ORIGINAL CONTRIBUTION

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Usefulness of nasal provocation tests in occupational rhinitis*

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SUMMARY

Objective: *The aim of the study was to determine whether Nasal Provocation Tests (NPT) could help in the diagnosis of occupational rhinitis (OR).*

Methods: *Changes in nasal airway resistance (NAR), measured by posterior rhinomanometry during specific nasal challenge associated with per and post test clinical scores, were compared to a prior probability, based on the patient's history, determined by occupational physicians, in 41 hairdressers and 33 bakers referred for suspected OR.*

Results: *A NAR ≥ 150% defined the positivity of the NPT. NAR demonstrated 50% sensitivity and a 86% specificity in hairdressers and a 95% sensitivity with 100 % specificity in bakers. NAR presented significant positive correlations with both per ($p = 0.0003$, $r = 0.48$) and post test clinical scores ($p < 0.005$, $r = 0.39$). The addition of clinical scores increased the sensitivity to 100% in hairdressers with 81% specificity.*

Conclusions: *The NPT constitutes a safe procedure of nasal reactivity with good levels of sensitivity and specificity in both hairdressers and bakers when nasal resistance and clinical scores are taken into account.*

Key words: flour, nasal provocation test, occupational rhinitis, persulfate, posterior rhinomanometry

INTRODUCTION

Allergies in the workplace are a significant source of illness, occupational rhinitis and asthma being the commonest occupational respiratory diseases in many industrialized countries [(1)]. Many agents may cause rhinitis symptoms, such as flour or persulfates [(2)]. Hairdressers and bakers are particularly at high risk for occupational airway disease [(3,4)]. The prevalence of respiratory diseases among hairdressers was shown to vary between 5 and 25% [(5)]. The bakers and pastry makers are commonly reported from population studies to be at high risk of developing asthma or rhinitis [(6)]. Subjects with allergic rhinitis have an increased risk of developing asthma [(7,8)], and the appearance of rhinitis in occupationally exposed subjects might be a marker of the likelihood of developing occupational asthma, thus early diagnosis of occupational rhinitis may prevent the development of asthma. Moscato et al. [(3)], studying 47 hairdressers, found that persulfate salts were the major agents involved in occupational asthma and occupational rhinitis. Karjalainen et al. [(9)] reported that occupational rhinitis carried a crude relative risk of asthma of 4.8, a risk which was high during the year following reported rhinitis but also for several years.

Identifying a workplace-related cause of disease is important because reversibility of symptoms is possible with an early detection; once the disease is established, withdrawal from the offending environment may not necessarily lead to symptom improvement. In most cases, timing of symptoms with respect to workplace exposure, detailed history with physical examination, skin tests and sometimes serologic testing allow the distinction between occupational rhinitis and perennial or seasonal rhinitis. However, due to the socio-economical consequences of occupational rhinitis diagnosis, efforts should indeed be made to objectively confirm occupational rhinitis. Using nasal provocation test (NPT) with rhinomanometry combined to a symptom score would allow obtaining an objective measurement of nasal allergic reactions, and consequently

List of abbreviations: NPT: nasal provocation test; OR: occupational rhinitis; NAR: nasal airway resistance; FEV1: forced expiratory volume in one second; HMW: high molecular weight

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would lead to the implementation of preventive measures, such as the relocation of affected workers to an unexposed job, and could prevent asthma from developing.

The aim of our study was to evaluate the usefulness of the NPT with rhinomanometric evaluation of nasal responses in diagnosing occupational rhinitis, and to compare the results to a clinical diagnosis made by two independent experts. We decided to assess the diagnostic value of NPT in two different kinds of allergy, namely flour- and persulfate-related, in as much as one may hypothesize that clinical rhinitis expression may be influenced by the kind of allergen.

METHODS AND MATERIALS

Subjects

We studied two groups of consecutive new patients suspected of having occupational rhinitis, referred by occupational physicians to the Occupational Medicine Department of the Centre Hospitalier Intercommunal de Créteil, France. The first group (Group 1) was composed of 33 bakers (29 males and 4 females) and the second one (Group 2) included 41 hairdressers (6 males and 35 females). A third group consisted of 10 healthy volunteers. All patients were clinically stable at the time of the study.

Patients with acute rhinosinusitis, exacerbation of allergic disease, a recent nasal surgery, nasal polyps, a respiratory tract infection, a history of airway obstruction defined as a ratio of forced expiratory volume in one second to forced vital capacity less than 70%, were not included. Antihistamines and nasal corticosteroids were withdrawn 5 days before the test. The protocol was approved by the local ethics committee.

Study design

Each subject underwent clinical and occupational histories, a physical examination with rhinoscopic examination, pulmonary function testing and a methacholine challenge test, skin-prick tests and a nasal provocation test. Before nasal provocation testing, two independent specialists in occupational diseases, working separately, determined which was the probability of having or not an occupational allergy for each subject, according to the results of all the examinations mentioned. Subjects were classified based on this prior probability, namely presence or absence of occupational disease, expressed as a binary variable having values 0 or 1.

Immunological test

Skin-prick tests for common and occupational inhalant allergens including tree and grass pollen, molds, feathers, house-dust mite, flours, persulfates, alpha-amylase, latex, were performed with commercial extracts (Allerbio, Varenne en Argonne, France), according to the method described by Pepys [10]. A phosphate-buffered saline solution was used as a negative control, and phosphate codeine served as a positive control. The results of the tests were examined after 15 minutes. They were considered positive when the wheal and red flare diameters were at least 4 mm and 5 mm, respectively.

Pulmonary Function and Methacholine Challenge Tests

Spirometry measurements and flow-volume curves were obtained using a spirometer (MedGraphics, PF/DX 1085D, St. Paul, MN, USA). The spirometry technique met international standards [11].

All study patients underwent a methacholine challenge test performed with an aerosol nebuliser (Mediprom FDC88, Paris, France), which delivered successively four increasing doses of methacholine: 100, 500, 1000 and 2000mg. A flow-volume curve was performed after each inhalation of methacholine. The methacholine challenge test was considered to be positive when a 20% fall in FEV1 was observed. After the test, the patient was given an inhaled dose of beta-adrenoceptor agonist (two 100 mg puffs) with FEV1 measurement 15 minutes later. If the FEV1 value was not similar to the baseline FEV1, an additional beta-adrenoceptor agonist dose was given and FEV1 was measured 15 minutes later. At the end of the test, all patients had FEV1 values ≥ 90% baseline FEV1.

Rhinomanometry

Active posterior rhinomanometry was used to determine nasal resistance according to international recommendations [12,13]. Briefly, while the subject was breathing through the nose, flow measurements were performed using a transparent nasal face mask (Respironics vinyl masks, Nantes, France) fitted with a Fleisch no. 1 pneumotachograph (Lausanne, Switzerland) connected to a differential pressure transducer (Validyne MP 45 ± 2 cm H_2O, Northridge, CA, USA). Oropharyngeal pressure was recorded via a catheter inserted through a hole drilled in a stopcock obstructing the cylindrical part of a modified mouthpiece placed between the lower lip and the protruding tongue. Nasal resistance was defined as the ratio between transnasal pressure and flow when the transnasal pressure reached 1 cm H_2O.

Bilateral, left and right resistances were measured allowing recognizing nasal cycling effects.

Resistance values were measured on patients who were seated after a 30 minutes-period of adaptation to the conditions in the testing room, to avoid the vascular effects of posture, physical exercise or exposure to pollutants.

Nasal provocation test

Meter-dose pump sprays were used for administration in both sides of the nose. The choice of the tests material was based on the patient's history and skin-prick tests.

After each challenge by 100 l spray, a patient was seated with a nose-clip during 10 minutes and without nose-clip during 3 minutes. An isotonic saline solution challenge was realized first and did not induce any significant nasal airway resistance change compared with the baseline value in any of the patients. Dose-response curves were constructed by adminis-

tering progressive doses of allergens. Nasal resistances were measured at intervals of 15 minutes. The ratios of the nasal airway resistances obtained after each dose of allergen over the NAR obtained after isotonic saline solution (NAR) were used to quantify the nasal obstruction.

Symptom score

To take into account clinical reactions such as sneezing, rhinorrhea, nasal obstruction and extranasal symptoms such as ocular, cutaneous or pulmonary reactions, scoring of the severity of each of these symptoms was noted during the test, 10 minutes after each dose, and at four hours after the end of the test [14,15] . The total symptom score ranged from 0 to 8 and represented the sum of the scores for sneezing (< 3 sneezes: 0 points; 3 - 4 sneezes: 1 point; > 4 sneezes: 2 points), nasal secretion (none: 0 points; moderate: 1 point; abundant: 2 points), nasal obstruction (none: 0 points; moderate: 1 point; nasal block: 2 points), and extranasal symptoms (none: 0 points; tearing or itching: 1 point; conjunctivitis with or without coughing 0 or dyspnoea: 2 points). A table with the scoring system was given to each patient for evaluation of clinical symptoms during the night and the day after.

NPT with persulfates salts

Persulfates salts, mix of 3 persulfates salts (1/3 sodium persulfate, 1/3 potassium persulfate, 1/3 ammonium persulfate), were prepared by Henri-Mondor Hospital's pharmacy.

Dose-response curves were constructed by administering progressive doses of allergens, i.e. 10 g, 100 g, 1mg.

NPT with flour

Flour extracts used were allergenic solutions promoted by Allerbio® (Varenne en Argonne, France). Dose-response curves were constructed by administering progressive doses of allergens, i.e. 10 g, 20 g, 30 g.

Statistical Analysis

All analyses were performed using a statistical software package (Statview 4; SAS Institute; Grenoble, France).

Comparisons of categorical data were made using the chi-squared test (X^2). Correlations between variables were evaluated using least-square linear regression techniques.

Sensitivity and specificity of the clinical scores for identifying subjects with occupational disease among patients were examined by receiver-operator characteristic (ROC) curves [16]. ROC curves made it possible to show the true positive rate (sensitivity) versus the false-positive rate (1-specificity) at various levels of symptoms scores and to determine the cut-off value corresponding to the largest number of well-classified patients according to the presence or absence of a significant increase in nasal airway resistance during the nasal provocation test. For all comparisons, p values < 0.05 were considered significant.

RESULTS

When analyzing all subjects, we noted that the sex distribution was significantly different between two groups ($p < 0.0001$), according to occupations that employ more males than females, as shown for bakers, and more females than males as shown for hairdressers, as previously reported [4,17,18]. No significant difference was found (chi-squared test, n.s.) in the methacholine challenge test, positive in 12 bakers (36.4%) and in 12 hairdressers (29.3%). A significant greater number of positive skin prick tests to common inhalant allergens was found in bakers as compared to hairdressers (60.6% vs 17.0%, $p < 0.001$).

Of the 74 study patients, 34 were found to be free of occupational rhinitis, and 61% of bakers (20 subjects) and 49% of hairdressers (20 subjects) to have an occupational rhinitis, according to the prior probability determined by two independent specialists. When comparing these specialist probabilities, similar results were noted ($r = 0.94$, $p < 0.0001$).

Mean bilateral nasal airway resistance (NAR) in 74 subjects at baseline was 2.1 ± 0.5 hPa.L.s-1. In control subjects, no symptoms and no significant increase in NAR were observed after NPT realized with flour or persulfates: ΔNAR = 104 ± 20%. According to these control subjects' results, and considering that the value of interest was the ΔNAR upper limit value, we calculated a one-sided limit with confidence probability 95%, and determined a ΔNAR cut-off value of 140% Because the control subjects sample size was not large enough to allow the limits of agreement to be estimated well, we calculated ΔNAR

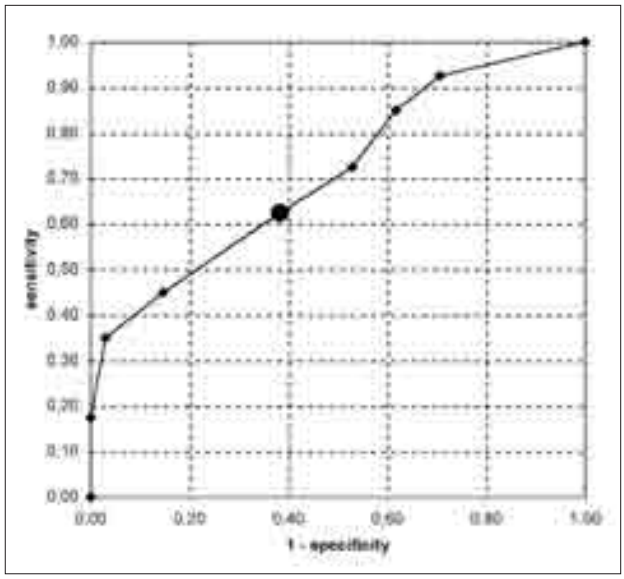

Figure 1. Receiver-operating characteristic (ROC) curves of per symptom score according to the prior probability. The receiver operating characteristic (ROC) curve is obtained by calculating the sensitivity and specificity of all possible cut points and plotting sensitivity (y axis) against 1 - specificity (x axis). Each point indicates the sensitivity and specificity of a possible score value. The cut-off value producing the best sensitivity and specificity (black round) is 4.

confidence intervals taking into account all patients with negative prior probability and obtained 115 ± 24%. After determining the upper limit, we then considered that a NPT was regarded as positive if the nasal resistance increased by at least 50% as compared with the post diluent measurement.

Evaluations of clinical symptoms during and after the test were combined with the assessment of NAR. A significant correlation was found between changes in nasal airway resistance (ΔNAR) and the score per test ($p = 0.0003$, $r = 0.47$), and between ΔNAR and the score post test ($p < 0.005$, $r = 0.41$). In our study, according to the ROC curve analysis (Figure 1), the symptom score cut-off value producing the best sensitivity and specificity was at least 4, which was in accordance with previous studies [14,15]. It allowed us to consider as negative a symptom score lower than 4 and positive a symptom score equal or greater than 4.

No systemic reactions were observed during the nasal provocation tests, nor were late reactions reported by the patients. All symptom scores assessed during the night and the day after the NPT were lower than 4.

Hairdressers group

Twenty patients were classified as having an occupational disease by physicians, and 10 of these subjects presented a positive NPT with a ΔNAR ≥ 150%. Among the 21 patients with a negative prior probability, 18 presented a negative NPT (chi-squared test: $p < 0.02$) (Table 1). The sensitivity of NPT was assessed as the proportion of the number of subjects with ΔNAR ≥ 150% in comparison to the number of subjects with a positive prior probability. The specificity of NPT was assessed as the proportion of the number of subjects with ΔNAR < 150% in comparison to the number of subjects with a negative prior probability. Sensitivity and specificity of NPT were 50% and 86%, respectively. No significant relationship was noted between ΔNAR and skin prick tests (chi-squared test: n.s.).

A significant relationship was observed between ΔNAR and the per test symptom score ($r = 0.47$, $p < 0.0025$). When adding the per test score results to nasal resistance changes, 16 of the 20 previous patients presented a positive NPT (chi-squared test: $p < 0.0001$), which corresponded to a sensitivity of 80% and a specificity of 86% (Table 1).

Table 1. Repartition of hairdressers according to NAR, to NAR and per symptoms scores and to NAR with symptoms scores evaluated during the test and four hours after the end of the test. NAR is the ratio of the nasal airway resistance (NAR) obtained after the last dose of allergen over the NAR obtained after isotonic saline solution.

	Positive prior probability	Negative prior probability
ΔNAR ≥ 150%	10	3
ΔNAR < 150%	10	18
ΔNAR ≥ 150% or per symptoms score ≥ 4	16	3
ΔNAR < 150% and per symptoms score < 4	4	18
ΔNAR ≥ 150% or symptoms scores ≥ 4	20	4
ΔNAR < 150% and	0	17

When considering the post-test symptom score, a significant correlation was observed with the change in nasal airway resistance ($r = 0.42$, $p < 0.02$). If adding the per and post test symptoms scores to nasal resistance changes, a positive NPT was noted in all the 20 patients suspected of having an occupational disease. A negative NPT, defined as ΔNAR < 150% and symptoms scores lower than 4, was observed in 17 patients with a negative prior probability (chi-squared test: $p < 0.0001$). Sensitivity and specificity were respectively 100% and 81% (Table 1). At last, no relationship was reported between skin prick tests results and ΔNAR associated with symptom scores.

Bakers group

Twenty patients were classified as having an occupational disease by physicians, with 19 subjects presenting a positive nasal provocation test with ΔNAR ≥ 150% (chi-squared test: $p < 0.0001$). All the 13 subjects with a negative prior probability presented a ΔNAR lower than 150% (Table 2). It corresponded to a sensitivity of 95% and a specificity of 100%. A significant relationship (chi-squared test: $p < 0.02$) was observed between skin prick tests and ΔNAR, 15 of the 19 patients with a positive NPT and 5 patients with ΔNAR < 150% presented positive skin prick tests.

One subject classified as having a high probability of occupational disease, presented a negative NPT with ΔNAR < 150% and per and post test scores lower than 4.

DISCUSSION

The results of this study demonstrated that NPT with measurement of nasal airway resistance as evaluated by posterior rhinomanometry, associated with per and post test clinical scores, is effective in diagnosing occupational allergic rhinitis in patients suspected of having this condition, exposed either to flour or persulfates. Occupational rhinitis is a disease of emerging relevance, and an early diagnosis is important, particularly in the prevention of occupational asthma, with regard to the association between rhinitis and asthma of occupational origin [19]. The different steps involved in the diagnosis of OR are the clinical history, nasal examination, immunological tests and NPT. Most evidence relating to the diagnosis of occupational rhinitis emanates from the clinical history, which may produce possibly false diagnoses. Indeed, occupational rhinitis is characterized by the episodic, work-related occurrence of

Table 2. Repartition of bakers according to NAR.

	Positive prior probability	Negative prior probability
ΔNAR ≥ 150%	19	0
ΔNAR < 150%	1	13

sneezing, itching, clear rhinorrhea, and nasal congestion. All these symptoms are frequently associated with nasal obstruction, difficult to evaluate with subjective measurement such as visual analogue scales or symptoms scores. Skin prick tests to common and occupational allergens are useful in detecting atopic patients, as atopy is a risk for the development of immediate allergy to HMW (high molecular weight) allergens. They also allow the demonstration of IgE-mediated sensitization to occupational agents, especially for OR caused by high molecular weight agents such as flour. In this study, we reported a high number of positive reactions in skin prick tests to flour and common inhalant allergens in bakers as compared to the few positive reactions in hairdressers.

According to clinical and occupational history, nasal examination and immunological tests, the occupational physicians may determine a probability of having or not an occupational rhinitis for each subject. Nevertheless, although an essential step of the diagnostic approach, the clinical history is not specific enough to establish a diagnosis of occupational rhinitis. Objective criteria such as NPT with rhinomanometry, which has been shown to provide a quantitative measurement of nasal airflow resistance (NAR), will be useful to confirm the diagnosis but also to confirm the relationship between symptoms and allergens [14]. Nasal obstruction can be monitored objectively by measurement of airways resistance, as evaluated by acoustic rhinometry or anterior or posterior rhinomanometry [20]. Posterior rhinomanometry, done during quiet voluntary respiration, allows the measurement of both unilateral and total nasal resistance. In our study, posterior rhinomanometry, previously described [21], was chosen as the reference technique as recommended by Nathan et al. [22], allowing to quantify the obstruction that may occurred during the provocation test. We observed mean bilateral nasal resistance at baseline similar to baseline NAR reported by previous studies [22]. One reason for false-positive results may be the effects of the nasal cycle, with daytime physiological fluctuations in nasal resistance due to a varying degree of vascular congestions, but these effects are minimized by the posterior rhinomanometry technique.

Whereas rhinomanometry has been accepted as the standard technique of measuring NAR, no formal cut-off value of increase in NAR is recommended in nasal provocation testing in as much as this value may depend on the dose and the nature of the allergen considered. The increase in NAR exploring only nasal obstruction, this measurement of nasal obstruction by rhinomanometry was supplemented with a symptom score as recommended [20,23]. Symptoms of rhinitis may be quite similar whatever the kind of allergen once the allergen dose exposure is sufficient. Our results support this latter hypothesis as similar cut-off values for both nasal resistance and clinical scores were found for flour and persulfates. Agents such as flour, a high-molecular-weight agent, act as complete antigens and induce rhinitis through a type 1 hypersensitivity reaction with the production of specific IgE antibodies. The mechanisms by which persulfate salts, low-molecular-weight agents, induce rhinitis seem more complex and are not clearly identified. Some authors suggested that occupational respiratory symptoms induced by persulfates might be mediated by an immunological mechanism, according to the delay between exposure and symptoms, and to the skin-prick test results [24,25]. On the contrary, Moscato et al. [3], studying occupational asthma and rhinitis in hairdressers exposed to persulfate salts, could not confirm the presence of an IgE mechanism as suggested by Munoz et al. [25]. Our results are in accordance with these findings in as much as all the 20 bakers with positive skin prick tests to common allergens were also positive to flours skin prick tests, whereas only 1 positive skin prick test to persulfates was reported in the 7 hairdressers with positive skin prick tests to common allergens. Nevertheless, the mechanism of rhinitis due to persulfate salts still requires further studies.

These different mechanisms may explain the better sensitivity of the NAR increase (ΔNAR) during the nasal provocation test in bakers, and the importance of clinical scores, in association with ΔNAR, in well-classifying patients exposed to persulfates. Our study has potential limitations. Indeed, we may hypothesize that occupational rhinitis could be irritative, being related to particular working environment especially in hairdresser salon. We did not analyze nasal lavage to find out the relationship between clinical symptoms and occupational exposure. However, the aim of our study was to develop an objective test allowing, in addition to the clinical history, to confirm occupational rhinitis, as such diagnosis has important medical and socio-economic consequences. From a clinical point of view, it may be hypothesized that the positivity of NPT would be an increase in nasal resistance ≥ 50% and per and post test clinical scores ≥ 4 points, whatever the allergen tested.

In conclusion, this study illustrates that NPT, including the assessment of NAR combined with evaluation of clinical symptom scores, allows to confirm the occupational origin of rhinitis in patients exposed either to persulfates or to flour. It appears to be a very useful and safe method for diagnosing occupational rhinitis.

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