Rhinology, 34, 86-90, 1996

# Nasal provocation test in the diagnostics of occupational allergic rhinitis*

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SUMMARY

*The diagnosis of occupational rhinitis (OR) must be better confirmed than in allergic rhinitis of other aetiology. A provocation test is required to confirm the causality between the disease and the work exposure. The purpose of this study has been to examine the feasibility of active anterior rhinomanometry and visual analogue scale in the diagnostics of OR, and to compare the results of these measurements to a nasal status change score. The study subjects have been 50 consecutive patients suspected of having OR. Altogether 148 bilateral nasal provocation tests (NPTs), 55 placebo- and 93 allergen-NPTs, have been done. Based on the change in the nasal status and change in the nasal airway resistance (NAR), there are 42 positive NPTs. Although overlapping between placebo and allergen provocations exists, an increase of >50% in NAR is recommended to regard the result as positive in NPT. The evaluation of the nasal reaction in the NPT is mainly based on anterior rhinoscopy and the change in the status score, but OR diagnostics should also include some physiological measurement.*

*Key words: allergy, nasal challenge, rhinomanometry, visual analogue scale*

## INTRODUCTION

The diagnosis of allergic rhinitis in clinical practice is based on the patient's history and symptoms, and the clinical findings. If necessary, the diagnosis is confirmed with skin-prick or RAST testing. There may, sometimes, be controversy between the history and laboratory testing. As allergy medication nowadays is mostly well-tolerated, the diagnosis of uncomplicated allergic rhinitis and the prescription of medication can mainly be based on these criteria.

The diagnosis of occupational rhinitis (OR) must be better confirmed than in allergic rhinitis of other aetiology. Thus, the diagnosis cannot only be based on the patient's history and laboratory tests. Few reports have been published on OR (Kup, 1985; Kanerva and Vaheri, 1993) or its diagnostics (Blainey et al., 1981; Okuda et al., 1982; Gervais et al., 1985; Schwartz et al., 1990). A positive provocation test is required to confirm the diagnosis and the causality between symptoms and signs of the disease and the work exposure. There are no standardized methods for the nasal provocation test (NPT), and different ways to perform the test have been reported (Holopainen et al., 1976; Pipkorn, 1988; Solomon and MacLean, 1989; Bachert et al., 1990; Druce and Schumacher, 1990). Reports on the use of NPT in clinical practice are scanty (Clarke, 1988).

Subjective symptoms cannot be the only criteria for a positive response in the NPT. There is often a need to transfer an employee having OR to a new job; sometimes, retraining is necessary. The question of financial compensation for the patient also arises, e.g. the costs of medication are paid by the insurance company. Thus, the diagnosis of OR must be better confirmed. This means that physiological measurements should be used in measuring the response in NPT. The use of rhinomanometry in evaluating nasal patency in allergy medication research, NPT (Sipilä et al., 1990) and nasal surgery (Broms et al., 1982b) has been well documented. However, the use of rhinomanometry in the diagnostics of OR has been rarely reported.

A patient having rhinitis symptoms associated with work complains of varying symptoms. Most often, he/she has symptoms of an immediate allergic reaction: itching, sneezing, watery secretion, and blockage of the nose. However, the symptoms can also be more obscure, such as a feeling of blockage, dryness of the nasal mucosa or crusts in the nose. These symptoms often worsen towards the end of the week. The latter symptoms are typical for rhinitis of a non-allergic occupational aetiology that can be called "toxic rhinitis." NPT has little or no value in the diagnosis of toxic rhinitis.

* Received for publication January 31, 1995; accepted May 8, 1995

Most of the diagnosed cases of OR are allergic diseases of the immediate type. The symptoms appear immediately after a sensitized worker is exposed to the allergen. NPT is suitable for the diagnostics of OR if an immediate nasal reaction is suspected. The patients in this study have had symptoms of an immediate allergic reaction.

This study reports a method of bilateral nasal provocation with occupational allergens, and rhinoscopic and rhinomanometric evaluation of the nasal response. The purpose of this study was to examine the feasibility of active anterior rhinomanometry (AAR) and visual analogue scale (VAS) in the diagnostics of OR, and to compare the results of these measurements to a nasal status change score. The purpose was also to compare the results of NPT with the results of prick skin tests.

## MATERIAL AND METHODS

The study subjects were altogether 50 consecutive rhinitis patients suspected of having OR, which were sent to our Institute. There were 29 women and 21 men, the average age was 39.8 years (range: 19–62 years). Careful working and exposure histories were taken during the first visit. Skin prick and RAST tests were done according to the information obtained from the patient and his/her employer concerning the possible allergen exposure at work. Before the NPT, the patient was examined by the otorhinolaryngologist who later performed the nasal provocation tests. If, during the first visit, an infection or considerable mucous membrane oedema was noted, an adequate treatment protocol was started. After infection, no provocation was done until 3-4 weeks after controlled healing. Antiallergy medication was stopped early enough.

Two to five nasal provocation tests were performed for each patient on consecutive days, and one test was performed daily between 10 a.m. and noon. Altogether, 148 NPTs were done. The test was done pseudo-randomly; the patient did not know which provocation material was tested until all the tests had been done. The provocation material was placed bilaterally onto the fronto-topical surface of the inferior turbinate. The choice of the test material was based on the patient's history and skin-prick or RAST tests, or previously done NPTs. Table 1 shows the provocations done.

The test series was started with placebo. Altogether 55 placebo tests were performed. The test material in the placebo tests was either prick control solution or NaCl plus lactose, depending on the allergen to be tested. In five cases the placebo test was repeated to exclude possible hyperreactivity, as the patients had developed a strong positive local reaction after an allergen provocation.

The application of allergen varied, depending on the material to be examined. In the tests for animal epithelium, acarus or molds, prick solutions (ALK, Copenhagen, Denmark) were used. A pressured cotton disk (diameter: 3 mm) was absorbed with two drops (approx. 120 ml) of allergen solution. If it was expected that cotton would cause a reaction itself (as in suspected cotton allergy), two drops of test solution were dropped onto the inferior turbinate.

Table 1. Number of NPTs, positive prick or RAST, and positive NPTs in this study (NPTs: the total number of provocations done; prick- or RAST-positive: the number of provocations with positive prick or RAST test; positive NPTs: number of positive nasal provocation tests).

| tested allergen | NPTs | prick- or RAST-positive | positive NPTs |
|---|---|---|---|
| *flours:* | | | |
| wheat | 15 | 7 | 9 |
| rye | 12 | 5 | 9 |
| oat | 5 | 1 | 2 |
| *animal epithelium:* | | | |
| pig, cow | 9 | 2 | 5 |
| fox, mink | 4 | 1 | - |
| laboratory rodents | 3 | 2 | 3 |
| acarus | 5 | 2 | 2 |
| molds | 6 | 4 | 4 |
| *wood dusts:* | | | |
| domestic (spruce, pine, birch) | 8 | - | 2 |
| foreign (mahogany, obeche, gabon, ash, oak) | 5 | - | 1 |
| pine resin | 2 | - | - |
| spices (white pepper, coriander, cinnamon, coffee bean, tobacco) | 6 | 3 | 3 |
| textiles (silk, linen, rayon) | 8 | - | 1 |
| flowers (freesia, rose) | 3 | - | - |
| ammonium persulfate | 2 | - | 1 |
| total | 93 | 27 | 42 |

To examine flours, wood dust or textile dust, a cotton disk was first moistened with 0.9% saline and then rolled in the flour or dust brought in by the patient from his working place. To test spices, a 1% NaCl solution was prepared by soaking in NaCl for 24 h. A 1% solution was prepared for ammonium persulfate provocation. In the tests with flowers, the flower was first defatted with acetone, dried and after that a 1% filtered solution was prepared. For the NPT a 3-mm cotton disk was moistened in the solution. When a new allergen preparation for NPT was taken into use, at least five healthy controls were done to exclude the probable irritant effect of the solution.

Anterior rhinoscopy was done and rhinorrhoea and nasal mucous membrane blockage of the both nasal cavities were scored separately, according to the scoring system in Table 2. The patient was asked to avoid blowing his/her nose and the status was scored every 10–15 min. The appearance of sneezing and itching were also noted. The test was continued for 30–45 min. The cotton disks were then removed. No late responses were registered. The change in the nasal status score ($\Delta_{status}$) was calculated: $\Delta_{status}$ equals the sum of the total blockage and rhinorrhoea after the NPT minus the sum of the total blockage and rhinorrhoea before the NPT. The NPT was regarded as positive if the $\Delta_{status}$ was ≥4 points.

Table 2. The scoring of nasal blockage and rhinorrhoea.

*rhinorrhoea:*
0: dry nasal mucous membrane
1: slightly moist mucous membrane
2: some mucus collecting at the bottom of the nasal cavity
3: mucus dropping out of the nose

*blockage of the mucosa:*
0: no swelling (the bony configuration of the inferior turbinate is seen)
1: slight mucous membrane swelling of the inferior turbinate
2: moderate mucous membrane swelling (if there is no septal deviation, the inferior turbinate is close to the septum)
3: the nasal cavity is (almost) completely obstructed

Inspiratory nasal airway resistance was measured before and immediately after the NPT, using an active anterior rhinomanometry technique (Rhinomanometer NR6; Mercury, Glasgow) with Broms radius-200 method (Broms, 1982a).

In 133 NPTs the nasal blockage was self-assessed by the patient with a 10-cm visual analogue scale. The ends of the scales were "the nose feels completely open" and "the nose feels completely obstructed."

The prick test was considered positive if the skin patch reaction was >50% of that caused by histamine (10 mg/ml; Kanerva et al., 1991). If the patch size was <50%, the prick test result was considered to be uncertain. The RAST test was positive if the IgE concentration exceeded 0.7 kU/l.

For comparison, the provocations were divided into groups based on the prick or RAST test result done with NPT allergen: group "Neg": prick and RAST negative (n=58); group "Unc": prick and/or RAST uncertain (n=8); and group "Pos"; prick or RAST positive (n=27). Group "0" includes the placebo provocations (n=55).

$\Delta_{NAR}$ is the percentual change in the nasal resistance, and $\Delta_{VAS}$ equals VAS scale value after the NPT minus VAS scale value before the NPT. The statistical significances between the groups were tested by Mann-Whitney U test. Kendall rank correlation coefficients ($r_K$) between $\Delta_{NAR}$, $\Delta_{VAS}$ and $\Delta_{status}$ were calculated.

## RESULTS

No systemic reactions were observed during the NPTs, nor were late systemic reactions reported by the patient in any of the NPTs.

Based on evaluation by anterior rhinoscopy the mean status in groups "0", "Neg", "Unc" and "Pos", was 1.27 (minimal -2, maximal 3), 1.40 (minimal -3, maximal 7), 3.25 (minimal 0, maximal 6) and 4.67 (minimal 0, maximal 8), respectively. Groups "Pos" and "Unc" differed from groups "0" and "Neg" significantly ($p < 0.05$). The frequencies of the sums are summarized in Figure 1. The number of NPTs in which the $\Delta_{status}$ was ≥4 in groups "0", "Neg", "Unc" and "Pos" were 0/55, 5/58, 5/8 and 21/27, respectively.

The NARs before each NPT are given in Figure 2. The mean nasal resistance prior to NPT on the first day was 0.271 Pa/cm$^3$/s (n=50) and on the following days 0.265 Pa/cm$^3$/s (n=50), 0.284 Pa/cm$^3$/s (n=38) and 0.256 Pa/cm$^3$/s (n=7), respectively. The mean resistances before NPT did not differ from each other on the consecutive days. Neither were there significant differences in the mean NARs between the different groups before NPTs.

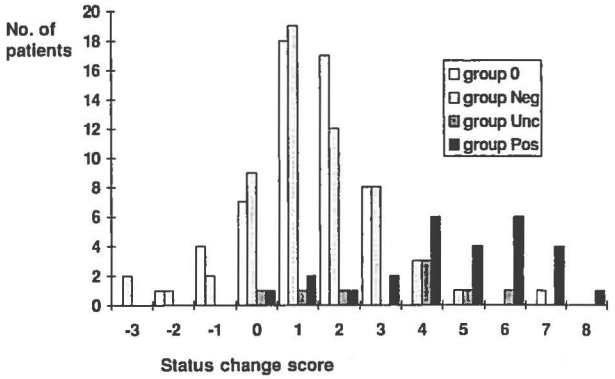


Figure 1. Change in the nasal status score after a nasal provocation test in different groups. Group "0": placebo provocation tests; group "Neg": prick test done with provocation test material negative; group "Unc": prick test uncertain; and group "Pos": prick test positive.

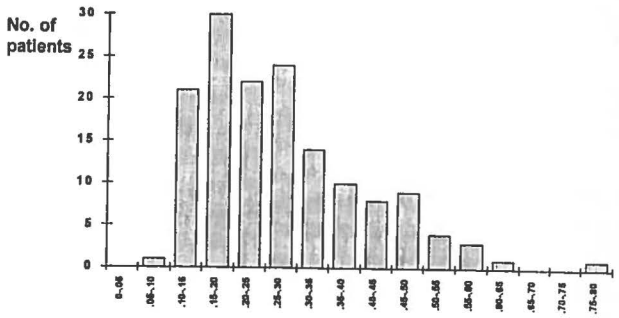


Figure 2. The distribution of nasal airway resistances before nasal provocation tests.

In the placebo NPTs, the mean change in NAR was 11.6% (minimal -36.4, maximal 102.6). If the placebo testing was done with NaCl plus lactose (n=43), the mean change was 13.3% (minimal -36.4, maximal 102.6). With control prick solution (n=12), the mean NAR was 0.3% (minimal -29.2, maximal 31.5). In group "Neg" the mean increase was 33.7% (minimal -33.6, maximal 288). In groups "Unc" and "Pos" the mean changes were 14.0% (minimal -33, maximal 51) and 83.1% (minimal -7.9, maximal 434), respectively. Although the means of NAR in the different groups differed, there was considerable overlapping within the groups (Figure 3). In 9% (5/55) of the placebo NPTs the NAR exceeded 50%. In five cases with repeated placebo tests no essential changes were seen in the status or in the NAR. Figure 4 shows the changes in the NAR in the provocations where the results according to the change in the status were positive ($\Delta_{status}$ ≥4; n=31) or negative ($\Delta_{status}$ <4; n=117). There was a significant ($p < 0.001$) correlation with $\Delta_{NAR}$ measurement and $\Delta_{VAS}$ (n=133). There was also a significant ($p < 0.001$) correlation with $\Delta_{VAS}$ and $\Delta_{blockage}$, and $\Delta_{blockage}$ and $\Delta_{NAR}$ (n=133).

The NPT was considered positive if either the status change was ≥4 points or the nasal resistance increased at least 50% and a change in the nasal blockage was seen. Based on the above-

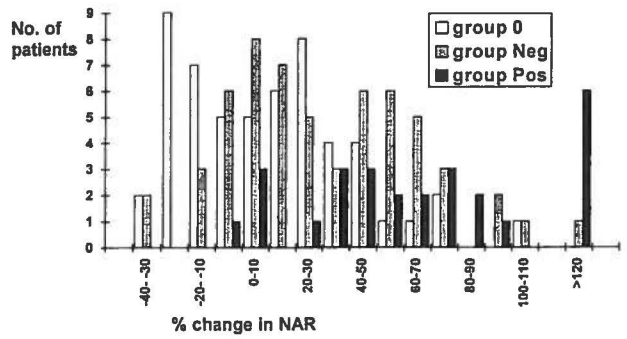


Figure 3. Percentual change in the nasal airway resistance (NAR) after a nasal provocation test. Group "0": placebo provocation tests; group "Neg": prick test done with provocation test material negative; and group "Pos": prick test positive.

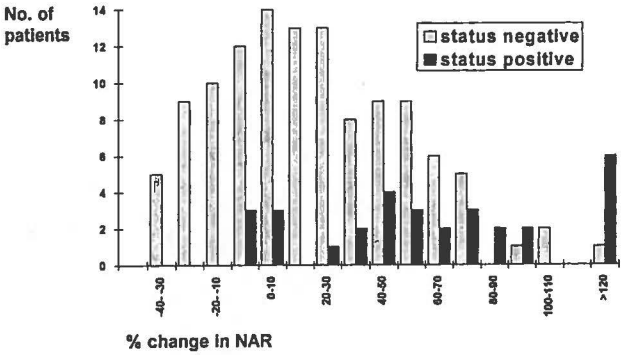


Figure 4. Change in the nasal airway resistance after a nasal provocation test. Status negative: the change in the nasal status score was <4; status positive: the change in the nasal status score was ≥4.

mentioned criteria, there were 42 positive provocation tests. Thus, 45% of allergen NPTs were positive (Table 1). If there was sneezing or the patients reported itching in the nose, this was considered to support the positive reaction, especially in cases with borderline response. In three allergen NPTs the test results were considered negative, although the nasal resistance increased over 50%, as no change was noted in the nasal status.

## DISCUSSION

Occupational rhinitis (OR) is a disease that considerably worsens the quality of life and the ability to work properly. Often, allergic OR is also an early sign of respiratory disease. If the exposure to allergens persists, the disease may develop into asthma (Machiels et al., 1991). This makes it important to find the cause of OR in its early stages. In the diagnostics of OR, provocation tests are essential not only to confirm the diagnosis, but also to confirm the causality between symptoms and signs of the disease and exposure. The provocation test may also give an idea of the intensity of the allergic reaction in the nasal mucosa.

A bilateral provocation is used, as it is more physiological (Okuda, 1977; Brooks et al., 1991) and resembles occupational exposure more than a unilateral test. The allergen used in occupational NPT should be the same, or as close as possible, to the material that the patient uses in his/her work. This means that there are many different test agents used in the different provocations. It is very time-consuming to do NPTs with different concentrations or even to do many control tests at one concentration.

As each NPT is done only with one allergen concentration, a false-negative NPT is possible. To minimize the possibility of false-positive reactions, five negative control-NPTs done with a new allergen are required to show that the test material itself does not cause a non-specific reaction. We have used glycerol-based solutions, although it has been reported that glycerol may cause in the nasal mucosa a non-specific reaction more easily than solutions without glycerol (Haahtela and Lahdensuo, 1979; Mygind et al., 1986). The prick solution containing glycerol did not cause essential changes in the nasal status or in the NAR. Based on that finding it is possible to use these solutions in NPTs. Our NPT system seems to be safe, as there were no systemic effects in the NPT.

The test was continued for 30 min when there was a clinically essential reaction, although in IgE-mediated allergy the reaction begins already within a few minutes after allergen exposure. If no reaction was noted, the test was discontinued after 45 min.

NPTs with nasal status scoring have been done for 20 years at our Institute. The increase of four or more points in the status score has proved to be a feasible limit for a positive nasal reaction. A change of three points is considered to be unreliable, and a change of one to two points is not relevant. Sneezing and itching in the NPT can point to a positive reaction. If present without changes or with only minor status changes, their value is uncertain in the diagnostics of occupational diseases. There is always the possibility of some degree of aggravation of the symptoms in the NPT. It is important that the patient does not know the material to be tested.

Active anterior rhinometry (AAR) was done routinely for all of our provocation patients. In some 5% of the cases the AAR could not be done due to the uncooperativeness. If the nasal reaction after the challenge is very strong, the watery secretions and the blockage of the nose may make the AAR difficult to perform reliably. However, in such cases the positive reaction is obvious even without NAR measurements.

We had expected a greater increase in the NAR than was actually measured in the allergen NPTs. The low increase may be due to the fact that all of our patients suffer from perennial OR symptoms. Some mucous membrane swelling can be present continuously, so the increase of the mucous membrane swelling in NPT is less than, for example, in seasonal rhinitis. The allergen was put to a relatively small area and the change in the nasal mucosa can concentrate on the inferior turbinate. Thus, the change in the blockage measured by $\Delta_{NAR}$ can be small. It is also possible that the test material concentrations were too low. AAR is also prone to technical artifacts, even when done by an experienced nurse.

The mean nasal resistances before NPT did not change in the consecutive days. However, this does not exclude the possible tachyphylactic or priming effect (Mygind and Lowenstein, 1982), although we did not see any essential change in the five repeated placebo provocation tests. Although the mean $\Delta_{NAR}$ of the different groups differed, there was considerable overlapping between the groups (Figure 3). Thus, it is difficult to

choose the limit of $\Delta_{NAR}$ change needed to regard NPT as positive. We recommend an increase of 50% or more as a limit for an significant change in the nasal resistance.

There was a correlation between VAS, nasal blockage status and AAR measurements. This means that VAS can be used in NPTs to give information on the grade of the nasal blockage.

Forty-two of the 93 NPTs done with allergen have given a positive result. However, as tested with skin prick test, only 27/93 give a positive result. This can partly be due to the fact that with increasing age the skin reactivity in prick tests decreases. Another reason might be that in occupational diagnostics the prick testing often has to be done with non-standardized extracts giving possible false-negative results. Over-evaluation of the nasal status change is also possible, resulting in false-positive NPTs. However, skin prick test and NPT do not measure the reactivity of the same organ. It is possible that an allergen causes only a local nasal reaction.

The relatively high number of positive NPTs on symptomatic but no prick- or RAST-positive patients, emphasizes the importance of provocation tests in occupational disease diagnostics. Although the concordance of skin and blood tests with provocation seems to be relatively good in asthma and allergic rhinitis (Räsänen et al., 1994) the diagnostics of OR cannot be based on these tests alone. The diagnosis of OR needs a positive exposition history and a positive reaction in a provocation test. Positive skin-prick test and/or RAST can confirm the IgE-mediated allergic aetiology. Although evaluation of the nasal reaction in the NPT is mainly based on anterior rhinoscopy and the change in the status score, the evaluation should include some physiological measurement, as AAR in this study.

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