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Guidelines for nasal provocations with aspects on nasal patency, airflow, and airflow resistance*

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SUMMARY

Under the auspices of the International Rhinologic Society (IRS) there is an 'International Committee on Objective Assessment of the Nasal Airways'. In 1984 Rhinology published the Committee's recommendations regarding rhinomanometry (Clement, 1984). During the last Congresses of the European Rhinologic Society (ERS) a subcommittee within that committee has discussed nasal provocations and the value of measuring nasal patency, airflow and airflow resistance to evaluate such provocations. The following is an effort to a consensus of indications and techniques for nasal provocation and to a critical analysis of methods to measure the effects. Only the most known methods will be discussed, i.e. acoustic rhinometry, rhinostereometry, nasal peak airflow and rhinomanometry with its different techniques.
For graded responses after provocations the use of such methods is of clinical value only in combination with scores from symptoms such as sneezes and secretion, as allergic rhinitis symptoms consist of obstruction, sneezing, itching and concomitant symptoms of the neighbouring organs. For research all methods can be recommended to be used and their respective value is depending on the specific scientific purposes.

Key words: nasal airflow, nasal challenge, nasal patency, nasal provocation, nasal airflow resistance

INTRODUCTION

Recommendations on and critical analysis of nasal provocations and methods to measure the effects of such provocations have been published many times before and some of those papers will be mentioned below as one of the purposes of this paper is to give useful references. In 1976 a Finnish group of otorhinolaryngologists gave in Rhinology their experience and opinion on allergen provocations and their rhinomanometric evaluation (Holopainen et al., 1976). In 1978 Rüdiger gave his view on the importance of rhinomanometry for nasal provocations in allergy diagnosis (1978). Schlenter (1982) was, however, the first to properly use statistical methods to evaluate rhinomanometric changes after nasal provocations.

In 1990 the German Society for Allergy and Immunology Research presented guidelines for nasal provocation in Allergology (Bachert et al., 1990). The authors, who were allergologists and otorhinolaryngologists, gave detailed recommendations concerning indications and contraindications for allergen provocations, quality and dosages of allergen and histamine solutions, evaluation of symptoms and of rhinomanometric results, etc.
In 1992 a consensus report from a 'Fireside Conference on Nasal Provocation Test', chaired by Schumacher from USA, was published in Rhinology (Schumacher et al., 1992). Schumacher had then since many years used nasal provocation testing and rhinomanometry (see e.g. Schumacher and Pain, 1979).
In 1994 an 'International Consensus Report on the Diagnosis and Management of Rhinitis' was published as a supplement in Allergy (Lund et al., 1994). Rather little regarding nasal airway assessment and nasal provocations was discussed.
In 1995 Acta Oto-Laryngology published 'Various methods for testing nasal responses in vivo: a critical review' by a Swedish group of otorhinolaryngologists (Andersson et al., 1995). The authors especially discussed different delivery systems for pro-

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vocations and different drugs for testing nasal reactivity. Nasal responses were mainly dealt with as symptoms, biochemical mediators and cellular events and less with methods to measure nasal patency, airflow, and airflow resistance.

In 1997 allergologists representing the European Academy of Allergy and Clinical Immunology (EAACI) gave their view on nasal provocations with historical notes, indications and applications, early and late responses, rhinomanometric evaluations etc (Melillo et al., 1997). Many textbooks and overviews in allergology give aspects on nasal provocations and one recent example is the book New Trends in Allergy (Bachert, 1997).

There are at least five European theses during the last decades that thoroughly have evaluated nasal provocations and the assessment of nasal reactivity regarding nasal patency, airflow, or airflow resistance (Schlenter, 1983; Wihl, 1986; Gerth van Wijk, 1991; Hallén, 1994; de Graaf-in 't Veld and Garrelds, 1995).

INDICATIONS AND TECHNIQUES FOR NASAL PROVOCATION

Our recommendation is to use the word 'provocation' instead of 'challenge' as the former word links up with words as Provocatione, Provokation, provocatie a.o. in other languages.

Recommended indications

I. Allergen provocations. In many occasions nasal provocation tests give more information than history and skin prick tests. Allergen provocation is particularly recommended:
   1. When discrepancies between history of allergic rhinitis and tests or between tests are present. If a positive nasal allergen provocation has been found in an asthma patient, the bronchial allergen provocation is not necessary (Clement et al., 1981). Argument against this is that very few well-documented studies are available.
   2. For diagnosis of occupational allergic rhinitis.
   3. Before immunotherapy for allergic rhinitis. Although it is still not very common to use nasal provocation before starting immunotherapy, the subcommittee considers it is important that a laborious long-lasting therapy is justified by a proper diagnosis. This holds true particularly in case of perennial allergic rhinitis. In seasonal allergic rhinitis a nasal provocation is seldom required. Nasal provocation to monitor an immunotherapy effect is even more uncommon, which makes a recommendation somewhat difficult.
   4. For research.

II. Lysine-aspirin

   Nasal provocation is recommended as a substitute for oral provocation at suspicious ASA (NSAID) intolerance (Milewski et al., 1998). Whenever such a nasal provocation test is negative, an oral one is still required.

III. To test non-specific hyperreactivity

   Nasal provocation tests with non-specific stimuli such as histamine, methacholine, cold dry air, etc are not relevant for individual diagnosis. In research at a group level these tests can be used. The inclusion of symptom scores, and scores for the number of sneezes and amount of secretion will discriminate somewhat better. However, non-allergic patients with mainly nasal blockage will not be captured by these tests.

Recommended techniques for both clinical routine and research

General

- Solution should have room temperature before application.
- Control solutions should be sprayed first and reactions thereto monitored.
- Deep inspiration should be performed before spraying in order to avoid deposition in the lower airways.
- Meter-dose pump sprays or disks can be used with a reproducible delivery of allergen.
- One or both nostrils may be challenged.[1]

Allergens

- Dilutions from freeze-dried stock solutions should be used where available.
- Standardised allergen extracts and units are recommended.

Non-specific stimulation with solutions

- To avoid non-specific stimulation with solutions, these should be isotonic and buffered to a pH close to 7.

Assessment of the nasal response

- It is recommended that symptom scores are combined with objective measurements (counting sneezes or attacks of sneezes, measuring volume or weight of nasal secretion, and results of changes of nasal patency, airflow, or airflow resistance).

[1]Regarding spraying in only one or both nostrils the subcommittee members differ in their opinion. Most of the members prefer spraying in both nostrils to avoid the influence of changing of the nasal cycle when monitoring the effects by nasal patency, airflow, or airflow resistance methods. If nasal provocation is performed in one nostril only, the other side should be measured also to recognise nasal cycling effects.

METHODS TO EVALUATE NASAL PATENCY, AIRFLOW, AND AIRFLOW RESISTANCE

The recordings of all the above-mentioned methods are depending on changes of the thickness of the nasal mucosa. Changes of the thickness are in turn depending on changes of the blood volume and on changes of transcapillary fluid changes i.e. increasing or decreasing oedema. Changes in blood volume are mainly parallel to changes in the tone of the capacitance vessels (mainly sinusoids)(Malm, 1974).

Acoustic rhinometry

Acoustic rhinometry, like rhinostereometry below, measures nasal patency; i.e. the degree of openness of the nose or parts of the nose.

The Aarhus mode has a coefficient of variation (c.v.) of 2% in repeated measurements of normal human subjects without nasal provocations (Hilberg et al., 1989). The c.v. in provocation protocols is not known, however. For decongested cavities measured at weekly intervals the Aarhus mode was found to

have a c.v. of 4% (Grymer et al., 1991). Lenders and Pirsig with their Ulm mode presented illustratively how the nasal patency is decreased gradually after challenges with increasing doses of allergen in a patient with nasal allergy (1990). The c.v. for allergen challenges is not given; repeatedly after a decongestant it was less than 6%.

A very careful study of the reproducibility of acoustic rhinometric measurements is published from Philip Cole's group in Toronto (Roithmann et al., 1995). The authors studied the variability for measurements minute-to-minute, hour-to-hour, day-to-day, and week-to-week and found the total minimal cross-sectional area to have a c.v. from 5-17% and the total nasal volume from 4-9%. They published no results from nasal provocations, however. Sipilä et al. (1996) gave figures for intra-individual variations from 8-32% with a mean of about 15% for one and the same nostril. Neither did they perform nasal provocations. Austin and Foreman performed provocations of noses with histamine and bradykinin and found acoustic rhinometry to be more sensitive than posterior rhinomanometry (1994). Pirilä also found acoustic rhinometry to be more sensitive than rhinomanometry to monitor nasal provocations (1998). Acoustic rhinometry, however, has limitations and pitfalls. Guidelines and recommendations to overcome technical difficulties have been given by Hilberg and the committee on standardisation of acoustic rhinometry (unpublished data, 1999).

The value of acoustic rhinometry to evaluate nasal responses after provocation in routine clinical work is not established yet; it is a promising method, which probably still can be improved.

Rhinostereometry

Rhinostereometry is in principle a very simple way of recording changes of the thickness of the nasal mucosa (Juto and Lundberg, 1982). The equipment consists of a surgical microscope placed on a micrometer table. The test subject is fixed exactly to the measuring apparatus by an individually made plastic splint adapted to the teeth. As the microscope has a small depth of focus, changes of the position of the mucosal surface on the medial side of the inferior concha can be registered along a millimetre scale. The method has an accuracy of 0.2 mm. The reactivity of the nasal mucosa has been studied after provocation with saline and increasing doses of histamine pipetted on the inferior concha. The method has e.g. been used in studies of non-allergic hyperreactivity (Hallén, 1994).

Rhinostereometry is a time-consuming method due to the need to have the test subject exactly fixed to the measuring apparatus. It seems useful for comparisons between well-defined groups of subjects and patients and between the same subjects or patients at different occasions.

Nasal peak airflow

The inspiratory flow meter is more suitable than the expiratory one because it avoids contamination with secretions. When studying nasal provocations with allergens or other substances it has been argued that with the inspiratory meter the mucosal surfaces will be sucked to each other and thus prevent measurements. Wihl and Malm (1988) found, however, in twelve allergic patients provoked with two types of allergens each at eight occasions, that only in 2% a total occlusion occurred. They also found significant correlations between results from both peak flow methods and active anterior rhinomanometry before and after decongestion. Holmström et al. (1990) in a study from UK did similar comparisons between inspiratory flow rate and nasal airway resistance (NAR) in allergic patients before and after allergen provocations and they also found a correlation between the results from the two methods ($p < 0.01$). Wihl (1987) could demonstrate the efficacy of a three-year tree pollen immunotherapy in patients with allergic rhinitis by testing the nasal reactivity with provocations once a year using different methods and symptoms among them nasal peak flow. The reactivity measured with the peak flow method decreased significantly between the four occasions the 31 patients were tested. He advocated, however, a total nasal provocation score to be used, also including scores for sneezes and secretion.

Peak inspiratory nasal flow and peak expiratory nasal flow (rate), especially the former, can be recommended for long-time control of pharmacologic or immunologic treatment of different types of rhinitis. For detecting nasal changes after provocations they are less accurate than active anterior rhinomanometry according to all publications found.

Rhinomanometry

Until now rhinomanometry is the best-evaluated and standardised technique.

Active anterior rhinomanometry was the rhinomanometric technique among others that was recommended by the above-mentioned Committee (Clement, 1984) and with two ways of presenting the nasal airway resistance (NAR); at a transnasal pressure of 150 Pa in a Cartesian co-ordinate system, or at a circle with a radius of 200 Pa on the abscissa and 200 ccm/sec on the ordinates in a polar co-ordinate system, or with both ways at the same time. The polar system (Broms et al., 1982) is used mainly in Scandinavian countries. It has the advantage that also airway resistances or flows not reaching a pressure of 150 Pa can be statistically compared with those reaching higher pressures. Also the above-mentioned German Society (1990) recommended active anterior rhinomanometry and for evaluation of rhinomanometric responses after nasal provocations a simple way; changes in percent of values obtained after application of solutions without allergen. By that different ways of obtaining the absolute figures of NAR or airflow does not matter. By convention both the Committee of ERS and the German Society specify NAR as transnasal pressure divided by airflow, which isn't the true value for a resistance with partly turbulent airflow. There is, however, no need of changing that convention in this context. The German Society recommended application of the allergen unilaterally. The drawback with active anterior rhinomanometry is then that the nasal cycle may affect the results. It is possible that that drawback is of minor importance when, as the German Society recommended, the application is done in the most open side. A similar way of performing the provocations was used by Wihl and Malm, who sprayed the allergen solutions with a de Vilbis nebulisator into the right nasal cavity

(1985). They studied ten patients with allergic rhinitis to grass pollen and found that active anterior rhinomanometry was clearly less sensitive than the patients own judgement of an allergic reaction. According to Schlenter a NAR increase of 60% or more above baseline (saline provocation) or a flow decrease of 40% or more is a sign of a positive nasal provocation (1982). He based his opinion on studies on over 700 patients and control subjects. Milewski et al. from Cracow in Poland recently presented a paper (1997) on nasal provocation with lysine-aspirin for diagnosis of aspirin-sensitive asthma. They used active anterior rhinomanometry, instilled the solutions in both nasal cavities and considered a nasal flow decrease of more than 40% in at least one side as compared with the post-saline baseline value as a positive reaction. The decrease in nasal airflow should also last for at least two consecutive measurements 10 minutes apart and it had to be accompanied by clinical symptoms persisting at least 30 minutes to be counted as a positive reaction.

As a measure of the reproducibility of NAR measurements in duplicate Holmström and Kumlien found the SD of the difference to be 3.8 before and 2.7 after decongestion (1988). In a similar study by Jessen et al. about twice those figures was obtained (1996). None of those studies dealt with provocations, however. In a recent Finnish study variations in NAR after nasal provocations with allergen have been very carefully evaluated (Pirilä et al., 1997). Provocations were done bilaterally. The authors found that a 100% increase in NAR was significant at the risk level of 5-10% for the observation time of 30-60 min. for an allergic reaction. They recommended other parameters to be used in addition, such as the amount of secretion. These intentions were followed up in a later paper (Pirilä, 1998), in which he presented studies on acoustic rhinometry, rhinomanometry and nasal secretion after nasal provocations. He found that an optimal threshold for a positive provocation was a secretion amount of 100 mg, a 15% decrease in the minimal cross-sectional area and a 50% increase in NAR for the observation period of 30 minutes and correspondingly 210 mg, 30% and 100% for 60 minutes. Allergen provocation was done in one nostril and diluent in the other in this latter study.

Active posterior rhinomanometry was used by Taylor and Shivalkar when they studied the effects of intranasal allergen provocations bilaterally with graded doses in 65 skin prick positive patients (1971). There was no correlation between skin prick sizes and NAR. Schumacher and Pain found no correlation between the threshold doses of allergens for positive provocations and the size of skin-test responses in a similar study (1979). Active posterior rhinomanometry was also the technique used by McLean et al., when they in the seventies challenged healthy subjects and patients intranasally with substances such as histamine, isoprenaline, and methacholine (e.g. 1977). Those authors and others (Guercio et al., 1979) found no differences in NAR between controls and allergic patients challenged outside the seasons with phosphate-buffered saline (PBS). After PBS aerosolised into each nostril McLean et al., found an increase of the mean NAR in 102 subjects of 22.5% (SD 24.5%) compared to values without spraying (1976). Pelikan used posterior rhinomanometry when he as one of the first investigators demonstrated a late phase reaction after allergen provocation (1978).

Shelton et al. found a c.v. for normal subjects of 14.0 and for patients with allergic rhinitis of 19.0 (1990). Those values were higher than the comparable ones for anterior rhinomanometry (normals 11.0 and rhinitics 18.0). Posterior rhinomanometry has the advantage of measuring the total nasal resistance, without need for calculations. However, using posterior rhinomanometry about 20% of patients can not, according to a general opinion among experts in the field, be measured due to closure of the catheter in the mouth or due to a positioning of the soft palate that prevents a connection between the mouth and the nose. Many experts also have the experience that with proper training that percentage can be markedly reduced.

Passive anterior rhinomanometry (PAR) was presented by Clement et al. in 1981 and was recommended by them as the most easy and suitable technique for measuring nasal resistance after nasal provocations.

They have thereafter published a number of studies with PAR both regarding specific and unspecific hyperreactivity (e.g. 1985) and when comparing PAR with other rhinomanometric methods (Gordt et al., 1989). There is also a study using PAR on the influence of the nasal cycle during nasal provocation in patients and normal test subjects (Wang and Clement, 1995). Also Corrado et al., have used PAR and they found a c.v. of 38% in repeated measurements of the resting NAR with individual fluctuations in repeated histamine provocations (1987). PAR is also the method used by Gerth van Wijk in his thesis 'Nasal Hyperreactivity' in 1991. Some of his final conclusions are: 'The measurements of NAR in histamine challenges does not differentiate between patients and healthy subjects.

With respect to the reproducibility of a nasal histamine provocation the use of reflex-mediated symptoms such as sneezing and secretion is advocated in the assessment of nasal responses. The use of NAR measurements yields a lower reproducibility. Although nasal provocations with non-specific stimuli may distinguish patient groups and healthy subject groups, the diagnostic value of these tests to determine nasal hyperreactivity is limited in the individual patient, because of the overlap in threshold concentration between the patients and healthy subjects.'

Other less common methods

With a *head-out body pletysmograph* NAR can be obtained just as well as with the above-mentioned rhinomanometric methods, with the advantage that the nose is free for inspection and available for observation and e.g. for electromyographic recording (Niinima et al., 1979).

Philip Cole's group in Toronto has presented a large number of studies with that method, however, none was found with allergen provocations.

With *oscillometry* nasal airway resistance can be calculated from the total resistance of the upper and lower airways. With that method Berdel et al. have measured nasal resistance during provocation with allergens (1981). A valuable review dealing mainly with less used methods to evaluate nasal patency and airflow was published in Facial Plastic Surgery (Eccles, 1990).

Nasal airway resistance, or nasal airflow at a certain pressure, has so far not convincingly been found to be able to select individual rhinitis patients from normal subjects with histamine or methacholine provocations intranasally even if all the precautions, such as rest before the measurements, as recommended by the Committee in 1984, are fulfilled. For graded responses after allergen provocations, NAR may be of clinical value only in combination with scorings from sneezes and fluid secretion.

Wihl (1986) and Gerth van Wijk (1991) in their respective theses, as well as Hasegawa et al. already in 1976, a group from Pittsburgh (Doyle et al., 1995) and recently Pirilä from Finland (1998), advocate a combined scoring for allergen and histamine challenges in the nose and the subcommittee shares that opinion. Regarding 'positive' cut-off levels for NAR values and also for values of the other methods mentioned above, it is important to emphasise that such levels are highly dependent of the method, the thickness of the mucosa before the provocations, and if the provocation is one- or twosided.

Symptom scores

In addition to the objective measurements of nasal patency and airflow a variety of methods to assess the response to allergen or non-specific stimuli are available. These methods comprise measuring nasal secretion, counting sneezes, assessment of severity of symptoms and VAS (visual analogue scores). The composite symptom score of Lebel (1988) has been validated in terms of responsiveness to treatment, correlation with daily nasal symptoms and discrimination between patients and healthy subjects (de Graaf-in 't Veld, 1995).

REFERENCES

1. Andersson M, Greiff L, Svensson C, Persson C (1995) Various methods of testing nasal responses in vivo: A critical review. Acta Otolaryngol (Stockh) 115: 705-713.
2. Austin CE, Foreman JC (1994) Acoustic rhinometry compared with posterior rhinomanometry in the measurements of histamine- and bradykinin-induced changes in nasal airway patency. Br J Clin Pharmac 37: 33-37.
3. Bachert C, Gonsior E, Berdel D (1990) Richtlinien für die Durchführung von nasalen Provokationen mit Allergen bei Erkrangungen der oberen Luftwege. Allergologie 13: 53-56.
4. Bachert C (1997) Nasal provocation test: Critical evaluation. In: J Ring, H Behrendt, D Vieluf (Eds.) New Trends in Allergy IV, Springer-Verlag, Berlin, Heidelberg.
5. Berdel D, Gast R, Huber B (1981) The simplified oscillation method for measuring nasal resistance during provocation with allergens. Clin Allergy 11: 385-393.
6. Broms P, Jonson B, Lamm J (1982) Rhinomanometry: A system for numerical description of nasal airway resistance. Acta Otolaryngol (Stockh) 94: 157-168.
7. Clement PAR, van Dishoeck A, van de Wal J, Stoop P, Hoek T, van Strick R (1981) Nasal provocation and passive anterior rhinomanometry (PAR). Clin Allergy 11: 293-301.
8. Clement PAR (1984) Committee report on standardisation of rhinomanometry. Rhinology 22: 151-155.
9. Clement PAR, Stoop AP, Kaufman L (1985) Histamine threshold and nasal hyperreactivity in nonspecific allergic rhinopathy. Rhinology 23: 35-42.
10. Corrado OJ, Ollier S, Phillips MJ, Thomas JM, Davies RJ (1987) Histamine and allergen induced changes in nasal airway resistance measured by anterior rhinomanometry: reproducibility of the technique and the effect of topically administered antihistaminic and anti-allergic drugs. Br J Clin Pharmac 24: 283-292.
11. Doyle WJ, Skoner DP, Seroky JT, Fireman P (1995) Reproducibility of the effects of intranasal ragweed challenges in allergic subjects. Ann Allergy Asthma Immunol 74(2): 171-176.
12. Eccles R (1990) Other techniques for assessing nasal function. Facial Plastic Surgery 7: 260-265.
13. Gerth van Wijk R (1991) Nasal hyperreactivity. Thesis. Faculty of Medicine. Erasmus University Rotterdam, The Netherlands.
14. Gordts F, Clement PAR, Derde MP (1989) Nasal provocation with histamin: A comparison of the determination of the threshold of reactivity by three methods of rhinomanometry. Rhinology 27: 263-269.
15. de Graaf-in't Veld C, Garrelds IM (1995) Nasal hyperreactivity and inflammation in perennial allergic rhinitis. Thesis. Faculty of Medicine. Erasmus University Rotterdam, The Netherlands.
16. Grymer LF, Hilberg O, Pedersen OF, Rasmussen TR (1991) Acoustic rhinometry: values from adults with subjective normal nasal patency. Rhinology 29: 35-47.
17. Guercio J, Saketkhoo K, Birch S, Fernandez R, Tachmes L, Sackner MA (1979) Effect of nasal provocation with histamine, ragweed pollen and ragweed aerosol in normal and allergic rhinitis subjects. Am Rev Respir Dis 119(suppl): 69.
18. Hallén H (1994) Nasal mucosa reactivity. Thesis. Karolinska Institute, Stockholm, Sweden.
19. Hasegawa M, Saito Y, Watanabe K (1976) The effect of sodium cromoglycate on the antigen-induced nasal reaction in allergic rhinitis as measured by rhinomanometry and symptomatology. Clin Allergy 6: 359-363.
20. Hilberg O, Jackson AC, Swift DL, Pedersen OF (1989) Acoustic rhinometry: evaluation of nasal cavity geometry by acoustic reflection. J Appl Physiol 66(1): 295-303.
21. Holopainen E, Tarkiainen E, Malmberg H (1976) Nasal challenge. Rhinology 14: 181-188.
22. Holmström M, Kumlien J (1988) A clinical follow-up of septal surgery with special attention to the value of preoperative rhinomanometric examination in the decision concerning operation. Clin Otolaryngol 13: 115-120.
23. Holmström M, Scadding GK, Lund VJ, Darby YC (1990) Assessment of nasal obstruction. A comparison between rhinomanometry and nasal inspiratory peak flow. Rhinology 28: 191-196.
24. Jessen M, Ivarsson A, Malm L (1996) Nasal airway resistance after decongestion with a nasal spray or a bellows device. Rhinology 34: 28-31.
25. Juto JE, Lundberg C (1982) An optical method for determining changes in mucosal congestion in the nose in man. Acta Otolaryngol (Stockh) 94: 149-156.
26. Lebel B, Bousquet J, Morel A, Chanal I, Godard P, Michel FB (1988) Correlation between symptoms and the threshold for release of mediators in nasal secretions during nasal challenge with grasspollen grains. J Allergy Clin Immunol 82: 869-877.
27. Lenders H, Pirsig W (1990) Diagnostic value of acoustic rhinometry: Patients with allergic and vasomotor rhinitis compared with normal controls. Rhinology 28: 5-16.
28. Lund V et al. (1994) International Consensus Report on the Diagnosis and Management of Rhinitis. Allergy Suppl 19: 1-34.
29. Malm L (1974) Responses of resistance and capacitance vessels in the feline nasal mucosa to vasoactive agents. Acta Otolaryngol (Stockh) 78: 90-97.
30. McLean JA, Mathews KP, Ciarkowski AA, Brayton PR, Solomon WR (1976) The effects of topical saline and isoproterenol on nasal airway resistance. J Allergy Clin Immunol 58: 563-574.
31. McLean JA, Mathews KP, Solomon WR, Brayton PR, Ciarkowski AA (1977) Effect of histamine and methacholine on nasal airway resistance in atopic and nonatopic subjects. J Allergy Clin Immunol 59: 165-170.
32. Melillo G, Bonini S, Cocco G, Davies RJ, de Monchy, Frölund L, Pelikan Z (1997) Standardisation of nasal provocation tests. Allergy Suppl 35: 26-33.
33. Milewski M, Mastalerz L. Nizankowska E, Szczeklik A (1998) Nasal provocation test with lysine-aspirin for diagnosis of aspirin-sensitive asthma. J Allergy Clin Immunol 101: 581-586.
34. Niinima V, Cole P, Mintz S, Shephard RJ (1979) A head-out exercise body pletysmograph. J Appl Physiol 47: 1336-1339.

35. Pelikan Z (1978) Late and delayed responses of the nasal mucosa to allergen challenge. Ann Allergy 41: 37-47.
36. Pirilä T, Talvisara A, Alho OP, Oja H (1997) Physiological fluctuations in nasal resistance may interfere with nasal monitoring in the nasal provocation test. Acta Otolaryngol (Stockh) 117: 596-600.
37. Pirilä T (1998) Acoustic rhinometry, rhinomanometry and the amount of nasal secretion in the clinical monitoring of the nasal provocation test. Clin Exp Allergy 28: 468-477.
38. Roithmann R, Cole P, Chapnik J, Zamel N (1995) Reproducibility of acoustic rhinometric measurements. Am J Rhinol 9: 263-267.
39. Rüdiger W (1978) Der Intranasaltest (INT) im Rhinomanogramm (Rhmg) und seine Bedeutung in der allergologischen Diagnostik. Allergologie 1: 140-144.
40. Schlenter WW (1982) Measurements in the course of intranasal provocation test (INT). Arch Otorhinolaryngol 234: 11-13.
41. Schlenter WW (1983) Der intranasale Provokationstest in der allergologischen Diagnostik. Hab. Schrift Med. Fakultät Albert-Ludwig-Universität Freiburg.
42. Schumacher MJ, Pain MC (1979) Nasal challenge testing in grass pollen hay fever. J Allergy Clin Immunol 64(3):202-208.
43. Schumacher MJ (1992) Nasal provocation test. Rhinology Suppl 14: 242-246.
44. Shelton DM, Perutze J, Gleeson MJ, Thompson J, Denman WT, Goff J, Eiser NM, Prode NB (1990) Comparison of oscillation with three other methods for measuring nasal airway resistance. Respir Med 84: 101-106.
45. Sipilä J, Nyberg-Simola S, Suonpää J, Laippala P (1996) Some fundamental studies on clinical measurement conditions in acoustic rhinometry. Rhinology 34: 206-209.
46. Taylor G, Shivalkar PR (1971) Arthus-type reactivity in the nasal airways and skin in pollen sensitive subjects. Clin Allergy 1: 407-414.
47. Taylor G, MacNeil AR, Freed D (1973) Assessing degree of nasal patency by measuring peak expiratory flow rate through the nose. J Allergy Clin Immunol 52: 193-198.
48. Wang D, Clement P (1995) Assessment of early- and late-phase nasal obstruction in atopic patients after nasal allergen challenge. Clin Otolaryngol 20: 193-198.
49. Wihl JÅ, Malm L (1985) Rhinomanometry in routine allergen challenge. Clin Otolaryngol 10: 185-189.
50. Wihl JÅ (1986) Assessment of nasal hyperreactivity. Thesis. Faculty of Medicine, University of Lund, Sweden.
51. Wihl JÅ (1987) Methodological aspects on nasal allergen challenges based on a three-year tree pollen immunotherapy study. Allergy 41: 357-364.
52. Wihl JÅ, Malm L (1988) Rhinomanometry and nasal peak expiratory and inspiratory flow rate. Ann Allergy 61: 50-55.

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