

Bilateral nasal allergen provocation monitored with acoustic rhinometry. Assessment of both nasal passages and the side reacting with greater congestion: relation to the nasal cycle

T. Gotlib*, B. Samoliński† and A. Grzanka‡

*Department of Otolaryngology, †Independent Laboratory of the Prevention of Environmental Hazards, Medical University of Warsaw, Warsaw, Poland and ‡Institute of Electronic Systems, Warsaw University of Technology, Warsaw, Poland

Summary

Background The effect of bilateral nasal provocation on nasal mucosa measured with the use of acoustic rhinometry (AR) can be assessed for both nasal passages or for the side responding with greater congestion. Assessment of changes in nasal congestion during the nasal provocation test (NPT) can be affected by the nasal cycle (NC). The aim of this study was to find out the most accurate method to evaluate changes observed during bilateral nasal provocation.

Methods Cross-sectional areas (CSA) at the level of inferior nasal turbinate (CSA-2) were recorded by AR in 26 volunteers with allergic rhinitis during the NC for 5–7 h and subsequently during NPT. The risk of spontaneous total and unilateral CSA-2 decrease was established.

Sensitivity of the NPT assessment for the total CSA-2 and for the side responding with greater congestion was evaluated at chosen thresholds. These thresholds were selected in a way that the risk levels of spontaneous decrease of unilateral and total CSA-2 were equal.

Results The assessment of the total CSA-2 was found to be more sensitive than the assessment of the side responding with greater congestion. The highest sensitivity and specificity of the test was achieved by using a combination of both assessments. Optimum thresholds of the CSA-2 decrease for assessment at 15 min after provocation, with this method, were 27% and 40% for the side responding with greater congestion and for the total CSA-2, respectively.

Conclusions Recognition of the risk of spontaneous unilateral and total CSA-2 decreases enables introduction of combined assessment of bilateral NPT. This assessment seems to be the most accurate method for evaluation of the test results.

Keywords acoustic rhinometry, allergic rhinitis, nasal challenge, nasal cycle, nasal provocation

Submitted 22 April 2004; revised 20 September 2004; accepted 23 November 2004

Introduction

Objective assessment of the nasal airways is an important part of the evaluation of mucosal reaction to allergen provocation. Most experts from the International Committee on Objective Assessment of the Nasal Airways favour bilateral allergen application [1]. So far, the commonest method used to evaluate nasal patency during the nasal provocation test (NPT) is active anterior rhinomanometry (AAR). The guidelines of the German Society for Allergy and Immunology Research recommended unilateral application of allergen to the more patent nasal cavity before AAR evaluation [2]. The main reason for this is that AAR assessment is impossible when one of the nostrils is totally blocked.

A drawback of another method used for the assessment of NPT, active posterior rhinomanometry, is that approximately

20% among patients do not tolerate a catheter placed in the pharynx [1].

Acoustic rhinometry (AR) is regarded as a quick, non-invasive, reproducible method, useful in the assessment of nasal obstruction during NPT [3]. In contrast to AAR assessment, AR can be performed when one or both nostrils are totally blocked and thus it seems more suitable for the assessment of bilateral NPT.

After bilateral provocation changes in nasal cross-sectional areas (CSA) can be assessed for the total CSA (sum of CSAs for both sides) or for one side only. Authors who observed more pronounced obstruction of one nostril in their patients, advocate assessment of the more reactive side (MRS) [4, 5]. Others use assessment of the total CSA stating that it allows the examiner to avoid the effect of the nasal cycle (NC) [6].

The NC has been reported to influence the response to unilateral nasal allergen provocation [7, 8]. The NC is a physiological phenomenon of spontaneous alteration in nasal patency. In their ideal form these alterations are rhythmic and bilaterally reciprocal while the total nasal patency remains unchanged. Recent studies have shown that the total nasal

Correspondence: Tomasz Gotlib, Department of Otolaryngology, Medical University of Warsaw, 02-097 Warszawa, ul. Banacha 1a, Warsaw, Poland.
E-mail: gotlib@amwaw.edu.pl

patency does not have to be stable and changes in nasal patency in the course of NC are often irregular [9, 10].

So far it is unknown which method of assessment (for MRS or total CSA) is superior and what influence the NC has on the results obtained with these methods. The aim of this study was to find out the most accurate method to assess bilateral NPT effects measured with AR.

Materials and methods

Patients

The study group consisted of 26 volunteers allergic to grass or birch pollen, including 11 women and 15 men, mean age 24 years (range 16–34 years). Diagnosis of allergic rhinitis had been established on the basis of history and positive skin prick tests (Allergopharma, Reinbek, Germany). Exclusion criteria: significant nasal deformity, nasal polyposis, immunotherapy (recently or in the past), respiratory tract infection or treatment with antihistamine drugs for at least 2 weeks before NPT (4 weeks for astemizole), treatment with steroids for at least 1 month or any other drugs for three days before NPT.

The protocol was approved by the Ethics Committee at the Medical University of Warsaw. The patients gave their informed consent before entering the study.

Study design

Subjects were challenged on two separate occasions (provocation 1 and 2). Before each challenge spontaneous changes in the patency of the nasal passages were observed. The total period of observation of the NC was 5–7 h. In order to avoid the priming effect the second provocation was performed after at least 4 weeks. The study was carried out in autumn and winter to avoid the interference of natural exposure to pollens. Assessment of the response to the control solution was performed during another session.

Allergens

Standardized grass or birch pollen extracts (Allergopharma) 5000 BU/mL were used. Two puffs (0.05 mL each) of the solution at room temperature were applied to each nasal passage with the use of a metered pump spray (total applied dose 1000 BU).

Acoustic rhinometry

AR was carried out with the use of the SRE 2000 rhinometer (Rhinometrics, Lynge, Denmark) according to the guidelines of the Standardization Committee on Acoustic Rhinometry [11]. The measurements were performed every 15 min during the NC and every 5 min for 30 min after the challenge. CSA at the second notch (CSA-2) were analysed. Because this point may change its position on the distance axis of the AR curve after the challenge and in the course of the NC, a special software enabling identification of the CSA-2 was developed.

Symptom scores were recorded on the visual analogue scale (VAS) scale for seven symptoms: itching, sneezing, rhinor-

rhoea, nasal blockage, dyspnoea, ocular symptoms and one additional symptom.

Data analysis

For each patient, maximum spontaneous decreases in the total and unilateral CSA-2 (for MRS) were estimated during a 15 and 30 min time span, respectively, over 5–7 h. Post-provocative changes in CSA-2 for MRS and for total CSA-2 at 15 min and in the maximum congestion recorded during 30 min after the challenge were calculated. Spontaneous and post-provocative decreases in the CSA-2 were calculated as a percentage of the *initial* value (Δ) according to the formula:

$$\frac{\text{CSA-2 after decrease} - \text{CSA-2 before decrease}}{\text{CSA-2 before decrease}} \times 100\% = \Delta$$

The percentage of patients in whom spontaneous changes could be greater than post-provocative changes at a given threshold was described as the risk level ($1 - \text{specificity}$).

Sensitivity was defined as a percentage of cases in which post-provocative changes appeared greater than a given threshold (percentage of cases considered positive at a given threshold).

The relationship between the risk level and sensitivity was plotted on the receiver-operating characteristic curve for MRS and total CSA-2, for assessment at 15 min and for the maximum congestion recorded up to 30 min after the challenge. Because of a diversity of response types (see below) another method of assessment was introduced. In this method reaction thresholds for MRS and total CSA-2 decrease after the challenge are used. These thresholds were calculated at equal risk of unilateral and total spontaneous CSA-2 decrease. This method was called combined assessment (Fig. 2).

Statistical evaluation

Student's *t*-test was used.

Results

Spontaneous changes in nasal patency (detected difference in the CSA-2 between the sides more than 30%) were found in 25 of 26 subjects during at least one session of the NC recording. Compared with the response to the control solution all the challenges were positive as demonstrated by the symptoms (VAS): 10 mm vs. 206 mm after provocation 1 and 213 mm after provocation 2 ($P < 0.001$).

Two main types of reaction to NPT were observed:

1. Typical reaction, with a decrease in CSA-2 on both sides, observed in 88% and 96% of subjects after provocation 1 and 2, respectively.
2. Atypical reaction, with a one-sided decrease in CSA-2 and a contralateral increase in CSA-2, observed in 12% and 4% of subjects after provocation 1 and 2, respectively (Fig. 1).

Sensitivity of the assessment for MRS, total CSA-2 decrease and combined assessment in provocation 1 and provocation 2, for the maximum congestion (up to 30 min after provocation) and at 15 min after provocation are presented in Tables 1 and 2.

The maximum sensitivity and specificity were achieved for the combined assessment at the following thresholds of CSA-2 decrease: 40% and 27% at 15 min after provocation and 62% and 27% at the maximum congestion after provocation (for the MRS and total CSA-2, respectively) (Table 2).

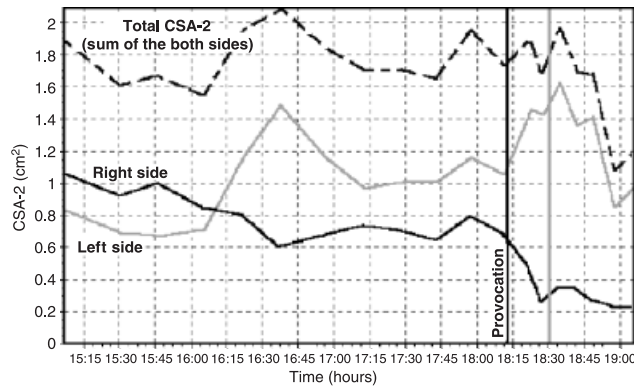


Fig. 1. Atypical reaction.

Assessment for total CSA-2 appeared to be more sensitive and specific than MRS assessment (Fig. 2).

Discussion

Awareness of the risk of a spontaneous decrease in nasal patency is crucial for establishing threshold values for NPT monitored with objective methods of nasal airway assessment. This risk increases with the duration of observation. Pirila et al. [7] observed spontaneous changes in nasal resistance using AAR. Comparison of their results with threshold values for significant resistance increase during NPT found in the literature reveal a high risk of false-positive results when these values are used. So far there have been no studies comparing decreases in CSA measured with AR after bilateral nasal provocation and during the NC.

Terrien et al. [6] who performed bilateral provocation and assessed a decrease in the total MCA (minimum CSA at the level of the inferior turbinate head, equivalent to CSA-2) established a threshold of 30%. Ganslmayer et al. [4] after

Table 1. Sensitivity of MRS and total CSA-2 decrease assessments for Prov. 1 and Prov. 2

Risk level of spontaneous CSA-2 reduction (1 – specificity) (%)	Threshold used (%)	Sensitivity at given threshold for Prov. 1 (%)	Sensitivity at given threshold for Prov. 2 (%)
<i>Total CSA-2 assessment for maximum congestion</i>			
0	45	31	38
4	31	58	73
15	29	65	85
<i>MRS assessment for maximum congestion</i>			
0	84	8	4
4	65	27	27
15	62	31	35
<i>Total CSA-2 assessment at 15 min after provocation</i>			
0	35	31	38
4	30	42	54
15	27	50	73
<i>MRS assessment at 15 min after provocation</i>			
0	64	12	19
4	51	35	31
15	40	46	50

Assessment for maximum congestion (up to 30 min after provocation) and at 15 min after provocation at the risk level (1 – specificity) of 0%, 4% and 15%. MRS, more reactive side; CSA, cross-sectional areas; Prov., provocation.

Table 2. Sensitivity of combined assessment for Prov. 1 and Prov. 2

Risk level of spontaneous CSA-2 reduction (1 – specificity) (%)	MRS threshold used in combined assessment (%)	Total CSA-2 threshold for used in combined assessment (%)	Sensitivity of combined assessment at given thresholds for Prov. 1 (%)	Sensitivity of combined assessment at given thresholds for Prov. 2 (%)
<i>Combined assessment for maximum congestion</i>				
0	84	45	23	38
4	65	31	69	73
15	62	27	85	88
<i>Combined assessment at 15 min after provocation</i>				
0	63	35	31	38
4	51	30	54	54
15	40	27	69	81

Assessment in maximum congestion after provocation (up to 30 min after provocation) and at 15 min after the provocation for the risk level (1 – specificity) 0%, 4% and 15%.

MRS, more reactive side; CSA, cross-sectional areas; Prov., provocation.

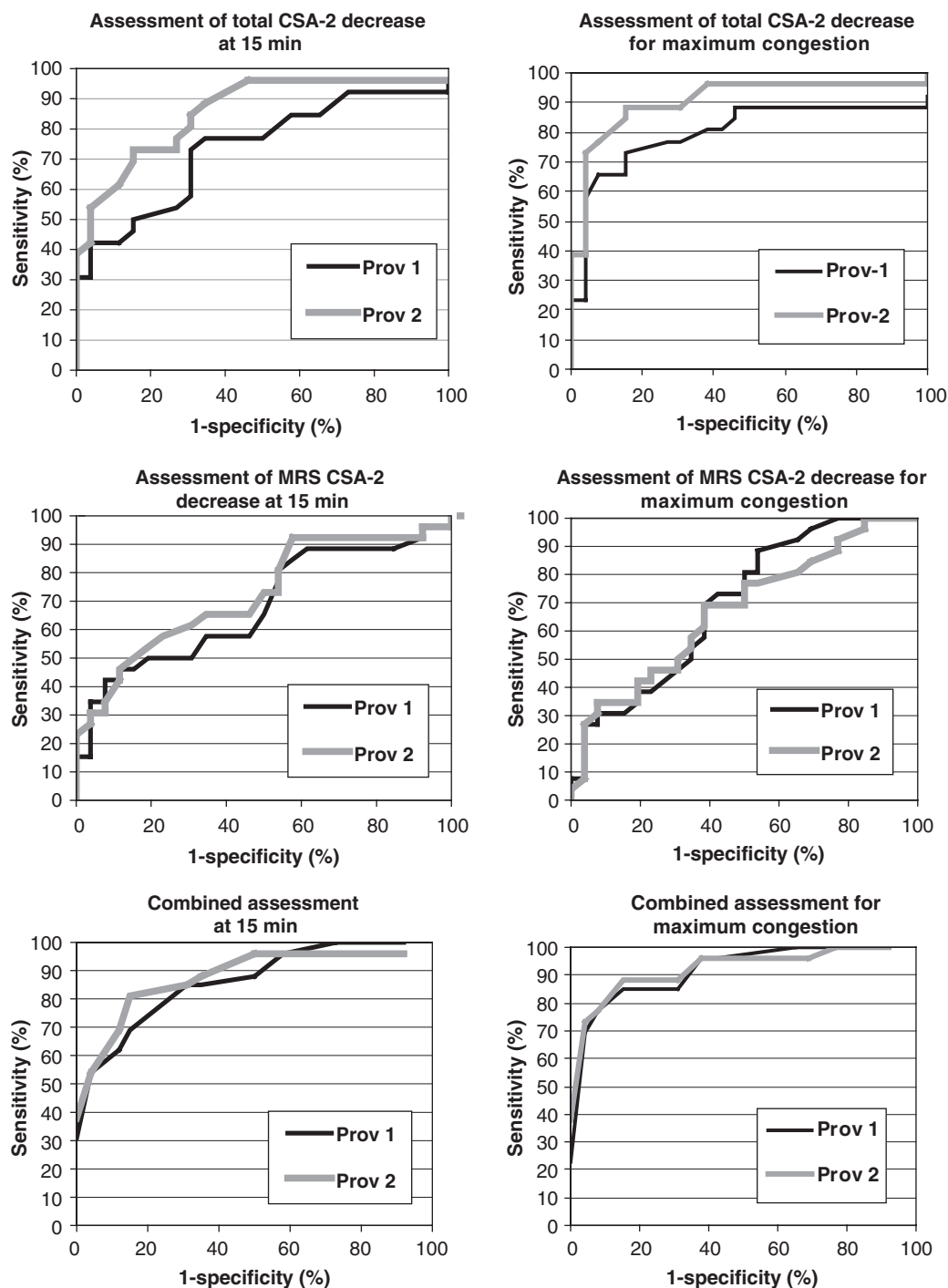


Fig. 2. Comparison of more reactive side (MRS) assessment, total cross-sectional areas (CSA)-2 and combined assessment at 15 min (left column) and for the maximum congestion after the provocation (right column).

bilateral nasal provocation assessed the MCA decrease on the MRS. The authors established a threshold of 29% for the MCA decrease [4]. In both studies each reaction to any allergen concentration was referred to the baseline value obtained after diluent application. Increased allergen concentrations were nebulized every 15 min in a study by Terrien et al. and every 10 min in a study by Ganslmayer et al. Seven allergen concentrations were used, so the maximum observation periods were 105 and 70 min, respectively. The threshold of 29% in the MRS assessment is too low according to our

results, because a spontaneous unilateral decrease of 30% in the CSA-2 could occur in 77% of the patients during 30 min of observation in the present study. A spontaneous total CSA-2 decrease of 30% during 30 min of observation could occur only in 15% of patients from our group (data not shown in the tables). However, during 105 min of observation such a decrease is more likely.

A single dilution of allergen was used in this study. Applied doses were threshold or supra-threshold because in none of the patients total occlusion of the nose was observed.

It can be hypothesized that atypical reactions observed in this study would have converted to typical ones (with a pronounced difference in congestion between the sides) if higher doses of the allergen had been subsequently used. Consequently, after higher allergen doses, optimum thresholds, at which no risk of spontaneous CSA-2 decrease exists, would be reached. So far, there has been no evidence that this hypothesis is correct.

Atypical reaction is not specific to the patient because in all cases it was observed only during one of the two challenges. This kind of reaction most probably results from the modification of the NC by provocation in the reflex mechanism. Unilateral provocation induces the glandular secretion not only in the ipsilateral but also the contralateral nasal passage. This well-documented reflex is mediated via parasympathetic neurons [12]. Nasal erectile tissue is predominantly innervated by sympathetic neurons. There is strong evidence that sympathetic nerves control filling of the nasal venous sinusoids and changes in nasal patency. Results of studies investigating the influence of unilateral provocation on the contralateral side airflow resistance are not consistent. However most of them suggest that the reflex mechanism may contribute to the congestion response after the provocation [13–15]. Numata et al. performed unilateral provocation and observed changes in the volume of the nasal passages using AR. Decrease of nasal volumes in both nasal passages was found in 10 of 20 subjects. Contralateral congestion reached 45% of that on the challenged side and persisted for 15 min. Ipsilateral nasal volume decrease was observed in 17 subjects, in one subject there was no change in the ipsilateral nasal volume and in two subjects ipsilateral increase in the nasal volume was observed (accompanied by contralateral decrease) [16]. The latter study suggests that centrally mediated reflex participates in induction of nasal mucosa congestion at least in the first 15 min after the provocation. Results of the present study seem to confirm this. In both studies in a small subset of patients paradoxical increase of patency in the provoked nasal cavity was observed.

Diversity of nasal mucosa reactions to NPT is the most reasonable explanation for the high sensitivity and specificity of the combined assessment. When the challenge is assessed on the basis of the total CSA-2 (a decrease in the sum of left and right CSA-2), in spite of a pronounced unilateral CSA-2 decrease an atypical reaction is considered negative because the total CSA-2 remains nearly unchanged (Fig. 1). On the other hand, moderate symmetric congestion on both sides (with a pronounced total CSA-2 decrease) can be considered negative when the MRS assessment is used. The use of combined assessment is justifiable only when there is a known risk of spontaneous unilateral and total CSA-2 decreases.

Surprisingly the assessment for maximum congestion showed highest specificity and sensitivity in spite of lengthening of the observation period, which should increase the risk of spontaneous CSA-2 decrease. The most probable reason for this is that maximum congestion seldom appears at 15 min and that in most cases maximum congestion is much more pronounced than observed at 15 min.

Differences in the duration of observation could be a potential reason for a minor inaccuracy in evaluation of the risk of a spontaneous CSA-2 decrease. In our opinion it did not really influence the results the study, however in further

evaluation of this risk of spontaneous CSA-2 decrease for practical use (reference values) equal periods of observation should be used.

Conclusions

Recognition of the risk of spontaneous unilateral and total CSA-2 decreases allows the introduction of combined assessment of bilateral nasal provocation measured with AR. This is more sensitive and specific than the bilateral assessment and assessment for the MRS. The most probable explanation for this is a diversity of reaction types observed at threshold and supra-threshold doses of allergen. Assessment of the MRS seems to be the least accurate method of NPT evaluation.

Acknowledgements

This study was supported by grant from Polish State Committee for Scientific Research.

References

- 1 Malm L, Gerth van Wijk R, Bachert C. Guidelines for nasal provocations with aspects on nasal patency, airflow, and airflow resistance. International Committee on Objective Assessment of the Nasal Airways, International Rhinologic Society. *Rhinology* 2000; 38:1–6.
- 2 Bachert C, Gonsior E, Berdel D et al. Richtlinien für die Durchführung von nasalen Provokationstests mit Allergen bei Erkrankungen der oberen Luftwege. *Allergologie* 1990; 13:53–5.
- 3 Scadding GK, Darby YC, Austin CE. Acoustic rhinometry compared with anterior rhinomanometry in the assessment of the response to nasal allergen challenge. *Clin Otolaryngol* 1994; 19: 451–4.
- 4 Ganslmayer M, Spertini F, Rahm F, Terrien MH, Mosimann B, Leimgruber A. Evaluation of acoustic rhinometry in a nasal provocation test with allergen. *Allergy* 1999; 54:974–9.
- 5 Samoliński B. Acoustic rhinometry for the purposes of rhinoallergological diagnosis: analysis of the results. Warsaw: Scholar, 1998.
- 6 Terrien MH, Rahm F, Fellrath JM, Spertini FS. Comparison of effects of terfenadine with fexofenadine on nasal provocation test with allergen. *J Allergy Clin Immunol* 1999; 103:1025–30.
- 7 Pirila T, Talvisara A, Alho OP, Oja H. Physiological fluctuations in nasal resistance may interfere with nasal monitoring in the nasal provocation test. *Acta Otolaryngol (Stockh)* 1997; 117:596–600.
- 8 Sipilä JI, Suonpää JT, Salmivalli AJ, Laippala P. The effect of the nasal cycle on the interpretation of rhinomanometric results in a nasal provocation test. *Am J Rhinol* 1990; 4:179–84.
- 9 Gilbert AN, Rosenwasser AM. Biological rhythmicity of nasal airway patency: a re-examination of the 'nasal cycle'. *Acta Otolaryngol* 1987; 104:180–6.
- 10 Gungor A, Moinuddin R, Nelson RH, Corey JP. Detection of the nasal cycle with acoustic rhinometry: techniques and applications. *Otolaryngol Head Neck Surg* 1999; 120:238–47.
- 11 Hilberg O, Pedersen OF. Acoustic rhinometry: recommendations for technical specifications and standard operating procedures. *Rhinology* 2000; (Suppl. 16):3–17.
- 12 Baraniuk JN, Silver PB, Kaliner MA, Barnes PJ. Effects of ipratropium bromide on bradykinin nasal provocation in chronic allergic rhinitis. *Clin Exp Allergy* 1994; 24:724–9.

- 13 Holmberg K, Bake B, Pipkorn U. Reflex activation in allergen-induced nasal mucosal reactions. *Acta Otolaryngol* 1989; 108:130–5.
- 14 Malmberg H, Binder E, Fraki J, Harvima I, Salo O, Holopainen E. Nasal reactions elicited by unilateral allergen challenge. *Acta Otolaryngol* 1989; 107:446–9.
- 15 Konno A, Togawa K, Nishihira S. Participation of vascular reflex in mucosal swelling in nasal allergy. *Acta Otolaryngol* 1982; 94:131–40.
- 16 Numata T, Konno A, Terada N, Hanazawa T, Nagata H, Tanikawa H. Role of vascular reflex in nasal mucosal swelling in nasal allergy. *Laryngoscope* 2000; 110 (Part 1):297–302.