

# Nasal Provocation Testing as an International Standard for Evaluation of Allergic and Nonallergic Rhinitis

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**Standardized nasal provocation testing (NPT) has been shown to be a safe and very useful tool in the diagnosis of allergic and nonallergic rhinitis. However, in the United States, its use has been mostly limited to scientific investigations, and it has not yet been widely accepted as a standard diagnostic procedure in clinical practice. NPT aims to identify and quantify the clinical relevance of inhalant allergens or occupational irritants. During NPT, nasal respiratory mucosa is exposed to an airborne substance suspected to cause symptoms in the respective individual. Clinical reactions are monitored in a controlled and standardized fashion. Nasal secretions, symptoms such as itching, sneezing and, most importantly, nasal obstruction are assessed as well as ocular, bronchial, cutaneous, and systemic reactions. To achieve objective data on changes in nasal airflow and patency after the challenge, anterior rhinomanometry and acoustic rhinometry have been included in the standard protocol of NPT. By monitoring changes of nasal airflow on one hand and of nasal geometry on the other hand, these methods display nasal function in a graphic way just as speech and pure tone audiometry do for auditory function. Also, by their objective nature, these methods offer a clear and internationally comparable standard. This review outlines a protocol for NPT and discusses practical applications and clinical indications. The use of rhinomanometry and acoustic rhinometry as objective diagnostic tools is emphasized. For the diagnosis of allergic and occupational rhinitis, standardized NPT should be regarded as an international diagnostic standard. **Key Words:** Nasal provocation testing, symptom scores, rhinomanometry, acoustic rhinometry.**

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## INTRODUCTION

Nasal provocation testing (NPT) has been widely used in scientific investigations involving the pathophysiologic mechanisms of allergic and nonallergic rhinitis. Because of the known similarities of these mechanisms in the upper and lower respiratory tract, some of these studies were able to unveil aspects of hyperreactivity in the lower respiratory tract as well.

Practically, NPT reproduces pathologic reactions of hyperreactive or allergic nasal mucosa to defined airborne substances under standardized and controlled conditions. Although NPT has been established as a standardized procedure of clinical evaluation in most European countries,<sup>1</sup> its acceptance within the United States, where it is mainly used for scientific investigations, is still limited.

The main diagnostic target of NPT being inhalant allergies, it is also applicable to other fields such as pharmacologic issues as well as questions concerning irritating effects of occupationally relevant substances. It offers the unique potential to differentiate between individuals with a relevant sensitization to a specific airborne substance from other individuals, who might show a sensitization but who remain asymptomatic under natural conditions of exposure to the respective substance. On the other hand, the test can be very helpful in cases where no specific immunoglobulin (Ig)E antibodies can be detected in skin or blood tests, but where NPT clearly proves a pathologic reaction of the nasal respiratory mucosa to the suspected substance. The latter is certainly rare, but it has been shown that specific IgE to various antigens can be locally produced within the nasal mucosa itself without any concomitant reaction being detectable in skin or blood tests.<sup>2</sup>

Several investigators have elaborated that there is not a general positive correlation between skin test reactivity and symptoms of allergic rhinitis.<sup>3</sup> In patients with symptoms of allergic rhinitis, skin testing can be positive for specific IgE even though these specific allergens prove to be irrelevant in terms of causing clinical symptoms.<sup>4</sup> This review is intended to evaluate the role of standardized NPT, objectively evaluated with the help of anterior rhinomanometry and acoustic rhinometry, in the diagnosis of allergic rhinitis.

## INDICATIONS

NPT can routinely be used for a safe and clear diagnosis of allergic rhinitis in cases where clinical symptoms and the results of skin or blood testing are conflicting or insufficient. It is also potentially important in the proper selection of an individual therapeutic concept in clinically complicated cases with sensitizations to various antigens.

It is subject to an ongoing discussion to what extent results of nasal provocations may be predictive of bronchial provocations by using the identical antigen for evaluation of bronchial asthma. It appears these two tests do not necessarily lead to correlating results in both target organs. On the other hand, if—in cases of a proven sensitization to a specific allergen—nasal provocation is followed by allergic nasal as well as bronchial symptoms, it may be obsolete to perform a bronchial provocation.<sup>5</sup> Generally, NPT offers a safer alternative to bronchial provocation when evaluating the relevance of specific allergens in the etiology of bronchial asthma.

The main clinical indications for NPT are as follows:

- To confirm the clinical relevance of a specific allergen in patients with positive reactions to multiple allergens in skin or blood tests.
- To identify relevant allergens in cases of multiple sensitizations if history of clinical symptoms does not point to a specific allergen because of overlapping pollen seasons or because of perennial exposure.
- To confirm nasal reactivity to a specific allergen before initiating immunotherapy.<sup>6</sup>
- To evaluate the role of allergens that are tested negative by skin or blood test but that are implicated in the patient's history.<sup>7</sup>
- To determine whether nasal application of a specific allergen can induce ocular or bronchial symptoms in addition to nasal symptoms.
- To confirm the role of a specific allergen in bronchial asthma in cases where bronchial provocation cannot be safely performed.
- To evaluate the role of specific occupational agents, suggested by the patients history, such as baker's yeast, dusts, or latex.<sup>8</sup>

## CONTRAINDICATIONS

The following contraindications should be regarded as absolute:

- Acute bacterial or viral rhinosinusitis.
- Acute exacerbation of allergic disease.
- History of previous anaphylactic reaction to an allergen.
- Severe general diseases, especially cardiopulmonary diseases with reduced lung capacity.
- Pregnancy.

In addition to these absolute contraindications, there are a couple of relative ones, which require a delay of a certain period of time before NPT can be safely and accurately performed:

- Episodes of allergic rhinitis (delay of 2–4 weeks).
- Nasal surgery (delay of 6–8 weeks).

Treatment with certain medications, which require a period of withdrawal before NPT: antihistamines (3 days), nasal corticosteroids (6 hours to 1 week), oral corticosteroids greater than 10 mg (1–2 weeks), nonsteroidal analgesics (1 week), central nervous antihypertensives (3 weeks), imipramines and other tricyclic drugs (1 week), astemizole (4–12 weeks), and ketotifen (2 weeks).

## ALLERGEN DOSING AND APPLICATION FOR NPT

Isotonic, buffered aqueous solutions with a neutral pH should be applied using defined allergen concentrations. The concentration of the respective allergen should be biologically standardized; however, hopefully, the new international standard suggested by the World Health Organization ( $\mu\text{g}$  of major allergen/mL)<sup>9</sup> will soon be accepted internationally. The following units have found acceptance for biologic standardization thus far:

- HEP/mL: histamine equivalent potency; 1 HEP will cause a wheal of equivalent diameter as will 10 mg/mL of histamine (1 HEP = 10,000 BU/mL).
- BU/mL: biologic units; deducted from HEP/mL following the Nordic Guidelines.
- IR/mL: index of reactivity; by definition, 100 IR/mL will result in a wheal of 7 mm in diameter.
- AU/mL: allergy unit; 100,000 AU/mL equals the amount of allergen extract that will cause an erythema of a defined size in highly sensitized patients.

The amount usually applied for NPT is 50 to 100  $\mu\text{L}$  of the test solution to one side of the nose. In case of a negative result but a positive clinical history of allergic symptoms to the suspected substance, NPT can be repeated in a concentration equivalent to that used in skin testing. If even at this concentration there is no measurable effect on nasal resistance but a strongly suggestive individual history, the reactivity of the nasal mucosa can be challenged by using a 50  $\mu\text{L}$  solution containing 4 mg/mL of histaminhydrochloride (pH 6–7).

## TECHNIQUE AND PRACTICAL PROTOCOL FOR NPT

Rhinoscopic examination including anterior rhinoscopy and nasal endoscopy should precede NPT to evaluate the baseline condition and to exclude possible pathologies such as nasal polyps or atrophic rhinitis. Before any patient undergoes NPT, evaluation for specific sensitizations by skin or blood test should have been completed.

Patients should be well adapted to room temperature for at least 30 minutes before a baseline evaluation by rhinoscopy and a clinical symptom score, anterior rhinomanometry, and acoustic rhinometry are performed. The wider side of the nose is used for the challenge; however, both sides will be monitored throughout the diagnostic procedure to identify possible false or unspecific variations in nasal patency caused by effects of the nasal cycle.<sup>1</sup> Before administration of the actual allergen solution, the nasal mucosa of the wider side of the nose is challenged for unspecific hyperresponsiveness by a known volume of iso-

TABLE I.  
Scoring System for Evaluation of Clinical Symptoms after  
Nasal Provocation.

| Symptom             | Severity                   | Score (points) |
|---------------------|----------------------------|----------------|
| Secretion           | No secretion               | 0              |
|                     | Little secretion           | 1              |
|                     | Heavy secretion            | 2              |
| Irritation          | 0–2 sneezes                | 0              |
|                     | 3–5 sneezes                | 1              |
|                     | >5 sneezes                 | 2              |
| Extranasal symptoms | None                       | 0              |
|                     | Tearing/itching            | 1              |
|                     | Conjunctivitis/chemosis +– | 2              |
|                     | Urticaria +–               | 2              |
|                     | Coughing/dyspnoea          |                |

tonic saline with a conserving agent using a metered dose-delivery device. Evaluation of the baseline scores is repeated after 10 minutes to check on clinical symptoms or significant changes in objective measurements of nasal patency. If no significant changes occur, the actual allergen provocation is performed on the wider side of the nose. The applicator of the delivery device is inserted into the nasal vestibulum and pointed upward and laterally toward the medial canthus of the eye to deposit allergen on the inferior and the middle turbinate mucosa when spraying 50 to 100  $\mu$ L of test solution into the nose. During allergen application, the patient must hold his or her breath to avoid inhaling the allergen into the lower airways. Patients are told to inhale before and to exhale right after the application. Instead of a pump spray device, pipettes can be used to deposit drops of allergen solution on the mucosa. Other alternatives such as vaporizers are infrequently used, and the use of cotton pads is obsolete.

For routine clinical use, application of one single concentration of allergen is sufficient because the test aims at a qualitative and not at a quantitative evaluation of nasal reactivity. Titrations of sequentially increasing doses of allergen solution is only indicated if changes in nasal reactivity before and after specific immunotherapy are to be quantified.

Ten minutes after allergen application, clinical signs and symptoms are reassessed, and objective measurements of nasal patency are repeated to define a positive or negative test result. In cases of uncertain results, a re-evaluation of all parameters can be conducted after a period of additional 10 minutes.

## EVALUATION OF CLINICAL SYMPTOMS

The clinical parameters of interest are nasal irritation, assessed by the number of sneezes, nasal secretion, assessed by anterior rhinoscopy, and extranasal symptoms such as ocular, cutaneous, or pulmonary reactions, as assessed by the investigators' judgment and patient complaints. A practical scoring system for a standardized quantification of these clinical parameters, which has been proposed by the ENT section of the German Society for Allergy and Clinical Immunology,<sup>9</sup> is summarized in Table I.

NPT is positive for the tested allergen if the symptom score as evaluated 10 minutes after the challenge is greater than 3. This clinical evaluation is always combined with the assessment of nasal airflow by anterior rhinomanometry. If the latter reveals a decrease of nasal airflow of greater than 40% at a transnasal pressure of 150 Pa after NPT, this is considered a positive test result regardless of the clinical symptom score. NPT is also positive if the symptom score is greater than 2, combined with a decrease in nasal airflow at 150 Pa of greater than 20%.<sup>9</sup>

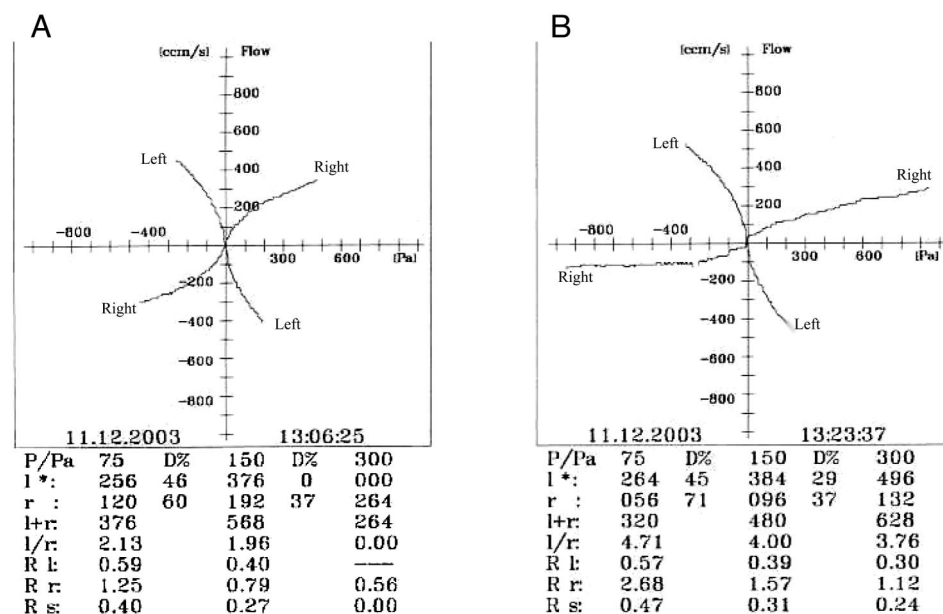


Fig. 1. Rhinomanometry before (A) and after (B) nasal provocation testing (NPT) of the right nasal cavity using house dust mite extract in a sensitized patient. The more horizontal orientation of the curve representing the right nasal cavity indicates less airflow at a given transnasal pressure after NPT when compared with the equivalent function of flow and pressure before NPT.

## OBJECTIVE MEASUREMENT OF NASAL PATENCY

Nasal air-space volume and patency can be assessed by a variety of different methods that are available such as nasal spirometry, nasal peak expiratory flow rate (NPEFR), or nasal peak inspiratory flow rate (NPIFR), but active anterior rhinomanometry has evolved to be accepted as an international standard for measurement of nasal resistance and nasal airflow.<sup>10</sup> It is designed to analyze the transnasal airflow in one nostril at a time depending on transnasal pressure, which is assessed contralaterally during tidal breathing. For complete and state of the art evaluation of nasal patency, this method is combined with acoustic rhinometry, which documents nasal geometry as cross-sectional area within the nasal cavity.<sup>11–15</sup>

Results of both methods, anterior rhinomanometry and acoustic rhinometry, are visualized graphically to facilitate analysis and documentation. Measurements before and after NPT can be easily compared and accurately assessed using these graphs in combination with the exact numbers for nasal airflow ( $\text{cm}^3/\text{s}$ ) and cross-sectional area ( $\text{cm}^2$ ), which are computed by the respective analyzers. Graphic display of detailed analysis of two different aspects of nasal function (flow and cross sectional area) gives these methods a great practical value comparable with the standard documentation of audiometric results (pure tone and speech audiometry), which have gained worldwide acceptance in audiology.

Figures 1 and 2 show the graphic documentation of anterior rhinomanometry and acoustic rhinometry before and after NPT of the right nasal cavity, using house dust mite extract in a sensitized patient. The curves display the positive result of the challenge as seen by a marked decrease of nasal airflow and of minimal cross-section area on the right as opposed to the left side of the nose.

## REASONS FOR FALSE-POSITIVE OR FALSE-NEGATIVE RESULTS

The most frequent reason for false-positive results in the measurements of nasal patency are effects of the nasal cycle. A general hyperreactivity of nasal mucosa preceding allergen exposure or episodes of rhinosinusitis (nasal priming) or preceding exposure to unspecific irritants are other frequent reasons for false-positive results.

False-negative results of NPT can occur after use or failure to withdraw from the discussed medications caused by nonstandardized and obsolete allergen solutions or by a very low nasal airflow before provocation. Previous sinonasal surgery with a consecutive lack of reactive mucosal tissue can also result in false-negative NPT.

## CONCLUSION

Standardized NPT is a diagnostic tool that reproduces nasal mucosal reactions to specific allergens or occupational irritants to define their clinical relevance. It is helpful in identifying the role of specific substances in case of sensitizations to multiple seasonal allergens or in cases lacking clinical evidence because of sensitization to perennial allergens. In cases of correlating results in nasal and bronchial mucosa, NPT can even be valuable as a surrogate for bron-

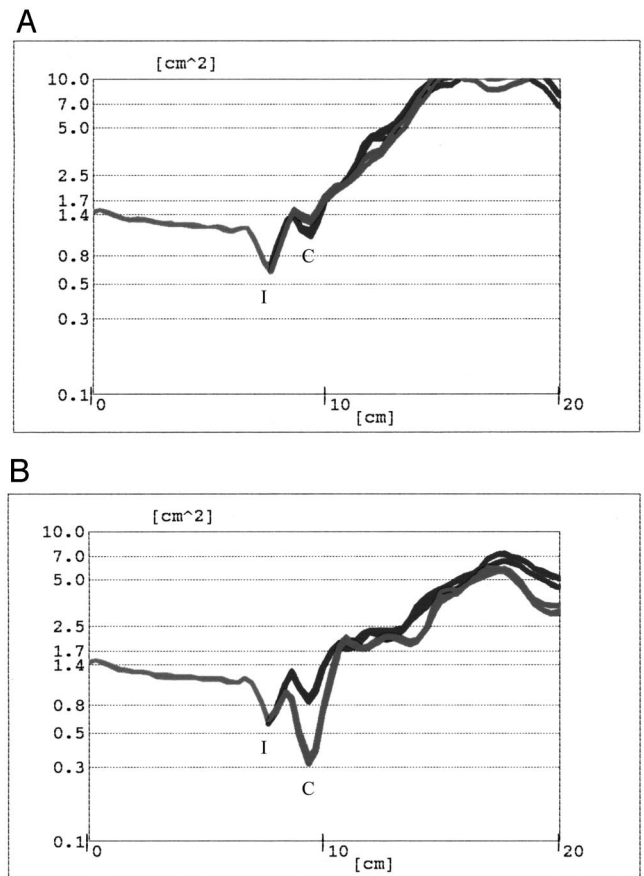


Fig. 2. Acoustic rhinomanometry before (A) and after (B) nasal provocation testing (NPT) of the right nasal cavity in the same patient as Figure 1. Cross-sectional area at the c-notch representing the level of the head of the inferior turbinate decreases dramatically after NPT, indicating marked mucosal swelling on the challenged side of the nasal cavity.

chial challenges. Evaluation of test results by a standardized symptom score and objective assessment of changes in nasal patency by anterior rhinomanometry and acoustic rhinometry help to establish this method as an international standard in the diagnosis of allergic airway disease.

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