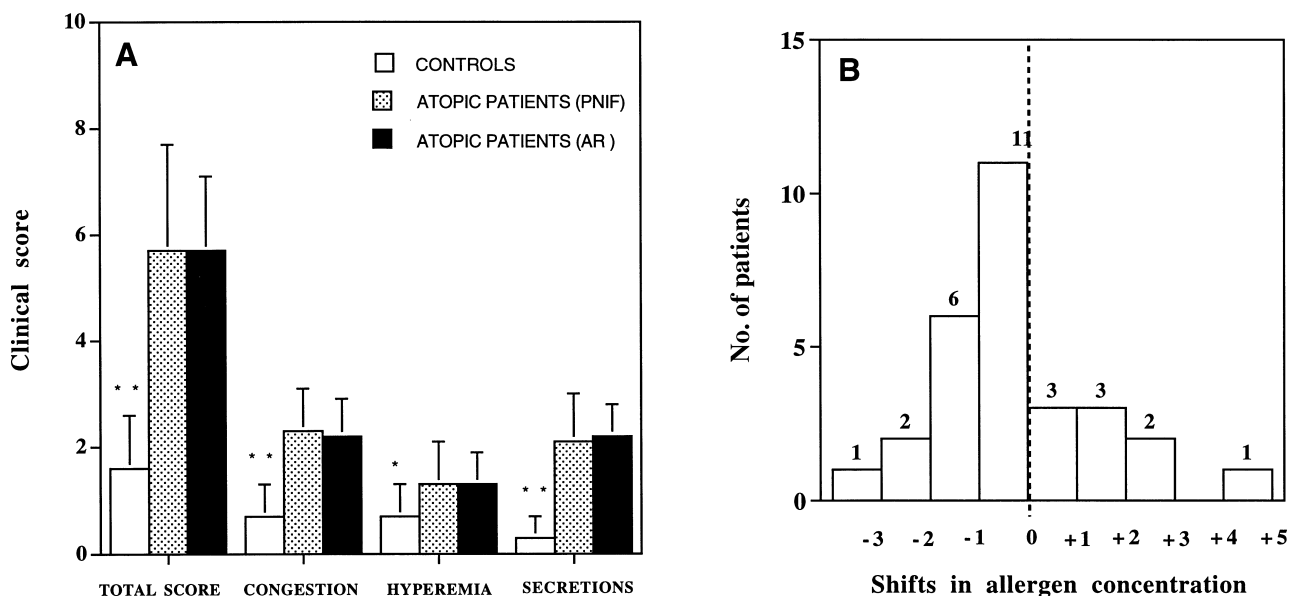


Figure 3. A) Clinical scores in control group at 100 000 U/ml are compared to clinical scores in atopic patients at reaction threshold for PNIF or AR; $**P<0.001$; $*P<0.01$ (Mann-Whitney test). B) Comparison of AR and PNIF at reaction threshold. Results correlate number of patients ($n=29$) who reached reaction threshold for PNIF with concentration of allergen measured at reaction threshold for AR, expressed in shifts in allergen concentrations. One patient of 30 did not reach threshold for AR.

lower concentration in two subjects (two shifts), and a 30-fold lower concentration in one subject (three shifts). In contrast, the reaction threshold was reached earlier for PNIF than for AR in another nine patients; i.e., by one shift in allergen concentration in three, two shifts in three, three shifts in two, and five shifts in one. As mentioned above, only one patient did not reach reaction threshold for AR, although he did so for PNIF. Taken together, these results allowed the calculation of a specificity of 100% and a sensitivity of 97% for AR, within the limits of the reaction threshold values considered in this study.

Discussion

In a limited number of patients, AR appeared to correlate with nasal congestion in the early and late allergic reaction (12). However, no reaction thresholds have been established for this method in atopic patients. The reaction thresholds we have established here (29% and 26% drop in MCA and PNIF, respectively) are in part the reflection of natural fluctuations of the nasal cycle (17, 18), and of nonspecific mucosal reactions to the diluent or the allergen itself in nonatopic volunteers. Within the frame of these cutoffs, the specificity of AR was optimal (100%). A limiting factor for AR appears to be the individual patient's nasal cavity anatomy. Very large cavities may never be sufficiently congested, even at maximal allergen concentration, to reach threshold for AR. Indeed, in eight of our patients, the reaction threshold for AR was not reached in one nasal cavity at least, if not in both (only one patient): in six of them, some degree of septal deviation was present. Therefore, we decided to include MCA results from a single nasal cavity, i.e., the nasal cavity in which reaction threshold was reached first. In most cases (20 of 30 patients with a difference of one shift in allergen concentration), there was actually a good correlation between reaction thresholds in the right and left nasal cavities. In this respect, PNIF was less dependent on nasal anatomy, since measurements with the peak flow meter integrated airflow in both nostrils.

Results obtained by AR and PNIF correlated closely with clinical scores, since there were no significant differences at reaction threshold between the two methods (Fig. 3A). Clinical scores obtained in the control group were significantly lower, even at maximal allergen challenge, and further validated AR and PNIF reaction thresholds. All but

one atopic patient reached reaction threshold for AR (sensitivity 97% vs 100% for PNIF). In support of these observations, we have recently challenged another group of 25 patients with grass-pollen rhinitis (14) and have evaluated their nasal reaction with AR, PNIF, and clinical score. All 25 patients reached the AR reaction threshold, as well as clinical score and PNIF reaction thresholds as defined in this study. A symptom score established in this second group of patients indicated that thresholds for AR and PNIF were reached at a similar level of subjective nasal congestion, confirming the close correlation between MCA variations and perception of nasal congestion.

The allergen concentration at threshold for AR and PNIF did not correlate for about one-third of the patients, taking one shift in allergen concentration as an acceptable difference in clinical practice (Fig. 3B). Three patients reached threshold for AR at an allergen concentration lower than for PNIF by two or three dilutions. In contrast, six patients required higher allergen concentration (two to five dilutions) to reach AR than to reach PNIF threshold. Again, these differences may be in relation to individual variability in nasal cavity anatomy and/or may reflect variations in the level of the patient's active cooperation with PNIF. Indeed, in this study, it was not always easy to obtain optimal cooperation from all patients in PNIF, despite careful explanation. On the other hand, if AR is independent of the patient's active collaboration, AR requires a particularly rigorous technique to ensure optimal reading quality with regard to the angle of incidence of the wave tube (about 45°), and configuration and sealing quality of the nose piece (16). Coupled with similar perception of nasal congestion at threshold, these observations indicate that PNIF and AR are two methods which indirectly give a close estimate of nasal congestion, but which measure different domains of the allergic response, and, as such, are more complementary than equivalent. In conclusion, AR appears to be as specific and sensitive as PNIF in evaluation of the allergic response to allergen provocation. Since AR is not dependent on the patient's cooperation, it can be considered a complement to PNIF in allergen challenges for clinical practice or research trials.

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