

Comparison of Conjunctival and Nasal Provocation Test in Allergic Rhinitis to House Dust Mite

Herbert Riechelmann Barbara Eppe Gunther Gropper

Department of Otorhinolaryngology, University of Ulm, Germany

Key Words

Allergic rhinitis · Allergic conjunctivitis · Nasal provocation tests · Conjunctival provocation test · Diagnostic techniques

Abstract

Background: Nasal allergen provocation tests (NPTs) are useful in confirming the diagnosis of allergic rhinitis, if data obtained by clinical history, skin tests and specific IgE determinations are not conclusive. Since NPTs are laborious, conjunctival provocation tests (CPTs) appear as an attractive alternative. The concordance of CPTs and NPTs with house dust mite allergen extract in sensitized and nonsensitized subjects should be evaluated. **Methods:** 50 otherwise healthy subjects with self-reported house dust mite allergy and positive skin prick tests and serum specific IgE to *Dermatophagoides pteronyssinus* and 45 sex- and age-matched healthy controls without allergic symptoms were included. For NPTs, 100 µl allergen extract [10,000 allergy units (AU/ml)] were applied to the less congested nasal cavity. A clinical symptom score and active anterior rhinomanometry were employed to assess the response. For CPTs, 50 µl low-concentrated *D. pteronyssinus* extract (1,000 AU/ml), and if negative, 50 µl normally concentrated extract (10,000 AU/ml) were

applied to the lower conjunctival sac. The response was assessed employing clinical symptom scores. **Results:** NPTs and CPTs yielded concordant results in 90% of the subjects successfully tested (Cohen's kappa = 0.78, $p < 0.0001$). The diagnostic efficacy of the CPT, with the NPT as the reference method, was 89%, whether or not conjunctival symptoms had been reported in addition to rhinitis symptoms. Both techniques were judged almost equally uncomfortable. **Conclusion:** CPTs are an acceptable alternative to NPTs in patients with allergic rhinitis to house dust mite, even if they have no conjunctival symptoms.

Copyright © 2003 S. Karger AG, Basel

Introduction

The nasal provocation test (NPT) reproduces the response of the upper airways to natural allergen exposure under controlled conditions. It tells whether a person is nasally sensitive to a certain allergen. It is indicated if clinical history, skin tests and/or specific IgE determinations are not conclusive [1, 2]. This rarely occurs in seasonal allergic rhinitis [3], but is more frequently encountered in patients with perennial allergic rhinitis [4]. In patients with perennial allergic rhinitis, NPTs help identi-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2003 S. Karger AG, Basel
1018–2438/03/1301–0051\$19.50/0

Accessible online at:
www.karger.com/iaa

Correspondence to: Dr. Herbert Riechelmann
Department of Otorhinolaryngology, University of Ulm
Prittwitzstrasse 43, D-89075 Ulm (Germany)
Tel. +49 731 50033002, Fax +49 731 50026703
E-Mail herbert.riechelmann@medizin.uni-ulm.de

fying appropriate candidates for immunotherapy [5]. However, NPTs are time consuming and not standardized in various countries, and the most commonly used method to objectively assess the nasal allergic response, i.e. active anterior rhinomanometry, may fail due to several causes [6]. As a consequence, conjunctival provocation tests (CPTs) have been employed as an alternative to NPTs in patients with allergic rhinitis in various studies. CPTs have been employed to confirm the clinical diagnosis of nasal allergy as an inclusion criterion in clinical studies and as a measure of outcome [7–10].

Data to support this practice are scarce and reports on whether CPTs are appropriate as a diagnostic test for nasal allergies are conflicting. In the study by Malmberg et al. [11], 17% of patients with allergic rhinitis had negative CPTs and positive NPTs and in 55% of the patients tested, the conjunctiva was less sensitive to allergen challenge than the nasal mucosa. Dissimilar allergen sensitivity of the nasal mucosa and conjunctiva was also reported in patients with allergic asthma to house dust mite [12]. Conversely, a strong concordance between NPTs and CPTs was reported in two studies with seasonal allergens [3, 13]. A systematic comparison of the results of NPTs and CPTs in patients with perennial allergic rhinitis has not yet been published.

The objective of this study was to systematically compare NPTs and CPTs in subjects with allergic rhinitis to house dust mite and healthy controls. A measure of concordance of these diagnostic techniques should be described. Moreover, the study also tried to establish whether the test concordance was different in patients with rhinitis symptoms only compared with patients suffering from concomitant conjunctivitis symptoms. The third objective of this study addressed the test-related discomfort experienced by the subjects investigated.

Material and Methods

Study Population

Fifty students of the University of Ulm with self-reported perennial allergic rhinitis to house dust mite volunteered in this study (rhinitis group). They were asked whether they suffered from rhinitis symptoms only or from both nasal and conjunctival symptoms. Forty-five sex- and age-matched healthy students who reported not to suffer from perennial nasal and conjunctival symptoms were recruited as controls. Exclusion criteria included manifest asthma symptoms, septal deformities considered functionally relevant by an experienced otorhinolaryngologist, signs of chronic sinusitis on nasal endoscopy, hyposmia and chronic midfacial numbness or pain indicative of chronic sinusitis, acute upper respiratory tract infection, any disease of the eye and orbit except allergic conjunctivitis or anoma-

lies of refraction, wearing of contact lenses, prior immunotherapy or any current antiallergic therapy. The study was performed in agreement with the requirements of the local ethics committee.

Skin Tests

Skin prick tests (SPTs) to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* were performed according to the recommendations of the Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology [14]. Test solutions containing 10,000 allergy units (AU)/ml (HAL Allergy, Düsseldorf, Germany) were employed. 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 for the allergen investigated served as control.

Determination of Allergen-Specific IgE

Serum specific IgE to *D. farinae* and *D. pteronyssinus* (ssIgE) was assayed using the Pharmacia CAP system (Pharmacia, Freiburg, Germany) according to the manufacturer's instructions.

Nasal Provocation Tests

NPTs with *D. pteronyssinus* or *D. farinae* extracts were performed according to the guidelines of the German Society for Allergy and Clinical Immunology (table 1) employing active anterior rhinomanometry as an objective measure of the allergic response [6, 15]. The guidelines are consistent with the guidelines of the European Academy of Allergy and Clinical Immunology [4]. For control and allergen provocation, test solutions for nasal provocation (HAL Allergy) were employed. Both solutions contain 0.4% phenol and are alike except for the allergen content. The solutions were delivered to the inferior turbinate with a nebulizer provided by the manufacturer. The nebulizer delivers 100 µl solution per actuation, the aerodynamic diameter of the droplets delivered ranges between 30 and 70 µm. Before application, the nebulizer was actuated several times outside the examination room to confirm appropriate spray delivery. Solutions were applied following deep inspiration when the patient stopped breathing to avoid allergen inhalation.

To assess unspecific hyperreactivity, 100 µl of control solution were initially applied to the less congested nasal cavity as determined by active anterior rhinomanometry. After 10 min, the absence of a reaction to the control solution was confirmed by symptom scoring and rhinomanometry. For actual nasal allergen provocation, 100 µl of a solution containing 10,000 AU/ml allergen were applied to the same nasal cavity. After 10 and 20 min, clinical symptoms and the change in nasal airflow at a transnasal pressure difference of 150 Pa were reassessed. NPTs were considered positive if the difference in the total symptom score (table 3) before and after allergen provocation was at least 4 or nasal airflow at 150 Pa was reduced by at least 40%. In addition, NPTs were 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. In contrast to the CPT, no symptomatic treatment was applied if NPTs were positive.

Conjunctival Provocation Test

Conjunctival provocation tests with *D. pteronyssinus* or *D. farinae* were performed according to Gronemeyer [16]. The test procedure is outlined in table 2. Modifications included the application of one drop of topical levocabastine 0.5 mg/ml once the test was consid-

Table 1. Flowchart for the NPT according to the guidelines of the German Society for Allergy and Clinical Immunology [15]

Step 1: Preparation
– Let patient adapt to room climate for 10 min
– Check test solutions (expiry date, control temperature, body temperature required)
– Allow rhinomanometer to warm up (10 min)
Step 2: Registration of baseline values
– Record baseline symptom score (see table 3): 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 µl of control solution in the less congested nostril
– Wait 10 min
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 decreased more than 20%: stop test
– Otherwise: administer 100 µl of allergen solution in the same nostril as the control solution
– Wait 10 min
Step 5: Registration of allergen response after 10 min
– 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 3 and text)
– If positive: finish
– Otherwise: wait 10 min
Step 6: Registration of allergen response after 20 min
– 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 3 and text)

Table 2. Flowchart for the CPT

Step 1: Preparation
– Let patient adapt to room climate for 10 min
– Check test solutions (expiry date, control temperature, body temperature required)
– Confirm that the eye is without irritation at the beginning of the investigation
– Exclude contraindications for CPT (eye diseases except for anomalies of refraction or allergic conjunctivitis, contact lenses, antiallergic therapy)
Step 2: Control
– Administer 50 µl of control solution identical to the allergen solution except for allergen content in the lower conjunctival sac of one eye (control eye)
Step 3: Provocation with low allergen concentration
– Immediately after application of control solution, administer 50 µl of low-concentrated allergen solution (1,000 AU/ml) in the lower conjunctival sac of the opposite eye (provocation eye)
– Inform the patient not to rub his/her eyes
– Wait for 10 min
Step 4: Response to low allergen concentration and rechallenge
– If positive (see below), administer topical antihistamine (e.g. levocabastine, azelastine, emedastine)
– If negative, repeat application of control solution to the control eye
– Immediately afterwards, administer 50 µl of normally concentrated allergen solution (10,000 AU/ml) in the lower conjunctival sac of the provocation eye
– Inform the patient not to rub his/her eyes
– Wait for 10 min
Step 5: response to normal allergen concentration
– If positive (see below), administer topical antihistamine (e.g. levocabastine, azelastine, emedastine)
– Otherwise: categorize as negative and stop

Table 3. Symptom scores recorded following NPTs

Nasal secretion on anterior rhinoscopy (examiner's judgment)	Irritation	Remote symptoms	Score per column-item
As before/normal	0–2 sneezes	none	0 points
Slight increase/minor amounts visible	3–5 sneezes	watery eyes and/or palatal itching and/or deep aural itching	1 point
Pronounced	>5 sneezes	conjunctivitis and/or chemosis and/or urticaria and/or cough and/or dyspnea	2 points

Table 4. Categorization of the response to allergen in the CPT (the CPT is considered positive if the response is stage II or higher)

Stage	Criteria
0	no subjective or visible reaction
I	itching, reddening, foreign body sensation
II	stage I and in addition tearing, vasodilation of conjunctiva, bulbi
III	stage II and in addition vasodilation and erythema of conjunctiva tarsi, blepharospasm
IV	stage III and in addition chemosis, lid swelling

ered positive to reduce the test-related discomfort. In a pilot investigation, CPTs occasionally caused severe eye symptoms and unpleasant late-phase reactions may occur [17]. Moreover, the staging of the test response (table 4) was slightly modified. A stage 0 response was included because nonallergic individuals commonly revealed no reaction at all to conjunctival allergen application. A CPT was considered positive if the response was stage II or higher. Test solutions were identical to the solutions employed for NPTs, except that the low-concentrated allergen solution was a 1:10 dilution of the 10,000 AU/ml standard provocation solution (HAL Allergy). Eye itching is usually the first symptom of a positive response but may also be due to unspecific irritation. Patients tend to rub their eyes following both control and allergen application, possibly causing false-positive results [18]. It is essential to inform the tested subjects not to rub their eyes. Late-phase reactions were not documented.

Assessment of Test-Related Discomfort

Approximately 30 min following NPTs and CPTs, the subjects were asked to assess the test-related discomfort on a 10-cm visual-analog scale ranging from no discomfort at all to maximum, intolerable distress.

Statistics

For normally distributed data, mean and standard deviation are provided, for continuous not normally distributed data, median and 95% confidence intervals (CI) for the median are given. To compare the distances on the visual-analog scale representing test-related discomfort, the Wilcoxon signed-rank test was employed. As a measure of agreement between NPTs and CPTs, Cohen's kappa statistics were performed using Statexact® software (Cytel Co., Mass., USA).

Results

Study Group Characteristics

Age and gender distribution in cases and controls were similar. The mean age ($\pm$ SD) of the 50 subjects with self-reported allergic rhinitis to house dust mite (rhinitis group) was 26 ± 7 years, 24 were males and 26 were females. All subjects of the rhinitis group reported perennial nasal obstruction worsening at night, nose itching and

sneezing, particularly in the morning, and positive skin test results to house dust mite in a prior allergy work-up. Seventeen volunteers of the rhinitis group reported not to suffer from concomitant eye symptoms (rhinitis-only), and 29 subjects reported to have concomitant eye symptoms such as conjunctival itching, dry and red eyes as well as a foreign-body sensation, particularly in the morning, and occasionally lid swelling (rhinitis-conjunctivitis). Four subjects were not able to make a clear statement on their conjunctival symptoms.

The participants in the control group reported not to suffer from chronic or recurrent nasal or conjunctival symptoms except for occasional common colds. The mean age of the controls was 28 ± 7 years, 21 were male and 24 female.

SPT, ssIgE, NPT and CPT

The test results of the rhinitis group ($n = 50$) are outlined in the tree diagram in figure 1. In the rhinitis group, 45 subjects had positive SPTs and/or ssIgE. In 40 of them, NPTs were positive, and CPTs were positive as well or not conclusive. In 3 of the 45 participants with positive SPTs, NPTs were inconclusive due to a positive response following application of the control solution. Two of these had positive CPTs and 1 had a negative CPT. Of the 45 participants in the rhinitis group with positive SPTs, 2 had negative NPTs and positive CPTs.

In the rhinitis group, 5/50 participants had negative SPTs and ssIgE. One of them had a positive NPT and negative CPT. In the remaining 4 participants, the NPTs were negative and the CPTs negative or inconclusive due to a positive reaction to the control solution.

The test results of the control group ($n = 45$) are summarized in the tree diagram in figure 2. In the control group, 8 participants had positive SPTs and/or ssIgE. In 2 of them, the NPTs and CPTs were also positive. One of 8 participants had an inconclusive NPT and concomitantly a positive CPT and 5/8 subjects of the control group with positive SPTs and ssIgE had negative NPTs. Two of these 5 subjects had a positive and 3 a negative CPT.

Thirty-seven of 45 participants of the control group had negative SPTs and/or ssIgE. Four of them had positive NPTs, and 1 of these had a positive and 3 a negative CPT. In 3/37 participants, the NPTs were inconclusive. Of these 3 participants, 1 had a positive, 1 an inconclusive, and 1 a negative CPT. Thirty of 37 subjects of the control group with negative SPTs and/or ssIgE had a negative NPT, and 28 concomitantly had negative CPTs. In 1 of these 30 subjects, the CPT was positive and in 1 it was inconclusive.

Fig. 1. Results of SPTs and assays of allergen-specific IgE (IGE), NPTs and CPTs in 50 subjects with self-reported perennial allergic rhinitis to house dust mite.

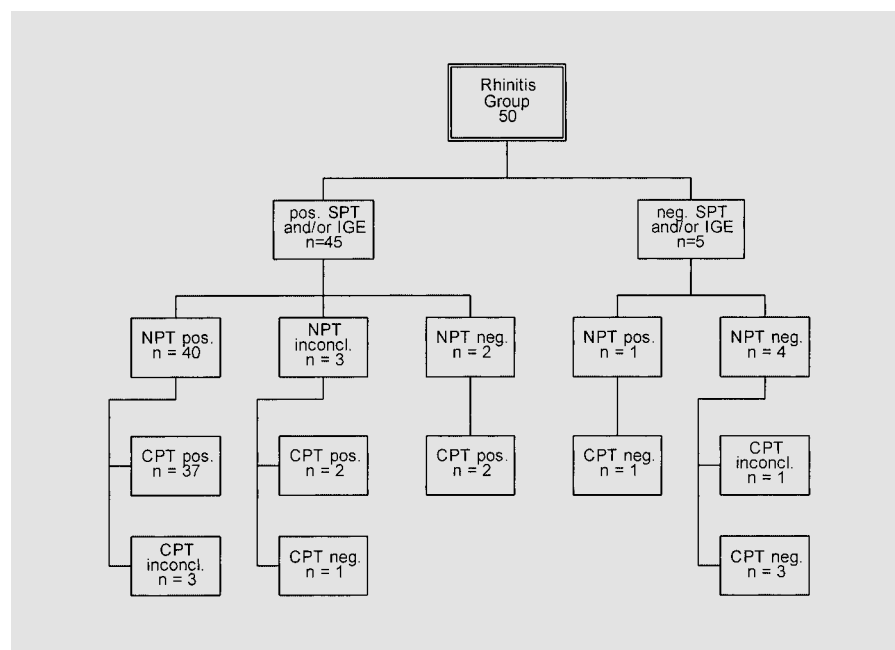
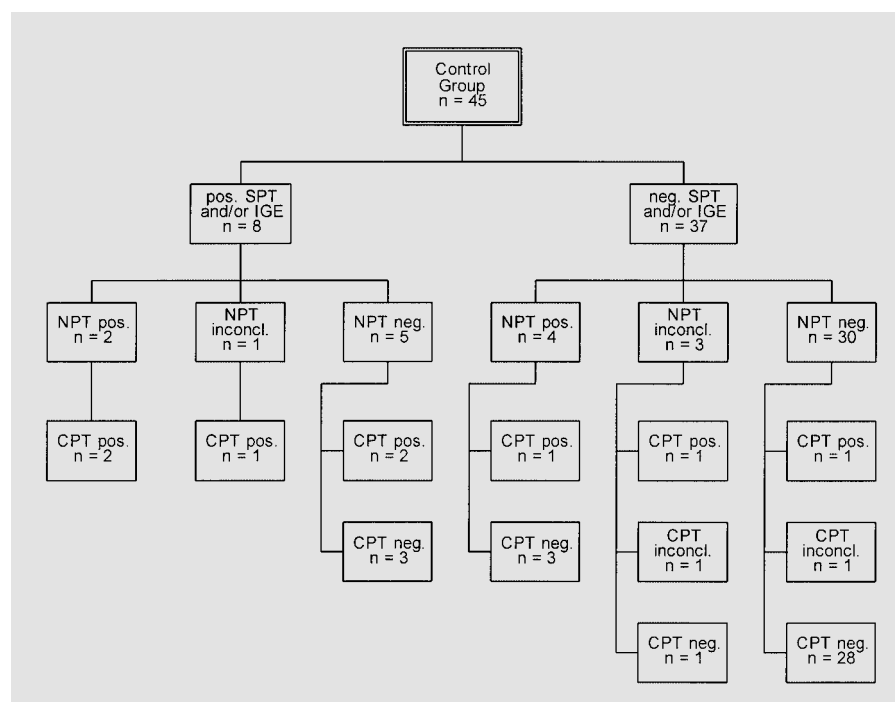


Fig. 2. Results of SPTs and assays of allergen-specific IgE (IGE), NPTs and CPTs in 45 subjects reporting no nasal or conjunctival symptoms consistent with perennial allergic rhinitis.



Evaluating the whole study group, CPTs and NPTs were both positive in 40 subjects, both negative in 34 patients, and both inconclusive in 1 subject. Discordant results were obtained in 20 participants (21%). The details are outlined in table 5. Cohen's kappa for nominal categories of the whole study group is 0.62 (95% CI 0.49–

0.76, $p < 0.0001$). If subjects with inconclusive NPTs and/or CPTs are omitted from the evaluation, concordant results for CPTs and NPTs were obtained in 74/83 (89%) subjects. Cohen's kappa is then 0.78 (95% CI 0.65–0.92, $p < 0.0001$).

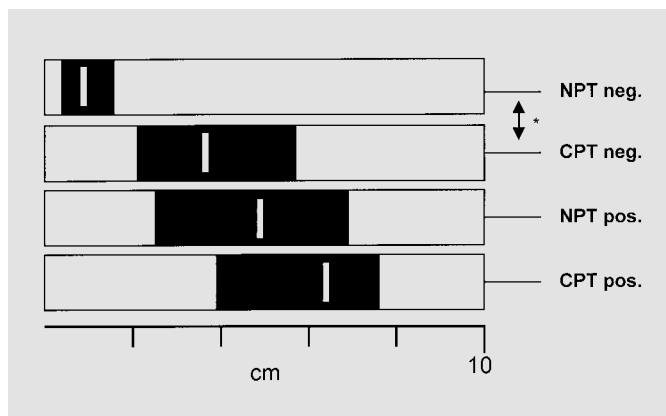


Fig. 3. Visual-analog scale plots of test-related discomfort (0 = no discomfort; 10 = maximum discomfort) in subjects with positive or negative responses to NPTs or CPTs with house dust mite extracts (white bar = median, black = 95% CI of median, * $p < 0.01$).

CPT in Subjects with Allergic Rhinitis with and without Conjunctival Symptoms

Whether the subjects had nasal symptoms only or both nasal and conjunctival symptoms did not influence the results. In 43 subjects of the rhinitis group, reliable data on concomitant conjunctival symptoms were available. All 5 subjects with negative CPTs suffered from conjunctival symptoms, and CPTs were positive in all 17 allergic subjects without conjunctival symptoms.

Discomfort Caused by NPTs and CPTs

Volunteers assessed the discomfort of the two diagnostic techniques on 10-cm visual-analogue scales ranging from no discomfort to maximum distress (fig. 3). A negative NPT (median 0.9 cm, 95% CI 0.4–1.6 cm) was less distressing than a negative CPT (median 3.6 cm, 95% CI 2.1–5.7 cm, $p < 0.001$). A positive NPT caused slightly less discomfort (median 4.9 cm, 95% CI 2.5–6.9 cm) than a positive CPT (median 6.4 cm, 95% CI 3.9–7.6 cm, $p = 0.07$). This difference was observed in spite of the fact that antiallergic eye drops were immediately administered when the subject had a clearly positive CPT, but no treatment was applied in subjects with positive NPTs.

Discussion

Provocation tests with allergens are used in the clinical diagnosis of allergic disorders caused by airborne allergens, because skin tests and in vitro tests may not always

Table 5. Concordant and discordant results of NPTs and CPTs in 50 subjects with perennial allergic rhinitis and 45 healthy controls

	NPT negative	NPT positive	NPT inconclusive	Total
CPT negative	34 (35%)	4 (5%)	2 (2%)	40
CPT positive	5 (5%)	40 (42%)	4 (4%)	49
CPT inconclusive	2 (2%)	3 (3%)	1 (1%)	6
Total	41	47	7	95

reflect the allergic situation at the organ level [15]. Moreover, provocation tests commonly serve as an inclusion criterion in clinical studies and as a tool to assess treatment outcome. Three organ systems are commonly targeted by provocation tests for type I allergy to airborne allergens. These include the bronchial system with bronchial provocation tests (BPTs), the nasal mucosa with NPTs and the conjunctiva with CPTs. Because CPTs are easy to perform, are cost-effective [19] and rarely complicated by systemic reactions [20], they would be an attractive alternative to NPTs and BPTs. In several studies, CPTs have actually been used as a surrogate for NPTs in patients with allergic rhinitis [7–10].

In this study, the concordance of CPTs and NPTs in subjects with allergic rhinitis was systematically investigated. Volunteers with perennial allergic rhinitis were chosen, because in seasonal allergic rhinitis, provocation tests are rarely required to confirm the clinical relevance of the suspected allergen [3]. Moreover, possible differences in test concordance in subjects with nasal symptoms only and in those with both nasal and conjunctival symptoms were explored. Finally, patient discomfort caused by the two diagnostic techniques was assessed. Although of significant clinical importance, late-phase reactions were not documented, as both provocation protocols only intend to facilitate the differentiation between allergic and nonallergic disease. Inclusion of late-phase reactions would substantially complicate the protocol and possibly prevent its use in clinical routine [15].

90% of the CPTs and NPTs that were both interpretable yielded concordant results ($p < 0.0001$). To assess the sensitivity, specificity and diagnostic efficacy of CPTs, with NPTs serving as the reference method, the results of CPTs in 83 participants with conclusive results on both tests were tabulated against those of NPTs (table 6). The positive predictive value was 89%, the negative predictive value 90% and diagnostic efficacy was 89%. The associa-

Table 6. Result of the CPT vs. the NPT, with the NPT serving as the reference method

	CPT+	CPT-	Total
NPT +	40	4	44
NPT-	5	34	39
Row total	45	38	83

In 12/95 participants, no conclusive result was obtained either in one or both tests due to a positive reaction to the control solution. The sensitivity of the CPT was 91% (95% CI: 78–98%), the specificity 87% (73–96%); there were 13% (4–27 %) false positives, 9% (3–21%) false negatives, and diagnostic efficacy was 89% (80–92%).

tion of nasal and conjunctival symptoms did not influence the results. CPTs are thus considered a reasonable alternative to NPTs in patients with perennial allergic rhinitis, even in the absence of conjunctival symptoms. Despite the fact that topical antihistamines were immediately given once a positive conjunctival response was observed, CPTs were more distressing than NPTs. Particularly controls with a negative CPT response complained of the conjunctival burning sensation caused by the test solutions, whereas negative NPTs did not cause major discomfort. This burning sensation is probably due to the preservative contained in the test solutions employed for CPTs. As an alternative, sterile IC test solutions free of preservatives could be employed. However, the concentrations commonly used for IC tests (100 AU/ml) are too low to elicit a positive response in the majority of allergic subjects.

If the subjects with differing results on CPTs and NPTs are analyzed in detail, 3 of 4 positive NPTs and negative CPTs are most likely false-positive NPTs. The subjects belonged to the control group, had no nasal symptoms and had negative SPT and ssIgE. The actual state of 1 subject with a positive NPT and a negative CPT remains unclear. In the 5 subjects with negative NPTs and positive CPTs, 2 false-negative NPTs were identified because all subjects had symptoms consistent with perennial allergic rhinitis and positive skin tests or ssIgE. In 3 participants with negative NPTs and positive CPTs, no concluding diagnosis of allergy could be made. Inconclusive results due to a positive reaction to the control solution were obtained in approximately 15% in both tests. This probably reflects hyperreactivity, which has been described in nasal and ocular allergy [17]. In the 11 patients who were hyperresponsive to one or the other test, the respective

alternative diagnostic test was well interpretable and the result was consistent with history, skin tests and the ssIgE assay. In 1 subject, neither the NPT nor the CPT were interpretable.

The results of this study are partially consistent with results reported in patients with perennial nasal allergy. Mosbech et al. [12] performed BPTs, NPTs and CPTs in 50 asthmatic patients with confirmed house dust mite allergy and found concordant results for the three diagnostic techniques in 40/50 patients. The authors concluded that only organ-specific allergen challenges provide valid information. An almost perfect concordance of CPT and NPT was reported in patients with seasonal allergic rhinitis [21]. In one study on 10 patients with allergic rhinitis without conjunctival symptoms and 20 patients with allergic rhinoconjunctivitis, 100% concordance was found between NPTs and CPTs. In patients with seasonal allergic rhinitis, 100% concordance between NPTs and CPTs was also found by Petersson et al. [3]. Whether the patients reported conjunctival symptoms in addition to respiratory symptoms had no influence on the results of CPTs in a previous study [22].

The study design was an open, case-control study in students with and without allergic rhinitis. Subjects with other diseases of the nose, paranasal sinuses or eyes were excluded. Students applied for participation in response to messages pinned on the notice board at the auditorium. Thus the two study groups are considered to be comparable except for the presence of allergic rhinitis. However, selection is biased towards younger, well-educated and otherwise healthy persons. It is thus unclear whether the results of this study can be extrapolated, for instance, to elderly patients with concomitant nasal or paranasal disease. Like previous studies comparing different provocation tests with allergen [3, 12, 21, 22], this study was not blinded. The reason is that volunteers are always aware of the result of the concomitant test, be it an NPT or CPT, and are thus subject to the placebo/nocebo effect. Accordingly, they are also able to voluntarily or involuntarily reveal the results of the concomitant test to the investigator. We thus chose to perform an open rather than a pseudo-blind trial [23]. Consequently, a possible observer bias cannot be ruled out and must be considered when interpreting the results of this study. The investigators were aware of this situation and attempted to observe the provocation-related effects critically and to base their judgment strictly on the criteria given in tables 3 and 4.

The CPT used in this study is based on a clinical score system [16]. In this system, typical symptoms and signs (redness and irritation, vasodilation and tearing, blepha-

rospasm and tarsal conjunctival involvement, and chemosis and lid swelling) are grouped together and classified according to the strength of the response in stages 0–4. The validity and reproducibility of CPTs based on clinical score systems were demonstrated in several investigations [8, 24, 25]. Evaluation of conjunctival redness and vasodilation with image analysis systems [26] have been used in order to obtain objective measures of the response to conjunctival allergen provocation. However, essential clinical signs, such as tearing, blepharospasm, and chemosis are difficult to assess with this method. Thermography has also been used in an attempt to obtain objective measures, but was found to be of little significance [25].

The result of CPT depends on the allergen concentration applied [8] and an allergen concentration equal to the SPT solution, i.e. 10,000 AU/ml, has been proposed [4]. However, in pilot investigations, this allergen concentration elicited an intense, distressing response in a few subjects. It was therefore decided to employ a 1:10 dilution (1,000 AU/ml) initially and to administer 10,000 AU/ml only if the initial response was negative. Actually, we have elicited a definitely positive response with the 1,000 AU/ml solution in 26/50 allergic subjects, making the use of the probably more distressing higher concentration unnecessary. Moreover, topical antihistamines were applied once the CPT was definitely positive. This is probably the reason why a stage IV response was not observed in the subjects investigated and why there was no correlation between the intensity of the responses to the CPTs and NPTs.

The advantages and disadvantages of NPTs have been discussed exhaustively in several publications [1, 4, 6]. In German-speaking countries, the NPT is standardized since 1990, reducing the problem of various concurring procedures for NPT [27]. Active anterior rhinomanometry is considered the method of choice to obtain an objective parameter on the allergic response of the nasal mucosa [6]. In Europe, the NPT is thought to provide valid information on whether or not a sensitized person is actually allergic to the suspected allergen [4, 6]. However, the method is laborious and has various disadvantages: it is unreliable in patients with recent nasal surgery, in severe nasal obstruction as is frequently seen in patients with concomitant rhinitis medicamentosa or nasal polyps; active anterior rhinomanometry, which is used to objectify the results of NPTs, yields invalid results in patients with septal perforation or nasal valve stenosis. In these patients, the CPT is a favorable alternative to the NPT in the diagnosis of allergic rhinitis.

In conclusion, the CPT appears to be a valuable tool in the diagnosis of perennial allergic rhinitis. It may serve as an alternative to NPT in the diagnosis of perennial nasal allergy also in patients without conjunctival symptoms. In this study, the CPT agreed better with allergic history, skin tests and IgE assays than the NPT.

References

- 1 Druce HM, Schumacher MJ: Nasal provocation challenge. The Committee on Upper Airway Allergy. *J Allergy Clin Immunol* 1990;86: 261–264.
- 2 Riechelmann H, Mewes T, Weschta M, Gropper G: Nasal allergen provocation with *Dermaphagoides pteronyssinus* in patients with chronic rhinitis referred to a rhinologic surgical center. *Ann Allergy Asthma Immunol* 2002;88: 624–631.
- 3 Petersson G, Dreborg S, Ingstad R: Clinical history, skin prick test and RAST in the diagnosis of birch and timothy pollinosis. *Allergy* 1986;41:398–407.
- 4 Melillo G, Bonini S, Cocco G, Davies RJ, de Monchy JG, Frolund L, Pelikan Z: EAACI provocation tests with allergens. Report prepared by the European Academy of Allergy and Clinical Immunology Subcommittee on provocation tests with allergens. *Allergy* 1997; 52:1–35.
- 5 Malling HJWB: Position paper: Immunotherapy. *Allergy* 1993;48:9–35.
- 6 Malm L, Gerth van Wijk R, Bachert C: Guidelines for nasal provocations with aspects on nasal patency, airflow, and airflow resistance. International Committee on Objective Assessment of the Nasal Airways, International Rhinologic Society. *Rhinology* 2000;38:1–6.
- 7 Kjellman NI, Andersson B: Terfenadine reduces skin and conjunctival reactivity in grass pollen allergic children. *Clin Allergy* 1986;16: 441–449.
- 8 Moller C, Bjorksten B, Nilsson G, Dreborg S: The precision of the conjunctival provocation test. *Allergy* 1984;39:37–41.
- 9 Lofkvist T, Agrell B, Dreborg S, Svensson G: Effects of immunotherapy with a purified standardized allergen preparation of *Dermatophagoides farinae* in adults with perennial allergic rhinoconjunctivitis. *Allergy* 1994;49:100–107.
- 10 La Rosa M, Ranno C, Andre C, Carat F, Tosca MA, Canonica GW: Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized *Parietaria judaica* extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1999; 104:425–432.
- 11 Malmberg CH, Holopainen EE, Stenius-Aarniala BS: Relationship between nasal and conjunctival tests in patients with allergic rhinitis. *Clin Allergy* 1978;8:397–402.
- 12 Mosbech H, Dirksen A, Madsen F, Stahl Skov P, Weeke B: House dust mite asthma. Correlation between allergen sensitivity in various organs. *Allergy* 1987;42:456–463.
- 13 Leonardi A, Battista MC, Gismondi M, Fregona IA, Secchi AG: Antigen sensitivity evaluated by tear-specific and serum-specific IgE, skin tests, and conjunctival and nasal provocation tests in patients with ocular allergic disease. *Eye* 1993;7:461–464.

- 14 Dreborg S, Frew A: Position paper: Allergen standardization and skin tests. The European Academy of Allergology and Clinical Immunology. *Allergy* 1993;48:48–82.
- 15 Riechelmann H, Bachert C, Goldschmidt O, Hauswald B, Klimek L, Schlenker W, Tasman A, Wagenmann M: Nasal provocation test in upper airway disease. Position statement of the German Association of Allergy and Clinical Immunology and the German Society of Otorhinolaryngology – Head and Neck Surgery. *Allergol J* 2002;11:29–36.
- 16 Gronemeyer U: Konjunktivaler Provokationstest; in Heppt W, Bachert C (eds): *Praktische Allergologie*. Stuttgart, Thieme, 1998, pp 67–68.
- 17 Bacon AS, Ahluwalia P, Irani AM, Schwartz LB, Holgate ST, Church MK, McGill JI: Tear and conjunctival changes during the allergen-induced early- and late-phase responses. *J Allergy Clin Immunol* 2000;106:948–954.
- 18 Raizman MB, Rothman JS, Maroun F, Rand WM: Effect of eye rubbing on signs and symptoms of allergic conjunctivitis in cat-sensitive individuals. *Ophthalmology* 2000;107:2158–2161.
- 19 Escudero AI, Sanchez-Guerrero IM, Mora AM, Soriano V, Lopez JD, Garcia FJ, Negro JM, Hernandez J, Pagan JA: Cost-effectiveness of various methods of diagnosing hypersensitivity to *Alternaria*. *Allergol Immunopathol (Madr)* 1993;21:153–157.
- 20 Anderson DF, McGill JI, Roche WR: Improving the safety of conjunctival provocation tests. *J Allergy Clin Immunol* 1996;98:1000.
- 21 Fennerty AG, Jones KP, Fifield R, Davies BH: Challenge tests and specific IgE in hay fever sufferers. *Clin Allergy* 1987;17:365–372.
- 22 Garcia-Ortega P, Costa B, Richart C: Evaluation of the conjunctival provocation test in allergy diagnosis. *Clin Exp Allergy* 1989;19:529–532.
- 23 Spriet A, Simon P: *Methodology of Clinical Drug Trials*. Basel, Karger, 1985.
- 24 Abelson MB, Chambers WA, Smith LM: Conjunctival allergen challenge. A clinical approach to studying allergic conjunctivitis. *Arch Ophthalmol* 1990;108:84–88.
- 25 Rimas M, Gustafsson PM, Kjellman NI, Björkstén B: Conjunctival provocation test: High clinical reproducibility but little local temperature change. *Allergy* 1992;47:324–326.
- 26 Horak F, Berger U, Menapace R, Schuster N: Quantification of conjunctival vascular reaction by digital imaging. *J Allergy Clin Immunol* 1996;98:495–500.
- 27 Bachert C, Berdel D, Enzmann H, Fuchs E, Gonsior E, Hofmann D, Keller H, Nitz U, Rudolph R, Rüdiger W, Schlenker WW: Richtlinien für die Durchführung von nasalen Provokationstests mit Allergenen bei Erkrankungen der oberen Luftwege. *Allergologie* 1990;2:53–55.