

Nasal provocation test using allergen extract versus cold dry air provocation test: Which and when?

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ABSTRACT

Background: Nasal provocation tests (NPTs) are useful for evaluation of patients with allergic rhinitis. The cold dry air (CDA) provocation test is useful for evaluation of patients with nonspecific nasal hyperreactivity (NHR). This study aimed to determine whether the NPT or CDA provocation would be more useful for patients with different clinical pictures.

Methods: We evaluated changes in nasal symptoms (visual analog scale [VAS]) and acoustic parameters after NPT or CDA provocation in healthy volunteers (group A, $n = 27$), patients with allergic rhinitis (group B, $n = 20$), and subjects with nonallergic rhinitis (group C, $n = 26$). According to their subjective cold hyperresponsiveness (SCH), we compared changes in VAS and acoustic parameters after each protocol. The correlation between results of the skin-prick test (SPT) and changes in VAS after each protocol was analyzed. Finally, we performed an analysis of correlation between NPT and CDA provocation.

Results: After NPT, group B showed a larger change in VAS for rhinorrhea, sneezing, and itching ($p < 0.01$). After CDA challenge, the change in VAS for nasal obstruction was larger in group C ($p < 0.05$). Changes in acoustic parameters were larger in groups B and C after NPT ($p < 0.01$). After CDA challenge, the SCH⁺ group ($n = 49$) showed a larger decrease of acoustic parameters than the SCH⁻ group ($n = 24$; $p < 0.01$). Significant correlation was observed between the size of SPT and degree of change in VAS after NPT. No significant correlation was observed between NPT and CDA.

Conclusion: CDA could be an adjunct tool for evaluating NHR in patients with self-reported SCH.

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Diagnosis of allergic rhinitis is based on the typical symptoms exhibited by patients and a positive laboratory result of the skin-prick test (SPT). However, observation of actual change of the nasal cavity, the target organ of allergic rhinitis, should be included in the diagnostic step. In this aspect, the nasal provocation test (NPT), which involves administration of allergen extract directly into the nasal cavity, is an ideal test.^{1,2} In our previous study, to evaluate the usefulness of NPT in diagnosis of allergic rhinitis, we performed an analysis of the change of nasal symptoms and the actual dimension and volume of the nasal cavity.³

Nonspecific nasal hyperreactivity (NHR) is defined as increased sensitivity of the nasal mucosa to several nonallergenic, nonspecific physical stimuli, such as sudden change of temperature, air pollutant, or smoking.⁴ The cold dry air (CDA) provocation test is one of several provocative protocols designed for evaluation of such NHR.^{5,6} We have shown the usefulness of CDA provocation with acoustic rhinometry in detection and evaluation of NHR.⁷ In addition, we have proposed criteria for use in diagnosis of NHR, using CDA provocation and acoustic rhinometry.⁸

Various patients with allergic or nonallergic rhinitis and those with or without NHR visit the outpatient clinics. Therefore, determination of the provocative protocol that would be most suitable for each patient is essential. In addition, study of the correlation between NPT and the CDA provocation test is also needed.

Therefore, we evaluated changes in nasal symptoms and acoustic parameters after NPT with house-dust mite (HDM) challenge and CDA provocation in healthy volunteers, patients with allergic rhinitis, and those with nonallergic rhinitis. Then, we grouped healthy volunteers and patients again according to their self-reported subjective hyperresponsiveness to cold air. We then compared changes in nasal symptoms and acoustic parameters after NPT or CDA provocation to

determine their usefulness in evaluation of NHR regardless of allergy. We also analyzed the correlation between the results of SPT and change in nasal symptoms after use of each provocation protocol to determine a more useful test for evaluation of systemic atopy. Finally, we analyzed the correlation between NPT and CDA provocation tests.

MATERIALS AND METHODS

Subjects

Healthy volunteers (group A, $n = 27$) with no nasal symptoms and negative SPT results were enrolled (If they had significant SPT reactions, they were disqualified even if they had no symptoms). Also, patients who had suffered from typical symptoms of rhinitis were enrolled in this study. All patients underwent SPT for >40 kinds of antigens, including HDM, fungi, pollen of various trees or weeds, cat, or cockroach. According to the results of SPT, patients who showed strongly positive results (>3+ to HDM) were classified as group B (allergic rhinitis, $n = 20$). And those who showed negative or only weakly positive results ($\leq 1+$) to HDM were classified as group C (nonallergic rhinitis, $n = 26$). For the homogeneity of the study population, those who had positive SPT results to any other allergen (pollens and other seasonal allergens) were disqualified. Patients who had used any antiallergic medication within 1 month, those with unstable systemic disease, pregnant or lactating women, those who had undergone nasal surgery within 3 months, those with nasal polyp or chronic sinusitis (which was confirmed by rigid endoscopy, plain paranasal x ray, and computed tomography), and those with chronic exposure to chemical irritants or smoking were excluded from the study. According to the Allergic Rhinitis and Its Impact on Asthma 2008 classification, there were no significant differences in patients' gender, age, and the severity of rhinitis between groups. The demographics of each group are summarized in Table 1. Before entry into the study, all patients provided written informed consent, and the study was approved by the Inha University Institutional Review Board Committee on Studies Involving Human Beings.

NPT Using HDM Extract and Acoustic Rhinometry

The detailed methodology for performance of NPT was described in more detail in our previous article.³ Briefly, an ECCOVISION

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Table 1 The demographic data of each group

Group	Age (yr)	Male/Female Ratio	ARIA classification (intermittent mild/intermittent moderate-to-severe/persistent mild/persistent moderate-to-severe)
A (n = 27)	13 to 64 (42.7 ± 15.5)	14:13	N/A
B (n = 20)	15 to 55 (29.5 ± 13.4)	14:6	1/0/5/14
C (n = 26)	19 to 62 (43.9 ± 12.7)	11:15	2/0/3/21

ARIA = Allergic Rhinitis and Its Impact on Asthma; N/A = not applicable.

Table 2 SCH questionnaire to assess patients' sensitivity to cold air

Q: How much is the discomfort you feel when you are exposed to cold air (e.g., when you get into the air-conditioned room or in the winter)?

A: (Please check one that is closest to you)

Absent (grade 0)	Mild (grade 1)	Moderate (grade 2)	Severe (grade 3)
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Source: Ref. 9.

SCH = subjective cold hyperresponsiveness.

acoustic rhinometer (E. Benson Hood Laboratories, Allergopharma, Hamburg, Germany) and *Dermatophagoides pteronyssinus* (DP) allergen extract (Allergopharma) were used. Fixed dose of DP extracts (50,000 standardized biological units [SBU]/mL) were diluted to 1:10 with 0.9% normal saline and were administered intranasally to each patient using a pump dosage sprayer. The sprayed dose was ~50 µL. During a 15-minute period of relaxation in a room at regular temperature (22°C) and relative humidity (50%), patients were asked to complete a visual analog scale (VAS) questionnaire for evaluation of nasal symptoms of nasal obstruction, rhinorrhea, sneezing, and itching by marking the severity of subjective discomfort on a 10-cm-long line on paper with marks at each centimeter. Acoustic rhinometry was performed for measurement of the minimal cross-sectional area (MCA) and total nasal volume (TNV). MCA was defined as the smallest cross-sectional area of the nasal cavity, and TNV was defined as the sum of the cross-sectional area from the nostril to 7 cm deep. After relaxation, patients received a challenge with DP antigen. VAS for each nasal symptom and acoustic rhinometry were repeated 15 minutes after the challenge. The change of TNV and MCA from the basal value was calculated as percentage.

CDA Challenge

The detailed protocol for CDA challenge was also described in our previous studies.⁷⁻⁹ Before the challenge, patients rested in a room at regular temperature and relative humidity for a period of 15 minutes, filling in the VAS questionnaire for evaluation of nasal symptoms and undergoing acoustic rhinometry for measurement of basal TNV and MCA. Before the actual CDA challenge, the subjective cold hyperresponsiveness (SCH) questionnaires, which were validated in our previous studies, were obtained from every patient (Table 2).⁹ According to their answer to the questionnaire, those with grade 2 or 3 were classified into the SCH⁺ group and those with grade 0 or 1 were classified into the SCH⁻ group.

For CDA challenge, air for medical use was made cold (~0°C) using a refrigerant air dryer, and was made dry (~10% humidity) by use of a mist separator. A microfilter was used for removal of any dust, particles, or microorganisms. A pediatric continuous positive airway pressure mask was used for delivery of the resultant CDA to the nose of the patient. Patients were instructed to inhale through the nose and exhale through the mouth during CDA challenge and to breathe according to their ordinary breath frequency and pattern. For a period of 6 minutes, 400 L of CDA was supplied to the patient's nose. None of the patients suffered from hyperventilation or other

major side effects during and after CDA challenge. After the challenge, patients again filled in their responses on the VAS questionnaire and underwent acoustic rhinometry for evaluation of their change. Between NPT and CDA challenge, there was more than a 1-week interval. In addition, for the order of test, the balanced design was used to control possible stimulus-carryover effects.

Statistical Analysis

Although the size of each group was >20, because of the significant standard deviation, we used nonparametric analysis, including the Kruskal-Wallis and Mann-Whitney *U* tests for comparison of changes in VAS scores, and acoustic parameters between groups. We used linear regression analysis for assessment of the correlation between the result of SPT and change of VAS score. A value of *p* < 0.05 was accepted as statistically significant.

RESULTS

After HDM challenge, subjects in group B (allergic rhinitis group) showed significantly larger changes in VAS score for rhinorrhea, sneezing, and itching, compared with those in group A (healthy volunteers) or group C (nonallergic rhinitis group; Fig. 1 *a*; *p* < 0.001 for rhinorrhea and itching; *p* = 0.002 for sneezing). For change in VAS for nasal obstruction, groups B and C showed a greater change in VAS, compared with group A (*p* < 0.001). However, no significant difference was observed between groups B and C.

In analysis of changes in acoustic parameters after HDM challenge, we observed that changes in TNV and MCA were larger in groups B and C, compared with those of group A (Fig. 1 *b*; *p* < 0.01). However, no significant difference was observed between groups B and C.

After CDA challenge, the change in VAS for nasal obstruction was significantly larger in group C, compared with those of group A and group B (Fig. 2 *a*; *p* < 0.05). However, changes in VAS for other nasal symptoms did not differ significantly between groups.

In analysis of changes in acoustic parameters after CDA challenge, we found that changes of TNV and MCA were larger in groups B and C, compared with those of group A (Fig. 2 *b*; *p* < 0.01). However, no significant difference was observed between groups B and C.

We further divided 73 patients according to those with subjective hypersensitivity to cold (SCH⁺ group, *n* = 49) and those without such hypersensitivity (SCH⁻ group, *n* = 24). After HDM challenge, subjects in the SCH⁺ group tended to suffer from greater aggravation of sneezing and itching, compared with those in the SCH⁻ group. How-

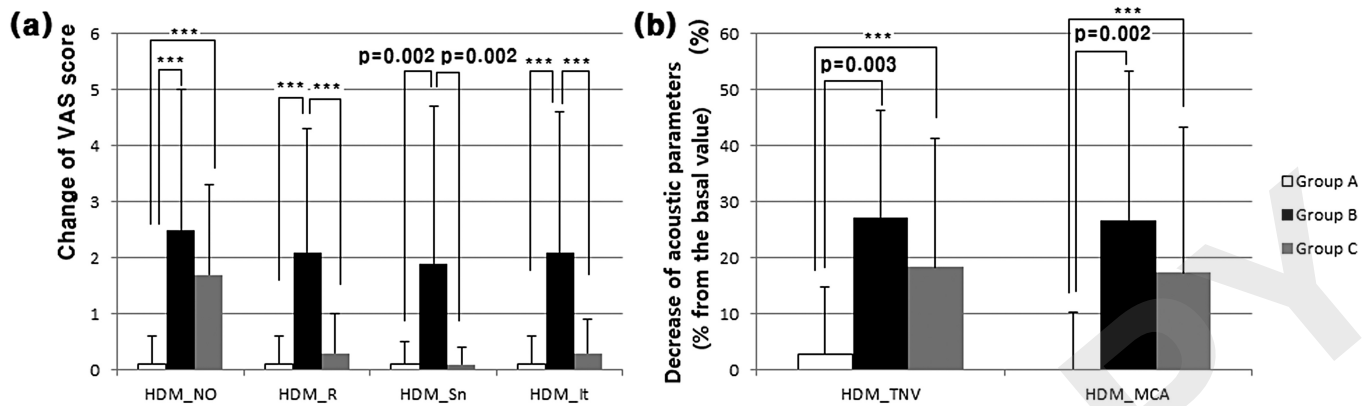


Figure 1. Change of (a) nasal symptoms and (b) acoustic parameters, including total nasal volume (TNV) and minimal cross-sectional area (MCA), after nasal provocation with house-dust mite (HDM) challenge. Group A—healthy volunteers; group B—patients with allergic rhinitis; group C—patients with nonallergic rhinitis. VAS, visual analog scale; _NO, nasal obstruction; _R, rhinorrhea; _Sn, sneezing; _It, itching sense; Kruskal-Wallis and Mann-Whitney U test; *** $p < 0.001$.

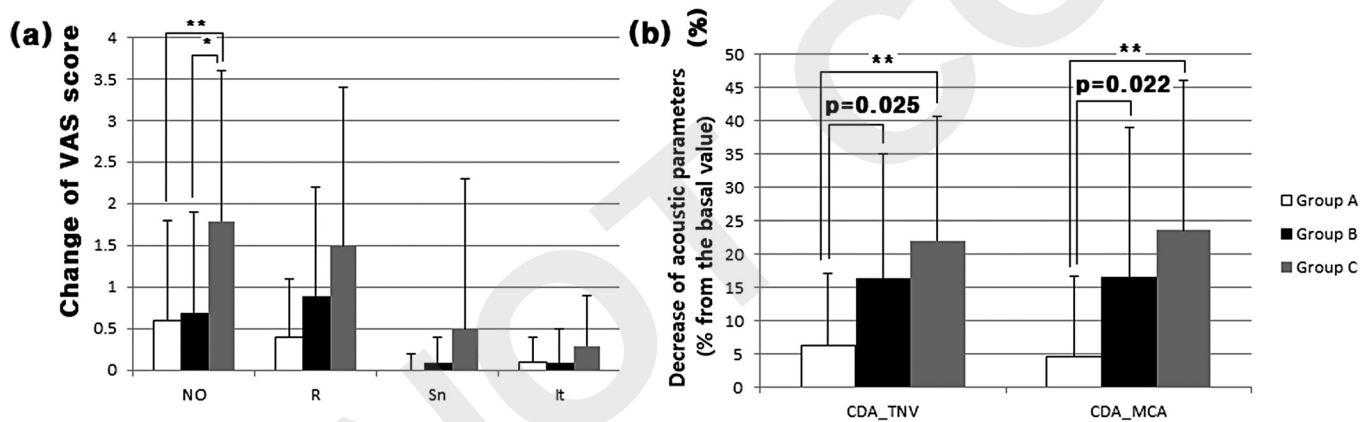


Figure 2. Change of (a) nasal symptoms and (b) acoustic parameters, including total nasal volume (TNV) and minimal cross-sectional area (MCA), after cold dry air (CDA) challenge. Group A—healthy volunteers; group B—patients with allergic rhinitis; group C—patients with nonallergic rhinitis. VAS, visual analog scale; NO, nasal obstruction; R, rhinorrhea; Sn, sneezing; It, itching sense; Kruskal-Wallis and Mann-Whitney U test; * $p < 0.05$; ** $p < 0.01$.

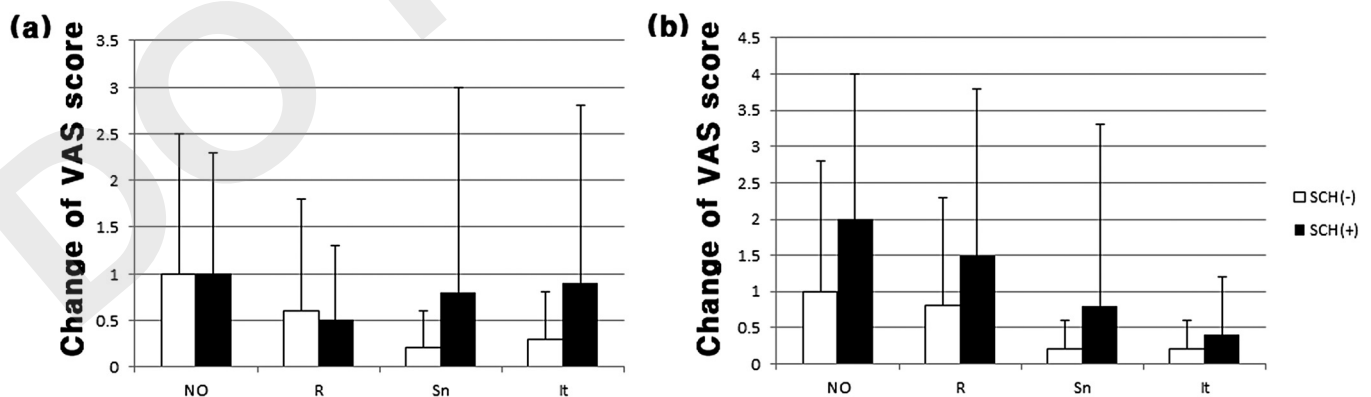


Figure 3. Change of nasal symptoms after (a) nasal provocation with house-dust mite (HDM) challenge and (b) cold dry air (CDA) challenge. SCH⁺—patients with self-reported subjective hyperresponsiveness to CDA. SCH⁻—patients without subjective hyperresponsiveness to CDA. VAS, visual analog scale; NO, nasal obstruction; R, rhinorrhea; Sn, sneezing; It, itching sense; Kruskal-Wallis and Mann-Whitney U test.

ever, there was no statistical significance ($p > 0.05$). In addition, after CDA challenge, subjects in the SCH⁺ group tended to complain of greater aggravation of nasal obstruction and rhinorrhea; however, the difference was not statistically significant (Fig. 3; $p > 0.05$).

In comparison of changes in acoustic parameters between the SCH⁺ and SCH⁻ groups, we found no significant difference in

changes of TNV and MCA after HDM challenge (Fig. 4 a; $p > 0.05$). However, after CDA challenge, the SCH⁺ group showed a larger decrease of TNV and MCA, compared with the SCH⁻ group, with statistical significance (Fig. 4 b; $p < 0.01$).

Using linear regression analysis, we observed significant correlation between the result for degree of SPT and change of VAS for each

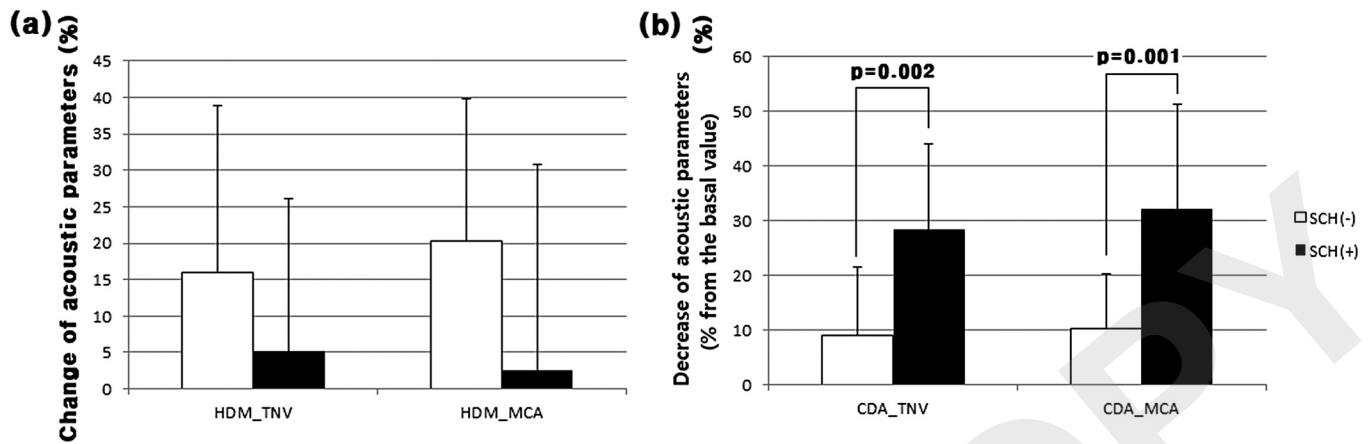


Figure 4. Change of acoustic parameters, including total nasal volume (TNV) and minimal cross-sectional area (MCA) after (a) nasal provocation with house-dust mite (HDM) challenge and (b) cold dry air (CDA) challenge. SCH⁺—patients with self-reported subjective hyperresponsiveness to CDA. SCH[−]—patients without subjective hyperresponsiveness to CDA. Kruskal-Wallis and Mann-Whitney U test.

Table 3 Correlation between the grade of SPT (SPT_grade) and change of each nasal symptom after challenge HDM or CDA

Independent Variable	Dependent Variable	R	p Value
SPT_grade	HDM_NO	0.250	0.033
	HDM_R	0.484	<0.001
	HDM_Sn	0.430	<0.001
	HDM_It	0.487	<0.001
	HDM_TNSS	0.485	<0.001
SPT_grade	CDA_NO	0.088	0.457
	CDA_R	0.044	0.713
	CDA_Sn	0.099	0.404
	CDA_It	0.064	0.590
	CDA_TNSS	0.097	0.414

_NO = nasal obstruction; _R = rhinorrhea; _Sn = sneezing; _It = itching; _TNSS = total nasal symptom score (sum of all nasal symptoms); SPT = skin-prick test; CDA = cold dry air; HDM = house-dust mite.

Table 4 Correlation for change of nasal symptoms or change of acoustic parameters after HDM challenge and after CDA challenge

Independent Variable	Dependent Variable	R	p Value
HDM_NO	CDA_NO	0.036	0.764
HDM_R	CDA_R	0.082	0.490
HDM_Sn	CDA_Sn	0.043	0.717
HDM_It	CDA_It	0.054	0.649
HDM_TNSS	CDA_TNSS	0.109	0.357
HDM_TNV	CDA_TNV	0.016	0.895
HDM_MCA	CDA_MCA	0.041	0.730

_NO = nasal obstruction; _R = rhinorrhea; _Sn = sneezing; _It = itching; _TNSS = Total Nasal Symptom Score (sum of all nasal symptoms); _TNV = change of total nasal volume; _MCA = change of minimal cross-sectional area; HDM = house-dust mite; CDA = cold dry air.

nasal symptom after HDM challenge. However, no significant correlation was observed between the result for degree of SPT and change of VAS for any nasal symptoms after CDA challenge (Table 3). No significant correlation was observed for change of VAS or change of acoustic parameters after HDM challenge and after CDA challenge (Table 4).

DISCUSSION

After HDM intranasal challenge, greater aggravation of rhinorrhea, sneezing, and itching was observed in group B (patients with allergic rhinitis), compared with group A (healthy volunteers) and group C (those with nonallergic rhinitis). This result is not so surprising, considering the release of several mediators from inflammatory cells, such as mast cells or eosinophils, in the nasal mucosa, as a result of antigenic challenge. However, vascular engorgement due to activation of the parasympathetic reflex is also involved in aggravation of nasal obstruction.¹⁰ In our study, compared with group A, subjects in group B and group C showed greater aggravation of nasal obstruction and a larger decrease in acoustic parameters, including TNV and MCA. However, no significance was observed between groups B and C. Therefore, the decrease of nasal patency after HDM challenge may be caused by (1) NHR caused by the diluent (0.9% saline in our study), (2) high concentration of HDM extract causing non-IgE-mediated effects, or (3) nonspecific irritant effects on the nasal mucosa rather than the allergic reaction.

On the other hand, compared with groups A and B, group C showed greater aggravation of nasal obstruction and a larger decrease of acoustic parameters after CDA, which was quite significant. This result shows strong correlation with results of previous studies. Braat and researchers insisted that nasal patency was the most important parameter after CDA.¹¹ In our previous study, we indicated that changes in nasal obstruction and rhinorrhea were more important in evaluation of NHR using CDA provocation machinery.¹²

To evaluate NHR itself, regardless of the presence of allergy, we grouped all healthy volunteers and patients again according to their self-report of subjective hyperresponsiveness to cold air. Therefore, we could observe that there was a substantial overlap between patients with allergic or nonallergic rhinitis in terms of CDA response. Therefore, CDA provocation is for evaluating NHR itself, rather than discriminating allergic or nonallergic rhinitis. In our prior studies, we proposed the SCH grade as a useful tool for evaluation of NHR, which has shown good correlation with change of nasal symptoms and acoustic parameters after CDA provocation.⁹ In this study, subjects in the SCH⁺ and SCH[−] groups showed no significant difference in their change of symptoms or decrease of TNV or MCA after HDM challenge. However, after CDA challenge, patients in the SCH⁺ group tended to experience more aggravated nasal obstruction and rhinorrhea (although without statistical significance) and showed a significantly greater decrease of TNV and MCA. Therefore, we were able to reach the conclusion that the protocol for CDA provocation is superior to that for HDM nasal provocation for evaluation of NHR.

Using linear regression analysis, we found significant correlation between the result for grade of SPT and change of each nasal symptom after HDM challenge. This result also shows strong correlation with results of our prior study.³ Therefore, NPT using HDM allergen extract could well reflect the degree of nasal allergy, which has shown significant correlation with systemic atopy. However, no correlation was observed between the SPT grade and change of any nasal symptoms after CDA challenge. These findings could be explained by the fact that CDA activates only the parasympathetic reflex in the nasal mucosa with minimal provocation of allergic responses. In addition, absolutely no correlation was observed between HDM challenge and CDA challenge, probably because of their different physiological mechanisms.

One important advantage of our study is that we have well-established protocols for NPT with HDM allergen and CDA provocation test. HDM is the most prevalent causative antigen in the Republic of Korea; therefore, we have routinely performed NPT for evaluation of changes in nasal symptoms and acoustic parameters, which was performed at a regular time of a day and by a single well-trained examiner. We have also developed CDA provocation machinery with the capacity to produce air at a regular temperature ($\sim 0^{\circ}\text{C}$) and humidity ($<10\%$). Although earlier researchers studying CDA had adopted -10°C , as a result of our several studies, we have shown that 0°C air was equally efficient for evaluation of NHR with less discomfort for patients.^{7-9,12}

One pitfall of our study is the small size of each group (~ 20 patients in each group). Although we have developed CDA machinery and performed it in >300 patients, we excluded many patients for the homogeneity. For example, we disqualified patients who showed positive results to any other allergen than HDM. We also disqualified patients with 2+ results to HDM. Only patients with strongly positive ($>3+$ or 3 mm of wheal) or nearly negative ($<1+$ to HDM) was included in this study. Because of the small study population, we were only able to perform nonparametric statistical analysis, including the Kruskal-Wallis and Mann-Whitney U tests. Additional study with a larger number of patients could yield additional meaningful results in the near future.

We could observe that subjective assessment as to cold air might be as valuable as doing the actual CDA provocation. This result is well correlated with our prior study, validating the usefulness of the SCH questionnaire.⁹ Therefore, performing the SCH questionnaire could be an effective and easy way in identifying NHR.

In conclusion, CDA provocation could be an adjunct tool for evaluating NHR in selected patients with self-reported SCH. We were

able to select an appropriate provocation protocol according to the clinical picture of patients, laboratory results, including SPT, and presence of SCH. Because the HDM and CDA provocation are independent in their provocative mechanism, parallel use of both provocation protocols could yield more meaningful information about the characteristics of each patient.

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