
Nasal allergen provocation with *Dermatophagoides pteronyssinus* in patients with chronic rhinitis referred to a rhinologic surgical center

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Background: Skin tests and specific immunoglobulin (Ig)E determinations identify the presence of some immune response to allergens, but frequently do not correlate to allergic disease in vivo.

Objective: To compare clinical history, skin tests and specific IgE determinations with the results of nasal provocation tests (NPT) to confirm clinically relevant allergy to *Dermatophagoides pteronyssinus* (DP) in patients with chronic rhinitis referred to a rhinologic surgical center.

Methods: Clinical data of 2,194 patients with chronic nasal disorders treated at two rhinologic referral centers between 1992 and 1998 were evaluated. Clinical allergy work-up was routinely performed corresponding to German and European guidelines providing consistent data in both centers.

Results: Of chronic rhinitis patients, 752 of 2,194 (34%) had at least one positive skin reaction to a perennial allergen common in Central Europe. Three hundred seventy-three patients had a positive skin test to DP and were paradigmatically evaluated in detail. In 235 patients, a complete dataset including structured allergic history, skin test, specific IgE determinations, and NPT was available. Quality and severity of symptoms, clinical history, skin tests, and allergen-specific IgE-determinations were unreliable predictors of the outcome of NPT with DP.

Conclusion: In patients referred for surgical treatment of chronic rhinitis, diagnosis of perennial allergy is unreliable unless confirmed with NPT.

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INTRODUCTION

Approximately 15% of the population in industrialized countries suffers from chronic nasal disorders. Nasal allergy to perennial allergens such as domestic mite, animal dander, or molds is a possible etiologic factor of this condition. Currently, diagnosis of nasal allergy is based on allergic history, skin tests, and in vitro determinations of allergen-specific immunoglobulin (Ig)E in peripheral blood samples.¹

Unlike seasonal allergic rhinitis with obvious allergic episodes during pollen or spore season, the correlation between allergen exposure and clinical symptoms is obscure in perennial allergic rhinitis. Allergic history is thus a less reliable diagnostic tool in perennial allergic rhinitis. To establish the diagnosis of perennial allergic rhinitis is particularly intricate in patients suffering from chronic nasal or paranasal complaints referred to a tertiary rhinologic surgical center. In addition to perennial allergic rhinitis, anatomical abnormalities and chronic rhinosinusitis of nonallergic etiology are frequently encountered in these patients and two or more pathologic conditions might coexist. Medical history can not reliably distinct between those entities,

because the symptoms of these conditions largely overlap.

Skin tests and specific IgE determinations merely recognize the presence of some immune response to allergens, but do not directly correlate to allergic disease in vivo.² In several studies, positive skin tests and specific IgE to various perennial allergens have been found in healthy individuals without nasal disease.^{3,4} In an extensive epidemiologic study, chronic rhinitis was not associated with skin test reactivity to common inhalant allergens.⁵ Further, in some investigations, the results of skin prick tests and allergen-specific IgE did not correlate with the results of nasal or bronchial provocation tests.^{6–8}

Nasal provocation test (NPT) is used to answer the question if a patient is nasally sensitive to a suspected allergen.^{9,10} The various recommendations how to perform NPT were recently summarized by Malm et al.¹¹ In 1990, the German Society for Allergy and Clinical Immunology presented guidelines for NPT.¹² Since then, NPTs according to these guidelines were performed in several rhinologic centers. Further, a revised version of a questionnaire for allergic airway disease¹³ became popular at that time. Concurrently, revised guidelines for skin tests used in type I allergy were published,⁴ and practicable assays for the determination of allergen-specific IgE had become readily available.¹⁴ On this basis, reliable clinical data on allergic history, skin tests, in vitro tests, and NPTs in patients with perennial rhinitis were routinely compiled during clinical allergy work up in the two rhinologic surgical centers participating in this study.

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Reviewing the data of the patients with chronic nasal and sinus complaints undergoing routine allergic work up between 1992 and 1998, we questioned how frequently positive skin tests or in vitro tests to house dust mites (HDM) are found in patients with chronic nasal or sinus disorders. Further we evaluated whether the quality of symptoms, several aspects of allergic history, and the results of skin tests and of specific IgE determinations allow the prediction of the outcome of NPTs with the suspected allergen.

METHODS

Study Population

All patients with chronic nasal and paranasal sinus symptoms such as nasal obstruction, hypersecretion, irritation, hyposmia, and midfacial pressure feeling or pain, lasting for at least 1 year treated at two tertiary surgical referral centers (Department of Otorhinolaryngology, Johannes Gutenberg University, Mainz, Germany and Department of Otorhinolaryngology, University of Ulm, Germany) between 1992 and 1998 were included in this retrospective study. Irrespective of the supposed etiology, allergy tests were performed as a part of the routine diagnostic work up in these patients. A subgroup of patients with positive skin tests to *Dermatophagoides pteronyssinus* (DP) was evaluated paradigmatically in detail. Not included were patients, who had undergone a previous allergy work up elsewhere resulting in the diagnosis or exclusion of allergic rhinitis. Further, patients with only seasonal symptoms were excluded.

Symptom Scores

Symptom scores for nasal obstruction, nasal discharge, itching/sneezing, and midfacial pressure-sensation or pain were recorded on numerical rating scales ranging from 0 (no symptoms) to 10 (maximum symptoms). Several other symptoms were evaluated in addition, such as hyposmia, gastrointestinal, bronchial, or skin symptoms, but were not included in this evaluation.

Allergy Work-Up

Structured allergic history was obtained using a questionnaire,¹³ including several items considered informative in the diagnosis of perennial allergic rhinitis. The item subset evaluated included positive family history, childhood eczema, worsening of symptoms at night and in the morning, improvement at the sea or in the mountains, symptoms worse at distinct locations with high allergen exposure, and worsening of symptoms when exposed to dusts and fumes. Next, a skin prick test with a set of 20 inhalant allergens common in Central Europe was performed according to the recommendations of the Subcommittee on Skin Tests of the European Academy of Allergology and Clinical Immunology.⁴ Test solutions containing 50,000 BU¹⁵ for prick tests and with 500 BU for occasionally performed IC-tests (Allergopharma, Reinbek, and ALK Scherax, Hamburg, Germany, respectively) were used. Prick tests were considered positive, if the wheal reaction was at least 3 mm in diameter, or at least 25% of the wheal area induced by simultaneous pricking with 1 mg/mL histamine solution. Saline solution identical to the test solutions except the allergen investigated served as control. Consistent with common diagnostic algorithms, no further allergic investigations were carried out if the skin tests were negative and allergic history was not considered indicative.² The patient was then categorized as nonallergic to common Central European inhalant allergens. In patients with positive skin tests and/or allergic history suggesting nasal allergy, determinations of allergen-specific IgE were performed using an enzyme immunoassay (Phadeyrm, Pharmacia, Freiburg, Germany) and the results were grouped in classes 0 to IV.¹⁴

NPT

In patients with positive skin tests to one or several perennial allergens, NPTs were performed according to the guidelines of the German Society for Allergy and Clinical Immunology (Fig 1).¹² The guidelines are consistent with

the guidelines of the European Academy of Allergy and Clinical Immunology.¹⁰ NPT was not performed in patients with manifest asthma symptoms. When the appointment for NPT was made, patients were instructed to stop any antiallergic treatment for an appropriate time interval (Table 1).

Before NPT, patients were allowed to adapt to indoor conditions for 15 minutes. For control and allergen provocation, test solutions for nasal provocation testing (Allergopharma and ALK Scherax) were used. Both solutions contain 0.4% phenol and are alike except the allergen content. The solutions were delivered to the inferior turbinate with a nebulizer provided by the manufacturer of the allergen solutions. The nebulizer delivers 50 μ L solution per actuation, the mean size of the droplets delivered ranges between 20 and 70 μ m. Before application, the nebulizer was held outside the examination room and actuated several times to confirm appropriate spray delivery. Solutions were applied after deep inspiration when the patient stopped breathing to avoid allergen inhalation.

To evaluate unspecific hyperreactivity, 100 μ L of control solution were initially applied to the less congested nasal cavity as determined by active anterior rhinomanometry. After 10 minutes, the absence of a reaction to the control solution was confirmed by symptom scoring and with rhinomanometry. For actual nasal allergen provocation, 100 μ L of a solution containing 5,000 BU of DP allergen were applied to the same nasal cavity. After 10 minutes and 20 minutes, clinical symptoms and the change of nasal airflow at a transnasal pressure difference of 150 Pa were reassessed. NPT was considered positive if the difference of the total symptom score (Table 2) before and after allergen provocation was at least 4 or nasal airflow at 150 Pa was reduced by at least 40%. In addition, NPT was considered positive if nasal airflow was reduced by at least 20% and the symptom score was at least 3. Late-phase reactions were not documented. The operators of NPT were

STEP 1) PREPARATION:

- LET PATIENT ADAPT TO ROOM CLIMATE FOR 15 MINUTES
- CHECK TEST SOLUTIONS (EXPIRY DATE, CONTROL TEMPERATURE, BODY TEMPERATURE REQUIRED)
- ALLOW RHINOMANOMETER TO WARM UP (10 MINUTES)

STEP 2) REGISTRATION OF BASELINE VALUES:

- RECORD BASELINE SYMPTOM SCORE (SEE TABLE 1): SECRETION (0-2), IRRITATION (0-2), REMOTE SYMPTOMS (0-2)
- PERFORM ACTIVE ANTERIOR RHINOMANOMETRY AND RECORD BASELINE FLOW AT 150 PA.

STEP 3) APPLICATION OF CONTROL SOLUTION:

- ADMINISTER 100 μ L CONTROL SOLUTION IN THE LESS CONGESTED NOSE
- WAIT 10 MINUTES

STEP 4) REGISTRATION OF CONTROL SOLUTION RESPONSE AND APPLICATION OF ALLERGEN SOLUTION:

- RECORD CONTROL SYMPTOM SCORE: SECRETION (0-2), IRRITATION (0-2), REMOTE SYMPTOMS (0-2)
- PERFORM ACTIVE ANTERIOR RHINOMANOMETRY AND RECORD CONTROL FLOW AT 150 PA.
- CHECK FOR UNSPECIFIC REACTION: IF SYMPTOM SCORE > 1 OR NASAL AIRFLOW AT 150 PA INCREASED MORE THAN 20%: ABORT TEST
- OTHERWISE: ADMINISTER 100 μ L ALLERGEN SOLUTION IN THE SAME CAVITY AS THE CONTROL SOLUTION
- WAIT 10 MINUTES

STEP 5) REGISTRATION OF ALLERGEN RESPONSE AFTER 10 MINUTES

- RECORD PROVOCATION SYMPTOM SCORE 1: SECRETION (0-2), IRRITATION (0-2), REMOTE SYMPTOMS (0-2)
- PERFORM ACTIVE ANTERIOR RHINOMANOMETRY AND RECORD PROVOCATION FLOW 1 AT 150 PA.
- CHECK FOR POSITIVE REACTION (CRITERIA SEE TABLE 2 AND TEXT)
- IF POSITIVE: FINISH
- OTHERWISE: WAIT 10 MINUTES

STEP 6) REGISTRATION OF ALLERGEN RESPONSE AFTER 20 MINUTES

- RECORD PROVOCATION SYMPTOM SCORE 2: SECRETION (0-2), IRRITATION (0-2), REMOTE SYMPTOMS (0-2)
- PERFORM ACTIVE ANTERIOR RHINOMANOMETRY AND RECORD PROVOCATION FLOW 2 AT 150 PA.
- CHECK FOR POSITIVE REACTION (CRITERIA SEE TABLE 2 AND TEXT)

Figure 1. Flow chart of nasal allergen provocation as recommended by the German Society of Allergy and Clinical Immunology¹² and performed in the evaluated patients. See Table 2 for judgment criteria.

not blinded to the skin test results of the subjects.

Statistics

Based on the results of NPT, patients were grouped in positives and negatives. Symptom scores and patient age were compared in these groups using the Mann-Whitney *U* test. The data of allergic history obtained by the questionnaire were categorized as indicative (positive) or not indicative for perennial allergy (negative) and tabulated against the outcome of NPT. For confirmatory analysis, the Fisher exact test

was used for each item. For the association between the skin test and specific IgE category and the result of the NPT, the Goodman and Kruskal γ coefficient has been calculated. Calculations were performed using the StatXact 4 statistical software (CYTEL Software, Cambridge, MA).

To evaluate, if the addition of various clinical parameters to skin test and specific IgE results would influence the outcome, a multivariate logistic regression model was used. Clinical parameters evaluated in this multivariate

model included symptom scores, patient age, sex, allergic history, skin test, and specific IgE. In a first step, an univariate χ^2 analysis of each variable grouped by NPT-outcome was performed and variables with *P* values >0.2 were excluded from further analysis. Variables with *P* values <0.2 were included in a backward selection logistic regression model with the result of NPT, ie, positive or negative, as the outcome variable. Variables with an adjusted *P* value >0.1 were eliminated. From the remaining variables, adjusted odds ratios with 95% confidence intervals (CIs) were calculated. Sensitivity and specificity of included independent variables were computed and displayed as a receiver operating characteristic (ROC) curve.

RESULTS

In total, 2,194 patients with chronic nasal and paranasal sinus disorders met the inclusion criteria and were evaluated; 752 of these (34%) had at least one positive skin reaction to one or more perennial allergens such as domestic mite, animal dander, or molds. Data of 373 patients with a positive skin reaction to DP were evaluated in detail. The mean age was 36 ± 13.6 years (mean $\pm$ SD), 209 were male and 164 were female. Because of simultaneous seasonal allergy, 61 patients were excluded from further evaluation, and in 5 patients with current asthma symptoms, NPT was contraindicated. Seventy-two patients did not meet the appointment for NPT, or no

Table 1. Time to Suspend Antiallergic Treatment before NPT

Substance	Treatment pause before NPT
Cromolyn sodium or nedocromil	3 days
Nasal steroids	7 days
Oral steroids	7 days
Nasal antihistamines	3 days
Oral antihistamines	3 days
Nasal decongestants	1 day
Inhaled broncholytics	no
Tricyclic antidepressants	3 days

Table 2. Symptom Scores Registered at Nasal Allergen Provocation

Nasal secretion at anterior rhinoscopy (examiner's judgment)	as before/normal	0 points
	slight increase/minor amounts visible	1 point
	pronounced	2 points
Irritation	0-2 sneezes	0 points
	3-5 sneezes	1 point
	> 5 sneezes	2 points
Distant symptoms	none	0 points
	watery eyes and/or palatal itching and/or deep aural itching	1 point
	conjunctivitis and/or chemosis and/or urticaria and/or cough and/or dyspnea	2 points

specific IgE determinations were available. Thus, a complete dataset including skin test, specific IgE-determination, and NPT with DP allergen extract was available in 235 of 373 patients sensitized only to HDM. The NPT was positive in 94 of 235 patients (40%). On average, the patients with negative NPT were elder (38.2 ± 12.9 years, mean $\pm$ SD) than the patients with positive NPT (32.4 ± 13.2 years, $P < 0.001$). The age distribution grouped by positive and negative NPT is outlined in Figure 2. Sex distribution did not differ significantly between NPT-positives and NPT-negatives. Quality and severity of symptoms were rather similar in patients with positive and negative NPT.

In 172 of 235 patients, a detailed questionnaire had been used. The frequencies of positive family history, childhood eczema, and increased symptom severity at night or at certain locations, indicating worsening during mite allergen exposure, were remarkably similar in patients with positive and negative NPT. Symptom deterioration when exposed to dusts and fumes, indicating unspecific nasal hyperreactivity, were more frequent in NPT-positives; however, differences were not significant.

The association of skin test results and results of NPT are summarized in Table 3 (column totals). A positive NPT was more common in patients with strong skin test reactions (γ coef-

ficient = 0.61 ± 0.08 , $P < 0.0001$); however, based on skin test reactivity alone, results of NPT could not be accurately predicted. Categorizing all patients with at least 1+ skin test as positives, 39% were categorized correctly and 61% incorrectly. Grouping patients with at least 2+ skin reaction as positive, 58% were categorized correctly, with 3+ positive skin test 64%, and with 4+ positive skin tests 67%.

Blood serum determinations of allergen-specific IgE also revealed a significant, but weaker association with the results of NPT (γ coefficient = 0.53 ± 0.09 , $P < 0.0001$). The frequency of IgE-positive patients categorized in classes 0 through IV and the outcome of NPT are detailed in Table 3 (row totals). The prediction of NPT outcome was slightly improved if IgE determinations were considered in combination with the results of skin tests.³ Categorizing, for instance, all patients with at least skin test 3+ and at least IgE class 1 as positive, 168 of 233 (72%) cases would have been classified correctly and 65 of 233 (28%) falsely. All other possible combinations of IgE and skin test categories yielded worse classification results.

Based on the results of univariate analysis, these variables were included in a linear logistic regression model: skin tests, IgE determinations, sex, age, symptom scores for nasal obstruction and nasal irritation, and symptom worsening at specific locations. Except skin test and IgE determinations, the included independent variables were eliminated because of P values > 0.1 in the multivariate analysis (sex $P > 0.8$, nasal obstruction $P > 0.5$, nasal irritation $P > 0.4$, age $P > 0.2$, and worsening at specific locations $P > 0.1$). The adjusted odds ratios predicting a positive outcome of NPT for stepwise increase in skin test positivity were 1.58 (CI 1.12 to 2.09, $P < 0.001$) and for stepwise IgE-class positivity 2.49 (CI 1.71 to 3.62, $P < 0.005$). The resulting ROC curve reveals a maximum for sensitivity and specificity at approximately 70% (Fig 3).

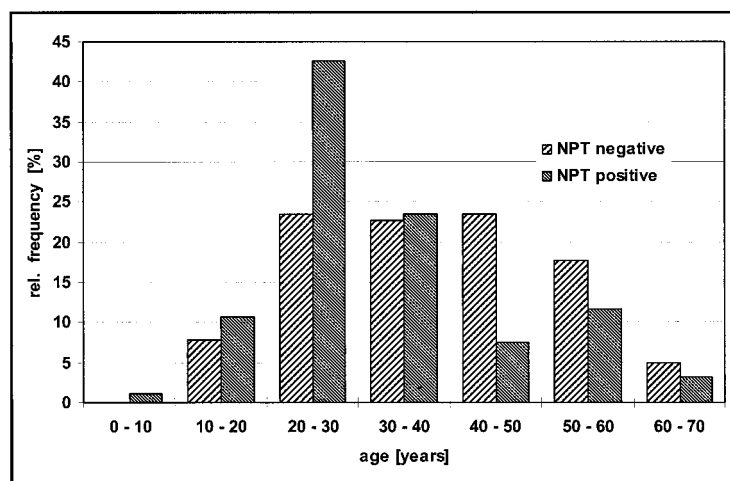


Figure 2. Relative age distribution of 235 patients with chronic rhinitis sensitized to DP grouped by positive or negative NPT to DP.

Table 3. Frequency of Positive NPT of Total Performed NPT to DP Grouped by Skin Test Reactivity and Determination Of allergen-Specific IgE

	Skin test 1+	Skin test 2+	Skin test 3+	Skin test 4+	Row total
IgE class 0	4/39 (0.10)	11/36 (0.31)	20/61 (0.33)	4/5 (0.8)	39/141 (0.28)
IgE class 1	2/11 (0.19)	2/5 (0.4)	6/11 (0.55)	0/0 (not def.)	10/27 (0.37)
IgE class 2	1/7 (0.14)	2/3 (0.67)	11/15 (0.73)	5/6 (0.83)	19/31 (0.6)
IgE class 3	1/1 (1.00)	1/3 (0.33)	7/10 (0.7)	5/5 (1)	14/19 (0.74)
IgE class 4	0/0 (not def.)	0/1 (0)	4/6 (0.67)	6/8 (0.75)	10/15 (0.67)
Col. total	8/58 (0.14)	16/48 (0.33)	48/103 (0.47)	20/24 (0.83)	92/233 (0.4)

Included were 233 patients with perennial nasal symptoms referred to two rhinologic centers. In brackets corresponding ratio of NPT positives of totally performed NPT per category. For instance, 11 of 15 patients with 3+ skin test and specific IgE class 2 had a positive NPT to DP.

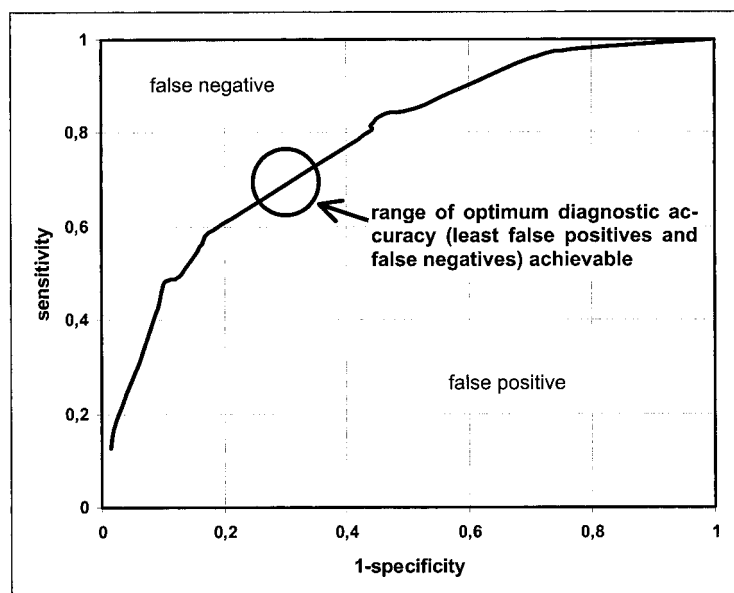


Figure 3. ROC curve of skin test reactivity and IgE determinations to DP in patients with perennial rhinitis. The ROC curve represents the trade off between the false negative and the false positive rates; the circle indicates the range of optimum diagnostic accuracy achievable with combined skin prick test and IgE-determinations (approximately 70%). Nasal allergen provocation in this context is considered the diagnostic reference method for perennial allergic rhinitis to DP.

DISCUSSION

Nasal provocation challenge was extensively applied in clinical routine in two tertiary rhinologic surgical centers in Germany. In general, data obtained during clinical routine do not reach the quality standards of prospective trials and must be interpreted with caution. For instance, the investigators performing NPT were not blinded to the results of skin testing, and data were retrospectively evaluated. Basic data consistency was attained using standardized questionnaires to evaluate allergic history and symptom severity.¹³ Operator variability with regard to skin testing and NPT have not been evalu-

ated in this study. Thus, increased data variability because of inconsistent classification of test results can be assumed, although skin tests were uniformly performed according to the recommendations of the European Academy of Allergy and Clinical Immunology⁴ and NPT according to the Guidelines of the German Society of Allergy and Clinical Immunology.¹²

The patients included are not representative for the general population nor for the population with nasal allergies in Central Europe, but represent a selected group referred to a rhinologic surgical center mainly for nasal or paranasal sinus surgery for chronic disease unre-

sponsive to conservative treatment. Of these patients, 752 of 2,194 (34%) had a positive skin test to at least one perennial allergen, predominantly DP and/or *Dermatophagoides farinae*. Sensitization to perennial allergens was thus more than twice as frequent as in an unselected Caucasian population.¹⁶ Isolated sensitization to molds or animal dander, including cat, was rare in the studied population. For further evaluation, patients with positive skin test to DP were paradigmatically evaluated. Cases with concomitant sensitization to other perennial allergens except *D. farinae* or seasonal allergens probably interfering with the results of NPT were excluded.

Neither specific nasal symptoms nor aspects of allergic history considered characteristic for perennial allergic rhinitis were effective to predict the result of NPT in this particular patient group. Further, the strength of skin test reaction and the level of allergen-specific IgE were unreliable predictors of the outcome of NPT.

These findings are consistent with previous publications demonstrating a weak correlation of skin test positivity and nasal reactivity to HDM allergen among patients with perennial rhinitis¹⁷⁻²⁰ and asthma.²¹ Further, serum IgE determinations did not correlate with symptom severity in allergic rhinitis.^{22,23}

Accuracy of NPT

Although nasal provocation is accepted as the reference method to evaluate the relevance of a specific allergen in allergic rhinitis in Europe, false results are reported to occur in approximately 15%.¹⁰ Unreliable evaluation of the allergic response might be one

reason for this inaccuracy. Most symptom scores reflect the investigator's judgment, with the exception of some subjective distant symptoms, such as palatal itching, which were reported by the patients. Some subjects with chronic rhinitis are adapted to their symptoms and tend to underestimate the severity of their symptoms²⁴; particularly in patients with longstanding chronic rhinitis included in this investigation, this might have biased the symptom scores obtained during NPT. As a surrogate marker for nasal irritation, the number of sneezes were counted. The amount of nasal secretion is also a vague parameter, because it reflects the investigator's impression. Accuracy of NPT might be improved if the amount of secretions was collected and weighted. To avoid bias attributable to elevated symptom scores before allergen application, baseline symptom scores should be subtracted from the scores after allergen application. However, the efficiency of NPT is significantly increased if rhinomanometry is used to confirm the results.^{11,25}

In addition to evaluation of the allergic response, a common reason for *false positive* NPT is unspecific nasal hyperreactivity. Application of a control solution before allergen application is likely to reveal such unspecific reactions. False-positive NPT may also result from unspecific changes of nasal airflow induced by the nasal cycle. This can be recognized by unilateral provocation and bilateral registration of nasal airflow. A positive reaction appears as a reduction of airflow of the provoked cavity. On the contralateral side, a minor concurrent reduction, no change, or at most an insignificant increase may be observed.²⁶ If the airflow on the contralateral side is more or less reverse to the provoked side, nasal cycle phenomena can be assumed. *False negative* results may result from several reasons, including inaccurate allergen application, low allergen concentration, previous topical or systemic medication, or unresponsive mucosa, eg, after nasal or paranasal sinus surgery. Further, the

nonchronic and nonrepetitive allergen exposure in NPT may lead to false negative results when compared with natural allergen exposure.²⁷ It has therefore been advocated to use two or three allergen concentrations to increase sensitivity of nasal allergen provocation.⁹

Allergen Dose Used for NPT

In the patients examined, 5,000 BU had been exclusively used. This concentration is considered sufficiently high to elicit a positive response in all patients with clinically relevant allergy. As previously reported, 25 ng/m³ HDM major allergen represents a high indoor concentration.²⁸ At rest, an adult would inspire approximately 10-ng allergen in 30 minutes under these conditions. With 100 μ L of a 5,000-BU DP extract, approximately 100-ng major allergen were applied to the nasal mucosa, representing a dose well above the ambient level in heavily contaminated rooms. In a series of 30 patients with known nasal allergy to DP, 50 BU was sufficient to elicit an allergic reaction in 3 of 30 patients (10%), 500 BU in 18 of 30 (60%), and 5,000 BU in all patients investigated.²⁹ It is assumed that false negative results attributable to low allergen concentrations were not likely to occur in this study.

Efficiency and Safety of NPT

The algorithm used for nasal provocation testing in this study takes the most common reasons for false results into account and the applied allergen dose is considered sufficient. The nasal challenge procedures performed in the two tertiary referral centers participating are thus considered reliable and valid. They are likely to reflect clinical relevant allergy to HDM in the studied population. Further, NPT with 5,000 BU HDM allergen as performed in this study is considered safe. No severe side effects, particularly no asthmatic reactions, had been observed in the 307 NPTS performed with various perennial allergens. Although a slight increase of bronchial responsiveness has been repeatedly found, noticeable asthmatic reactions after NPT are rare.³⁰⁻³²

Thus it is not considered necessary to use lower concentrations for NPT with HDM for safety reasons.

Study Population and Selection Bias

The data presented in this evaluation were obtained in a selected group of patients with chronic nasal disorders referred to the rhinologic centers participating in this study. Nasal deformities, septal abnormalities, conchal hyperplasia, or chronic sinusitis unresponsive to conservative treatment, atrophic rhinitis, mucosal dryness, and various other complex nasal conditions were common in the studied population. These disorders occurred alone or in combination and with or without concomitant nasal allergy. Assigning certain symptoms or aspects of clinical history to a definite condition such as nasal allergy is intricate in these patients. Further, the complex etiology of the complaints occasionally remained obscure. In a general population, skin prick test, specific IgE, and nasal symptoms revealed better consistency³³ than in the population studied. However, within the patient population evaluated in this study, no patients were systematically excluded and a selection bias is not assumed. Of 373 patients with positive skin test to DP, 61 patients were regularly excluded from the evaluation attributable to coexistent seasonal allergy and 5 because of asthma symptoms, resulting in 307 patients regularly included. Seventy-two patients could not be evaluated either because they did not meet the appointment for NPT or because no IgE determinations were available, resulting in 235 patients with a complete dataset.

Sensitivity of Skin Prick Test

According to common diagnostic algorithms, skin tests were used as a screening method for IgE-mediated disease. Therefore, only patients with positive skin tests were included for further systematic evaluation of allergic disease. No systematic evaluation of NPT in patients with negative skin tests had been obtained and no assumptions on sensitivity or diagnostic efficiency of skin tests in perennial rhinitis can be made. However, in the 2,194 patients investigated, NPT with

HDM were unsystematically performed in seven cases with negative skin prick tests. Three of 7 patients revealed a positive NPT. Intradermal skin testing is more sensitive than skin prick testing and might have yielded correct positive results in these patients.³ However, positive NPT in patients with negative skin tests have been reported by several authors and are likely attributable to local IgE production.³⁴⁻³⁶ Thus, additional studies on the relevance of perennial allergens in skin test negatives are required.

CONCLUSION

NPT is indicated if interpretation of skin tests or other IgE-mediated tests is difficult.⁹ This is the case in patients with chronic nasal disorders referred to a rhinologic center. Supposing that nasal allergen provocation is the best method currently available to discriminate allergic from nonallergic perennial rhinitis, allergy diagnosis based on allergic history, skin test, and serum-specific IgE determinations resulted in approximately 30% false results. It is unlikely that antiallergic treatment is of benefit in individuals without allergy. In view of high costs for allergen avoidance strategies, immunotherapy or medical therapy, this figure is considered unacceptably high. Further, conducting clinical studies targeting perennial allergic rhinitis, several participants would not respond to treatment because of false inclusion.

In addition, a considerable number of patients with perennial allergy would remain undetected unless allergy is confirmed by NPT even in cases with low skin test reactivity and low specific-serum IgE. Because perennial allergy adversely affects quality of life and may result in life-threatening asthma, early reliable diagnosis is mandatory. In patients with chronic nasal disorders sensitized to perennial allergens, NPT is not only a useful model to study the pathophysiology of nasal allergy,^{1,37,38} but a mainstay of clinical diagnosis in patients referred to a rhinologic surgical center.

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