Nonspecific Hyper-reactivity and Localized Allergy: Cause of Discrepancy Between Skin Prick and Nasal Provocation Test

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Abstract

Objective. Disagreement between results of skin prick test (SPT) and nasal provocation tests (NPT) causes difficulty in differential diagnosis of allergic rhinitis (AR) and nonallergic rhinitis (NAR). We hypothesized this discrepancy could be due to the nonspecific hyper-reactivity (NHR) and localized allergy of the nasal cavity.

Study Design. Prospective pilot.

Setting. Academic tertiary rhinologic practice.

Subjects and Methods. Sixty patients with AR and 62 with NAR were enrolled. We categorized patients according to results of SPT and NPT. We compared: (1) the clinical characteristics and severity of the disease, (2) change of minimal cross-sectional area (MCA) and total nasal volume (TNV) after normal saline (NS) challenge, and (3) change of nasal symptoms and acoustic parameters after intranasal house dust mite (HDM) challenge between groups.

Results. Patients in groups A (SPT+/NPT+) and C (SPT–/NPT+) complained of more persistent discomfort than those in groups B (SPT+/NPT–) and D (SPT–/NPT–). The proportion of moderate to severe symptoms was significantly higher in groups A, B, and C compared to group D. After NS challenge, MCA/TNV showed a significantly greater decrease in groups A (MCA: 27.6% ± 16.4%) and C (MCA: 31.2% ± 24.0%) compared to groups B (MCA: 0.1% ± 13.2%) and D (MCA: 2.1% ± 12.1%). After HDM challenge, groups A/B showed a greater decrease in MCA (Group A: 62.4% ± 16.1%, Group B: 6.4% ± 11.3%) compared to groups C/D (Group C: 45.5% ± 14.4%, Group D: −3.0% ± 9.5%).

Conclusion. NHR and/or localized allergy should be considered in patients with rhinitis whose SPT and NPT results are not in agreement.

Keywords

nasal provocation tests, skin tests, allergic rhinitis, nonspecific hyper-reactivity, allergy

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Introduction

The diagnosis of allergic rhinitis (AR) is dependent on patients’ clinical symptoms and strongly positive results of skin prick test (SPT) to a clinically suspected allergen. If the SPT result is negative and other possible causes of rhinitis (hormone, medication, pregnancy, etc) can be ruled out, the patient is diagnosed as nonallergic rhinitis (NAR).

However, in reality, the clinical picture is not so simple. Some patients whose clinical characteristics are strongly suggestive of AR show a negative SPT result. Still other patients with features of NAR often show a strongly positive SPT result. Therefore, direct provocation of the target organ, the nasal cavity itself, would be a more reasonable method. The nasal provocation test (NPT), which evaluates the change of the nasal cavity induced by intranasal allergen challenge, has drawn significant attention from several researchers. Olive-Perez suggested that NPT could be an appropriate standard method for evaluating AR.

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In performance of NPT, we have used acoustic rhinometry to measure changes in the volume and dimension of the nasal cavity after allergen provocation. In our large population-based study, we proposed the diagnostic criteria of AR using NPT. However, some patients with typical AR symptoms and strongly positive SPT results showed absolutely no change of nasal cavity volume and dimension after NPT. On the contrary, other patients with negative SPT results often showed a dramatic decrease of acoustic parameters after intranasal allergen challenge. This discrepancy between SPT and NPT could cause confusion in diagnosis of AR and NAR.

According to our clinical experience, we framed the hypothesis that the discrepancy between the results of SPT and NPT could be due to the nonspecific hyper-reactivity (NHR) of the nasal cavity and localized mucosal allergy of the nasal cavity. To confirm our hypothesis, we categorized patients with symptoms of AR or NAR according to their results of SPT and NPT. We then compared: (1) the clinical characteristics and severity of the disease, (2) the change of nasal cavity volume and dimension after normal saline (NS) challenge, which represents NHR, and (3) the change of nasal symptoms and acoustic parameters after intranasal allergen challenge (NPT) between groups.

**Materials and Methods**

**Subjects**

Sixty patients with AR (40 males and 20 females, 11 to 69 years old, 37.2 ± 13.0 years) who suffered from typical clinical symptoms of rhinitis (watery rhinorrhea, stuffy nose, and sneezing) for more than 1 year were enrolled. We performed SPT, using more than 40 kinds of allergen extracts, including house dust mites (HDM), fungi, trees or weed pollen, cat, dog, and cockroach. Only those showing strongly positive results (wheal size ≥ 3 mm or larger than the positive control) to HDM were enrolled as AR patients. For the homogeneity of the study population, patients with positive SPT results to any other allergens than HDM were disqualified. Another 62 patients with NAR (37 males and 25 females, 14 to 78 years old, 39.3 ± 17.0 years) who also suffered from typical symptoms of rhinitis for more than 1 year were enrolled. The result of SPT in these NAR patients was negative to all tested allergens. We excluded patients who had used anti-allergic medications within 1 month, those with unstable systemic diseases, pregnant or lactating females, those who had undergone nasal surgery within the previous 3 months, those with chronic sinusitis and/or nasal polyp (confirmed by endoscopic examinations and/or para-nasal radiography), and those under chronic exposure to chemical irritants or smoking. The protocol for this study was approved by the Inha University Institutional Review Board Committee on Studies Involving Human Beings. All subjects had signed the informed consent before enrollment.

**Baseline Clinical Characteristics of Patients**

All patients were asked to complete a questionnaire, composed of visual analogue scale (VAS) for nasal symptoms such as nasal obstruction, rhinorrhea, sneezing, and itching sense. For VAS, patients marked the severity of their subjective discomfort on a 10-cm-long line with marks at each centimeter (0 cm: no discomfort at all, 10 cm: agonizing discomfort). The subjective severity of rhinitis symptoms was also graded using the Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 classification.

**NPT Using HDM Allergen Extracts and Acoustic Rhinometry**

The detailed protocol for NPT was well described in our previous article. Briefly, patients were asked to wait for 15 minutes for acclimatization in a room at regular temperature (22°C) and relative humidity (approximately 50%). While waiting, they responded to the VAS questionnaire for each nasal symptom before any challenge. Using acoustic rhinometry (E. Benson Hood Laboratories, Allergopharma, Hamburg, Germany), the minimal cross-sectional area (MCA) and the total nasal volume (TNV) were measured before any intranasal challenge (basal value). MCA was defined as the smallest cross-sectional area of the nasal cavity and TNV as the sum of the cross-sectional area from the nostril to 7 cm deep. For evaluation of NHR, 0.9% NS was sprayed into both nasal cavities using a 5-ml pump dosage sprayer (amount about 50 μL). Five minutes after the saline challenge, acoustic rhinometry was repeated for measurement of MCA and TNV. After 10 minutes of additional waiting for the effect of the NS to disappear, *Dermatophagoides pteronyssinus* (DP) allergen extract (50,000 standardized biological units [SBU]/ml, diluted to 1:10 with 0.9% NS, amount approximately 50 μL) (Allergopharma, Hamburg, Germany) was sprayed into both nasal cavities using the same dosage sprayer. Fifteen minutes after the DP challenge, the VAS questionnaire and acoustic rhinometry were repeated. The change of nasal symptoms was calculated by post-DP-provocation VAS score minus pre-DP-provocation VAS score. The change of MCA and TNV after NS or DP challenge from the basal value was calculated as percentage.

All tests were performed by a single experienced examiner who did not know about the aim of this study. Patients and investigators were totally blinded to any of the test results until the end of the study.

According to the result of SPT and NPT using HDM allergen extract, all patients were categorized according to 4 groups (Table 1). Decrease in MCA of more than 30% after DP challenge was considered as “[+] NPT result” and less than 25% of decrease as “[–] NPT result.” The degree of nasal symptoms, subjective severity according to ARIA 2008 classification, change of VAS score after DP challenge, and change of MCA and TNV after NS or DP challenge were compared between groups.

**Statistical Analysis**

Although the size of each study population was more than 20, we adopted nonparametric statistical analysis such as chi-square, Kruskal-Wallis, and Mann-Whitney U tests.
because the standard deviation was so significant. Linear regression analysis was used to determine any correlation between each parameter. SPSS 19.0 software (SPSS, Chicago, Illinois) was used and P values < .05 were considered as statistically significant.

**Results**

Sixty AR patients were classified into group A (SPT[+]/NPT[+], n = 29) and group B (SPT[+]NPT[–], n = 31). Another 62 patients with NAR were also divided into Group C (SPT[–]/NPT[+], n = 22) and Group D (SPT[–]/NPT[–], n = 40). Demographic parameters such as sex ratio and age were not significantly different between groups.

Before any challenge, no significant difference in the VAS score for each nasal symptom was observed between groups (P > .05) (Figure 1). According to the ARIA classification, patients in groups A and C (those with [+]NPT results, group A: 86.2%, group C: 86.4%) complained of more persistent discomfort than those in groups with NPT[–] results (group B: 61.3%, group D: 47.5%) (Figure 2A). Regarding the severity, the proportion of moderate to severe symptoms was significantly higher in groups A (69.0%), B (74.2%), and C (77.3%) than in group D (42.5%, P < .05) (Figure 2B).

After NS challenge for evaluation of NHR, a significantly greater decrease of MCA and TNV was observed in groups A and C (MCA: 27.6% ± 21.3%, TNV: 24.6% ± 16.4%) and group C (MCA: 31.2% ± 24.0%, TNV: 24.1% ± 23.4%) compared to group B (MCA: 0.1% ± 13.2%, TNV: 3.9% ± 13.5%) and group D (MCA: 2.1% ± 12.1%, TNV: 2.0% ± 17.2%, P < .05) (Figure 3).

After DP challenge, the change of each nasal symptom was significantly greater in group A compared to groups B, C, and D. In addition, patients in groups B and C also complained of greater aggravation of VAS score compared to those in group D (Figure 4). Linear regression analysis revealed significant correlation between the result of SPT/NPT and change of nasal symptoms after DP challenge (Table 2).

In comparison of the change of acoustic parameters after DP challenge, we found that groups A and C (NPT[+] groups) showed a significantly greater decrease in MCA and TNV than groups B and D (NPT[–] groups, P < .001). In addition, a statistically significant difference in decrease of MCA was observed between groups A and C (group A: 62.4% ± 16.1% vs group C: 45.5% ± 14.4%, P < .001) and between groups B and D (group B: 6.4% ± 11.3% vs group D: –3.0% ± 9.5%, P = .004) (Figure 5).

Linear regression analysis revealed significant correlation between the result of SPT and the decrease of MCA and TNV after DP challenge (P < .001). However, no significant correlation was observed between the result of SPT and the decrease of these acoustic parameters after NS challenge (P > .05). On the other hand, significant correlation was observed between the result of NPT and the decrease of MCA/TNV after NS challenge (P < .001) (Table 3).

Grouping all 122 patients with AR or NAR according to their age, we found that elderly patients (more than 56 years) showed larger proportion of localized mucosal allergy (25.0%) compared to younger patients (11 to 25 years old, 14.0%) and adults (26 to 55 years old, 19.2%) (Table 4).

**Table 1. Groups of patients according to results of skin prick test (SPT) and nasal provocation test (NPT).**

<table>
<thead>
<tr>
<th>Result of SPT</th>
<th>Result of NPT</th>
<th>Sex ratio (male:female)</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Positive (&gt;3+ to HDM)</td>
<td>Positive (&gt;30% of MCA decrease after HDM challenge)</td>
<td>21:8</td>
</tr>
<tr>
<td>Group B</td>
<td>Positive</td>
<td>Negative (&lt;25% of MCA decrease after HDM challenge)</td>
<td>19:12</td>
</tr>
<tr>
<td>Group C</td>
<td>Negative</td>
<td>Positive</td>
<td>14:8</td>
</tr>
<tr>
<td>Group D</td>
<td>Negative</td>
<td>Negative</td>
<td>23:17</td>
</tr>
</tbody>
</table>

Abbreviations: HDM, house dust mite; MCA, minimal cross-sectional area.
Figure 2. Proportion of patients' severity of symptoms according to Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 classification.

Figure 3. Decrease of minimal cross-sectional area (MCA) and total nasal volume (TNV) after normal saline (NS) challenge. Significantly greater decrease of MCA and TNV was observed in groups A and C \( (P < .05) \).

Figure 4. The change of nasal symptoms after house dust mite (HDM) intranasal challenge was significantly greater in group A, compared to the other groups.
45.5% ± 14.4%) compared to NPT[–] groups (group B: 6.4% ± 11.3%, group D: −3.0% ± 9.5%).

However, the clinical symptoms of these 4 groups were similar (no difference of VAS score for each symptom before any challenge). Therefore, diagnosis of AR and NAR by assessment of symptoms alone is nearly impossible. Therefore, laboratory tests such as SPT and NPT could be useful in evaluation of these patients. However, in patients showing discordant results for SPT and NPT (SPT result strongly positive to HDM but no response to DP allergen extract in NPT, and vice versa), diagnosis as AR or NAR is more confusing. In a previous study, Agarwal and researchers suggested that the result of SPT to fungi and patients’ nasal hypersensitivity to fungal allergen showed poor correlation.9 In studies using alternaria and timothy grass, Krouse and colleagues found that results of skin testing and NPT showed poor correlation and discordant results for SPT and NPT (SPT result strongly positive to HDM but no response to DP allergen extract in NPT, and vice versa), diagnosis as AR or NAR is more confusing. In a previous study, Agarwal and researchers suggested that the result of SPT to fungi and patients’ nasal hypersensitivity to fungal allergen showed poor correlation.9

### Table 2. Correlation between the result of skin prick test (SPT)/nasal provocation test (NPT) and the change of visual analogue scale (VAS) score for nasal symptoms.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Dependent variable (change of VAS score)</th>
<th>R (correlation coefficient)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result of SPT ([+]/[-])</td>
<td>Nasal obstruction</td>
<td>0.380</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Rhinorrhea</td>
<td>0.541</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Sneezing</td>
<td>0.351</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Itching</td>
<td>0.491</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Result of NPT ([+]/[–])</td>
<td>Nasal obstruction</td>
<td>0.747</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Rhinorrhea</td>
<td>0.473</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Sneezing</td>
<td>0.184</td>
<td>.043</td>
</tr>
<tr>
<td></td>
<td>Itching</td>
<td>0.315</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

### Table 3. Correlation between results of SPT/NPT and change of acoustic parameters.a

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Dependent variable (decrease of acoustic parameters, %)</th>
<th>R (correlation coefficient)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result of SPT ([+]/[-])</td>
<td>MCA_DP</td>
<td>.319</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>TNV_DP</td>
<td>.398</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>MCA_NS</td>
<td>.021</td>
<td>.270</td>
</tr>
<tr>
<td></td>
<td>TNV_NS</td>
<td>.101</td>
<td>.816</td>
</tr>
<tr>
<td>Result of NPT ([+]/[–])</td>
<td>MCA_NS</td>
<td>.626</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>TNV_NS</td>
<td>.526</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: DP, after Dermatophagoides pteronyssinus challenge; NS, after normal saline challenge.

*Significant correlation was found between the result of skin prick test (SPT) and the decrease of minimal cross-sectional area (MCA) and total nasal volume (TNV) after Dermatophagoides pteronyssinus (DP) challenge. On the other hand, significant correlation was observed between the result of nasal provocation test and the decrease of MCA/TNV after normal saline (NS) challenge.

Figure 5. The change of acoustic parameters after Dermatophagoides pteronyssinus (DP) intranasal challenge. Groups A/C showed a significantly greater decrease in minimal cross-sectional area (MCA) and total nasal volume (TNV) than groups B/D.
stated that skin testing could not accurately assess allergy of the nasal cavity compared to NPT.\textsuperscript{10,11} To the best of our knowledge, this is the first study that attempted to elucidate the cause of this discrepancy between SPT and NPT, using HDM.

Irrespective of their SPT results, according to ARIA guidelines, NPT[+] groups (groups A and C) had a higher proportion of persistent disease. In addition, patients in group C (NAR with NPT[+] results) reported more severe impairment of quality of life compared to those in group D (NAR with NPT[−]). Therefore, we could postulate that the result of NPT could be related to more persistent and more severe disease.

Localized mucosal allergy is defined as the localized allergic reaction of the nasal cavity in the absence of systemic allergic sensitization.\textsuperscript{12,13} In our study patients in group C could be diagnosed as localized mucosal allergy, as their NPT results were positive while those for SPT were negative. In order to rule out nonallergic rhinitis with eosinophilia, the number of eosinophils in the nasal smear was counted. In our previous study, patients with localized mucosal allergy showed similar clinical characteristics to those with AR.\textsuperscript{14} Also in this study, the symptoms of patients in group C were quite indistinguishable from those of other groups. Localized mucosal allergy is thought to be caused by the local Th\textsubscript{2} response in the nasal cavity by the causative allergen.\textsuperscript{15} As NPT evaluates the local allergic response in the nasal cavity, it could be more useful in differentiating diagnosis of localized mucosal allergy and NAR, as in our study.

For assessment of NHR, we measured the decrease of MCA and TNV after intranasal NS challenge. As a result, we found that NPT[+] groups (groups A and C) showed more significant NHR, which was detected by a greater decrease of MCA and TNV after NS challenge, compared to NPT[−] groups (groups B and D). Therefore, we suggest that the presence of NHR, as well as the local allergic reaction of the nasal mucosa, could be responsible for the result of NPT.

It is not so surprising that NPT[+] groups (groups A and C) reported a greater change of VAS score after DP challenge, compared to NPT[−] groups (groups B and D). As NPT[+] groups were characterized by a greater decrease in the volume and dimension of the nasal cavity after DP challenge, the nasal symptoms would also be more aggravated as well. However, it is striking that in comparison of groups A and C, both NPT[+] groups, group A showed more symptom change after DP challenges. Regarding acoustic parameters, group A showed a greater decrease of MCA after intranasal HDM challenge compared with group C (group A: 62.4% ± 16.1%, vs group C: 45.5% ± 14.4%, \(P < .001\)). This tendency is also evident in comparison of groups B and D, both NPT[−] groups (group B: 6.4% ± 11.3% vs group D: −3.0% ± 9.5%, \(P = .004\)). This result could not be explained by the local allergic response, since the response to HDM challenge was similar in each group. Therefore, it could be due to the influence of NHR. In fact, in interpreting the result of NPT, since the HDM allergen extract is diluted to 1:10 using NS, we cannot rule out the effect of NHR to NS. The significant correlation between the result of NPT and the degree of NHR (decrease of MCA/TNV after NS challenge) further supports our hypothesis.

Results of our correlation analysis revealed that the degree of symptom change after DP challenge showed significant correlation with the results of both SPT and NPT. In our previous study, we demonstrated significant correlation between the change in symptoms after intranasal allergen provocation and the degree of SPT results.\textsuperscript{7} We also suggested that the degree of SPT results and decrease of MCA/TNV after HDM intranasal challenge had significant correlation.\textsuperscript{7} Therefore, evaluation of the symptom changes could be a reasonable alternative when more objective measurement using rhinomanometry or acoustic rhinometry is not available. In fact, we have proposed “the change of VAS score > 2 after HDM intranasal challenge” as the diagnostic criteria for AR.\textsuperscript{6}

Using linear regression analysis, we proved significant correlation between the SPT result and the change of MCA/TNV after HDM challenge. However, no significant correlation was observed between the SPT result and the change of acoustic parameters after NS challenge (Table 3). Therefore, we could suggest that the systemic sensitization to provocative allergen had nothing to do with NHR of the nasal cavity. On the other hand, significant correlation was observed between the result of NPT (after HDM challenge) and the decrease of MCA/TNV after NS challenge. Therefore, it is probable that NHR could be responsible for the response of the nasal mucosa to the provocative allergen.

To investigate the pathophysiologic mechanism underlying NHR and localized mucosal allergy, further studies including analysis of nasal secretions and histopathologic examination of nasal mucosa should be conducted. In
addition, recruitment of healthy volunteers could yield more meaningful comparison.

**Conclusion**

NHR and/or localized mucosal allergy should be considered in patients with symptoms of rhinitis who have discordant results for SPT and NPT. In elderly patients, especially, localized mucosal allergy could be more responsible for this discrepancy compared to their young counterparts.

**Author Contributions**

Geun Uck Chang, main writer, data analysis; Tae Young Jang, main writer, data acquisition and statistical analysis, final decision for the script to be submitted; Kyu-Sung Kim, secondary writer and English interpretation, data analysis and article revision; Hyuk Choi, data acquisition and interpretation, figure work, English editing and article revision, responsibility for the paper; Young Hyo Kim, study design, conception, responsibility for the paper.

**Disclosures**

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**References**