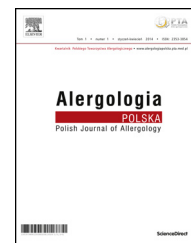


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Review/Praca poglądowa

Practical implications of nasal allergen provocation testing



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ABSTRACT

Due to its high sensitivity and specificity, nasal allergen challenge has a special place among differential diagnostic tests for allergic rhinitis. Such assessment of early and late phases of allergic reactions not only provides information on the local nasal mucosa response, but helps determine the degree of sensitivity to specific allergens as well.

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Introduction

Nasal allergen provocation testing (NAPT) plays a role in nasal allergy diagnostics due to its high sensitivity and specificity. Moreover, in case of significant discrepancies between the patient's history, skin prick test results, and/or sIgE levels, NAPT often has the decisive role in qualifying the patient for immune therapy (Fig. 1). Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines define allergic rhinitis as “the symptoms caused by immunologically mediated (most often IgE-dependent) inflammation after the exposure of the nasal mucous membranes to offending allergens. Symptoms of allergic rhinitis include rhinorrhea,

nasal obstruction or blockage, nasal itching, sneezing and postnasal drip that reverse spontaneously or after treatment.” [1].

Nasal allergen challenge

Allergen challenge produces an immediate response within the nasal mucosa. This involves mainly mast cell and macrophage activation. Coated with immunoglobulins, these cells stimulate the release of mediators, such as tryptase, histamine, CysLT, and PGD₂, which in turn activate sensory nerve and blood vessel receptors within the nasal mucosa [2, 3]. Moreover, mast cells release chemotactic

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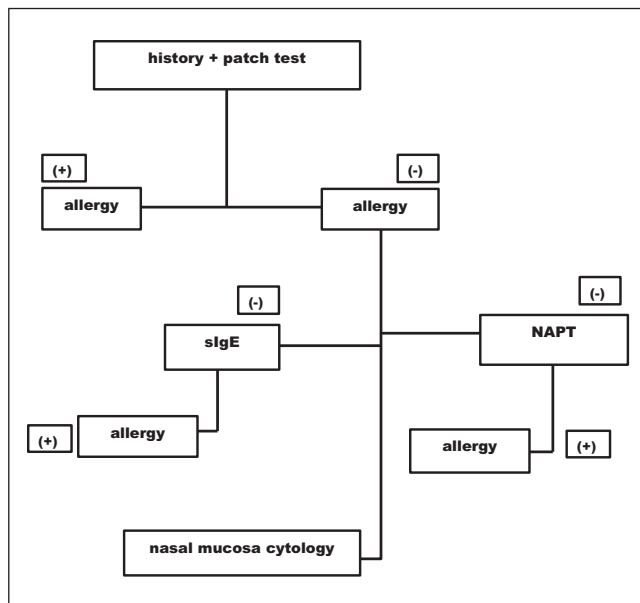


Fig. 1 – The protocol for allergic

agents and the platelet activating factor (PAF), which enhance the inflammation [3].

The early phase of an allergic reaction typically lasts up to 20–30 min and (in approximately 30–40% of subjects) may continue into the late phase, with an onset approximately

4 h after the initial nasal allergen challenge [4]. The early phase includes the following symptoms:

- itching within the first minute
- sneezing and increased production of serous secretion at 2–3 min
- swelling of nasal mucosa at approximately 10 min [2].

Following localized allergen challenge, nasal symptoms last usually up to 30 min, with their intensity depending on individual sensitivity and the extent of the allergic reaction. Despite generally being considered a relatively safe method, due to the potential NAPT-related side effects, this examination technique requires the allergy testing office to be equipped with an anti-anaphylaxis drug kit [5–7]. Kupczyk estimated the rate of NAPT-related side effects to be approximately one in several hundred tests [8].

The late phase of allergic reactions is characterized by the release of cytokines and chemokines into the blood-stream, which leads to the recruitment of eosinophils from the bone marrow and the secretion of eosinophil cationic protein (ECP) and major basic protein (MBP). The signs and symptoms of the late phase of allergic reactions are:

- nasal congestion
- sneezing
- nasal discharge [2, 4]

The International Committee on Objective Assessment of the Nasal Airways [9] and 2010 Polish Consensus on Standardization of Nasal Allergen Provocation Testing [2] guidelines include:

- Testing protocol (Fig. 2) – provocation testing is typically assessed via acoustic rhinometry, rhinomanometry, or

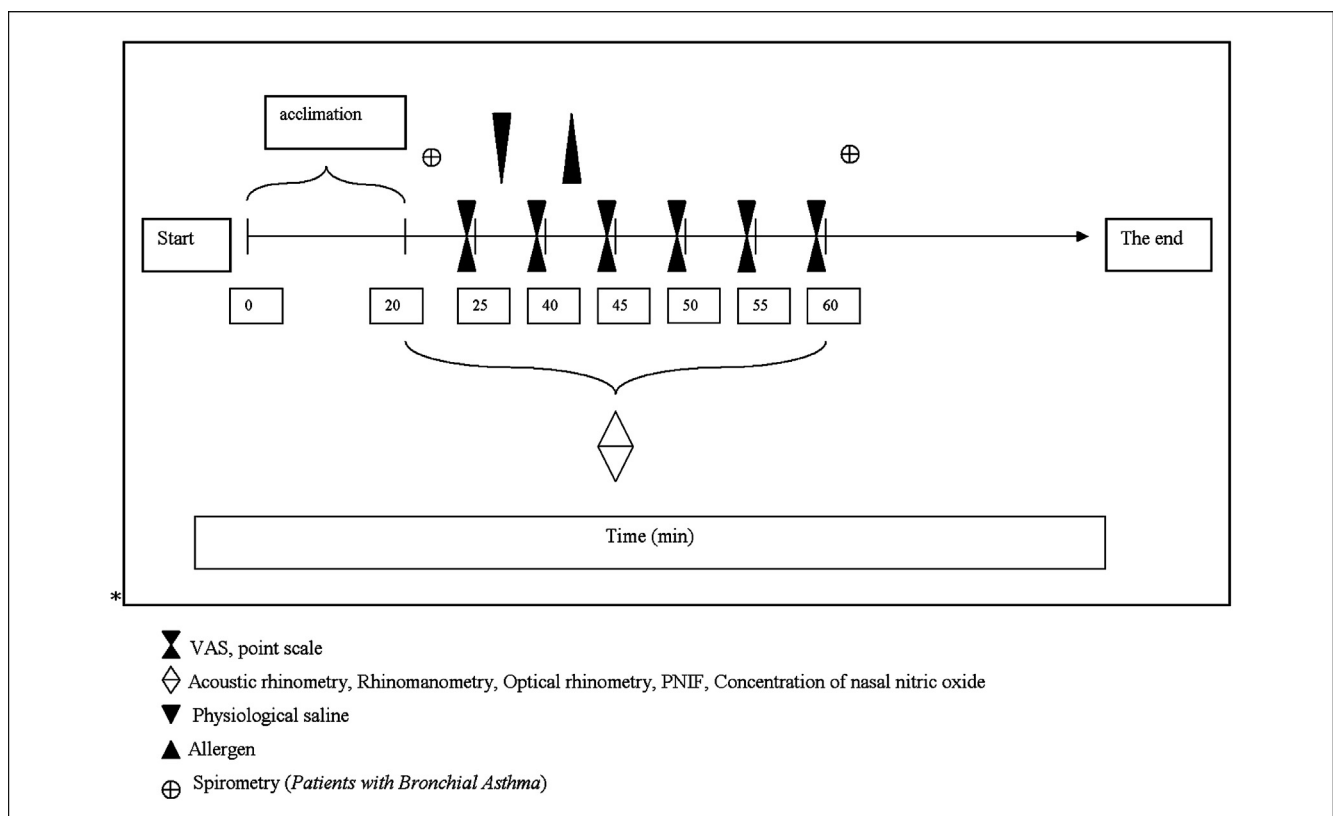


Fig. 2 – Testing protocol

Table I – Objective and subjective NAPT assessment techniques

Objective and Subjective Techniques	Principle	Positive NAPT result
Subjective Techniques		
Bachert's scale of symptoms	The measurement covers the following nasal symptoms: nasal discharge, sneezing, nasal patency, and the following non-nasal symptoms: eye watering, itching of the palate, conjunctivitis, nettle rash, cough, breathlessness	More than 4 points over the score obtained following saline administration
VAS	A 10-cm horizontal line is used to measure, in percentage terms, the values of nasal symptoms	More than 4 points over the score obtained following saline administration
Objective Techniques		
Anterior rhinoscopy	This method measures the level of swelling and the congestion of the mucous membrane of the nasal concha.	Observed swelling of the nasal mucosa
Acoustic rhinometry*	This is used to measure the nasal cavity by recording a picture of the cross-sections of the nasal cavity	A reduction of the transverse nasal cross-sectional area by 30% in comparison to that following saline administration [10]
Optical rhinometry*	(Emission spectroscopy) This method measures changes in blood flow through blood vessels and the oxygen saturation of hemoglobin	Infrared light extinction of optical density (OD) = 0.37–0.43 [11–13]
Rhinomanometry*	This measures the resistance of the air flowing through the nasal cavity by measuring the volume of air in a unit of time and the difference in pressure levels between the posterior nares and the anterior nares	An increase in respiratory tract resistance to airflow by at least 100% in comparison to that following saline administration [14]
PNIF*	In this method, the subject breathes in as much air as he or she can into a specially designed mask, with the mouth closed	A reduction by 40–50% in comparison to the baseline value following saline administration [15, 16]
The concentration of nitrogen oxide in the air exhaled from the upper airways*	The patient breathes out the air calmly against resistance (at least 10 cm H ₂ O) in accordance with the American Thoracic Society's principles	A reduction by 22.6–19.2% in comparison to the baseline value following saline administration [17, 18]
The concentration of reaction mediators in nasal lavage fluid	This method measures the levels of inflammation mediators, e.g. the concentration of eosinophil cationic protein ECP and Trypsinase	An increase by 14.5 mcg/L in comparison to the baseline value following saline administration [19]

peak nasal inspiratory flow (PNIF) measurement (Table I). Due to limited accessibility and standardization problems in the case of the two former techniques, the last one seems to be the most useful. A PNIF assessment involves several attempts (until repeatability is achieved) of a maximum, forced inhalation through the nose (with the mouth closed) into a mask connected with a flow meter calibrated in L/min. An attempt to establish PNIF reference values for the Polish population (also to establish a baseline for NAPT), which was part of the Epidemiology of Allergic Diseases in Poland (ECAP) study, demonstrated significant increase in PNIF values with age (Table II) [20]. The manifestations (edema of the nasal mucosa) measured via objective nasal occlusion assessment techniques require concomitant assessment of subjective techniques for measuring nasal and extra-nasal discomfort via the visual analog scale (VAS) or Bachert's point scale.

- The placebo/allergen solutions used – an NAPT kit consists of a saline solution with phenol (0.9% NaCl + 0.4% Phenol) and an allergenic extract (5000 BE/mL). Allergenic extracts are to be reconstituted with the phenol-containing saline solution from dry formulations of pH = 7 and subsequently applied with a metered atomizer at the volume of 0.2–0.05 mL to the head of the inferior turbinate. Due to their biological properties, NAPT kit formulations should be refrigerated both before and after their reconstitution in

the phenol-containing saline solution (maximum storage duration: 3 months of the reconstitution date).

- Unilateral or bilateral nasal provocation – a considerable majority of experts recommend a bilateral nasal challenge with simultaneous assessment on both sides. This preference is due to the phenomenon of physiological nasal cycle, which involves sympathetically mediated alternating changes in nasal passage patency (with a mean duration of approximately 2.5 h) [21]. Allergen solutions are to be administered intranasally, following a forced inhalation, to seated patients with their head tilted forward. The atomizer is to be directed laterally toward the alae nasi (septal application should be avoided).
- Patient preparation to NAPT in terms of a review of indications and contraindications, as well as drug discontinuation (Tables III–V) – following a nasal allergen challenge conducted in an outpatient setting, patients should be closely monitored for a minimum of 60 minutes and, in the event of a positive reaction to nasal allergen application, receive an antihistamine or a decongestant (e.g. 0.1% Xylometazoline).

As mentioned above, NAPT-related side effects occur in a small percentage of patients only and may include:

- nasopharyngeal pruritus and edema,
- Eustachian tube occlusion,
- sinusitis,

Table II – Mean PNIF values in the study population

Study criteria	Females N = 9956			Males N = 8560		
	Mean L/min	Median	Min-max	Mean L/min	Median	Min-max
6–7 y.o.	91.84	90.0	40–300	92.3	90.0	51–290
13–14 y.o.	93.19	82.5	60–300	93.98	80.0	59–300
20–44 y.o.	94.17	80.0	64–300	94.28	93.98	66–350
Body weight of 6–7 y.o.						
20–30 kg	58.68	60.0	33–150	51.61	50.0	39–140
Body weight of 13–14 y.o.						
40–50 kg	98.68	90	30–170	91.67	90	30–220
Body weight of 20–44 y.o.						
50–60 kg	96.87	90	60–280	105.7	100	66–300
60–70 kg	111.3	110	61–270	116.7	100	70–320
70–80 kg	125.3	120	70–290	117	100	73–350
80–90 kg	129.9	120	70–300	107.9	100	78–290
Height of 6–7 y.o.						
100–120 cm	52.65	50	37–100	50	50	30–100
Height of 13–14 y.o.						
140–150 cm	65.0	65.0	50–80	85.38	80	50–140
150–160 cm	101.6	100	59–200	101.2	90	62–220
Height of 20–44 y.o.						
160–170 cm	105.7	100	50–300	97.84	90	40–250
170–180 cm	114.5	110	66–330	122.2	120	79–300
180–190 cm	129.4	130	50–310	119.7	110	70–230

Table III – Preparation for NAPT [21]

Drugs	Discontinue for preparation
glucocorticoids	8 days
nasal glucocorticoids	2–4 weeks
cromones	3–5 days
Ketotifen	7 days
first-generation antihistamines	2–4 days
second-generation antihistamines except astemizole	4–7 days
astemizole	6 weeks
anti-leukotrienes	2–4 days
theophylline-retard	2 days
α-sympathomimetics	1 day
β-sympathomimetics	12 h
anticholinergics	2–3 days
NSAIDs	7 days
hypotensives (Rauvolfia, clonidine, alpha-methyldopa and tricyclic antidepressants)	3 weeks

Table IV – Contraindications to NAPT [21]

Absolute contraindications	Relative contraindications
An acute anaphylactic reaction to the tested allergen in another organ	Allergic or infectious rhinitis exacerbation 2–4 weeks prior to the scheduled test
Acute rhinitis, acute sinusitis	The period of 6–8 weeks after the pollen season in patients with suspected seasonal allergic rhinitis
Exacerbated allergic rhinitis or exacerbated bronchial asthma	History of nasal or sinus surgery during previous 6–8 weeks Polyps, atrophic rhinitis, deviated nasal septum Unstable asthma Taking drugs that inhibit the nasal mucosa reaction to an allergen The period of 6 weeks following the administration of intranasal vaccine containing live viruses

- conjunctivitis,
- laryngeal signs and symptoms,
- bronchospasm,
- generalized anaphylactic reaction (urticaria or anaphylactic shock),
- nasal and bronchial late-phase allergic reaction [7].

A nasal allergen challenge produces a bronchial response; and, conversely, allergen application into the bronchial tree triggers a local response in the nasal mucosa. This is a result of a common response mechanism for the respiratory system. The phenomenon of bronchial hyper-sensitivity in response to NAPT was observed in one third of

the study population without evidence of bronchial asthma [102]. A much more common finding is a reduction in forced expiratory volume in 1 second (FEV1) in the group with concomitant asthma. The late-phase allergic reaction is characterized by: (1) the spread of inflammation from the upper to lower respiratory tract, for example via gravitational flow into the bronchi of nasal discharge rich in cells that play a role in allergic rhinitis; (2) IgE released at the site of allergen application; (3) elevated IL-5 that is transported to the pulmonary circulation, which increases nitrogen oxide concentration in the exhaled air and (4) bronchial hyperresponsiveness [23].

Table V – Indications for NAPT [22]

Diagnostic indications	Pathophysiological indications	Pharmacological indications
Suspected allergic rhinitis	Investigation of allergic-inflammatory reaction mechanisms in the respiratory tract	Investigation of mechanism of action and effectiveness of various drugs affecting the course of allergic-inflammatory reactions in the nasal mucosa
Difficulty in identifying the causative allergen in patients with allergic rhinitis	Investigation of non-specific hyperreactivity of the upper and lower respiratory tract	Assessment of the effectiveness of various allergen immunotherapies
Difficulty in identifying the causative allergen in patients with bronchial asthma		
Suspected respiratory tract hypersensitivity to aspirin and NSAIDs		
Identification of the agent responsible for occupational allergy		

Conclusion

NAPT should be the golden standard in the differential diagnostics of allergic rhinitis along with skin prick tests, sIgE levels or lung function tests, as it helps monitor the body's response in natural conditions. However, it is worth remembering that conducting consecutive allergen provocation tests without a minimum 7-day interval may result in over-sensitization of the nasal mucosal epithelium and lead to false-positive results.

Authors' contributions/Wkład autorów

EK-F – study design, data collection and interpretation, literature search. AN – study design, literature search. AS – study design, data interpretation. BP – literature search. BS – study design, acceptance of final manuscript version.

Conflict of interest/Konflikt interesu

None declared.

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None declared.

Ethics/Etyka

The work described in this article have been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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