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Diagnostic Criteria of Nonspecific Hyperreactivity Using Cold Dry Air Provocation With Acoustic Rhinometry

Young Hyo Kim, MD, MPh, and Tae Young Jang, MD, PhD

Objectives. The authors aimed to (1) compare symptom changes in patients with or without nonspecific hyperreactivity, (2) compare changes in total nasal volume (TNV) and minimal cross-sectional area (MCA) using acoustic rhinometry after cold dry air (CDA) challenge, and (3) set the diagnostic criteria using receiver operating characteristic (ROC) curve analysis.

Methods

Subjects and Methods. CDA provocation was performed on 45 patients with self-reported hypersensitivity to cold dry air (group A) and on 53 patients without such hypersensitivity (group B). Symptoms (as measured by visual analog scale [VAS]), TNV, and MCA were checked before and after provocation.

Results. The changes in nasal obstruction (1.8 ± 2.1 vs 0.0 ± 2.3) and rhinorrhea (0.8 ± 2.1 vs −0.5 ± 2.3) were significantly greater in group A (P < .01 in each case). There were no significant differences between groups in VAS scores for sneezing and itching. From the ROC curve, the authors set the diagnostic criterion as “TNSS (total nasal symptom score) change larger than 1.5,” and its sensitivity and specificity were 75.6% and 86.8%, respectively. The criteria “TNV decrease larger than 19.5%” and “MCA change larger than 15.0%” had higher sensitivity and specificity (TNV: 84.4% sensitivity and 77.4% specificity; MCA: 93.3% sensitivity and 77.4% specificity).

Conclusions. The authors were able to propose diagnostic criteria of nonspecific hyperreactivity using a CDA provocation test with acoustic rhinometry. These results are also helpful for understanding the pathophysiologic mechanisms of nonspecific hyperreactivity.

Keywords

allergic rhinitis, acoustic rhinometry, nasal provocation tests

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MAST, Multiple Allergo-Sorbent Test.

Exclusion criteria

Inclusion criteria for the whole cohort (group A or group B)

Table 1. The 5-Point-Scale Used to Check Patients’ Sensitivity to Cold Air

Q: Do you feel more uncomfortable when you are exposed to cold air (for example, when you get into an air-conditioned room or in the winter)?

A: Please check one that is closest to you

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<th>Absolutely so</th>
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17-59 years old) and 53 patients who “never” felt discomfort (group B, 36 men and 17 women, 15-60 years old) were enrolled. Patient gender and age were not significantly different between groups. Thirty patients with allergic rhinitis and 15 patients with nonallergic rhinitis were included in group A. Forty-three healthy volunteers, 9 allergic patients, and 1 nonallergic patient were included in group B. The criteria for inclusion or exclusion are listed in Table 2. No patient took medications that could affect the result of the CDA challenge. All patients gave informed consent before entry, and the study was approved by the Inha University Institutional Review Board Committee on Studies Involving Human Beings.

Cold Dry Air Challenge

Patients were acclimatized to room temperature (20°C) for 15 minutes prior to blowing their nose to remove nasal secretion and nasal rinsing 5 times with normal saline irrigation. About 15 minutes after humidification, baseline symptom scores for nasal obstruction, rhinorrhea, sneezing, and itching were obtained using a visual analog scale (VAS). The VAS used a 10-cm line with a dot at every centimeter, and patients marked the severity of their symptoms from 0 to 10 on the line. TNV and MCA were obtained by acoustic rhinometry in both nasal cavities. The method for performing acoustic rhinometry is well described elsewhere.9

The CDA provocation test was then performed on each patient. Air for medical use was cooled to about 0°C by passing through a refrigerating air dryer. The cooled air was dried (to less than 10% humidity) by passage through a mist separator, and particles, dust, and microorganisms were removed by passage through a filter. The cold dry air was delivered to patients’ noses via a pediatric continuous positive airway pressure (CPAP) mask. Patients were instructed to inhale through the nose and exhale through the mouth during the air challenge and to maintain their ordinary breathing frequency. About 400 L of cold dry air was supplied over 6 minutes. For the patients’ safety, the provocation was stopped immediately in the case of hyperventilation or other major discomfort.

Five minutes after provocation, symptoms were measured by VAS. TNV and MCA were obtained in both nasal cavities by repeating acoustic rhinometry, and the changes were expressed as a percentage. The larger of the values between the right and left nasal cavity was selected. To avoid diurnal variation and intertest error, all the provocations were performed at a fixed time of the day by a single experienced examiner.

Statistical Analysis

Because the data were not normally distributed, the Mann-Whitney U test was used to compare the change in symptoms and TNV and MCA values between groups. Data were reported as mean ± standard deviation. To set a diagnostic standard and evaluate its sensitivity and specificity, the authors used a ROC curve. SPSS 12.0 statistics software (SPSS, Inc, an IBM Company, Chicago, Illinois) was used, and P < .05 was accepted as statistically significant.

Results

The changes in nasal obstruction (1.8 ± 2.1 vs 0.0 ± 2.3) and rhinorrhea (0.8 ± 2.1 vs –0.5 ± 2.3) were significantly greater in group A (P < .01 in each case). However, there were no significant differences between groups in VAS scores for sneezing and itching (Figure 1). Defining the total nasal symptom score (TNSS) as the sum of the values above, the change in TNSS was significantly larger in group A (2.5 ± 4.3 vs –1.3 ± 7.1, P < .01). The change of TNV and MCA values was also larger in group A (TNV: 31.6% ± 14.1% vs 12.4% ± 14.0%; MCA: 33.9% ± 18.2% vs 8.9% ± 16.0%, P < .001 in each case; Figure 2).

By drawing a ROC curve, the authors found that the changes of nasal obstruction and rhinorrhea had some value as diagnostic parameters, whereas changes of sneezing and itching had no value (Figure 3). The areas under the curve (AUCs) of nasal obstruction, rhinorrhea, sneezing, and itching were 0.772, 0.712, 0.559, and 0.564, respectively. The AUC of TNSS change was 0.784. When the authors set the diagnostic criterion as “TNSS change larger than 1.5,” the sensitivity and specificity were 75.6% and 86.8%, whereas the positive and

Table 2. Inclusion and Exclusion Criteria for the Study

Inclusion criteria for the whole cohort (group A or group B)

Age: 16 to 65 years
Free of any nasal symptoms (healthy volunteers group)
More than 1 year of suffering from allergic or nonallergic rhinitis (allergic or nonallergic patients)
Strongly positive (more than 3+) to house dust mites (allergic patients)
Negative skin prick or MAST results to any antigen (nonallergic rhinitis)

Exclusion criteria

Use of inhaled or systemic corticosteroids within a month
Use of inhaled cromoglycates, astemizole, or nedocromil sodium within a month
Inability to stop medication that could affect nasal function
A serious or unstable, systemic disease
Pregnant or lactating woman
History of nasal surgery within 3 months
Nasal polyp or chronic sinusitis proved by plain X-ray or computed tomography of the paranasal sinus
Exposure to chemical irritants
Use of inhaled or systemic corticosteroids within a month
Use of inhaled cromoglycates, astemizole, or nedocromil sodium within a month
A serious or unstable, systemic disease
Inability to stop medication that could affect nasal function
Pregnant or lactating woman
History of nasal surgery within 3 months
Nasal polyp or chronic sinusitis proved by plain X-ray or computed tomography of the paranasal sinus
Exposure to chemical irritants

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MAST: Multiple Allergo-Sorbent Test.
negative predictive values were 82.9% and 80.7%, respectively. Because there were no significant changes in sneezing and itching, the authors also drew a ROC curve for change of nasal obstruction and rhinorrhea combined (Figure 4). The criterion of “larger than 1.5 change of nasal obstruction and rhinorrhea combined” had a slightly lower sensitivity (68.9%) and specificity (84.9%).

The ROC curve of TNV change revealed that the AUC was 0.836, and when the diagnostic criterion was set as “TNV decrease larger than 19.5%,” the sensitivity and specificity were 84.4% and 77.4% (Figure 5). When the criterion was set as “MCA change larger than 15.0%,” the ROC curve of MCA change revealed a sensitivity of 93.3%, a specificity of 77.4%, a positive predictive value of 77.8%, and a negative predictive value of 93.2% (Figure 6).

**Discussion**

In our study, the aggravation of nasal obstruction and rhinorrhea was more prominent in patients with nonspecific hyperreactivity. However, this was not the case for sneezing or itching, and the ROC curves of sneezing and itching were not diagnostic either. These results are in agreement with previous findings, with Togias and colleagues reporting a very low incidence of sneezing and other researchers who also used nasal patency and mucus production as the main parameters suggesting that sneezing was not useful. Sneezing and itching are caused by the activation of afferent fibers of the trigeminal nerve in the nasal mucosa. In allergic rhinitis, immunologically triggered inflammation thus plays a central role in causing sneezing and itching. On the other hand, the glandular and vascular systems are regulated by parasympathetic and sympathetic reflexes. Thus, cholinergic reflexes are responsible for symptoms such as nasal congestion and secretion. Therefore, the authors suggest that the mechanism of CDA hypersensitivity is different from that of allergic rhinitis.

Upon allergenic provocation, mast cells degranulate, and several mediators such as histamine, prostaglandins, and leukotrienes are released. Histamine causes nasal congestion, rhinorrhea, sneezing, and tickling sensation when applied in high concentrations inside the nose. The chemical mediators such as histamine, PGD, and leukotrienes are also increased in the nasal lavage fluids after CDA provocation. However, the lack of induction of sneezing and itching after CDA provocation suggests that these mediators might only play a limited role in the pathogenesis of nonspecific hyperreactivity. In fact, the role of these mediators in the response to cold dry air is still unknown. And the fact that intranasal antihistamine and topical steroids were not effective in alleviating symptoms after CDA provocation further supports this hypothesis.
Instead, the parasympathetic nervous system plays a pivotal role in CDA-induced rhinitis. This hypothesis is supported by the fact that pretreatment with anticholinergic agents decreased the secretory response to cold dry air, and atropine had a significant suppressive effect on rhinorrhea. Togias and others suggested that because the nasal congestion and albumin levels of nasal lavage fluid are unchanged after atropine application, there could be yet another mechanism involving, for example, plasma transudation or nonmucinic nasal glands.
Since there is still no single test to diagnose and evaluate nonspecific hyperreactivity (especially to cold dry air), the authors used self-reported hypersensitivity as the gold standard. To our knowledge, this is the first study to establish diagnostic criteria using CDA provocation and acoustic rhinometry with reasonable sensitivity and specificity. Although earlier studies used air of temperatures below \(-10^\circ\text{C}\), \(1^,1^6\) recent studies have used air of 0°C, which is more physiologic. \(2^0\) The authors also used air of 0°C, which caused much less discomfort and greater compliance of patients.

The authors set the diagnostic criteria of nonspecific hyperreactivity as (A) “symptom change as measured by VAS of more than 1.5” and (B) “MCA change larger than 15%” after the CDA challenge. Applying the criteria as “(A) or (B),” the sensitivity was 100%, but the specificity was 64.2%. In contrast, the criteria of “(A) and (B)” had a sensitivity of 68.9% and a specificity of 100%. Therefore, clinicians should bear both these criteria in mind and apply them with careful consideration of the clinical picture.

The patient and control groups each had allergic and nonallergic patients. This is because the authors tried to evaluate the nonspecific hyperreactivity of the nasal cavity itself, regardless of the etiology. The fact that allergic patients and nonallergic patients coexist in the clinical setting supports the logic of our choice.

The pathophysiologic mechanisms of nonspecific hyperreactivity are still to be elucidated. Although not included in the scope of this study, the pathophysiologic mechanisms beyond parasympathetic activity should be studied in the near future by analysis of nasal lavage fluid or other methods.

In conclusion, patients with nonspecific hyperreactivity experienced greater aggravation of nasal obstruction and rhinorrhea after CDA provocation than those without hyperreactivity. This tendency was proved by greater decreases of TNV and MCA as measured by acoustic rhinometry. On the basis of these results, the authors were able to propose diagnostic criteria of nonspecific hyperreactivity using a CDA provocation test with acoustic rhinometry. These results are also helpful for understanding the pathophysiologic mechanism of nonspecific hyperreactivity.

**Author Contributions**

**Young Hyo Kim**, acquisition of data, primary writing of article, English interpretation; **Tae Young Jang**, study design, analysis and interpretation of data.

**Disclosures**

**Competing interests:** None.

**Sponsorships:** None.

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