Nasal Hyperreactivity: Nonspecific Nasal Provocation Tests. Review by the Rhinoconjunctivitis Committee of the Spanish Society of Allergy and Clinical Immunology

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Abstract

Nasal hyperreactivity is the abnormal reaction of nasal tissue to a stimulus that is innocuous to most people. This response is caused by dysregulation of the autonomic nervous system at various levels of the nasal autonomic reflex arc. Various stimuli (methacholine, histamine, adenosine 5´-monophosphate, cold air, mannitol, capsaicin, phentolamine, and distilled water) have been used in an attempt to find the test that most reliably differentiates between healthy individuals and patients and also between different types of rhinitis. Despite the small number of publications available, in the present review, we provide an update on current nonspecific nasal provocation techniques. The studies published to date are not comparable: the stimuli applied act through different mechanisms and are used to assess different pathways, and the methodologies differ in terms of selection of participants, concentrations used, and assessment of response (criteria for positivity). Given the limited use of nonspecific nasal provocation tests in routine clinical practice, we believe that more studies are warranted to address the research issues we present at the end of the present review, for example, the need to standardize the methodology for each test or even the clinical benefits of knowing whether or not a patient has nasal hyperreactivity.

Key words: Nasal provocation. Nasal hyperreactivity. Rhinitis. Methacholine. AMP. Histamine. Mannitol. Cold air.

Resumen

La hiperreactividad nasal es la reacción anormal del tejido nasal frente a un estímulo inocuo en la mayoría de las personas. La respuesta nasal es un mecanismo de defensa fisiológico que puede verse híper-regulado cuando existe inflamación, como en la rinitis alérgica, pero también en ausencia de ésta. Mecanismos inmunes inflamatorios y neurogénicos se interrelacionan generando cambios inflamatorios y diferentes tipos clínicos. Metacolina, histamina, manitol, AMP, capsaicina, fentolamina así como aire frío o agua destilada, se han usado para medir la hiperreactividad nasal. Los estudios publicados hasta la fecha no son comparables; difieren en la selección de pacientes, las concentraciones usadas para la provocación y la valoración de la respuesta en cuanto a métodos y criterios de positividad. La falta de estandarización de estas pruebas, y la dificultad que han mostrado en discriminar entre sujetos con rinitis de sujetos sanos, y entre los diferentes tipos de rinitis, hacen escasa su utilidad en la práctica clínica diaria y actualmente su uso está limitado al campo de la investigación. En esta revisión hacemos una puesta al día de las técnicas de provocación nasal no específica de que disponemos en la actualidad.

Palabras clave: Provocación nasal. Hiperreactividad nasal. Rinitis. Metacolina. AMP. Histamina. Manitol. Aire frío.

Introduction

A healthy nasal response is part of homeostatic and defense functions against physical and/or chemical stimuli. Through a complex network, the sympathetic nervous system, parasympathetic nervous system, and C nerve fibers transmit signals of nasal mucosal sensations such as itching or sneezing and motor reflexes that cause changes in glandular and vascular systems.

In a consensus article about nonspecific nasal provocation published in 2007, the EAACI-GA^{2}LEN group [1] defined nasal hyperreactivity as the abnormal reaction of nasal tissue to a stimulus that is innocuous to most people. The authors stated that this response is caused by dysregulation of the autonomic nervous system at various levels of the nasal autonomic reflex arc.

The first studies demonstrating the existence of nasal hyperreactivity were published in the 1960s. Connell [2] described the priming effect, demonstrating that repeated exposure to ragweed pollen increased the sensitivity of the histamine response.

Such an abnormal response is common to all types of rhinitis, although its pathogenesis remains unclear. The many mechanisms involved include increased permeability of the mucous membrane, increased excitability of trigeminal afferent fibers, changes in the central control of the reflex arc, and an inflammatory mechanism involving mast cells, eosinophils, and neutrophils with a lower activation threshold [1,3]. In allergic rhinitis (AR), where the inflammatory mechanism is predominant, and in idiopathic noninfectious nonallergic rhinitis, there is evidence of mucosal hyperinnervation with overexpression of neuropeptides in periglandular nerve fibers (calcitonin gene–related peptide and substance P). Inflammatory mediators in turn activate afferent nerve fibers, leading to the release of neutrophins (nerve growth factor, brain-derived growth factor), neuropeptides (calcitonin gene–related peptide, substance P), and neurokinins A and B, all of which exert an immunomodulatory effect on eosinophils and mast cells. These neurogenic and inflammatory immune mechanisms interact to generate inflammatory changes and various clinical profiles. It is unknown which of these prevails and how they overlap in each type of rhinitis [4-6].

Inflammation and hyperreactivity are characteristic of AR, and it seems that both are so closely related that the greater the inflammation, the higher the degree of nasal reactivity. This possibility is considered in the studies of Terada et al [7,8] and Gerth et al [9], who suggest that inflammation induced by a single nasal provocation with allergen can generate an increased response to histamine and that this is proportional to the degree of inflammation, since patients presenting a dual response have a more pronounced response to histamine than those who only have an immediate response [10,11]. The findings of other studies, however, contradict this observation [12].

Measurement of nasal hyperreactivity involves the use of various stimuli to find the test that differentiates most reliably (in terms of sensitivity, specificity, and reproducibility)

between healthy individuals and patients and between different types of rhinitis. These stimuli can act directly on cell receptors in the nasal mucosa or indirectly by releasing inflammatory mediators.

The aim of this literature review is to perform an update on the different techniques used in the evaluation of nonspecific nasal hyperreactivity. Therefore, we performed a literature search in scientific databases with the following key words: *Non-specific Nasal Provocation Test, Nasal Challenge Test, Nasal Hyperreactivity, Methacholine, AMP, Histamine, Mannitol, Capsaicin*, and *Cold dry air*.

As the number of publications found was low, we included all papers regardless of the date of publication.

Nonspecific Nasal Provocation Testing With Direct Stimuli (Tables 1A and 2A)

Histamine

Histamine acts directly on the mucosal receptors by activating neuroreflexive mechanisms through the trigeminal vascular and glandular pathways. It is the most potent mediator and produces vasodilatation and nasal secretion leading to edema and congestion.

Histamine has an irritant effect that universally causes dose-dependent positive responses. High concentrations also cause systemic effects such as hypertension, flushing, headache, and tachycardia. In general, allergic individuals have a more intense response than controls, with overlapping values between groups and with no concentration or cut-off able to distinguish between patients with rhinitis and controls.

According to the EAACI-GA^{2}LEN [1], the test involves the administration of histamine in an aqueous solution (1-2 mg/mL), although the methodology used in published studies varies considerably.

Hilberg et al [13] used acoustic rhinometry to compare the response to histamine and pollen extract in pollen-allergic patients and controls. The authors performed bilateral provocations with nebulized histamine (0.1, 1, and 10%) and histamine 10% on filter paper applied to the inferior turbinate. They found that patients with AR have increased sensitivity to histamine 0.1% and show a prolonged response. For the remaining concentrations, the results did not differ significantly between the groups.

Wuestenberg et al [14] unilaterally applied different concentrations of histamine in patients with AR, patients with vasomotor rhinitis, and a group of healthy controls. They administered increasing double concentrations (0.25 to 16 mg/mL) and measured the response using a symptom score and anterior rhinomanometry. Although the response was dose-dependent, the concentration of 1 mg/mL appeared to discriminate better between patients with rhinitis and healthy controls (100% sensitivity and 83% specificity). No differences were detected between patients with AR and patients with vasomotor rhinitis. The authors suggested that unilateral provocation would be valid and more comfortable for the patient.

Kölbeck et al [15] performed a provocation test with histamine in patients with AR to pollens and measured the response using rhinosterometry. By administering concentrations of between 0.13 mg/mL and 8 mg/mL, they determined that nasal mucosa can be considered hyperreactive when there is a 0.4-mm increase in edema 5 minutes after application of the 2-mg/mL concentration. Using this measure as the cut-off, the authors considered it would be possible to differentiate healthy individuals from those with rhinitis with a specificity of 80%.

Table 1A. Nonspecific Nasal Provocation Tests With Direct Stimuli

	Methodology	Mechanism	Advantages	Disadvantages
Histamine	Aqueous solution at several concentrations Measurement of obstruction (VAS/AR/ARM)	Activation of neuroreflexive mechanisms via trigeminal, vascular, and glandular pathways Induces nasal obstruction and secretion Activation of nerve endings (sneezing, itching)	Good indicator of vasomotor reflex response	Nonstandardized technique Dose-dependent irritative response Difficult to discriminate between hyperreactive and healthy individuals Does not discriminate between allergic and nonallergic rhinitis Risk of systemic reactions at high doses
Methacholine	Administration of increasing doses of methacholine (0.0038-48 mg/mL) Measurement of secretions and/or obstruction (AR and PRM)	Interaction with cholinergic receptors in glandular tissue Increased secretion with minimal obstruction	Good indicator of mucosal reactivity No tachyphylaxis No contralateral secretion reflex	Nonstandardized technique Does not reflect changes in nasal resistance Difficult to discriminate between hyperreactive and healthy individuals Does not discriminate between allergic and nonallergic rhinitis

Table 1B. Nonspecific Nasal Provocation Tests With Indirect Stimuli

	Methodology	Mechanism	Advantages	Disadvantages
AMP	Variable concentrations: - Serial dilutions of 25-800 mg/mL - Single dose of 6.5-320 mg	Stimulation of mast cell A2b receptors: release of mediator	Safe, sensitive, and reproducible technique Good correlation with the specific challenge Sufficiently sensitive to evaluate the effectiveness of various treatments	Nonstandardized technique Does not replace allergen-specific provocation
Cold air	Nasal inhalation of cold dry air (0-5°C and relative humidity <10%) for 15 minutes at flow of 26 L/min Nasal instillation of drops of cold water at 0-5°C Assessment by ARM, AR, and VAS	Change in the osmolarity of the mucous membrane (water evaporation)	Easy to perform Useful in studies of nasal physiology Good tolerance in general	Low specificity and sensitivity Little clinical utility
Mannitol	Mannitol solution 200 mg/mL	Hyperosmolar stimulus that leads to release of epithelial cell mediators	Simplicity	Induces burning in both healthy individuals and patients with rhinitis
Distilled water	Nebulizing hypotonic distilled water for 30-60 s Change in volume with AR or ARM	Dilution of luminal epithelial surface and creation of a transepithelial gradient with mediator release	Total absence of side effects Does not require patient cooperation (even in children <5 years) Detects nasal hyperreactivity in early stages	Does not discriminate between allergic and nonallergic rhinitis
Phentolamine	Spray instillation of 0.2 mg per nostril Assessment by ARM	Powerful alfa-blocker that blocks the autonomic regulation of the vascular bed in rhinopathy	Produces significant increase in nasal resistance in allergic patients	Poor diagnostic value Induces nasal reactivity only in the late phase of the nasal disease when the ANS is compromised
Capsaicin	Application of capsaicin nasal drops Measurement using VAS/ARM	Direct stimulation of unmyelinated C nerve fibers and release of neuropeptides: increase in vascular permeability and mucus secretion	Can distinguish between patients with nasal hyperreactivity and healthy controls	Nonstandardized technique Difficult to perform Nonspecific Hardly reproducible

Abbreviations: AMP, adenosine 5'-monophosphate; ANS, autonomic nervous system; AR, acoustic rhinometry; ARM, anterior rhinomanometry; PRM, posterior rhinomanometry; VAS, visual analog scale.

Table 2A. Summary of Studies With Direct Stimuli

Study	Discriminates Rhinitis/ Healthy	Methodology/Design	Results	Discriminates Between Rhinitis Types
Histamine				
Hilberg et al, 1995 [13]	Yes	AR pollen/controls 0.1, 1, 10% bilateral Acoustic rhinometry and VAS	Concentration 0.1% greater response in AR vs controls $P<.05$	–
Wustenberg et al, 2004 [14]	Yes	AR/NAR/controls 0.25-16 mg/mL, unilateral PARM and symptoms	Concentration 1 mg/mL S 100%, Sp 83%	No
Kolbeck et al, 1999 [15]	Yes	AR and controls 0.13-8 mg/mL, bilateral Rhinosterometry	2 mg/mL differentiates AR from controls with Sp 80%	–
Giannico et al, 1996 [16]	Yes	Children chronic AR due to mites/ controls 0.3-4 mg/mL, bilateral AARM	0.5 mg/mL discriminates with S 91%, PPV 80.8% More sensitive than methacholine	–
Wandalsen et al, 2010 [22]	Yes	Children and adolescents with AR and controls 0.15-8 mg/mL, bilateral AARM, acoustic rhinometry, and symptoms	AR greater NHR than controls AARM $P<.01$, and reduction of volume from 0 to 5 cm^3 in AR $P<.04$	–
McLean et al, 1977 [17]	No	Atopic subjects with/without rhinitis vs nonatopic 0.0001-1 mg/mL PARM	Similar nasal response in the 3 groups	No
Simola and Malmberg, 2000 [19]	No	AR 0.025-1.6%, bilateral AARM and symptoms	Weak positive correlation between histamine and allergy status	–
Methacholine				
Márquez et al, 2000 [25]	Yes	AR pollen/NAR/controls 0.5-16 mg/mL, bilateral Acoustic rhinometry	Reduction ≥20% volume at 2 mg/mL predicts rhinitis to 75% S 83%, Sp 92%, PPV 93.7%, NPV 79.3%	Does not differentiate AR/ NAR
Borum 1979 [23]	No	Perennial AR/NAR and controls 3-48 mg/0.4 mL Bilateral PARM, symptoms, and secretions	No changes in nasal resistance. Increased secretion in perennial NAR vs controls $P<.001$	–
McLean et al, 1977 [17]	No	Atopic patients with/without rhinitis vs nonatopic 1-27 mg/mL PARM	Similar nasal response in the 3 groups	No
Giannico et al, 1996 [16]	No	Children AR mites/control 0.025-10 mg/mL, bilateral AARM	S 55%, PPV 75% Less sensitive than histamine	–

Table 2B. Summary of Studies With Indirect Stimuli

Study	Discriminates Rhinitis/ Healthy	Methodology/Design	Results	Discriminates Between Rhinitis Types
Mannitol				
Koskela et al, 2000 [54]	Yes	AR with or without symptoms/ controls 200 mg/mL, bilateral NPIF, symptoms and levels of tryptase, α2 macroglobulin, substance P, 15-HETE	PNIF and symptoms: Reduction in symptomatic AR No variations in asymptomatic AR and controls Elevated 15-HETE in AR $P<.0006$	Yes Symptomatic/ asymptomatic AR
Cold air				
Kim et al, 2010 [45]	Yes	AR/NAR and controls Cold air 0º and <10% humidity, bilateral Acoustic rhinometry/VAS/weight of secretions	More rhinorrhea and reduction in volume and minimal cross-sectional area in AR/NAR than in controls $P<0.01$	Yes Differentiates rhinitis with /without symptoms of NHR
Braat et al, 1998 [53]	Yes	NANIR and controls Cold air –10ºC and <10% humidity Compared with histamine ARM and weight of secretions	Detects NHR in NANIR S 87% and Sp 71% Discriminates better than histamine (S 100%, Sp 0%)	–
Shusterman and Tilles, 2009 [44]	Yes	NANIR with symptoms of NHR after physical or chemical stimuli and controls Cold air 0ºC and 5% humidity, bilateral PARM and symptoms	Increased nasal resistance in NANIR by physical stimuli vs controls $P<.05$	Does not differentiate NANIR from NHR after physical or chemical stimuli
Van Gerven, 2012 [46]	Yes	Idiopathic rhinitis vs controls Cold air –10ºC, <10% humidity bilateral, 15 minutes Symptoms, PNIF	Obstruction only in rhinitis S 66.7% and Sp 100%	No
Distilled water				
EAACI-GAL²EN, 2007 [1]	Yes	Nebulizing hypotonic distilled water 30-60 s, bilateral Acoustic rhinometry or AARM	–	No (does not differentiate NNHR/SNHR)
Phentolamine				
EAACI-GAL²EN, 2007 [1]	Yes	0.2 mg bilateral	Variation nasal resistance only late stages with autonomic nervous system involvement	No
Capsaicin				
Stjarne et al, 1989 [57]	Yes	VMR/VMR with predominant rhinorrhea and controls Capsaicin $3.3x10^{-3}$ M in 70% ethanol and saline, unilateral Secretions	Greater secretion in VMR with secretion than in VMR and controls	Yes Vasomotor rhinitis with/without rhinorrhea as the predominant symptom

Abbreviations: AARM, active anterior rhinomanometry; APRM, active posterior rhinomanometry; AR, allergic rhinitis; NANIR, nonallergic noninfectious rhinitis; NAR, nonallergic rhinitis; NHR, nasal hyperreactivity; NNHR, nonspecific nasal hyperreactivity; NPV, negative predictive value; PARM, passive anterior rhinomanometry; PNIF, peak nasal inspiratory flow; PPV, positive predictive value; S, sensitivity; SNHR, specific nasal hyperreactivity; Sp, specificity; VAS, visual analog scale; VMR, vasomotor rhinitis; 15-HETE, 15-hydroxyeicosatetraenoic acid.

Giannico et al [16] compared hyperresponsiveness measured by histamine and methacholine in a group of children and young adults with mite AR and controls using histamine concentrations of 0.03 mg/mL to 4 mg/mL and applying drops bilaterally. They measured the response with anterior rhinomanometry and concluded that histamine at 0.5 mg/mL achieved positive responses in 82.6% of patients with rhinitis, compared with 45.5% of the healthy controls. This gave the test a sensitivity of 91% with a positive predictive value of 80.8%, which is higher than that obtained with methacholine (sensitivity of 55% and positive predictive value of 75%), leading to the conclusion that histamine is more appropriate for differentiation between children with AR and healthy controls.

Other authors, however, did not consider this technique useful for differentiating between patients with rhinitis and healthy controls [17,18]. In addition, there is no association between the result of the histamine challenge and the patient's allergic state measured with skin testing or allergen challenge [19].

Nasal hyperreactivity measured with histamine is reduced when the patient is treated with antihistamines [13,20] or nasal corticosteroids [21,22] (Table 3A).

Key Points

Histamine challenge is subject to limitations.

The nasal mucosa responds to histamine in a dose-dependent manner. Although this response seems more pronounced in patients with rhinitis than in healthy controls, values overlap between groups.

A cut-off or histamine concentration capable of differentiating between patients and controls has not yet been established, and no study has shown that this test can differentiate between the different types of rhinitis.

Methacholine

Methacholine is a synthetic analog of acetylcholine. It acts primarily on cholinergic receptors at the glandular level, thereby producing hypersecretion and nasal obstruction.

According to the methodology described by EAACI-GA²LEN [1], the technique consists of administering increasing double doses of methacholine from 7.5 mg/mL to 120 mg/mL and measuring the secretions collected on tissue paper every 15 minutes.

Borum et al [23] published a study in patients with perennial rhinitis who were challenged with increasing concentrations of nebulized methacholine (3 mg/mL to 48 mg/mL). Although posterior rhinomanometry revealed no changes in nasal resistance, the changes observed in the amount of the secretion led the authors to conclude that this would be a more reproducible and useful parameter. Pretreatment with anticholinergics such as ipratropium bromide reduced the response, whereas lidocaine did not modify it (Table 3A).

Naclerio and Baroody [24] compared provocations with methacholine and histamine in a group of patients with perennial rhinitis. They placed filter paper discs on the middle turbinate with methacholine and histamine at varying concentrations, using measurement of nasal secretion as an outcome variable. Both substances increased nasal secretion in a dose-dependent manner, although methacholine did not cause tachyphylaxis or reflex contralateral secretion, unlike histamine. This reflex histaminergic response could be caused by a parasympathetic mechanism that is inhibited by anticholinergics such as atropine and ipratropium bromide.

Conversely, other studies revealed changes in nasal resistance after methacholine challenge. Márquez et al [25] compared the nasal response to several concentrations of nebulized methacholine (0.5 mg/mL to 16 mg/mL) in 3 groups: nonatopic healthy individuals, patients with AR due to pollens, and patients with nonallergic rhinitis (vasomotor rhinitis and nonallergic rhinitis with eosinophilia). Although they obtained a dose-dependent response in all cases, this was higher in patients with rhinitis than in the controls ($P<.01$). There were no differences between the 2 groups of patients with rhinitis. Using a receiver operating characteristic curve analysis, the authors suggested that 2 mg/mL could be the cutoff concentration that would differentiate between individuals with rhinitis and controls (sensitivity, 83%; specificity, 92%; positive predictive value, 93.7%; negative predictive value, 79.3%).

Table 3A. Action of Drugs in Nonspecific Nasal Provocation Tests With Direct Stimuli

	Histamine	Methacholine
Antihistamines		
Topical azatadine	↓ Togias et al, 1987 [20]	
Cetirizine	↓ Hilberg et al, 1995 [13]	
Topical corticosteroids		
Mometasone	↓ Wandalsen et al, 2010 [22] and Wilson et al, 2003 [21]	
Anticholinergics		
Ipratropium bromide		↓ Márquez et al, 2000 [25] and Borum 1979 [23]
Local anesthetic		
Lidocaine		= Borum 1979 [23]

Abbreviations: ↓, reduces response; =, no changes.

Key Points

The methacholine test is not standardized in terms of concentrations or assessment methods. It seems to have the same limitations as histamine challenge for differentiating between patients with rhinitis and healthy controls. Similarly, it cannot distinguish between different types of rhinitis.

Nonspecific Nasal Provocation Testing With Indirect Stimuli (Tables 1B and 2B)

Adenosine 5'-Monophosphate

Adenosine is a nucleotide that is generated naturally from intracellular adenosine 5'-monophosphate (AMP) after the action of 5'-nucleotidase. Its levels are increased in inflamed tissue. AMP has a clear role in the pathogenesis of asthma and AR, and increased levels have been detected in asthmatic patients. Previous studies have shown that inhaled adenosine causes bronchoconstriction in asthmatic patients and in patients with AR, although it does not cause changes in healthy individuals [26].

AMP acts by stimulating mast cell A2b receptors and inducing the release of inflammatory mediators such as histamine, cysteine leukotrienes, prostaglandins, and interleukins (IL-8). The response to AMP intensifies in cases of allergic inflammation, possibly owing to an increase in the number of activated mast cells.

The methodology of nasal challenge with AMP varies across published studies, and provocations based on both serial dilutions and single doses have been used.

Provocation with AMP induces more symptoms and increased tissue histamine in patients with rhinitis than in healthy controls. Polosa et al [27] reported this finding after nasal provocation with a single dose of AMP (6.5 mg). Delivery of 1 spray per nostril (50 mg/mL of solution) led to a significant increase in histamine levels in nasal lavage after 3 minutes in allergic patients. Levels remained unchanged in healthy controls.

AMP appears to be a more sensitive marker of inflammation than histamine. It can detect residual inflammation in asymptomatic pollen-allergic individuals outside the pollen season, as reported by Vaidyanathan et al [28] in a study measuring the response to AMP and histamine before, during, and after the pollen season in patients with pollen AR. The authors used AMP concentrations of between 25 mg/mL and 800 mg/mL and histamine concentrations of between 0.25 mg/mL and 8 mg/mL and measured the response

Table 3B. Action of Drugs in Nonspecific Nasal Provocation Tests With Indirect Stimuli

	AMP	Mannitol	Capsaicin	Cold
Antihistamines				
Fexofenadine	↓ Lee et al, 2004 [31]			
Fexofenadine, desloratadine, levocetirizine	↓ Lee et al, 2004 [29]			
Levocetirizine	↓ Vaidyanathan et al, 2009 [30]			
Desloratadine		↓ Lee et al, 2003 [55]		
Topical azatadine				= Togias et al, 1987 [20]
Topical corticosteroids				
Mometasone	↓ Barnes et al, 2006 [33] and Wilson et al, 2003 [32]			
Fluticasone	↓ Lipworth et al, 2012 [38] and Barnes et al, 2007 [34]			
Beclomethasone				= Cruz et al, 1991 [52]
Antileukotrienes				
Montelukast	↓Lee et al, 2004 [31]	↓Lee et al, 2003 [55]		
Anticholinergics				
Ipratropium bromide			↓ Stjarne et al, 1989 [57]	↓ Assanasen et al, 2000 [39]
Atropine				↓ Jankowski et al, 1993 [43]
Beta-agonists				
Salmeterol	↓ Lipworth et al, 2012 [38]			
Salbutamol	↓ Russo et al, 2005 [37]			
Petasites hybridus	↓ Lee et al, 2003 [35]			
Inhaled heparin	↓ Zeng et al, 2004 [36]			
Local anesthetic				
Lidocaine			= Stjarne et al, 1989 [57]	
Lidocaine + naphazoline			↓ Stjarne et al, 1989 [57]	

Abbreviations: ↓, Reduced response; =, No change

by peak nasal inspiratory flow (PNIF) and active anterior rhinomanometry. They also calculated the dose required to produce a 30% drop in PNIF (PC_{30}) and 60% in resistance (PC_{60} of active anterior rhinomanometry) and measured the recovery curve 60 minutes after provocation. Patients kept a symptom diary and monitored PNIF values at home. Provocation with AMP during the pollen season led to a reduction in PC_{30} and PC_{60} values compared to preseasonal values, although this was not the case with histamine, indicating that AMP could be a more sensitive marker of inflammation. After the pollen season, provocation with AMP continued to generate an abnormal curve, indicating residual hyperreactivity and, indirectly, inflammation, even when the patient was clinically asymptomatic. These findings point to mast cell memory or a priming effect and indicate that other arachidonic acid–derived mediators such as leukotrienes or other T_H2 cytokines may be involved.

The AMP test showed high sensitivity when used in studies assessing the efficacy of antihistamines [29,30,31], topical corticosteroids [32,33,34], herbs such as *Petasites hybridus* (butterbur) [35], leukotrienes [31], heparin [36], and $ß_2$ agonists [37,38] (Table 3B).

Key Points

Nasal provocation with AMP appears to be a more sensitive marker of inflammation than methods based on histamine or methacholine.

Nasal provocation with AMP is a safe, sensitive, and reproducible test, although it is not yet standardized. Studies differ in terms of the concentrations used and the application methods.

Cold Air

Cold air rhinitis is characterized by rhinorrhea, nasal congestion, and burning sensation on exposure to cold air. It can affect individuals with and without underlying rhinitis, in which case only cold air is the trigger of symptoms.

One of the main functions of the nose is to warm and humidify the air we breathe, a process in which the mucosa loses heat and water.

Vasoconstrictors reduce the temperature of the nasal mucosa, and locally applied anticholinergic agents such as ipratropium bromide enhance the ability of the anticholinergic agents to humidify and heat the air, even though they reduce the secretory response after challenge with cold air [39].

Activation of the sympathetic nervous system by processes such as cholinergic stimulation and inflammation may increase the secretion of chloride and water into the airway. Assanasen et al [40] reported that in patients with AR, the mucosa was much more able to produce water 24 hours after allergen challenge and that this ability decreased if a topical corticosteroid was administered 2 weeks earlier.

The possible association between nasal response to cold and asthma is interesting. Hanes et al [41] reported that the response to cold was more marked in patients with asthma and rhinitis than in those with only rhinitis. Kauffman et al [42] reported that the nasal response to cold was a risk factor for reduced FEV_1, suggesting that this defect in the conditioning of the nasal mucosa might be involved in the pathogenesis of asthma.

According to the methodology described by EAACI-GA^{2}LEN [1], nasal provocation with cold air is performed by instilling drops of cold water (0°C-5°C) in the nose or by breathing or administering cold, dry air through a spray (0°C-5°C) at a flow of 26 L/min and a relative humidity of <10%. The negative control used is hot air at 37°C and 100% humidity at the same flow. Cold air provocation produces mainly obstruction and rhinorrhea [43].

Shusterman and Tilles [44] reported findings from patients with nonallergic noninfectious rhinitis who reported predominant symptoms with physical or chemical triggers and a control group without rhinitis. They found that patients with rhinitis symptoms due to physical stimuli experienced a greater change in nasal resistance when challenged with cold dry air than the rest of the groups.

Kim et al [45] reported that cold air provocation makes it possible to differentiate between patients with rhinitis and healthy controls and between patients with rhinitis who do or do not present clinical nasal hyperreactivity. Patients with rhinitis who had symptoms of nasal hyperreactivity exhibited greater variations than those without symptoms; however, the study did not differentiate between allergic and nonallergic rhinitis.

Van Gerven et al [46] recently advocated the use of a short exposure to cold air to distinguish patients with rhinitis from control patients (sensitivity, 66.7%; specificity, 100%).

Provocation with cold air increases levels of mast cell mediators (histamine, prostaglandin D2 and tryptase) and markers of glandular activation and plasma extravasation (lysozyme and albumin) [47,48]. It also generates activation of nerve endings and cholinergic secretion, and stimulation of a nostril triggers a contralateral response that is reduced when a local anesthetic is applied in the nostril [49].

Atropine reduces secretion and levels of glandular activation markers but not mast cell activation and plasma exudation, indicating that mechanisms other than cholinergic activation are involved [50].

Repeated application of capsaicin as treatment reduces nasal hyperresponsiveness (as measured using cold air provocation) by acting on the transient receptor potential cation channel and reducing levels of substance P [51]. Corticosteroid treatment administered a week earlier does not change symptoms but reduces histamine levels [52] (Table 3B).

The histamine challenge does not distinguish between individuals with or without a response to cold, and antihistamines are not effective in relieving symptoms after provocation with cold air. Compared with histamine, provocation with cold air seems to be more specific in differentiating nasal hyperreactivity in patients with nonallergic noninfectious rhinitis [53].

Key Points

Nasal provocation testing with cold air is easy to perform but shows low sensitivity and specificity. It could be useful in the study of nasal physiology and serve as a model for the study of similar reactions at bronchial level.

Mannitol

The administration of mannitol produces a hyperosmolar stimulus that causes the release of mediators. The cells and mechanisms involved in this response are unknown, although it is postulated that mast cells, epithelial cells, and C nerve fibers could be involved [54].

Koskela et al [54] performed provocations with mannitol solution (200 mg/mL) in patients with symptomatic and asymptomatic AR and a control group. All patients experienced a burning sensation, although congestion and increased levels of 15-hydroxyeicosatetraenoic acid (15-HETE) were only observed in patients with rhinitis. The results of this study indicate that epithelial cells are the cell type mainly affected by this type of stimulus.

Administration of both loratadine and montelukast 12 hours before challenge reduces the response to mannitol [55] (Table 3B).

Key Points

The administration of mannitol causes a nonspecific burning sensation; the technique is not standardized and few studies have determined its clinical utility.

Other Techniques

Techniques such as ultrasonic nebulization of distilled water, phentolamine [56], and capsaicin [57] have been described in the literature, although data are scarce.

Utility of Current Techniques for the Assessment of Nonspecific Nasal Hyperreactivity

At present, the evaluation of nonspecific nasal hyperreactivity has limited use in research. It enables us to expand our knowledge of the pathophysiology of rhinitis and its various clinical types and to assess the changes that different treatments produce in nasal hyperreactivity in order to establish their clinical utility.

In the context of the single airway, the study of rhinitis would make further information on the pathophysiological mechanisms shared with asthma more accessible.

The usefulness of evaluation of nonspecific nasal hyperreactivity in clinical practice is limited by factors such as the lack of standardization, the absence of defined concentrations and cut-off values to establish test positivity, and the difficulties in discriminating between patients with rhinitis and healthy individuals and between different types of rhinitis.

Provocation methods are not comparable: they act by different mechanisms and assess different pathways, so that there is no correlation between them. In addition, studies published to date are very heterogeneous, even for the same test, as they differ in patient selection, concentrations used, method of administration, assessment methods (eg, visual analog scale, PNIF, anterior rhinomanometry, and acoustic rhinometry), and criteria for positivity. In summary, we can conclude that the use of these tests is limited to the field of research and, based on existing data, they do not provide the practical clinical utility necessary to recommend their routine use.

Research Issues in the Assessment of Nasal Hyperreactivity

Given the limited use of nonspecific nasal provocation tests in routine clinical practice, more studies would be warranted to address the research issues we propose below.

1. It is necessary to standardize the methodology for each test in terms of concentrations, cutoffs, and positivity criteria.
2. In the field of research, both the test and the criteria should be defined depending on the predominant symptom, the drug whose therapeutic effect we are assessing, and the pathophysiological mechanism that we wish to study.
3. A decision should be taken on whether to continue using known techniques (whose ability to discriminate between healthy persons with rhinitis or between different types of patients with rhinitis is unclear) or whether to investigate new avenues of study using other mediators as markers of hyperreactivity.
4. Finally, if standardized tests did become available, the benefit of knowing whether or not a patient has nasal hyperreactivity should be defined from the clinical practice standpoint.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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