Objective monitoring of nasal patency and nasal physiology in rhinitis

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Nasal obstruction can be monitored objectively by measurement of nasal airflow, as evaluated by nasal peak flow, or as airways resistance/conductance as evaluated by rhinomanometry. Peak flow can be measured during inspiration or expiration. Of these measurements, nasal inspiratory peak flow is the best validated technique for home monitoring in clinical trials. The equipment is portable, relatively inexpensive, and simple to use. One disadvantage, however, is that nasal inspiratory peak flow is influenced by lower airway as well as upper airway function. Rhinomanometry is a more sensitive technique that is specific for nasal measurements. The equipment, however, requires an operator, is more expensive, and is not portable. Thus, it is applicable only for clinic visit measures in clinical trials.

Measurements require patient cooperation and coordination, and not all can achieve repeatable results. Thus, this objective measure is best suited to laboratory challenge studies involving smaller numbers of selected volunteers.

A nonphysiological measure of nasal patency is acoustic rhinometry. This sonic echo technique measures internal nasal luminal volume and the minimum cross-sectional area. The derivation of these measures from the reflected sound waves requires complex mathematical transformation and makes several theoretical assumptions. Despite this, however, such measures correlate well with the nasal physiological measures, and the nasal volume measures have been shown to relate well to results obtained by imaging techniques such as computed tomography scanning or magnetic resonance imaging. Like rhinomanometry, acoustic rhinometry is not suitable for home monitoring and can be applied only to clinic visit measures or for laboratory nasal challenge monitoring. It has advantages in being easy to use, in requiring little patient cooperation, and in providing repeatable results.

In addition to nasal obstruction, allergic rhinitis is recognized to be associated with impaired mucociliary clearance and altered nasal responsiveness. Measures exist for the monitoring of these aspects of nasal dysfunction. Although measures of mucociliary clearance are simple to perform, they have a poor record of reproducibility. Their incorporation into clinical trials is thus questionable, although positive outcomes from therapeutic intervention have been reported. Measures of nasal responsiveness are at present largely confined to research studies investigating disease mechanisms in allergic and nonallergic rhinitis. The techniques are insufficiently standardized to be applied to multicenter clinical trials but could be used in limited-center studies to gain insight into the regulatory effects of different therapeutic modalities. (J Allergy Clin Immunol 2005;115:S442-59.)

Nasal obstruction is a common and important symptom of rhinitis.[1] Visual analogue scales or symptom rating scores may evaluate this subjectively. It is appreciated, however, that the subjective sensation of nasal obstruction can be difficult to quantify accurately, because patient perceptions of nasal obstruction vary considerably, often bearing no relationship to the actual resistance to airflow in the nose.

Consequently, objective methods have been developed to assess nasal patency quantitatively.[2] These methods include measurement of nasal peak inspiratory flow (NPIF) and nasal peak expiratory flow (NPEF), anterior and posterior rhinomanometry, acoustic rhinometry, and

the peak flow nasal patency index.[3] Nasal adapters have also been fitted to spirometers to enable measurement of nasal FEV_1, nasal forced inspiratory volume in 1 second, and nasal forced vital capacity.[4,5] Peak flow and rhinomanometry represent physiologic measures. Rhinomanometry involves the simultaneous measurement of nasal airflow and the pressure required to achieve that flow, from which nasal airway resistance (NAR) can be calculated. Depending on the technique used, this provides either information about each nostril separately (anterior or modified posterior rhinomanometry) or an integrated measure for both nostrils together (posterior rhinomanometry). Nasal peak flow is an indirect index of nasal obstruction, because increasing nasal resistance modifies nasal airflow and hence the peak inspiratory or expiratory nasal airflow achievable. Differences exist in the cost of equipment required for these physiologic measures and their practical applicability for clinical trial purposes.

An alternative approach used to gain information of relevance to nasal obstruction is acoustic rhinomanometry. This is not a physiologic measure, because it provides no information about nasal airflow but provides information about the nasal luminal anatomic structure, either as a measure of nasal volume over a predetermined set distance into the nostril or as the minimal cross-sectional area within the nasal cavity.

Mucociliary clearance is an important upper airway defense mechanism. Defects in mucociliary clearance may promote mucus retention within the nasal cavity and indirectly reduce nasal airflow. The assessment of mucociliary function can be achieved by measures such as the saccharine test, which is in part subjective, as well as more objective tests such as the measurement of ciliary beat frequency and ciliary ultrastructure. The latter would not be applicable to clinical trials.

Another nasal physiologic parameter for which methods have been established for measurement is nasal reactivity. Tests of nasal reactivity have been used to investigate how rhinitis alters the nasal response to exogenous chemical or physical stimuli and have been primarily used as a research approach to understand the nature of altered physiology in disease. These tests may use one of the measures of nasal obstruction as an outcome parameter in association with nasal challenge, or may use an alternative outcome, such as number of sneezes or quantity of anterior rhinorrhea, depending on the nature of the challenge and the protocol involved. Some tests of nasal reactivity have shown an altered nasal responsiveness in rhinitis, which is distinct from that in the normal nose.

MEASUREMENT OF NASAL PEAK FLOW

One of the attractions of nasal peak flow is the simplicity of the method. A mini-Wright peak flow meter, equipped with an airtight face mask instead of a mouthpiece, can be used to measure NPEF. This measure is quick, non-invasive, inexpensive, and relatively easy. The equipment is portable and useful for repeated examinations. During this procedure, patients are instructed to inspire to total lung capacity and, keeping lips tightly closed, to expire with maximal effort through the nose.[6] Maximal flow rate is read from a cursor in liters per minute. A potential drawback to the expiratory peak flow technique is the blowing of mucus into the peak flow meter.[7]

Alternatively, NPIF can be measured by using a Youlten peak nasal inspiratory flow meter (an inverted mini-Wright flow meter) attached to an anesthesia mask. During this procedure, the patient places the mask over the nose and mouth, secures an airtight seal around these areas, and inspires forcefully (a vigorous sniff) through the nose, with lips tightly closed. The measurement of NPIF is associated with a small risk of nasal vestibular collapse. If the alar muscles are contracted during maximal inspiration leading to flaring of the nostrils, this counteracts the tendency for vestibular collapse.[1] In a study of patients with allergy, 2% (6 of 327) of NPIF measurements were not obtained because of total occlusion of the nose.[1] Recent mathematical modelling has indicated that nasal wall compliance, in addition to nasal patency, is an important determinant of NP1F.[8]

Reproducibility and variation in nasal peak flow

Reproducibility in nasal peak flow measurement is dependent on variation resulting from characteristics of the flow meter, variation related to subject technique, and variation caused by changes in airway size and shape that arise because of interindividual differences. Both the mini-Wright and Youlten flow meters are reported to offer highly reproducible results. Proper technique is more difficult with NPIF than NPEF, but most subjects still achieve reproducible values after less than 5 minutes of instruction.[9,10]

Secretions in the mini-Wright meter can influence NPEF readings. Both NPEF and NPIF are effort-dependent, and variability of results might come from fatigue or subtle changes in technique. In addition, nasal patency can change quickly. Other factors that can affect NPIF measurements include severe nasal obstruction, poor coordination, alar collapse, and poor inspiratory reserve.[10] Taking the best of 3 readings with less than 10% variation is a more useful result than taking the mean of the 3 maneuvers.

For NPIF, proper fit of the mask is important—that is, the mask must be small enough to provide an airtight seal yet large enough to avoid compression of the external nares.[6] Wihl and Malm[1] reported that leakage through the mouth during NPIF and NPEF could result in false maximal values, whereas failure to relax the soft palate during maximal expiration could result in false low values. The investigators found that in patients with partially blocked noses, the eustachian tube can be pressurized during maximal expiration, causing discomfort and a decreased expiratory effort.[1]

Confounding factors in nasal peak flow measurements

One inherent flaw of nasal peak flow is the failure of this method to account for abnormalities in pulmonary function.[11] Nasal peak flow is dependent on both nasal patency and the ventilatory capacity of the lungs.[1] Lower airway obstruction and a reduced respiratory effort can affect nasal peak flow. Findings from a study by Phagoo et al[12] demonstrated that NPIF and, to a lesser extent, NPEF were altered by changes in intrapulmonary airway dimensions. The authors stated that NPIF and NPEF may give a false impression of nasal patency when effort is submaximal, intrapulmonary dynamic resistance is increased, or nasal dynamic resistance is low. They suggested that false readings could be avoided by comparing mouth peak flow and/or mouth peak inspiratory flow with that of NPIF and NPEF.[12]

Similar to peak expiratory flow rate in patients with asthma, there is a diurnal variation in nasal peak flow measurements, with readings lower in the morning and highest at dinner. There are no reported normal values for either NPEF or NPIF, and accordingly, nasal peak flow can be used only as a relative measurement in the same individual over time, although a NIPF of greater than 2.5 L/s has been proposed as being normal.[13]

Some investigators have argued that NPIF should not be used to assess a very obstructed nose quantitatively. Gleeson et al[14] found that many patients with marked subjective nasal blockage were unable to obtain NPIF readings greater than 20 (on a scale from 20 to 350 units, which correspond roughly to L/min). Furthermore, a variety of stimuli can acutely influence nasal patency. Exercise and warm air increase patency. Recumbency, pain, cold air, smoking, and hypoventilation decrease patency. Hormonal factors can also influence nasal patency, although small studies in pregnancy and through the normal menstrual cycle have failed to show significant changes in NPIF.[15,16]

Nasal peak expiratory flow can be influenced by a flow meter contaminated from nasal secretions, which is common in individuals with allergy. Subjects must be instructed to evacuate secretions from the nose by sniffing or blowing before taking a measurement. False results occur if the device is not cleaned regularly.

Relevance of dose timing to measurement

Nasal peak flow meter portability allows measurements to be obtained during a symptomatic state to document environmentally and occupationally induced nasal obstruction. Twice-daily measurements would be adequate for determining a chronic pharmacologic effect, and measuring nasal peak flow before and 10 minutes after would examine the effects of nasal provocation. The domiciliary use of nasal peak flow meters to monitor objectively the magnitude of nasal obstruction has been found valuable, and the measures have been found to correlate significantly with the severity of symptom reporting.[17]

How nasal peak flow relates to other indices of disease: Comparison with rhinomanometry and subjective measures

Rhinomanometry provides a well-established, objective, quantitative measure of NAR. Several studies have compared nasal peak flow measurements with rhinomanometry and visual analogue scales in the determination of nasal obstruction with conflicting results. Gleeson et al[14] and Enberg and Ownby[9] found nasal peak flow to be an unreliable measure of nasal obstruction. Clarke et al[18] found nasal peak flow a relatively insensitive measure compared with rhinomanometry. Larsen and Kristensen[19] saw a poor intraindividual correlation. Jones et al[20] and Fairley et al[21] saw a strong correlation with subjective nasal sensation. In addition, Jones et al[20] found a high correlation between NAR, as measured by anterior rhinomanometry, and NPIF and concluded that NPIF was as good an indication of objective nasal patency as NAR measured by rhinomanometry.[20] Holmstrom et al[10] found a good correlation of NPIF with rhinomanometry, and a significant correlation has also been shown between NPIF and forced inspiratory volume in 1 second.[22] Frølund et al[6] studied the relationship between posterior rhinomanometry and NPEF in healthy subjects and patients with rhinitis. A significant correlation was found between posterior rhinomanometry and NPEF when patients were stratified by rhinitis diagnosis and height. The authors concluded that posterior rhinomanometry is an appropriate method for clinic use, and that NPEF is an easy method for measuring nasal patency and may be suitable for home use.

Marais et al[23] used nasal peak flow and acoustic rhinometry to evaluate patients undergoing septoplasty alone and septoplasty combined with trimming of the inferior turbinates. Patients who had both procedures had the greatest increase in both minimal cross-sectional areas (measured by acoustic rhinometry) and nasal peak flow fraction (the ratio of oral peak expiratory flow rate to peak nasal expiratory flow rate). Both measurements were closely correlated with patient satisfaction. The authors concluded that acoustic rhinometry and nasal peak flow fraction were accurate and easily performed perioperative measurements for patients undergoing surgery for nasal obstruction.

Gleeson et al[14] concluded that although anterior and posterior rhinomanometry have advantages for some research applications, consideration of cost and convenience makes nasal volume or NPIF measurements more practical for routine medical or surgical use.

Clinical relevance

Various opinions circulate about the role of nasal peak flow measurements in clinical practice.[24,25] However, nasal peak flow is the only method suitable for home monitoring to investigate circadian variation, day-to-day changes, or environmental effects on nasal patency. Its portability allows objective assessment of occupationally induced nasal obstruction. Nasal peak flow can assess the acute effect on nasal blockage before and after dosing with a pharmacologic agent or with a provocative stimulus. It can also assess changes over longer periods. For example, after nasal allergen provocation, nasal peak flow measurements can assess the late phase reaction at home. This technique can establish the effect of corticosteroids on nasal polyposis and can be used for preoperative and postoperative assessment of septoplasty or turbinectomy. Nasal peak flow is also potentially useful in assessing functional nasal problems and for medical legal assessment.

Use as a measure of work-related nasal blockage

Ahman[26] investigated the value of serial NPEF measurements in detecting nasal blockage in different work environments. Eleven patients who had nasal blockage caused by airway irritants were compared with 11 control subjects. Compared with the control subjects, NPEF values for patients exposed to irritants decreased gradually over the workweek, with gradual improvement during the weekend. Changes in bronchial peak expiratory flow rates were similar but less pronounced. The author concluded that NPEF was an effective means of detecting changes in the sensation of nasal blockage.

In another study, Ahman and Soderman[27] evaluated the usefulness of serial NPEF as a measure of work-related nasal obstructive symptoms in woodwork teachers and control subjects. Compared with control subjects, the teachers reported a higher level of nasal blockage (as assessed by symptom ratings). A gradual increase in nasal blockage during the week corresponded moderately with a gradual decrease in NPEF. No statistically significant difference was observed between the proportion of teachers and control subjects who had a meaningful decrease in NPEF. The authors concluded that NPEF is useful in evaluating subjects with work-related nasal obstruction, but because of its variability, a large number of subjects should be evaluated, with several measurements taken daily.

Use as an efficacy measure in clinical drug trials

Nasal peak inspiratory flow has been used successfully in combination with other measures in several placebo-controlled trials to demonstrate the efficacy of steroid nasal sprays in patients with a variety of conditions. Greiff et al[28] used daily patient-assessed NPIF and nasal index scores to compare the efficacy of mometasone furoate and budesonide aqueous nasal sprays in patients with seasonal allergic rhinitis (SAR), and NPIF was also used to show improvement objectively in nasal obstruction with triamcinolone acetonide and fluticasone propionate therapy in SAR.[29] Daily NPIF (patient-assessed), in combination with other assessments, has been used to demonstrate the efficacy of fluticasone propionate nasal spray in patients with allergic rhinitis,[30] recurrent sinusitis,[31] chronic eosinophilic rhinitis,[32] and nasal polyposis.[33] NPIF has also been used in a clinical trial of an H_1-antihistamine in combination with either a cys-leukotriene 1 receptor antagonist or pseudoephedrine to demonstrate efficacy of combination therapy on nasal obstruction.[34] In a study of patients with nasal polyps, NPIF, polyp size scores, and total symptom score were used to evaluate various doses of budesonide aqueous nasal spray as primary treatment of nasal polyps.[35] Also, NPEF measurements have been used in several placebo-controlled trials to demonstrate improvements in patients with nasal polyposis after steroid therapy.[36-39]

MEASUREMENT OF NAR BY RHINOMANOMETRY

Rhinomanometry is the measurement of nasal pressure flow relationships during normal breathing. Rhinomanometry is generally accepted as the standard technique of measuring NAR and assessing the patency of the nose[40-43] and provides a sensitive and functional measure of nasal patency during normal breathing.

Normal NAR

In subjects free from signs of nasal disease, mean total resistance has been reported to be around 0.23 Pa $cm^{-3}s^{-1}$, ranging between 0.15 and 0.39 Pa $cm^{-3}s^{-1}$.[44] A total nasal resistance to airflow of 0.3 Pa $cm^{-3}s^{-1}$ can be considered a reasonable upper limit of the normal range in healthy volunteers.

Nasal resistance is highest in the infant, at around 1.2 Pa $cm^{-3}s^{-1}$,[45,46] and declines to the adult value at around 16 to 18 years of age, showing only a slow decline with increasing age.[47] In a study in healthy volunteers, Vig and Zajac[48] reported a relationship between age and nasal resistance, with resistance declining with increasing age from 0.6 Pa $cm^{-3}s^{-1}$ (age 5-12 years) to 0.29 Pa $cm^{-3}s^{-1}$ (age 13-19 years), and 0.22 Pa $cm^{-3}s^{-1}$ (age >20 years) in male subjects. The relationship between age and nasal resistance was similar in female subjects, but in general, nasal resistance was lower in female subjects than male subjects.[48]

If the nose is decongested by exercise or application of a topical decongestant, then this eliminates any physiologic variation in resistance and allows investigation of the anatomical factors influencing resistance. Studies by Broms[49] have provided a table of predictive values for

height and nasal resistance in the decongested nose that are useful in assessing the extent of any deviation from normality in patients with nasal skeletal stenosis.

Total nasal resistance gives an overall measure of nasal function, but it is a very crude measure because it provides no information about the separate nasal passages. Rhinologists have a dilemma when assessing nasal function, because the nose consists of 2 separate dynamic airways. The ophthalmologist or audiologist would never consider using a bilateral measure of vision or hearing when assessing function, because this could fail to detect blindness in one eye or deafness in one ear. Similarly, the measurement of total resistance may fail to detect unilateral nasal obstruction. However, it is not very informative to quote the mean of unilateral resistance when measured over a period of several hours, because this mean value will have a large SD because of the instability of unilateral resistance. The range of unilateral NAR in a group of healthy volunteers when recorded over a period of 6 to 8 hours has been shown to vary from 0.36 to 1.36 Pa cm^{-3}s^{-1},[50] and from 0.28 to 0.63 Pa cm^{-3} s^{-1}.[51] This indicates that there is almost a 4-fold change in unilateral resistance associated with the spontaneous natural congestion and decongestion of the nasal venous sinuses.

One way to overcome the dilemma of spontaneous changes in unilateral nasal resistance is to decongest the nose before assessment. This solution is of use to a surgeon who is interested only in assessing the extent of any nasal anatomical problem.[49] However, decongestion of the nose is of no use in studying nasal physiology and pathophysiology, because it is the spontaneous changes in unilateral resistance that are of interest to the physiologist and clinician. One solution is to quantify the extremes of unilateral resistance or the amplitude of the unilateral changes in resistance over a period of several hours. This approach has been used to determine the unilateral changes in resistance in health,[52] common cold,[50] and hay fever,[53] to assess the effects of oral decongestants,[54] and to assess the efficacy of nasal surgery.[55] The disadvantage of unilateral nasal measurements is that to assess the amplitude of changes in unilateral nasal resistance it is necessary to make measurements over several hours. The advantage of unilateral measurements is that they give a comprehensive assessment of the dynamic nose rather than the crude snapshot provided by a single measure of total resistance. In the laboratory, under conditions of bilateral nasal challenge, however, a single measurement will provide information relating to the overall effect of the provocation.

How measurements should be performed

Active posterior rhinomanometry can be used to measure both unilateral and total nasal conductance. Conductance is defined as the airflow through the nose at a sample pressure of 75 Pa. Conductance is a more useful measure than resistance, because resistance measurements tend toward infinity when the nose becomes completely obstructed, whereas conductance declines toward 0.

A face mask is used to make a seal around the nose, and the patient breathes through a flow head attached to the mask. A pressure-sensing tube is held in the mouth and detects the posterior nares' pressure when the soft palate allows an airway to the mouth, as shown in Fig 1. Total nasal airflow can be measured from both nasal passages, or, by taping off one nostril, the right and left nasal air flows can be measured separately. Total nasal conductance can be determined directly from the total nasal airflow and transnasal pressure with this method. A disadvantage of this method compared with the anterior method is that not all subjects can open an airway around the soft palate into the mouth. With some training of subjects, using feedback from the pressure flow curve on the computer monitor, it is possible to obtain satisfactory results from almost all subjects, and in studies on many hundreds of subjects, very few have been unable to perform this technique.

Some centers recommend anterior rhinomanometry in preference to the posterior method. In active anterior rhinomanometry, the pressure-sensing tube is normally taped to one nasal passage. The sealed nasal passage acts as an extension of the pressure-sensing tube to measure pressure in the posterior nares. With this method, nasal airflow is measured from one nostril at a time and the pressure-sensing tube is swapped from one side to the other. Therefore, the pressure/flow curves and nasal resistance or conductance measurements are determined separately for each nasal passage and the total is then calculated. The major disadvantage of the anterior method is that it is impossible to make any measurements if one of the nasal passages is completely obstructed. This is a significant limitation of the anterior rhinomanometric method and a deciding factor in preference for posterior rhinomanometry as a standard technique, because patients with rhinitis often have obstruction of one nasal passage, and it would not be possible to include these patients in any study in which anterior rhinomanometry was the preferred measure of nasal conductance.

When making measurements of NAR, it is important to take several measurements with repositioning of the mask between measurements. This is to control for air leaks around the mask, a common source of error. A single measurement of NAR is unreliable, and a standard operating procedure should be implemented to prevent investigator bias when gathering data. The equipment should be calibrated daily.

Ease of measurement

Rhinomanometry is a relatively easy measurement when performed in a laboratory by trained personnel using a standard operating procedure. Training of subjects to perform posterior rhinomanometry and obtain the first measurement takes 10 to 15 minutes, and after this first measurement, subsequent measurements take only around 5 minutes. Measurements using anterior rhinomanometry can be made more quickly because training of subjects is not required. At present, rhinomanometers are interfaced with computers. This makes them rather expensive and not very portable for use in a clinic or hospital ward.
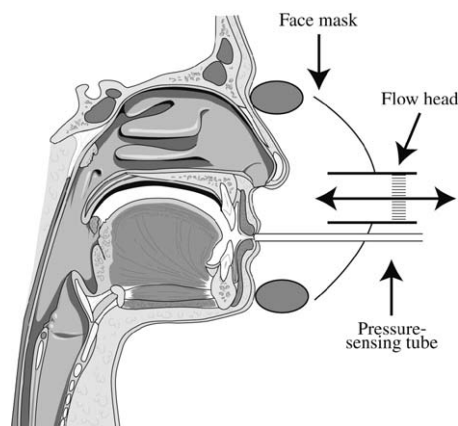
FIG 1. The technique of posterior rhinomanometry involves a pressure-sensing tube in the mouth, which detects the changes in pressure in the posterior nares, and a flow head to measure nasal airflow.

FIG 2. Spontaneous changes in left and right nasal resistance recorded in 1 patient with common cold. Reproduced with permission from *Acta Oto-Laryngologica*.[50]

Repeatability

Nasal airflow resistance is unstable as a result of spontaneous and often reciprocal changes in resistance associated with the so-called *nasal cycle*.[50,56] An example of the spontaneous changes in unilateral nasal resistance in a patient with rhinitis associated with the common cold is shown in Fig 2. Similar fluctuations in nasal resistance are associated with allergic rhinitis[57] and are also found in healthy subjects.[51] Because of the inherent instability of nasal resistance, any study on repeatability of measurements can examine only short-term comparisons made over a period of 10 to 15 minutes.

The results of a study on 21 patients (mean age, 23 years) with the common cold are illustrated in Fig 3. In this study, total NAR was measured by the technique of posterior rhinomanometry by 2 different operators using 2 different rhinomanometers. The 2 measurements of resistance were separated by no more than 6 minutes to limit the occurrence of spontaneous changes in resistance. The results show that the measurement of total resistance over this period is repeatable, although there is a tendency for more discrepancy between the 2 measurements in those patients with high nasal resistance. The mean $\pm$ SD nasal resistance for each measurement respectively was 0.34 ± 0.13 Pa cm^{-3}s^{-1} and 0.34 ± 0.15 Pa cm^{-3}s^{-1}, showing that the measurements were repeatable over the 2 time points, even with different operators and separate rhinomanometers.

Although total resistance may be unstable over a period of hours because of the nasal cycle, it is possible to demonstrate the effects of medication on nasal resistance in patients with common cold[54,58] and allergic rhinitis.[59]

Source of variation

Some of the sources of variation have been mentioned. The spontaneous changes in nasal resistance associated with the nasal cycle are a natural source of physiologic variation, and other factors such as changes in posture,[57,60] exercise,[61,62] cold air,[63] and ingestion of alcohol[64] also
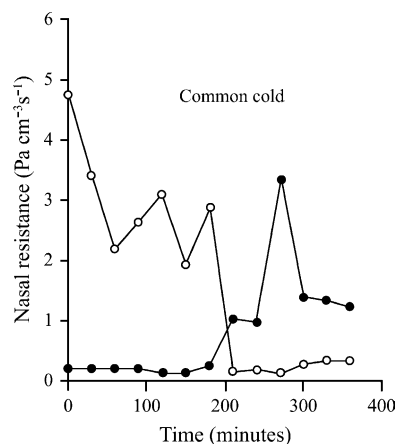
influence nasal resistance. During measurement, the main source of variation is an air leak around the face mask, which can be controlled by taking the mean of paired measurements and discounting those measurements with a high coefficient of variation.[65]

Confounding factors

Rhinomanometry is performed more as a research measurement in the laboratory than as a standard clinical measurement, because the equipment is bulky and expensive. The spontaneous changes in nasal resistance associated with the nasal cycle and other factors described make nasal resistance relatively unstable, although it is possible to demonstrate the efficacy of medications such as nasal steroids by measuring changes in total nasal resistance.[59] The presence of mucus in the nose can confound measurements of nasal resistance, because sniffing and nose blowing will remove mucus and lower resistance (especially in patients with rhinitis). To overcome this problem, patients are asked to blow their nose gently before each measurement of nasal resistance.

How rhinomanometry relates to other indices of disease

Nasal obstruction is a dominant symptom associated with all types of rhinitis[66]; it is an indirect reflection of nasal inflammation, providing that there are no significant permanent nasal anatomical abnormalities contributing to reduced nasal airflow. Any medication or disease process that causes dilation of nasal blood vessels, leading to swelling of the nasal venous sinuses, will be associated with nasal obstruction. The anti-inflammatory effects of nasal steroids account for the sustained reduction in NAR in patients with allergic rhinitis caused by treatment with intranasal steroids.[59]

What is a significant alteration of disease?

Any objective reduction in nasal resistance that is also detected by the patient by the use of subjective scores could be deemed a clinically significant alteration.
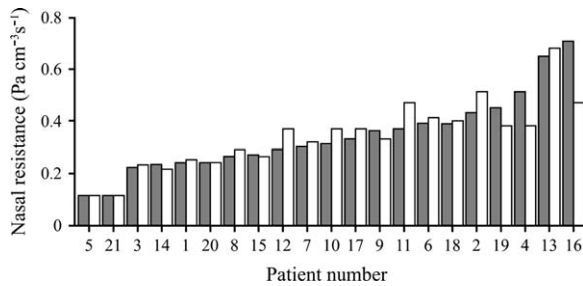
FIG 3. Paired measurements of total nasal resistance measured in 21 patients with common cold. Measurements were made no more than 6 minutes apart on 2 separate rhinomanometers with different staff making the measurements. The *shaded and unshaded bars* represent separate readings for each patient. The figure shows the repeatability of rhinomanometer measurements. Eccles, unpublished data, 2002.

Objective changes in resistance, as measured by rhinomanometry, that are not detected by the patient should not be considered a significant alteration of the disease.

A major problem in this area is that the objective measures of nasal resistance do not correlate very well with subjective measurements.[67-69] This is because the nasal valve region primarily determines nasal resistance, whereas the sensation of nasal obstruction may be related to congestion in other areas of the upper airway, such as the ethmoid region.[70]

If one considers the main function of the nose to be an airway to the lungs, then when the nose is obstructed, any decrease in nasal resistance brought about by treatment could be considered a significant alteration in the disease. As a general rule, one could defend a 20% reduction of total nasal resistance as being clinically significant, although this is very much a matter of opinion.

Relevance of dose timing to measurement

The relevance of dose timing to measurement depends on the type of medication under investigation. For treatment with topical decongestants, the maximal reduction in nasal resistance occurs as long as 45 minutes after treatment,[65] whereas the effect of treatment with nasal steroids on nasal resistance has been reported to occur only after 5 days of treatment.[59]

Power calculations

The power of a study is dependent on the magnitude of the change in nasal resistance expected on treatment. For studies on topical nasal decongestants in which a large reduction in nasal resistance is expected, group numbers as low as 8 will suffice.[65] For carefully controlled studies using nasal allergen challenge in patients with SAR, groups of 12 patients have been used to demonstrate significant changes in nasal resistance on treatment after 5 days' treatment with nasal steroids.[59]

ACOUSTIC RHINOMETRY

In acoustic rhinometry, a sound impulse, termed the *incident wave*, is generated and transmitted through a tube

of known dimensions into the nostrils, with analysis of the reflected echoes. The principal behind this method of measurement is that the size and pattern of the reflections are an indication of the structure and dimensions of the airways, and that the timing of the reflected wave provides information about the distance into the nostril. This method has been applied to the determination of the cross-sectional area as a function of distance into the nasal airways. The technique assumes 1-dimensional sound propagation and the lack of cross-mode waveforms. The devices and the frequency of sound used are designed to facilitate these requirements, and technologic developments in microcomputers have enabled the sampling, storage, and interpretation of the sound reflections. The conversion of the echo measurements to derive a measure of nasal volume requires complicated mathematical transformation[71] in addition to several theoretical assumptions.[71-74] However, the validity of acoustic rhinometry has been proven by comparison of measures by this technique with those obtained by imaging, such as with computerized tomography (CT) or magnetic resonance imaging scanning.[74-76] Studies have indicated that measurements as far as 6 cm from the entrance to the nostril are accurate, but that beyond this distance, access of air to the maxillary sinuses through the ostiomeatal complex distorts the information from the reflected sound, at least in the decongested nose, and leads to inaccuracies in measurement.[77-79] Measures are thus usually made from 0 to 5 cm into the nostrils. In the congested nose, there is a less good correlation between CT scan evaluation of the nasal air passage dimensions and those obtained with acoustic rhinometry.[78] This is predominantly because of sound distortion in the posterior end of the nasal cavity, whereas anteriorly good agreement is evident. In addition to measuring nasal volume, for a set distance into the nostril, acoustic rhinometry standardly also provides information relating to the minimal cross-sectional area within the nose (a-min). This is usually at the level of the nasal valve, but in the congested nose, it can be at the anterior tip of the inferior turbinate.

Method of measurement

A major advantage of acoustic rhinometry over other methods is that it is a very simple technique to use and requires minimal patient cooperation. For measurement, the patient sits in the upright position, clears their nose of secretions, and places the disposable nosepiece attached to the end of the acoustic rhinometry tube into a nostril. Different size nosepieces are available and should fit comfortably but firmly into the external nares to ensure an airtight seal. In some instances, it may be necessary to apply a proprietary soft paraffin wax to ensure an airtight seal. Measurements are made separately for each nostril. It is suggested that subjects keep their eyes focused on a point marked on a wall to keep the same head position during repeated measurements. Studies have evaluated the use of a head frame to fix the head rigidly in a set position, but this approach has not been found to provide better results[80]; rather paradoxically, the results have been

reported to be less repeatable under such circumstances. However, the angle of the rhinometry tube is important, because the axis at which the sound travels in the nasal cavity should be parallel to the nasal floor from the nasal valve, and alterations influence the measurement.[81,82] Measurements are made during breath holding, as the area-distance function may be affected by breathing.[83] The measurements are passive and require no other co-operation from the patient.

Repeatability

Repeated measurements of nasal parameters by acoustic rhinometry and by rhinomanometry in 6 normal subjects over a 2-month period identified a reproducibility of 5% to 10% with acoustic rhinometry and 8% to 15% with rhinomanometry.[84] Such a measure incorporates not only machine/program variability but also subject-related variations. Studies in cadavers, which eliminate the subject variability, report a variation of less than 5% in repeated measurements of the nasal cavity volume by acoustic rhinometry.[85]

Sources of variations/confounding factors

The main basis for poor repeatability of values is a nasal air leak, and it is important that the nasal nosepiece fits closely.[86] As with other measures that reflect nasal cavity volume/airflow, there is the influence of both the nasal cycle and of diurnal variations in nasal airway caliber. Thus, for repeated measures on separate days as part of a drug intervention study, measures should be undertaken at the same time of day. Because a classic nasal cycle is associated with alternating congestion/decongestion cycles matched by the opposite in the other nostril, the sum of the 2 sides is usually constant. In contrast with measures of nasal airflow, which have indicated that such reciprocating cycles occur in as many as 80% of subjects,[87] acoustic rhinometry measures of nasal volume have revealed such changes in only 25% to 50% of subjects.[75,88,89] In one small study of 12 subjects without allergy, repeated measurements of nasal volume, minimal cross-sectional area, and the area of the anterior end of the inferior turbinate every 15 minutes for 6 hours revealed a coefficient of variation of 9.4%, 11.3%, and 17.8%, respectively.[90] The variability was significantly larger in subjects with allergy, with a coefficient of variation for the nasal volume measurement of 14%.[90]

Factors other than allergic disease that may influence intersubject variability or baseline measurements are race and height.[91-93] In a study of 106 subjects with a range of racial origins in North America, there were racial differences between white, Asian, and black noses.[92] Another study has reported no difference between Anglo-Saxon and Indian noses.[93] In a Swedish study of 334 healthy individuals, a weak correlation was found between the minimal cross-sectional area, as measured by acoustic rhinometry, and weight, height, age, and body mass index.[94] A correlation has been found between the dimensions of the external nose and the minimal cross-sectional area.[95]

Because acoustic rhinometry measures internal nasal cavity dimensions, any structural alterations, independent of mucosal swelling, such as those related to a deviated nasal septum, will influence nasal cavity measures. Changes resulting from mucosal swelling will be modified by a nasal decongestant, whereas those related to structural airway abnormalities will not.

During exercise, the increased sympathetic tone decongests the nasal mucosa, and measures of nasal volume by acoustic rhinometry have indicated that exercise at 75% of the maximum expected heart rate for 15 minutes has the same decongestant effect as a topical α-agonist vasoconstrictor decongestant.[71,90] It is thus important that before any measures, subjects rest quietly for 15 minutes. It has been shown that such an acclimatization period reduces the variability in measurements.[96]

Changes in relationship to disease

Intranasal challenge with substances such as histamine, kinins, or allergen results in a dose-related decrease in nasal volume and in a-min that correlates well with the subjective sensation of nasal obstruction.[97-99] In naturally occurring disease, there is a tendency for a smaller nasal volume and a reduced a-min, consistent with enhanced mucosal congestion.[90,100,101] Consistent with this, there is a greater response to nasal decongestants.[90] However, the subjective reporting of nasal obstruction in unselected clinical cases does not correlate well with acoustic rhinometry measures.[102,103] This may well be because the sensation of nasal obstruction can also be influenced by changes in the ostiomeatal complex rather then purely reflecting nasal cavity size.

Relationship to other measures

Acoustic rhinometry as a volume measurement has been compared with other imaging methods for measurement of nasal volume, such as CT and magnetic resonance imaging scanning.[74-79] As discussed, in the decongested nose, these provide very comparable measurements, particularly within the anterior part of the nasal cavity.[77,78] Acoustic rhinometry obviously has considerable advantage over these other methods of measurement in being considerably less expensive, easy to conduct, rapid to perform, and without radiation risk. Studies have also compared changes in acoustic rhinometry measures after intranasal challenge with measures of nasal airflow, such as rhinomanometry and nasal peak flow.[82,97,98,104-108] Although studies have found minor variations, in general the information gained by the different techniques is very comparable, with nasal congestion leading to a decrease in nasal volume and a-min in association with a reduction in nasal inspiratory peak flow and an increase in NAR (Fig 4). Acoustic rhinometry is noted to be user-friendly.[97,98]

Similarly, improvements can be seen with all methods of measurement with nasal decongestants that increase nasal volume and improve nasal airflow.[82,109] One study found acoustic rhinometry to be more sensitive then rhinomanometry.[110]
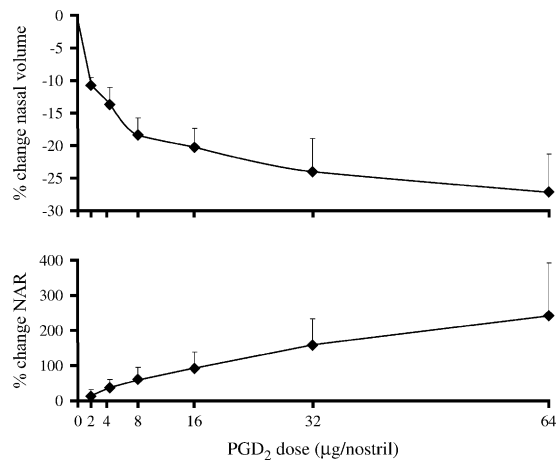
FIG 4. Changes in nasal volume *(upper panel)*, as measured by acoustic rhinometry, and in NAR *(lower panel)*, as measured by active posterior rhinomanometry, with prostaglandin D_2 (PGD_2) intranasal challenge in healthy subjects. Howarth, unpublished data, 2003.

Theoretically, acoustic rhinomanometry and rhinomanometry may provide complimentary but slightly different information, because the resistance of a cross-sectional area may differ considerably depending on the shape, despite a constant area.[107,111] In practice, however, under challenge situations in which large changes are induced, the methods are very comparable, and changes relate to the subjective sensation of induced nasal obstruction.[112] Under clinical circumstances, however, there is a poor correlation between the subjective scoring of nasal congestion and measures both by acoustic rhinometry and rhinomanometry.[102,103]

Changes in nasal cavity size after intranasal allergen challenge do not relate to measures of nitric oxide, and at rest, the concentration of nasal nitric oxide is independent of measures of nasal cavity volume.[113,114] Both these findings suggest that nitric oxide per se is not a major determinant of nasal cavity dimensions. One study in patients with coronavirus-induced common cold identified a correlation between changes in olfaction and changes in nasal dimensions, as assessed by acoustic rhinometry.[115] It is probable, however, that this relationship is purely a reflection of the viral infection affecting 2 separate variables, because studies with nasal decongestants in the common cold have dissociated these measures.[116,117] Decongestants improve nasal dimensions but have no effect on olfaction. Similarly, no significant correlation has been found between olfaction and nasal patency after nasal allergen challenge.[118]

MUCOCILIARY CLEARANCE MEASUREMENTS IN RHINITIS

The function of the mucociliary system relates to the characteristics and dynamics of the cilia, including the number of ciliated cells, the frequency, effectiveness, and coordination of ciliary beating, and the quantity and physiochemical composition of the secretions that coat the mucosal membrane. The overall function of the mucociliary clearance system within the nose may be measured by recording the transport rate of particles. Measurement of mucociliary clearance thus potentially provides an overall integrated measurement of cilial function and allows assessment of the net effect of disease processes, such as those associated with allergic inflammation. Important information may also be obtained by analyzing the characteristics of the cilia and the secretions. However, these additional measurements will not be further evaluated.

Measurement of mucociliary clearance

Traceable particles that may be soluble, such as saccharin, insoluble, such as charcoal, or radioisotopes may be placed on the surface of the inferior turbinate for measurements of mucociliary clearance within the nose. An estimate of the mucociliary activity can be obtained by recording the time until the tracer can be tasted (saccharin) or visually observed in the pharynx (charcoal). The transport rate of radioactive particles can be calculated by following them over a certain distance for a certain period.[119] The saccharin test is most frequently used for screening purposes, because it is easy to perform both for the investigated and the investigator. The radioisotopic technique gives a more exact mucociliary transport rate in millimeters per minute.

Repeatability/source of variation

The clinical and scientific applicability of measurements of the mucociliary system is, unfortunately, considerably limited by great interindividual, intraindividual, interday, and regional variations in mucociliary transport, probably reflecting both biologic and test-related features.[119,120] The transport rate in one nostril may differ considerably from the corresponding parameter in the other nostril at the same time, probably reflecting the nasal cycle. There may also be regional differences in clearance velocity within the same nostril. Some individuals have a rapid clearance rate, whereas others are slow clearers. Perfectly healthy individuals may not have recordable mucociliary transport.[121] Generally, it is recommended to measure the transport rate bilaterally to avoid misdiagnosis of mucociliary transport defect.

Confounding factors

In vitro studies on cilial function have indicated that temperature, humidity, and pH are all factors that can affect performance,[119,122-126] although changes *in vivo* in these parameters are unlikely to be very significant within the nose, because rapidly adapting changes in mucosal blood flow, glandular secretion, and nasal patency maintain homeostasis. Other endogenous confounding factors are age,[127] sex,[128] posture,[129] exercise,[130] and sleep,[131] as well as neurotransmitters and neurohormones.[122]

The effect of exogenous factors on mucociliary clearance, such as environmental pollution from tobacco smoke, car exhaust fumes, and the burning of fossil fuel, have also been evaluated. The results from studies of the effect of acute exposure to tobacco smoke on the mucociliary system are inconsistent. Consequently, it appears that there are individual variations in the mucosal tolerance to toxins such as tobacco smoke.[132,133] The functional consequences of sulfur dioxide, nitrogen dioxide, and ozone on the respiratory epithelium are controversial. Although there are reports about impairment of ciliary activity[134,135] and mucociliary clearance,[136] other studies indicate an unchanged or enhanced transport of secretions[137] after exposure to these substances.

Influence of allergic rhinitis on mucociliary function

A diseased mucociliary apparatus is characterized by defects in the ciliary and/or secretory components of the mucociliary system that interfere with the normal mechanical, physiologic, and biologic protective functions of the airway mucosa.[138,139] Secondary to the allergic inflammation, there are changes in the rheological properties of the respiratory secretions and in the morphology and function of cilia. Whether these alterations favor the overall mucociliary clearance is a matter for further studies.[119,140]

Influence of nasal therapy on mucociliary clearance

Consistent with the variability of assessments of mucociliary clearance, there are no clear results in this outcome measure. Nasal steroids have been found to improve measures,[141] to have no effect,[142] and to be no different to antihistamines.[143] Oral and intranasal antihistamines have not been found to influence mucociliary clearance,[144,145] and no effect has been seen with the leukotriene receptor antagonist zafirlukast, even though this treatment reduced the nasal lavage eosinophil count significantly.[146]

Concern has been raised about whether mucociliary function may be adversely influenced by components of medication. Both *in vitro* and *in vivo* studies have shown that that a preservative frequently used in topical nasal drugs, benzalkonium chloride, may structurally and functionally affect both the cilia and the mucosa from which they originate. The clinical consequences of this have been a matter of debate,[147,148] although a recent review of the literature concluded that products containing the preservative benzalkonium chloride appear to be safe and well tolerated.[149]

NASAL RESPONSIVENESS

The term *nasal responsiveness* refers to the functional responses of the nasal mucosa to a variety of stimuli, some of which are of physical and some of chemical nature. On the basis of convention, immunologic responses are excluded. Reactions of the nasal mucosa to such stimuli should be considered part of the protective function of the nose that is meant to benefit the entire respiratory tract. For example, cold air induces significant water loss, especially under conditions of hyperventilation. To preserve homeostasis and avoid mucosal desiccation and damage, water is being constantly replenished by passive transfer through the paracellular spaces of the nasal airway epithelium. When the water loss is excessive, hypertonicity develops and sensory nerves are activated to induce glandular secretions through a reflex mechanism. The large amounts of water in these secretions compensate for the loss. Similarly, the nose will react with sneezing, glandular secretions, and vascular engorgement (congestion) against chemical irritants or against inhaled particles. The nasal obstruction protects the nasal mucosa by limiting the access of the stimulus.

The term *hyperresponsiveness* refers to exaggerated protective responses. This may arise because of alterations in the normal response as a result of changes in inflammatory cell behavior, sensory neural function, central information processing and gating, efferent messaging, end-organ sensitivity, or end-organ responsiveness. Different stimuli will test different components. Altered responsiveness within the nose is described in both inflammatory (allergic) and noninflammatory (nonallergic) rhinitis.

Clinical relevance of nasal hyperresponsiveness

In the clinical setting, it is believed that hyperresponsiveness manifests itself with nasal symptoms induced by various exposures or by intrinsic processes that would have gone unnoticed in the absence of this condition. For example, more than 50% of patients with allergic rhinitis complain of nasal symptoms induced by smoke, strong odors, and other irritants, with the prevalence of these complaints higher in perennial than seasonal disease.[150] Patients with some forms of nonallergic rhinopathy[151] report similar symptoms. In allergic rhinitis, hyperresponsiveness may also be involved in the phenomenon of priming to allergen, which has been described by several investigators.[152,153] Priming can be viewed as an augmentation of the acute allergic reaction to allergen by repeated exposures. Although priming probably involves several mechanisms, it may be partly explained by allergen-induced increased responsiveness to the products of an allergic reaction, namely histamine,[154] sulfidopeptide leukotrienes, or prostaglandin D_2.

Methods for measuring nasal responsiveness

A major misconception regarding hyperresponsiveness is that it is a phenomenon that globally affects every aspect of nasal function. It is important to realize, however, that the nasal mucosa comprises several functional elements, including sensory and effector nerves, submucosal glands, respiratory epithelium, goblet cells, subepithelial capillaries, capacitance vessels, and so forth, all of which are regulated by distinct mechanisms and have a certain

degree of independence. Nasal symptoms are produced by the activity of 1 or more of these elements. For example, sneezing is produced by activation of nasal sensory nerves or by sensory nerves at a distant part of the body. Rhinorrhea, on the other hand, requires activation of the glandular apparatus, which may occur directly by a chemical stimulus or, most commonly, through cholinergic activation, via a central reflex. In the latter case, several elements of the mucosa are involved, namely sensory nerves, cholinergic effector nerves, and submucosal glands. Nasal symptoms do not always occur in concordance and, depending on the patient or the condition, different nasal symptoms may predominate. Allergic rhinitis characteristically involves sneezing and pruritus, something that is rather rare in patients with nonallergic rhinopathies.[151] Also, clinical observations have suggested that patients with rhinitis can be separated into sneezers, runners, or blockers on the basis of the predominance of the respective symptom.[155]

Given this complexity, one has to attempt to define hyperresponsiveness as an attribute of a specific functional element of the nasal mucosa and not as a global condition. The terms *sensorineural hyperresponsiveness*, *glandular hyperresponsiveness*, and so forth should therefore be used. The problem arises as to which tests—that is, which stimuli—can reliably offer information on the responsiveness of specific functional elements of the nose. Unfortunately, only a few stimuli with single specificity for a particular functional element have been identified.

Methacholine. One of the most specific stimuli is methacholine. In the nasal mucosa, it induces glandular secretions by activating cholinergic receptors on the basal surface of glandular epithelial cells.[156] Methacholine does not appear to affect the nasal vasculature, although the theoretical potential for vasodilation exists.[157] Clearly, methacholine does not activate sensory nerve endings.[158] The outcome of a methacholine nasal provocation can be the amount of nasal secretions produced by the stimulus or the content of nasal secretions in biochemical markers of mucus or serous gland activation. These can include mucus glycoproteins (which are very difficult to measure), the content of fucose (a characteristic sugar of the mucus glycoproteins), lysozyme, or lactoferrin (serous cell products).[159]

Is there evidence of nasal hyperresponsiveness to methacholine—that is, of nasal glandular hyperresponsiveness? Several publications support the notion that such a form of nasal hyperresponsiveness does indeed exist.[160-164] There is also some evidence that nasal provocation with allergen can increase nasal responsiveness to methacholine.[165] Unfortunately, not all studies reproduce these findings. One study examined the effect of methacholine applied to the septal mucosa through filter paper discs in patients with perennial allergic rhinitis who were distinguishable from healthy controls when other tests for hyperresponsiveness were applied. There was no difference between the groups,[166] and no good explanation for this discrepancy was apparent.

Capsaicin. Another stimulus with high specificity for a particular functional element of the nasal mucosa is capsaicin, the pungent component of hot peppers. Capsaicin stimulates a specific vanilloid receptor[167,168] on sensory nerve endings to induce a central reflex with its efferent arm leading to cholinergic glandular activation.[168,169] Capsaicin induces a strong burning sensation but only induces sneezing at very low doses. In addition to the generation of neural reflexes, capsaicin can result in local release of neuropeptides by sensory nerve endings. These peptides can also stimulate glands and may induce plasma exudation from adjacent blood vessels. In the human nose, high doses of capsaicin may yield evidence of plasma exudation, but only in patients with active allergic rhinitis.[170] Despite this, it is difficult to define rhinitis by capsaicin provocation because of a considerable variability in response, and intranasal challenge cannot identify a particular type of nasal hyperresponsiveness. On the other hand, the ipsilateral and contralateral nostril secretory response to unilateral capsaicin provocation using the filter paper technique allows for a clear differentiation between healthy subjects and patients with active allergic rhinitis, with the ED_{50} 100-fold lower in the latter.[171]

Histamine. Very little controversy exists about the ability of histamine to differentiate between active allergic rhinitis and the healthy state.[161,163,171-175] In addition, hyperresponsiveness to histamine has been convincingly demonstrated to occur after experimental nasal allergen provocation and to be inhibited by nasal corticosteroids, linking this phenomenon to allergic inflammation.[154,172,176,177] Most impressively, nasal responsiveness to histamine, with symptoms as the outcome, was found to correlate moderately well with clinical indices of perennial allergic rhinitis (PAR), such as daily symptom scores and the score from the rhinitis quality of life questionnaire.[178] Histamine is by far the most commonly used stimulus in studies assessing nasal hyperresponsiveness.

Histamine has multiple effects on the nasal mucosa. It induces sensory nerve activation leading to sneezing, pruritus, cholinergically mediated glandular secretions, and possibly even reflex vasodilation, which may be a cholinergic effect. In addition, histamine has a direct effect on the vasculature leading to vasodilation of the capacitance vessels and plasma exudation from the postcapillary venules of the subepithelial plexus. It is not clear whether histamine can directly activate the nasal glandular apparatus.[179] Despite the complicated effects of histamine on the nasal mucosa, the methodology of the provocation permits differentiation of various aspects of nasal hyperresponsiveness. First, histamine-induced sneezing is a quite clean outcome, reflecting sensory neural function, and can be used to assess sensorineural hyperresponsiveness. Second, evaluation of the content of histamine-induced nasal secretions in markers of plasma extravasation can be used as a measure of vascular hyperpermeability, a form of nasal hyperresponsiveness.

One can also measure changes in nasal airflow after unilateral histamine challenge and separate the ipsilateral from the contralateral to the challenge nostrils. This technique may allow an assessment of the direct effects of histamine on the capacitance vessels (by subtracting the changes in the contralateral from the ipsilateral nasal passage). Alternatively, pretreatment of the challenged nostril with a local anesthetic may reveal only the direct, as opposed to the indirect (neural), effects of histamine provocation on nasal airflow.

Bradykinin. Bradykinin is a product of allergic reactions.[180] Its most evident effect on the nasal mucosa is plasma extravasation. In this respect, bradykinin does not appear to differentiate patients with active allergic rhinitis from healthy controls.[181] However, in a study by Riccio and Proud,[181] healthy subjects or patients with SAR, when tested out of the pollen season, generate minimal secretory responses to bradykinin and no sneezing. In contrast, both ipsilateral and contralateral secretions to unilateral, localized bradykinin provocation, as well as sneezes, are induced in patients with PAR and in those with symptomatic seasonal disease. This indicates that, in the presence of active allergic disease, a sensorineural response to bradykinin is induced. However, there are some discrepancies between this study and a study reported by Baraniuk et al.[182] Thus, more work with bradykinin in the nose will be required to obtain a more concrete impression of its potential usefulness as a tool to examine specific forms of nasal hyperresponsiveness. Studies on the effects of anti-inflammatory agents on hyperresponsiveness to bradykinin have not been performed. Neither do we know whether experimental allergen provocation can change as well as augment the qualitative characteristics of the responsiveness to bradykinin. However, it is worth mentioning that, in the lower airways of patients with asthma, responsiveness to bradykinin increases dramatically 24 to 48 hours after allergen inhalation challenge, much more so than the responsiveness to methacholine.[183] Inversely, bronchial responsiveness to bradykinin can be dramatically reduced with inhaled glucocorticosteroids.[184]

Other pharmacologic and biochemical stimuli. Other products of the nasal allergic reaction could turn out to be useful in assessing nasal hyperresponsiveness. These include the sulfidopeptide leukotrienes, prostaglandin D_2, platelet-activating factor, and so forth. There is very limited experience, however, with nasal provocations involving these agents. Also, other endogenous substances that are capable of inducing nasal symptoms but have not been clearly associated with allergic reactions should be considered, including serotonin, endothelin, and neuropeptides such as substance P or neurokinin A.

Physical and environmental nonantigenic stimuli. Nasal symptoms can be produced by physical stimuli. The most common and well-characterized physical stimulus is cold, dry air and, associated with that, hyperosmolar solutions. Many individuals complain of nasal symptoms on exposure to cold, windy conditions, particularly during winter skiing, a phenomenon termed *skier's nose*.[185] Cold, dry air nasal challenges have been performed in the laboratory, and nasal responsiveness to this stimulus has been well characterized.[186-191] Although many individuals without allergy have a specific sensitivity to cold, dry air, which is not associated with any other kind of nasal dysfunction, patients with active allergic rhinitis respond more vigorously to this stimulus compared with healthy subjects.[189] Furthermore, patients with allergic rhinitis and asthma have stronger nasal reactivity to nasal challenge with cold, dry air compared with patients with allergic rhinitis alone.[192] Finally, nasal allergen provocation augments the nasal reaction to cold, dry air.[193] Interestingly, cold, dry air has been shown to differentiate patients with nonallergic, noninfectious perennial rhinitis from healthy subjects with higher sensitivity than histamine.[194] Although the exact mechanism through which cold, dry air induces a nasal reaction is not known, available data support the concept that this is primarily a sensorineural reaction initiated by increased tonicity (osmolarity) of the nasal surface, which is in turn induced by excessive water loss.[195] The main outcome of the reaction, however, is glandular activation.[196]

In accordance with the theories regarding the mechanism of nasal reaction to cold, dry air, various forms of nasal challenges with hyperosmolar solutions have been developed.[55,197,198] The outcomes from these provocations support the concept that hyperosmolarity and cold, dry air share common pathways.[195] As with cold, dry air, hyperosmolar challenges reveal stronger nasal responsiveness in patients with PAR compared with healthy controls.[55] Studies in healthy volunteers have shown that intranasal hypertonic saline enhances the exudative and secretory effects of histamine and methacholine respectively.[199]

Shusterman and Balmes[200] and Shusterman et al[201] have developed a methodology to stimulate the nose with chlorine gas and with carbon dioxide. These stimuli are quite relevant to daily environmental exposures, and nasal responsiveness assessed through such methodologies has direct clinical implications. These studies have so far demonstrated that patients with SAR, even when tested outside the pollen season, develop nasal airflow limitation on exposure to chlorine gas with lower threshold, compared with healthy controls.

Techniques for nasal challenge

The methodologies through which nasal provocations are performed to assess hyperresponsiveness can be largely categorized into 3 groups: whole-nose challenges, localized challenges, and environmental exposures. In the last case, provocations are performed either inside environmental chambers or with equipment designed to deliver gases into the nasal passages via face masks.[186,201]

Whole-nose challenges are usually performed with the use of a metered pump spray that delivers a known amount of stimulus into the mucosa. A large airway surface can be reached in this fashion. Objective outcomes from such provocations can be obtained with evaluations of airflow, blowing of secretions, or nasal lavage. Nasal lavage offers

the advantage of collecting large volumes of secretions and performing extensive evaluations.[202]

The localized provocations are performed by using filter paper discs or strips impregnated with the chemical stimulant that can be introduced into one nostril and left in contact with the septal or the inferior turbinate mucosa for a specific period.[158] Secretory outcomes can be assessed by introducing preweighed dry discs or strips, of the same size as those used for stimulation, onto the same mucosal areas. Secretions induced by the stimulus are absorbed by the filter paper, and the change in the weight of these collection discs is a reliable marker of the secretory response. Collected secretions can be eluted from the filter paper, and limited biochemical evaluations can be performed. The major advantage of the localized challenge technique is that it allows secretions to be collected from both the ipsilateral and the contralateral side to the unilateral provocation. Thus, neurally mediated outcomes involving central reflexes can be assessed.

An alternative approach to whole-nose and to localized challenges is the nasal pool device and related instruments.[203] According to this technique, a lavage is performed only in one nostril by instilling the fluid through a pump-like device (the nasal pool) and retracting it after a set period.

Nasal responsiveness as an outcome measure with therapeutic intervention

The major problem in efficacy trials of therapeutic modalities in allergic rhinitis is the lack of objective measures. Obviously, the importance of reported nasal symptoms should not be underestimated, because the definition and diagnosis of rhinitis is also based on symptomatology, and it is the symptoms of this ailment that drive its morbidity and its economic effect on society. Unfortunately, questions are consistently raised regarding the reliability of symptom scales or other subjective measures such as quality of life, which are associated with impressive placebo effects. From this perspective, objective measures should be sought as complementary outcomes in clinical trials to strengthen the validity of therapeutic efficacy conclusions.

Some trials have begun to use nasal peak flow measurements to provide objective measure support. The problem with this approach is that nasal airflow limitation is only 1 of several nasal symptoms, and not all patients with allergic rhinitis report congestion as a major complaint. Furthermore, nasal symptomatology is frequently episodic, and daily measurements of airflow may not track the natural presentation of the disease. By assessing nasal hyperresponsiveness, one can obtain a better picture of the propensity of a patient to develop symptoms in response to frequently encountered environmental stimuli. Most importantly, if measures of nasal hyperresponsiveness are performed by using methodologies that can dissect the various functions of the nose, as discussed, various clinical phenotypes and their response to treatment could be correlated to a particular aspect of hyperresponsiveness in a patient-tailored fashion. Unfortunately, the lack of

standardization and validation of methodologies to assess nasal hyperresponsiveness means that only scattered data are available on the effects of therapeutic agents, and, even worse, none from large-scale clinical trials.

As discussed, nasal corticosteroids have been found to affect various aspects of nasal responsiveness in a limited number of short-term laboratory trials. Pretreatment with nasal corticosteroids for 1 week has been shown to reduce allergen-induced increase in some aspects of nasal responsiveness to histamine.[176,177] It appears that this effect can be obtained even with a single dose of steroids administered 2 hours before the allergen challenge.[204] Klementsson et al,[165] using therapeutic agents other than corticosteroids, showed that pretreatment with cetirizine and terfenadine, 2 of the second-generation nonsedating antihistamines, inhibited the small increase in nasal secretory responsiveness to methacholine that was induced 24 hours after nasal allergen challenge.

The few clinical trials in which aspects of nasal responsiveness were assessed can be summarized as follows. In 1981, Malm et al[205] showed moderate reduction by a nasal corticosteroid of the secretory responsiveness to methacholine in patients with nonallergic rhinitis. In 1982, Toft et al[206] showed that sneezing induced by the spraying of beclomethasone in the nose was reduced after chronic treatment in patients with nasal polyposis. Finally, in 1991, it was reported that budesonide given nasally during the birch pollen season was able to reduce the seasonal increase in nasal secretory responsiveness to methacholine.[207] Veld et al[208] performed the only clinical trial with antihistamines that attempted to assess nasal responsiveness, in which treatment with topical levocabastine failed to reduce methacholine secretory responsiveness in patients with PAR.

SUMMARY

Objective measures exist for the measurement of nasal patency. Nasal peak flow is an inexpensive, noninvasive, portable, and relatively simple measure that reflects changes in nasal luminal patency. Nasal peak flow is the only validated method suitable for home use, and studies have demonstrated that, when used correctly, the method is reproducible, correlates with both subjective and other objective measures, and may therefore provide a viable method for the outpatient monitoring of nasal patency. NPIF has better reproducibility than NPEF and is the best validated and studied nasal peak flow measurement. Such use would be most appropriate in persistent rather than intermittent disease, because measurement at set times of the day may not reflect episodic events. Within the laboratory, rhinomanometry is the standard technique used for the measurement of nasal resistance, and measurements are relatively easy and are reproducible. This approach is thus commonly used in nasal challenge studies. Such measures are more discerning than those of peak flow. The equipment is not portable and thus not available for home monitoring. The instability of nasal

resistance means that only relatively large changes in resistance can be studied in clinical trials, when occasional clinic visit measurements are made, but despite this, such measurements have been able to demonstrate the efficacy of medications such as nasal steroids in allergic rhinitis. A nonphysiologic measure of nasal patency is acoustic rhinometry. Using sound waves and their echo reflection, this technique measures intranasal volume and a-min within the nose. This method of measurement correlates well with rhinomanometry and NPIF and is easy to undertake. Acoustic rhinometry has advantages in that it needs little patient cooperation in the measurements and is a repeatable method of measurement. Measures of nasal patency, although they provide objective outcome measures, reflect only 1 aspect of rhinitis and may thus not encompass all aspects of the disease. It is recognized that there may be altered mucociliary clearance and abnormal nasal airway reactivity in rhinitis. Measures of mucociliary clearance, although simple and easily applicable clinically, are poorly repeatable. To provide a more integrated measure of abnormal nasal airway physiology, nasal challenge testing to measure nasal reactivity has been used.

Nasal responsiveness testing theoretically reflects the propensity of a patient to develop nasal symptoms in response to exogenous or endogenous stimuli, and if this response is abnormally exaggerated, this is termed *nasal hyperresponsiveness*. From this perspective, evaluation of this phenomenon can potentially complement currently assessed parameters, such as symptoms, quality of life outcomes, and use of rescue medications. However, hyperresponsiveness is a very complex phenomenon that involves a range of potential abnormalities in the various functional elements of the nasal mucosa. Standardized methodologies assessing these abnormalities are not sufficiently developed, and the relationship between such abnormalities and disease presentation has not been vigorously examined. In the effort to develop objective tools to test efficacy of nasal therapeutic modalities, the area of nasal hyperresponsiveness needs to be developed.

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