

ORIGINAL RESEARCH–ALLERGY

Evaluation of optical rhinometry for nasal provocation testing in allergic and nonallergic subjects

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ABSTRACT

OBJECTIVE: Optical rhinometry is a new method that quantifies light extinction in optical density to assess nasal blood volume as a measure of nasal patency. The purpose of this study is to evaluate optical rhinometry as an objective evaluation of nasal patency using nasal provocation testing with histamine and oxymetazoline.

STUDY DESIGN: Prospective pilot.

SETTING: Academic tertiary rhinologic practice.

SUBJECTS AND METHODS: Convenience sample of five adult subjects with allergic rhinitis and five adult normal subjects who underwent challenge with histamine and oxymetazoline. Patients underwent challenge with increasing concentrations of histamine to determine the amount of histamine needed to cause a positive optical rhinometry reading. The same subjects then underwent histamine challenge with this amount followed by oxymetazoline. Nasal patency was assessed subjectively after each challenge with the visual analog scale.

RESULTS: The median histamine amount needed to cause a positive response was statistically lower in allergic rhinitis as compared with nonallergic subjects at 150 μ g and 300 μ g, respectively ($P = 0.04$). When comparing the optical rhinometry with subjective nasal congestion after histamine and oxymetazoline challenges, there was a statistically significant correlation with $r = 0.79$ ($P = 0.00003$).

CONCLUSION: This initial study demonstrates a correlation between subjective symptoms of nasal patency and objective measurements with the optical rhinometer. Less histamine amount necessary to incite nasal congestion in allergic rhinitis suggests that these patients may be primed to the effects of histamine. These preliminary data suggest that optical rhinometry is able to assess changes in nasal patency during challenges with histamine and oxymetazoline.

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Nasal provocation testing (NPT) with antigen represents a direct means of evaluating the nasal end organ response to suspected inhalant allergens. The antigen is intro-

duced into the nasal cavity, and response in terms of nasal mucosal swelling is then monitored. In a positive hypersensitivity response, the nasal mucosa swells from the influx of blood to the cavernous sinusoids, and the cross-sectional area of the nasal airway is reduced. In most European countries, NPT is well standardized and is incorporated into the clinical evaluation of inhalant allergies.¹ The clinical use of NPT in the United States has been limited to date. Rather, the diagnosis of allergies has relied primarily on history and either skin testing or measurements of serum allergen-specific immunoglobulin (Ig) E levels.

Inhalant allergies are first suggested by a clinical history of allergy symptoms such as rhinorrhea, sneezing, watery/itchy eyes, and nasal congestion. For confirmation and identification of inciting allergens, patients undergo either skin or blood testing. Several investigators have argued that skin test results have unreliable correlations with nasal challenges unless coupled with serum IgE levels in a patient with allergic rhinitis (AR) symptoms.² The sensitivity of epicutaneous skin testing is dependent on the allergen and is reported between 50 to 87 percent.^{3,4} Given limitations of skin and modified radioallergen sorbent testing (mRAST) for the diagnosis of clinically relevant inhalant allergies, NPT represents an alternative diagnostic tool for inhalant allergies.

The clinical value of NPT has been limited partly by the lack of an ideal objective measuring device. Several techniques have been utilized to assess the response to NPT, including acoustic rhinometry, anterior and posterior rhinomanometry, and rhinosterometry. Acoustic rhinometry transforms the analysis of a sound pulse within the nasal cavity to an area-distance plot. This technique has the potential of providing a rapid and reproducible intranasal dimension; however, it involves placement of a tube within the anterior aspect of the nasal cavity and prevents continuous monitoring from the introduction of the antigen. Anterior and posterior rhinomanometry represent traditional techniques for assessment of nasal patency by calculations

Received December 15, 2009; revised March 18, 2010; accepted March 24, 2010.

of nasal airflow resistance. Although rhinomanometry is well standardized, anterior rhinomanometry is not valid in subjects with septal perforations or unilateral complete obstruction, and placement of the catheter within the posterior pharynx for posterior rhinomanometry measurements is not tolerated by many patients. Rhinostrometry allows direct visual measurements of changes in nasal mucosal swelling. However, it has not been widely utilized because it requires individually adapted tooth splints, is more vulnerable to investigator bias, and only allows evaluation of relative changes in the mucosal thickness. The limitations of these techniques have consequently limited the clinical value of NPT.

Optical rhinometry (ORM) has recently been introduced as a means of assessing nasal airway patency. An 808-nm wavelength light emitter and optical sensor are placed across the nasal bridge. This wavelength corresponds to the isobestic point of hemoglobin. Consequently, changes in hemoglobin within the nasal tissue is measured independent of its oxygenation state. Hemoglobin and water are a few of the chromophores within tissue that absorb this wavelength of light. Because endonasal tissue swelling affects nasal patency and this swelling is caused primarily by increased blood volume to the sinusoids and edema of the tissue within the turbinates, measurements of the blood volume within the nasal tissue by the optical rhinometer provide a means of assessing nasal congestion. Rhinolux (Rhios GmbH, Grosserkmannsdorf, Germany), one such optical rhinometer, assesses nasal airway patency by detecting changes in blood volume within the nasal mucosa. Endoscopic evaluation shows that the emitted wavelength passes through the inferior and middle turbinates.⁵ This technique was recently compared with anterior rhinomanometry in nonallergic subjects for NPT. Compared with anterior rhinomanometry, ORM had better correlation with patient symptoms.⁶ The primary advantages with ORM are the ease of use and the ability to obtain continuous measurements during the nasal provocation study.

The purpose of this study was to evaluate the optical rhinometer in healthy controls (HC) and symptomatic AR subjects with histamine and oxymetazoline, which will increase and decrease blood volume to the endonasal tissue, respectively. In addition, we evaluated the ability of ORM to measure challenges in each nasal cavity separately.

Methods

Subjects

A convenience sample of five HC and five AR subjects was recruited for this study after Institutional Review Board approval from the Cleveland Clinic Foundation. The HCs had no history of allergy symptoms such as sneezing, rhinorrhea, and/or itchy eyes; no history of using antihistamines or nasal steroid sprays; and a negative skin test to *Dermatophagoides farniae* antigen. AR subjects had symptoms of AR consisting of sneezing, rhinorrhea, and/or itchy

eyes and a skin test positive for *D. farniae*. Allergic rhinitis was defined by a positive skin test to *D. farniae* rather than by quantification of *D. farniae*-specific IgE blood levels or by NPT because skin testing has been shown to be more sensitive than mRAST, and NPT is not widely used clinical for diagnosing AR. One of the goals of this study was to determine whether nasal congestion could be assessed with ORM in subjects with a clinical diagnosis of AR.

Subjects with an acute or chronic rhinosinusitis were excluded from the study. In addition, subjects with asthma were excluded. Finally, subjects on antihistamines, topical nasal steroids, or systemic glucocorticoids were asked to hold these medications for at least two weeks prior to testing.

Study Design

This study was conducted over two days. On the first day, each subject underwent NPT with three increasing amounts of histamine (ALK-Abello, Round Rock, TX) (150 µg, 300 µg, and 450 µg) in one nostril. The subjects were monitored by ORM during the entire course of the NPT. Prior to the first challenge, a baseline visual analogue scale (VAS) rating for subjective nasal congestion was recorded, with 10 representing agonizing nasal congestion and zero representing no sensation of nasal congestion. A two-minute baseline ORM reading was first recorded. Starting at 150 µg of histamine challenge to the right nasal cavity, continuous measurements with the optical rhinometer were obtained for at least 10 minutes at each dose of histamine. If a change in optical density (OD) of less than 0.2 was noted by ORM, then the next higher histamine amount was administered until there was at least a 0.2 change in OD or the maximum 450 µg amount was given. The change in 0.2 OD is the published value of a positive response for the optical rhinometer.⁵ VAS assessments for nasal congestion were recorded at this time. Measurement with the optical rhinometer was continued for 20 minutes at this histamine amount. The goal of this first day of testing was to determine the minimum histamine amount that would incite a positive response as detected by ORM.

The first goal for day two was to evaluate ORM during NPT with histamine and oxymetazoline. Histamine will incite a positive change in the OD (as determined from day 1), and oxymetazoline should cause a fall in the change in OD. Prior to the histamine challenge, VAS assessments were recorded for subjective sensation of nasal congestion. Then a two-minute baseline ORM reading was obtained. Each subject underwent nasal challenge with histamine at the amount that resulted in a positive OD response as determined from the first day of testing. The subjects were monitored for five minutes at this positive OD level by ORM. Another VAS assessment was recorded. Next, the subjects were challenged with 0.1% oxymetazoline hydrochloride. An additional 15 minutes of monitoring by ORM was completed. A final VAS assessment of nasal congestion was recorded.

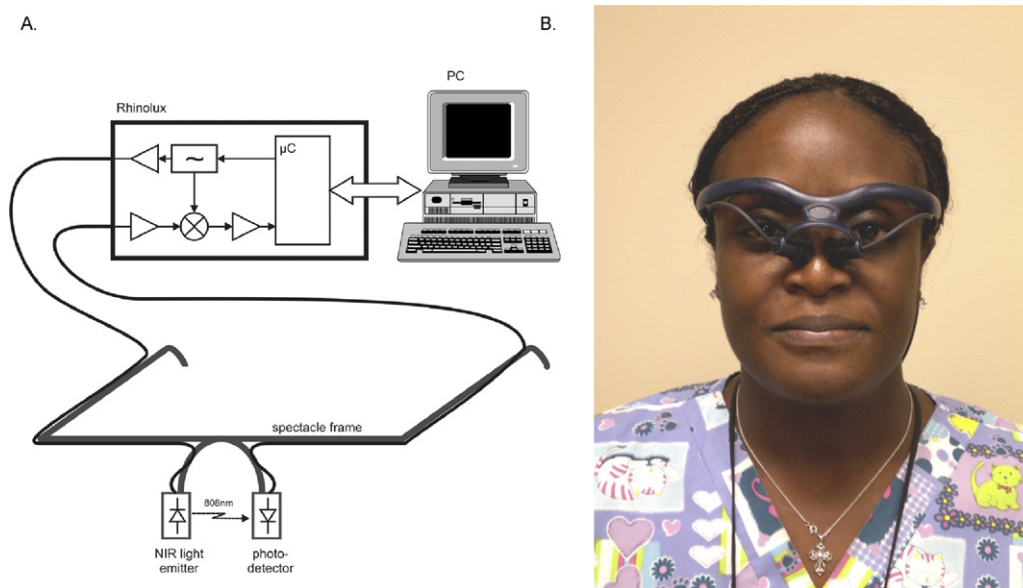


Figure 1 Optical rhinometer. (A) Schematics of the optical sensor, which consists of an optical emitter and detector that resides in the nasal pieces of a spectacles-like frame. (B) Optical sensor is placed across the nasal bridge during measurements.

The second goal for day two was to determine whether the contralateral nostril could be evaluated by ORM during NPT. After the monitoring period following the application of oxymetazoline, the contralateral nostril was challenged with the histamine dose that was determined to incite a positive response from day one. If a change of 0.2 OD was noted by ORM, then a VAS assessment was obtained, and 20 minutes of continuous measurements with ORM were recorded. If there was less than a 0.2 OD change, then the next higher amount of histamine was applied to the nose until a positive ORM reading was elicited. A VAS assessment was obtained after this histamine challenge. Continuous measurements were obtained for 20 minutes with the optical rhinometer after the final histamine challenge.

NPT and ORM Monitoring

Prior to NPT, the subjects were fitted with the spectacles-like frame of the optical rhinometer, which house the optical emitter and sensor within the nosepieces (Fig 1). The principle behind ORM is that an optical detector is placed opposite of an optical emitter across the nasal bridge when placed on a subject. The 808-nm wavelength used correlates to the isobestic point of hemoglobin, which allows measurements of hemoglobin independent of oxygenation state of the molecule. Nasal congestion is the clinical sensation caused by influx of blood volume and edema within the endonasal tissue. The 808-nm wavelength is emitted through one external surface of the nose and passes through the nasal tissue intervening between the optical emitter and detector. Changes in blood volume through the nasal tissue are detected by the extinction of light as the light passes through the nasal tissue, which is measured in OD. The output from the device is the change in extinction relative to the baseline extinction value. This baseline value was ob-

tained during the two-minute reading with ORM prior to the histamine challenge. Consequently, ORM allows assessment of nasal congestion via measuring changes in hemoglobin content within the nasal tissue.⁶

Once the frames were fitted on the subject, a two-minute baseline ORM reading was first obtained prior to provocation. Next, the subjects were provoked with either histamine or oxymetazoline as described above. The provoking agent was introduced into the nasal cavity via a mucosal atomizer device at a fixed volume of 150 μ L. The change in light extinction (ΔE), as measured in OD by the optical rhinometer, represents the change before and after nasal provocation (Fig 2).

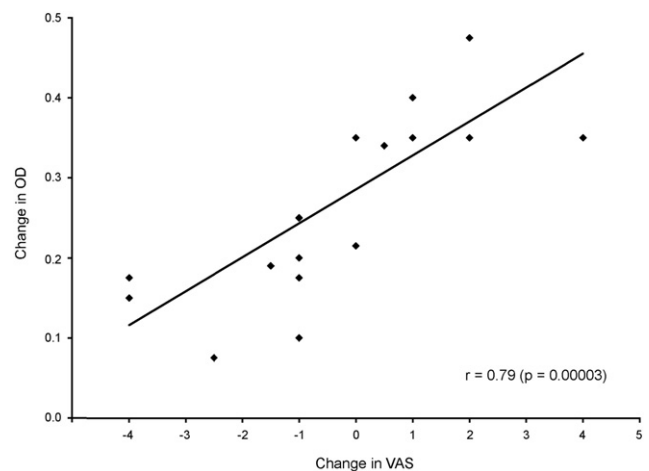


Figure 2 Correlation of change in OD by ORM with change in subjective VAS for nasal congestion in allergic rhinitis subjects challenged with histamine followed by oxymetazoline (10 measurements in 5 subjects).

Table 1
Comparison of histamine amount to incite positive response by optical rhinometry in nonallergic rhinitis and allergic rhinitis subjects

	Histamine amount (μg)
Nonallergic rhinitis	450
	300
	300
	300
	300
Median	300*
Allergic rhinitis	150
	300
	150
	150
	300
Median	150

* $P = 0.0353$.

Statistical Analysis

The comparison between changes in OD and the changes in subjective ratings of nasal congestion based on the VAS from challenges with histamine and oxymetazoline was analyzed by Spearman nonparametric correlation. Mann-Whitney U tests were used to identify the difference between the median histamine amount needed to elicit a response between HC and AR subjects. The critical α level was set at $P = 0.05$ for all tests, and all P values are two-tailed.

Results

A total of 10 female subjects, five HC and five AR subjects, was recruited for this study. The mean age for each group was 43.2 ± 10.9 years and 43.4 ± 5.2 years, respectively.

ORM Correlates with Subjective VAS for Nasal Congestion

Figure 2 compares the maximal ORM ΔE readings with the subjective changes in ratings of nasal congestion on the

VAS after histamine and oxymetazoline challenge conducted on day two. The overall correlation coefficient between the ΔE and the ΔVAS subjective ratings of nasal congestion was $r = 0.79$ ($P = 0.00003$). The correlation coefficient between ΔE and ΔVAS for the AR subjects was 0.78 ($P = 0.008$) and 0.67 ($P = 0.03$) for the non-AR subjects.

Less Histamine Needed in AR versus non-AR Subjects to Incite Positive Response in NPT

Table 1 lists the amount of histamine for each subject, separated into HC and AR subjects, that resulted in a positive response as detected by ORM on NPT. The median baseline OD readings were 0.00 and 0.02 for the HCs and AR subjects, respectively. The amount of histamine required for AR subjects (median amount = $150 \mu\text{g}$) was significantly less than HCs (median amount = $300 \mu\text{g}$, $P = 0.04$) to incite a positive response. Figure 3 shows representative ORM readings from an allergic and nonallergic subject. The nonallergic subjects typically required a greater amount of histamine to cause a change in OD necessary to incite a positive response by ORM ($\text{OD} \geq 0.2$).

PT of the Contralateral Nasal Cavity Can Be Detected by ORM

Given that the optical emitter and sensor on the optical rhinometer is placed across the nasal bridge, we tested whether the contralateral nasal cavity could undergo NPT following challenge of one nasal cavity. The nasonasal reflex should cause an increase of blood volume in the challenged as well as in the contralateral nasal cavity tissue.⁷ The ORM has no ability to discern between each nasal cavity. The ORM reports change in blood volume within both nasal cavities, so the nasonasal reflex cannot be specifically demonstrated with ORM. However, a response to antigen challenge in the contralateral nasal cavity can be detected by ORM after one nasal cavity has undergone challenge with both histamine and oxymetazoline. Figure 4 depicts a representative response from an AR subject. The contralateral nasal cavity can undergo immediate NPT, and

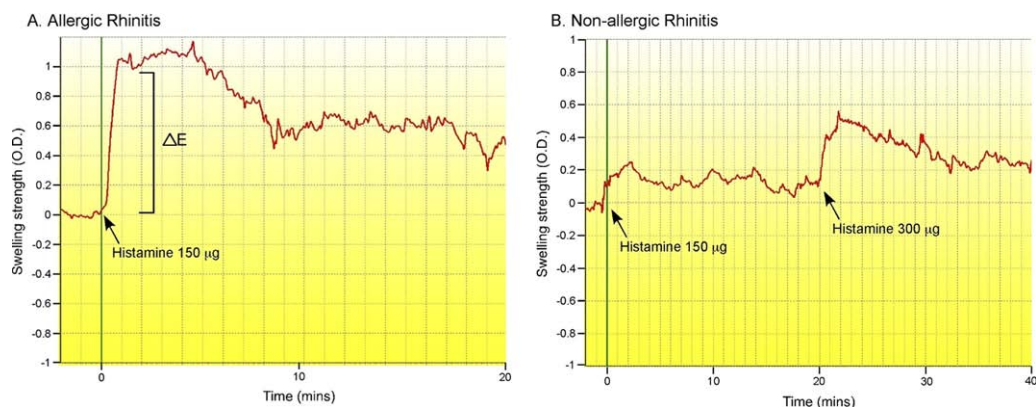


Figure 3 Graphic representation of ORM in (A) AR and (B) HC subjects undergoing NPT with increasing amounts of histamine.

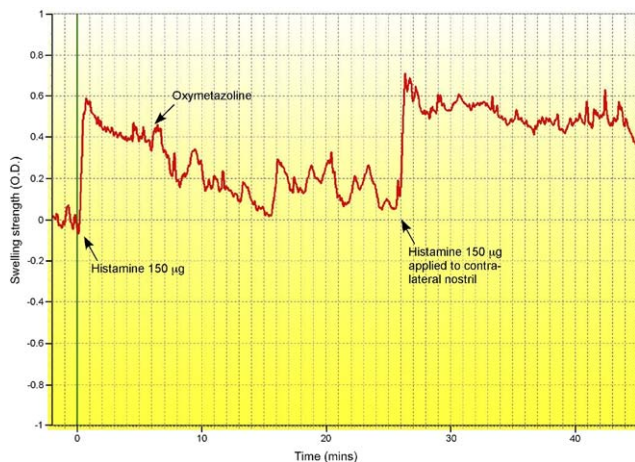


Figure 4 Graphic representation of readings from ORM in allergic subject undergoing NPT with histamine and then oxymetazoline in one nasal cavity followed by histamine challenge in the contralateral nasal cavity.

the response can be detected by ORM following challenge of one side.

Discussion

Although NPT is more direct than skin testing, NPT is not routinely used for the diagnosis of inhalant allergies. One reason stems from the lack of a clinically useful tool to objectively measure the resultant nasal congestion. The ideal measuring device should be easy to use, comfortable to the patient, and accurate in its assessment of nasal congestion. In addition, the device should not interfere with the mechanics of administering the NPT. The current tools, acoustic rhinometry, rhinomanometry, and rhinostereometry, do not meet many of these criteria, and this is why NPT is not widely used clinically.

The optical rhinometer represents an ideal device for NPT. It is worn similar to a pair of glasses (Fig 1). Consequently, the device is comfortable and does not require obstructing the nasal cavity during the monitoring process. In addition, ORM provides continuous measurements throughout the entire NPT. Moreover, the correlation coefficient of 0.79 ($P = 0.000034$) between the OD readings and the subjective rating of nasal congestion as measured with the VAS supports a strong correlation (Fig 2). This correlation is present in both the allergic and nonallergic subjects with correlation coefficients of 0.78 ($P = 0.008$) and 0.67 ($P = 0.03$), respectively. Our results are similar to the published correlation coefficient of 0.81 ($P < .001$) between subjective nasal congestion and ORM when tested in HC.⁶ This correlation suggests that ORM may represent a means of assessing the subjective rating of nasal congestion whether the patient does or does not have AR.

A recent systematic review of the literature investigating the correlation between subjective and objective evaluation of nasal airway patency concluded that such correlation

remains inconclusive because of the variability in the techniques to measure and to report the objective and subjective symptoms.⁸ Of the 16 studies included in the review, one study similar to the present found a strong correlation between subjective symptoms on a VAS and objective measurements of nasal airway resistance by active anterior rhinomanometry after histamine challenge in allergic and nonallergic subjects.⁹

Although ORM measures blood volume across both nasal cavities concurrently, the optical rhinometer can collect data from nasal cavities that are challenged consecutively. Figure 4 illustrates the challenge of one nasal cavity with histamine followed by oxymetazoline. Once the optical rhinometer has reset close to the zero OD baseline with the oxymetazoline, challenge with histamine of the contralateral side can result in a positive response. For safety reasons, we did not test whether the contralateral nasal cavity could be challenged without resetting the initially challenged nasal cavity with oxymetazoline. Consequently, NPT challenges can be performed in both nasal cavities during one testing session.

The nasal cavities of AR subjects appear primed to respond to histamine. The amount of histamine needed to incite a positive response on NPT as detected by ORM in AR subjects was significantly lower than the amount needed to incite a positive response in nonallergic HCs. In addition, the degree of response as noted by the severity of the nasal congestion as detected by ORM and subjective ratings was generally greater in the AR group (Fig 3). Our observations are consistent with published findings of increased expression of histamine H1 receptor messenger RNA in the mucosa from AR subjects as compared with nasal mucosa from non-AR subjects.¹⁰

When considering use of ORM in the clinical setting, potential drawbacks should also be considered. First, ORM was difficult to use in subjects with wide, flat nasal bridges, and readings varied when there was significant facial movement. The ORM frame is designed to keep the light emitter and detector across from each other. This orientation is distorted with the flat nasal bridge, and, consequently, the readings had greater variability. Similarly, the orientation of the emitter and detector is distorted with movement of the soft tissue around the nose. Therefore, subjects were instructed to minimize conversation while being monitored. Also, significant variations in the readings were noted during sneezes.

With this requisite background information, current studies are addressing the effectiveness of ORM in monitoring NPT with specific antigen challenges in AR and non-AR subjects. In addition to assessing correlation with subjective nasal congestion, ORM will be compared with established methods of assessing the effects of NPT, such as acoustic rhinometry.

In conclusion, ORM represents a novel technique for monitoring NPT with a strong correlation to subjective assessment of nasal congestion. Measuring by ORM, a less

amount of histamine was needed to incite a positive response in AR subjects. Additional physiologic studies showed that each nasal cavity could undergo NPT separately using ORM during the same sitting. These initial studies serve to create the foundation for further exploration of the utility of ORM in NPT.

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This article was presented at the American Academy of Otolaryngic Allergy Fall Meeting, San Diego, CA, October 2-3, 2009.

Author Contributions

Amber Luong, conception and design of study, data acquisition, writer; **Esther J. Cheung**, data analysis; **Martin J. Citardi**, conception and design of study, edit manuscript; **Pete S. Batra**, conception and design of study, edit manuscript.

Disclosures

Competing interests: **Martin J. Citardi**, consultant: Medtronic; **Pete S. Batra**, consultant: Medtronic, Karl Storz; research grant: Xoran.

Sponsorships: This study was generously funded by the American Academy of Otolaryngic Allergy.

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