Nasal provocation test: how to maximize its clinical use?

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Summary

In order to diagnose allergic rhinitis (AR), skin prick tests and serum specific IgE level are the most common used methods. But there are some conditions which the results of both methods do not correlate with the clinical presentation of AR. Nasal provocation test is the method of detecting local IgE at the shock organ. There are some variations of NPT in terms of dosage, allergen administration, evaluation and scoring system. This article summarized the usefulness of NPT, its indication and contraindication, dosage and instillation techniques for allergens and evaluation of outcome in the hope that if we can standardize the procedure and make it easier to perform, NPT will be applied more in clinical practice. In addition normal values among Asian ethnics are presented for appropriate interpretation of the test *(Asian Pac J Allergy Immunol 2010;28:225-31)*

Key words: *Allergic rhinitis, Diagnosis, Skin prick test, Nasal provocation test, Peak nasal inspiratory flow, Acoustic rhinometry, Rhinomanometry*

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Introduction

Skin prick tests are recommended as the test of choice for the diagnosis of allergic rhinitis (AR) due to its simplicity and reproducibility[1]. In cases when skin prick testing is not possible, such as inability to discontinue oral antiallergic drug, responsible practitioners may request for serum specific IgE as an alternative diagnostic test.

Although skin tests and serum specific IgE levels are the most reliable method for determining specific hyperreactivity and sensitization, some discrepancies between serum specific IgE and local production specific IgE in the nasal mucosa have been observed[2]. For example, positive skin tests and increased serum level of specific IgE could be present in individuals who do not have any clinical manifestations of allergic disease[3]. In contrast, some patients with symptoms of AR do not have any positive skin tests or serum specific IgE. In such cases, the nasal provocation test (NPT) with specific allergens could help in the establishment of reliable diagnosis of AR. Upon instilling the culprit allergen into the nasal cavities an allergic reaction is produced. Nasal provocation with specific allergens is therefore considered the gold standard for the diagnosis of AR. However, the NPT is not popular in clinical practice and is limited to tertiary care centers due to its complexity and inability to test more than one allergen at once. Moreover, results of skin prick tests and serum specific IgE levels could not be correlated with NPT response in some investigations[4-6]. Such drawback could be due to several reasons including the absence of universally accepted method for NPT procedures. In addition, the dosage of available provocation extracts may vary from one manufacturer to another. The scoring and recording criteria for defining positive NPT reaction are varied as well as the objective tools to measure the degree of nasal blockage. Currently, the widely accepted

criteria and techniques are adapted from European Research Centers[7].

This article summarized the usefulness of NPT, its indication and contraindication, dosage and instillation techniques for allergens and evaluation of outcome in the hope that if we can standardize the procedure and make it easier to perform, NPT will be applied more in clinical practice. In addition normal values among Asian ethnics are presented for appropriate interpretation of the test.

Application of NPT and its importance

Skin Prick testing (SPT) is a standard testing for allergy diagnosis. Patients with larger wheal sizes from SPT are the ones with higher clinical correlation than those with smaller wheal sizes. Some patients with negative SPTs but with positive intradermal tests (IDT) do not react to allergen challenge. However, this has recently been questioned by reports from Bodtger in 2006 and Scadding in 2007. These authors reported that patients with ab definate allergic history but with negative skin tests could later become develop both positive skin test and NPT results [8,9]. Such patients with convincing allergic history could make it difficult for clinicians to make a correct diagnosis during their first encounter with the patient. When there is doubt regarding the diagnosis of nasal allergy, NPT could be a useful procedure for such patients[10,11]. Moreover, those with multiple sensitivities, i.e., those who react to several allergens by skin testings, should be candidates for NPT in order to identify the culprit allergens. Thus, such patients could be improved through environmental control measures and the physician could select appropriate allergens for allergen immunotherapy.

To date, the indications of NPT are:

1. To confirm the diagnosis of allergic rhinitis in patients with negative allergy skin tests or without serum specific IgE.
2. To confirm the clinical relevance of a specific airborn allergen in patients with multiple sensitivities, as determined by skin testings[12].
3. To confirm nasal reactivity to specific allergen before initiating immunotherapy[13].
4. To assess the hyper-reactive state of non-allergic rhinitis, using capsaicin- or lipopolysaccharide (LPS)- challenge[14].
5. To confirm the role of a specific allergen in patients with bronchial asthma in which bronchial provocation test could not be safely performed[7].
6. To confirm the role of a specific occupational agent[15,16].
7. To study patho-physiology of allergic and non allergic reactions.
8. For allergy research such as the identification of new allergens or in the process of evaluating new treatments for allergic conditions.

Nevertheless, NPT is still not used as often as it could be in clinical practice.

NPT can be carried out safely with only a few minor side effects. In order to avoid side effects, NPT should not be performed during an exacerbation of the allergic condition or in patients with a history of severe systemic reactions (anaphylactic shock) to the particular allergen of interest.

To minimize false positive results, NPT should be avoided during an acute episode of rhinitis since the increase vascular permeability and nasal hyper-reactivity could alter the results [17].

To minimize false negative results, certain medications should be discontinued prior to NPT. These are listed in Table 1.

Principle of NPT

An allergen extract or other provocative agents is instilled intranasally and the intensity of nasal symptoms such as itching, sneezing, rhinorrhea and nasal obstruction occurred are recorded. Distant symptoms, such as ocular and bronchial, can be observed as well. The most important outcome parameter is nasal obstruction which can be assessed by various methods such as peak nasal inspiratory flow (PNIF), rhinomanometry (RMM) or acoustic rhinometry (ARM) [19,20].

Table 1. Medications should be stopped before nasal provocation test.

Medications	*Duration to stop before nasal provocation test*
Oral antihistamine	3 days
Intranasal corticosteroid	1 week[7] to 6 weeks[18]
Oral corticosteroid (greater than 10 mg/day)	2 weeks
Topical nasal decongestant	1 day
Antihypertensive (ACE inhibitors)	3 weeks

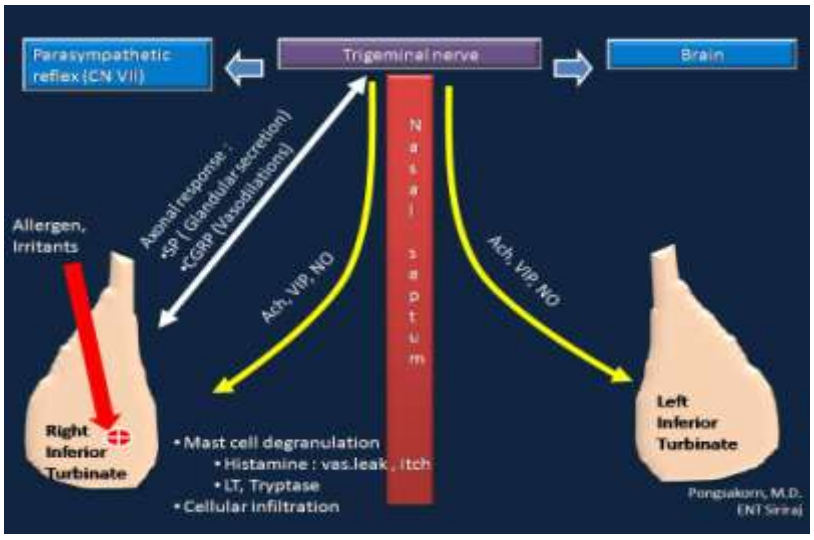

Figure 1. Nasal provocation test and its response. SP = substance P, CGRP = Calcitonin-gene related peptide, Ach = Acetylcholine, VIP = Vasoactive intestinal peptide, NO = Nitric oxide, LT = Leukotriene.

Regarding the immediate allergic response, the reactions observed in the ipsilateral nostril are increased nasal secretions (rhinorrhea), nasal blockage, and itching. Rhinorrhea and nasal obstruction are the main symptoms occurring on the contralateral side. This nasonasal reflex involves ipsilateral activation of sensory nerves and a bilateral parasympathetic reflex which can be reduced by atropine-like drugs[18,21,22].

Technique

Nasal endoscopy and patient preparation

Intranasal examination with an endoscope is the first necessary step to evaluate the pre-existing condition or pathology within the nose. Some conditions, such as nasal septal deviation, nasal polyp or atrophic rhinitis, could influence the nasal patency assessment before and after NPT. Patients, who have had recent surgery to the nose, should have NPT postponed for at least 8 weeks. To minimize the influence of nasal cycle or irritation in daily life, NPT should be performed at the same time, i.e., in the morning and at least 30 minutes after patients arrival, in order to be adapted to the temperature in the laboratory.

Allergen administration

Before challenging the nose by allergen extract, both nasal cavities should be examined to identify nonspecific anatomical variations of nasal patency caused by the nasal cycle[23]. Nonspecific nasal hyper-reactivity can also be investigated by challenging the nasal mucosa with isotonic saline sprayed into the wider side of the nose[7]. This should be done as a baseline challenge.

Allergens are available in various forms such as solution, powder or pollen grains. Such allergen can be administered into the nasal cavity by several methods i.e. pump spray, paper disc, atomizer, pipettes, or dropper. Important issues which have to be considered before delivering allergen are adverse effects, ease of instillation, amount of solution per delivery and distribution of mast cell in the nose. NPT can be performed unilaterally or bilaterally depending on the method of allergen administration. Unilateral challenge may be easier but bilateral challenge should give higher number of positive reactions. According to our current knowledge of nasal physiology, unilateral challenge should also provide relevant information regarding the intensity of the nasonasal reflex elicited in the contralateral side of the nose[18,23].

Impregnated paper discs could be used as a means to introduce allergen into the nose. They could be placed on particular sites, such as on anterior tip of the inferior turbinate or the anterior part of the middle meatus (agger nasi area). Okuda reported the greatest sensitivity in the

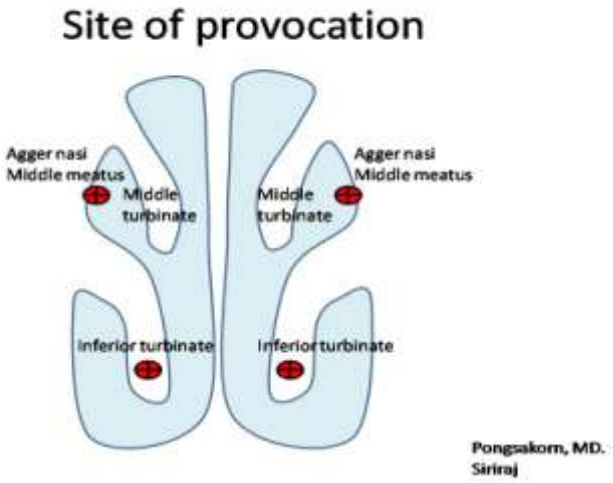

Figure 2. Intranasal area ⊕ used for provocation testing , i.e., anterior end of inferior turbinate, agger nasi and middle meatus.

agger nasi area when compared to the inferior turbinate or nasal septum[24]. However, due to the ease of placing discs on the inferior turbinate, this method is recommended by the author. On the other hand, physicians unfamiliar with forceps handling could make iatrogenic injury to the intranasal structures. Due to these shortcomings, some researchers prefer other delivery methods.

Bottle droppers and micropipette methods are easy to use delivery devices. Nonetheless, they may have some disadvantages since the area in the nose where the allergen has been applied is not seen. Moreover, allergen could be aspirated into the larynx, inducing cough, laryngeal irritation, edema or bronchospasm[18].

A better method of delivery could be by using hand-operated nasal spray. With the spray method, a reasonable contact area would be to the anterior part of nasal cavities. Because of ease of use and the predictability of the amount of allergen administered, most of research centers in Europe recommend this method as a standard delivery system[23]. Atomizers also generate larger particles which help avoiding aspiration of allergens into the lower airways.

Allergen dosage

Some investigators use titration doses but some use one single concentration of allergen for routine clinical NPT[7]. For titration NPT, the lowest allergen concentration should be started from 1:10,000 to 1:5,000 w/vol or 50 allergen unit (AU)/ml or 50-100 protein nitrogen unit (PNU)[7,25]. If the initial concentration does not induce any symptom or clinical signs, then the next concentration is increased by a 3-fold increment, e.g. 1:10,000, 1: 3,000, 1: 1,000[26].

It should be noted that such recommended doses have been applied to European subjects. According to a study by Roongapinun et al. performed in 44 Thai patients with perennial allergic rhinitis, significant changes in total nasal symptom score (TNSS) and nasal airway resistance (NAR) were observed at the concentration of500-1,000 AU/ml[27].

The dosage of allergen will also depend on the delivery technique. For the paper disc technique, Okuda used 3mm diameter disc soaked with 5-500 ug house dust extract[24]. Schumacher et al. used 4 mm disc with 10 µl dose[28]. We have modified the Okuda-paper disc method by using 5mm disc with a 0.01 ml dose[29]. For the atomizer-dosimeter, 0.1 ml of allergen per spray is used. The test solution is applied into the nose by pointing the device upwards and laterally to deposit allergen solution on the middle and inferior turbinates, while avoiding spraying directly to the back of the nose[7].

- ***Evaluation***

Four cardinal symptoms of allergic rhinitis are assessed before and after instillation of allergen extract into the nasal cavity. They are itching, sneezing, rhinorrhea and nasal obstruction.

Extranasal symptoms such as coughing and ophthalmic symptoms are also recorded. Symptoms are assessed subjectively by patients usually using a 4 point rating scale. Objective evaluations such as weighing nasal secretion, measuring nasal airflow and/or nasal airway resistance, or analysis of inflammatory mediators could also be employed.

Peak nasal inspiratory flow (PNIF) is a simple method to assess nasal airflow (Clement Clark, Harlow, UK) . The normal value of PNIF among 92 healthy Thai volunteers is 112.3 L/min. If the nasal airflow and nasal airway resistance (NAR) as measured by active anterior rhinomanometry (RMM) is used, pressure difference at 150 Pa is recommended as a reference pressure in Europe. However, in a study of Bunnag et al. including 130 healthy Thais, 75 Pa was recommended as a reference pressure difference since 13.79% of Thai subjects were not able to reach the pressure difference recommended in Europe(150 Pa) [30].

Nasal patency can be assessed by acoustic rhinometer (ARM) which provides a minimal cross-sectional area (MCA) of the nasal cavity and a calculated nasal volume (NV). Table 2 lists normal values for minimal cross sectional area and nasal volume among 135 healthy Thais [31].

Scoring system

NPT is considered positive if the nasal airflow decreases by more than 40% of the baseline value, regardless of the clinical symptom score. It is also considered positive if nasal airflow decreases by greater than 20% of the baseline value, combined with a symptom score greater than 3 [32] (Table 3). Another scoring system considers a change of NAR of 100% from baseline as a cut-off value[33]. Recently, the study of Chusakul et al. compared

Figure 3. Peak nasal inspiratory flow measurement (PNIF). (Picture used with subjected permission).

Table 2. Mean value of minimal cross sectional area (MCA) and nasal volume (NV) by acoustic rhinometer (ARM) in 135 healthy Thais[31].

	Before Decongestantion	***After Decongestantion***
MCA (cm2)	0.61 +/- 0.6	0.64 +/- 0.1
NV (cm3)	3.66 +/- 0.6	4.18 +/- 0.7

the cutoff value of symptom scores by visual analog scale (VAS) and PNIF after NPT to house dust mite extract. They demonstrated the superior diagnostic value of VAS change when compared with the change in PNIF[34].

Research applications of NPT

The outcome measurements fo NPT, as mentioned earlier, focus on the immediate allergic response, characterized by itching, sneezing, rhinorrhea and nasal blockage which is enable the investigator to identify the causative allergen(s). However, cellular inflammation, cytokines and neuro-hormones in the nasal secretions from the late phase nasal allergic reaction can also be studied[35,36]. Therefore, NPT can also be used to elucidate the patho-physiological mechanism of AR. Cellular changes after NPT can be assessed by nasal smear or scraping methods. Nasal secretions produced after NPT can be collected by blowing or nasal lavage techniques and further analyzed for plasma proteins, mediators and cytokines.

Clinical applications of NPT

NPT for diagnosis of AR or for determining the hyper-reactivity status of non-specific rhinitis is still much underused in clinical practice because of the time-consuming nature of the

Table 3. Scoring system of nasal provocation testing[32]

Symptom	***Severity***	***Score***
Rhinorrhea (judged by examiner)	No secretion	0
	Slightly increase	1
	Profuse	2
Sneezing	0-2 sneezes	0
	3-5 sneezes	1
	More than 5 sneezes	2
Extranasal symptoms	None	0
	Watery eyes	1
	Cough or urticaria	2

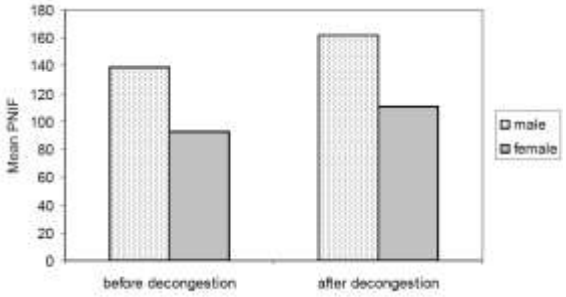

Figure 4. Bar graphs show mean value of peak nasal inspiratory flow (PNIF) before and after decongestion.

procedure and complexity of the methods for objective nasal airway assessment. From the above review, we think that the method of NPT could be simplified for easy use in clinical practice as follows:

- Administration by nasal spray with 0.125-0.15 ml per puff
- Challenge both sides of the nose
- Single dose challenge is preferred i.e. 50 or 100 AU of allergen extract
- Scoring system according to Table 3 and assess nasal airflow by PNIF change 20-40%

Conclusions

NPT is a useful method in diagnosis of allergic diseases and in determining the hyper-reactive status in non-specific rhinitis. Its indications, contraindications, technique, outcome measures and criteria for positive test results are reviewed. There are variations in challenge dosages, methods of allergen application, outcome measurements and criteria for a positive test and the normal values among different population. Due to such differences, it is currently difficult to compare results of NPT between different centers. For allergy research, there is an urgent need for an international consensus to overcome these variations in order to establish this test as a gold standard. Such consensus should contribute to more use of NPT as a diagnostic tool for chronic rhinitis. To maximize its use in clinical practice, the simplified method and the criteria suggested by this article may make it easier to utilize for diagnosis AR/NAR.

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