



Proposed diagnostic standard using visual analogue scale and acoustic rhinometry in nasal provocation test in allergic patients

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Abstract

Objective: The authors aimed to analyze symptom change after nasal provocation and acoustic rhinometry results of a larger number of allergic rhinitis patients and also aimed to propose a new diagnostic threshold by investigating the difference between patients with allergic and non-allergic perennial rhinitis.

Methods: The authors checked symptom change and performed acoustic rhinometry before and after nasal provocation in 208 patients (114 males and 94 females, 19–58 years old) with allergic rhinitis and 222 patients (116 males and 106 females, 20–74 years old) clinically diagnosed with non-allergic perennial rhinitis (control group). Then the authors compared VAS (visual analogue scale), TNV (total nasal volume), MCA (minimal cross-sectional area), length of MCA and change of these values between allergic patients group and control group, to propose the new diagnostic standard.

Results: The change of symptom score and number of sneezing after nasal provocation were significantly different between allergic patient and control group. The basal TNV, MCA, length of MCA, and changes of these values were also significantly different. By drawing the ROC (receiver operator characteristic) curve and evaluating the sensitivity and specificity for each criteria, we could set the diagnostic criteria as follows: (1) symptom change: more than 2 points in the case of nasal obstruction and more than 1 point for the case of rhinorrhea or itching, (2) more than 24.5% change of the TNV, and (3) more than 20% change of the MCA.

Conclusion: VAS change and acoustic rhinometry in nasal provocation test could be a valuable tool in diagnosing allergic rhinitis with high sensitivity and specificity.

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Keywords: Acoustic rhinometry; Allergic rhinitis; Nasal provocation

1. Introduction

The principle of acoustic rhinometry is based on sound reflection. By analyzing the sound reflected, the researchers could get information about the cross-sectional area and volume of the nasal cavity. Acoustic rhinometry is useful as an adjunctive method in diagnosing the nasal pathology [1]. The procedure is superior in that the patients' cooperation is not required, it takes less time, it is non-invasive, and

quantitative analysis is possible. Roithmann and researchers suggested that acoustic rhinometry is especially useful in evaluating the response of nasal mucosa to allergen in allergic patients [2]. But it is used only as an adjunctive diagnostic method, and the threshold for positive response is still needed.

There was a study evaluating the TNV (total nasal volume) and MCA (minimal cross-sectional area) in symptom-free Korean subjects [3]. But there is still no definite diagnostic standard of acoustic rhinometry in nasal provocation test in allergic patients. Furthermore, there is no study comparing allergic patients with non-allergic perennial rhinitis patients by acoustic rhinometry. As the previous studies involved less than 100 patients, the authors

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aimed to analyze symptom change after nasal provocation and acoustic rhinometry results of a larger number of allergic rhinitis patients and also aimed to set a new diagnostic threshold by investigating the difference between patients with allergic and non-allergic perennial rhinitis.

2. Materials and methods

Between January 2003 and December 2006, the authors selected 208 patients (114 males and 94 females, 19–58 years old) who had suffered from typical symptoms of allergic rhinitis and had been diagnosed as allergic rhinitis patients. They showed the clinical symptoms and signs of allergic rhinitis and their MAST (multiple allergeo-sorbent test) results were strongly positive (4+) for house-dust mites (*Dermatophagoides pteronyssinus*) allergen. The authors also selected 222 patients (116 males and 106 females, 20–74 years old) clinically diagnosed with non-allergic perennial rhinitis and whose MAST results were negative (0+) for house-dust mites allergen, as the control group. All subjects with allergic rhinitis were only sensitized for house dust mite and all subjects in the control group were negative against all other antigens including house dust mite. The patient characteristics such as gender, age and rhinitis severity according to ARIA 2008 guideline were not significantly different between groups. The infectious rhinitis and NARES (non-allergic rhinitis with eosinophilia syndrome) were excluded by endoscopic examination, eosinophilia in nasal cytology and serum IgE level. All patients of allergic rhinitis and control group underwent the nasal provocation test and acoustic rhinometry. The patients with other nasal pathology such as chronic sinusitis or severe septal deviation (diagnosed with nasal endoscopy), patients less than 20 years old, patients taking antihistamine or systemic steroid medication, patients with asthma or aspirin sensitivity, and pregnant or lactating women were excluded. We got an international review board (IRB) approval before initiating the study. Histamine and normal saline were used as positive and negative control, respectively.

We used E. Benson Hood Laboratories' ECCOVISION Acoustic rhinometer as the measuring equipment. This equipment consists of an IBM-486 personal computer, a wave tube (internal diameter: 1.5 cm, length: 30 cm), a calibration tube, nose tips and a HP 550C color printer. The room temperature was set at 22 °C (± 2 °C) and the relative humidity at 50% (± 5 %). We inserted a nose tip with size identical to that of the anterior nares taking care that the shape of nostril was not changed as the patient was encouraged to relax and breathe gently after being seated on a chair for 15 min. Before the challenge, acoustic rhinometry was performed for the baseline data. The patients were asked to complete the VAS (visual analogue scale), which consists of a 10 cm long line on paper with markings at every 1 cm interval. Then they received a control challenge, which consisted of 0.9% normal saline.

After 15 min of saline challenge, VAS and acoustic rhinometry were repeated. After a waiting period of 10 min to allow the effects of the challenge to disappear, the challenge with Dp antigen was performed. Fifteen minutes later, the VAS and acoustic rhinometry were performed again. With nasal provocation test, both nasal side were challenged in order to account for the effects of the nasal cycle. No patient showed any severe side effects such as bronchospasms during or after the challenge.

The allergen used was Allergopharma's *D. pteronyssinus* antigen, contained in a 5 ml pump dosaging sprayer where the antigen was diluted at 1:10. The amount to be sprayed at once was 40–50 μ l. Before spraying, both the normal saline and allergen were brought to normal body temperature to minimize the irritating effect caused by low temperature. Both allergen and saline were sprayed twice into both nasal cavity.

The MCA was defined as the smallest cross sectional area of the nasal cavity. TNV was defined as the sum of the cross-sectional area from the nostril to 7 cm deep. The authors chose the larger value change between the values of the right and left nasal cavity. The authors measured the changes in symptoms such as nasal obstruction, rhinorrhea and itching, after the allergen challenge, using a VAS. The authors also measured the number of sneezing before and after the provocation. All tests were done by the same examiner.

We compared VAS, TNV, MCA, length of MCA and change of these values between allergic patients group and control group. To propose the new diagnostic standard, we used ROC (receiver operator characteristic) curve analysis. We used the independent *t*-test and the paired *t*-test using SPSS 12.0 for the statistical analysis.

3. Results

The change of symptom score showed significant difference between allergic patient and control group. The change of nasal obstruction, itching and PND were 3.4 ± 2.4 , 3.4 ± 3.3 and 3.1 ± 2.1 in allergic rhinitis patient group, which were significantly greater than 0.6 ± 1.0 , 0.2 ± 0.7 and 0.2 ± 0.7 of control group (Fig. 1). The number of sneezing 15 and 30 min after Dp provocation were 3.6 ± 4.5 and 0.1 ± 0.6 in patient group, which were also significantly greater than 0.1 ± 0.6 and 0.0 ± 0.0 of control group (Fig. 2). These results were also statistically significant ($p < 0.001$). The authors defined total nasal symptom score (TNSS) as the total sum of nasal obstruction, itching and PND. The change of TNSS was 10.0 ± 5.7 in allergic rhinitis group, which was significantly greater than that of control group (1.0 ± 1.9 , $p < 0.001$).

The basal TNV and MCA values were smaller and the length of MCA was rearer (Fig. 3) in the case of allergic rhinitis patients group as compared to the control group. These differences were statistically significant ($p < 0.01$). The changes in TNV, MCA and the length of MCA after the

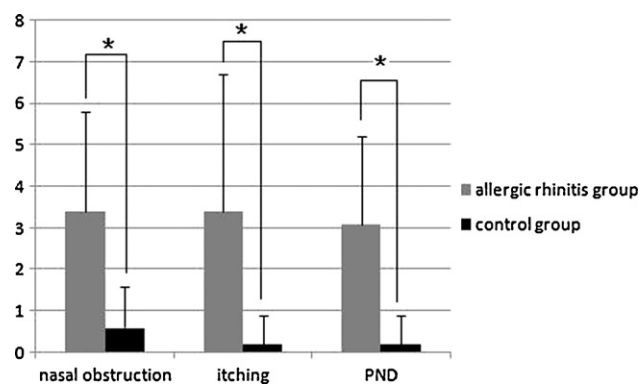


Fig. 1. The change of nasal obstruction, itching and PND in allergic patients and control group (AR: allergic rhinitis)

allergen challenge were 32.8%, 34.6% and 28.6%, which were greater than those in the control group, namely, 10.5%, 5.6% and 11.1%, respectively ($p < 0.01$) (Fig. 4).

By drawing the ROC curve, we found that the change of symptoms was quite valuable for use as diagnostic criteria according to the AUCs (Areas Under the Curve) of the symptoms, and all the AUCs were all above 0.84 (nasal obstruction: 0.845, rhinorrhea: 0.905, itching: 0.883, all $p < 0.01$, Fig. 5). The ROC curve for the number of sneezes revealed that it was valuable up to 15 min, but it was of no value after that (Fig. 6). The change of the TNV and MCA were also proven to be quite valuable for the diagnostic criteria. With the criteria “change of the TNV more than 24.7%”, the sensitivity was 70.2% and the specificity was 77.8%. With “change of the MCA more than 20%”, the sensitivity was 70.6% and the specificity was 80.5% (Fig. 7).

Thirty-one patients in group B showed more than a 30% decrease of the MCA after house dust mite provocation. Because these patients could be classified as having ‘localized mucosal allergy’ as compared to the healthy volunteers, we again compared each of the parameters between the groups with excluding these 31 patients. As a result, the specificity of the TNV criteria (more than 24.7%) increased to 87.2% and that of the MCA criteria (more than 20%) also increased to 91.6%, respectively (Fig. 8).

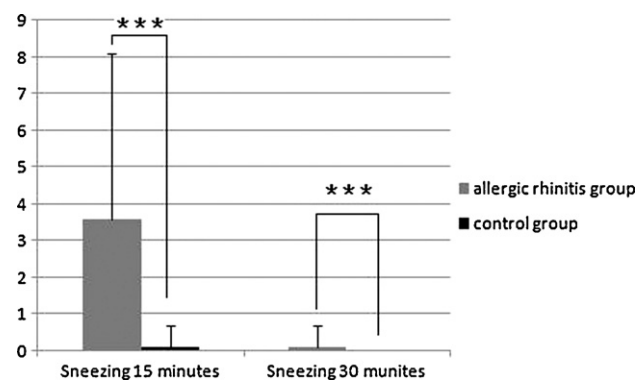


Fig. 2. The number of sneezing 15 and 30 min after Dp provocation in allergic patients and control group.

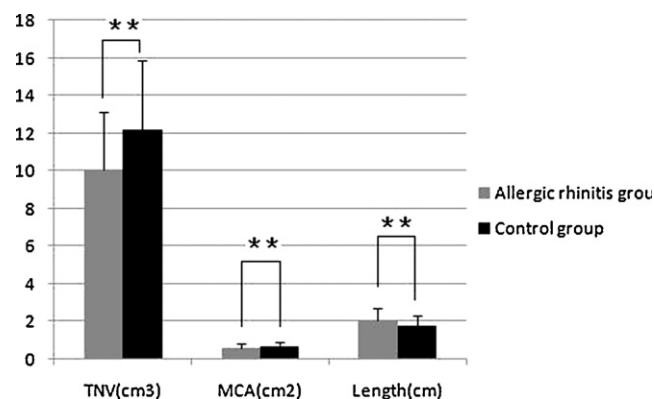


Fig. 3. The basal TNV, MCA and length of MCA of allergic patients and control group.

4. Discussion

The diagnosis of allergic rhinitis is made by patient’s history, physical examination by nasal endoscopy, and the results of skin prick test or MAST to evaluate the causative antigen. However, the clinicians should examine the target organ itself, in other words the nasal mucosa, to confirm the allergic ‘rhinitis’.

The nasal provocation test is useful in evaluating the hypersensitivity of nasal mucosa to allergens by provoking the nasal cavity directly. But it is time-consuming, may cause anaphylactic reaction, generates lots of false positive or negative reports, and is more subjective because of its dependency on the patients’ symptoms [4]. Kirkman and researchers first reported a case of hay fever-like clinical symptoms after exposure to weed antigen in 1835 [5]. Later many researchers studied various methods of allergen exposure into the nasal cavity without severe adverse effects. For example, there are methods such as intranasal spray [5,6], positioning the antigen directly into the nasal cavity [7], inhalation of antigen [8–10], and positioning the antigen-coated gauze into the nasal cavity. We selected the intranasal spray method. It has some pitfalls in that the amount of sprayed antigen is uneven and it has some risk of

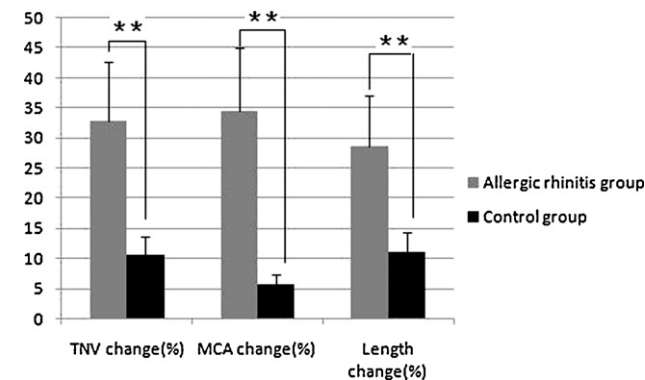
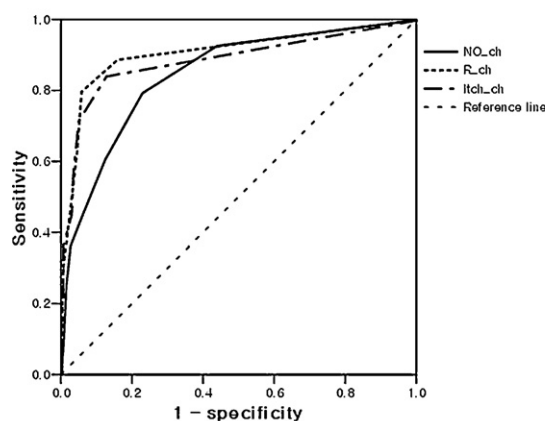


Fig. 4. change in TNV, MCA and length of MCA with Dp allergen challenge.



	Positive if Greater Than or Equal To(a)*	Sensitivity	1-specificity
NO_ch	-2.0000	1.000	1.000
	-1.5000	.996	.981
	-1.0000	.925	.440
	-0.5000	.792	.230
	0.0000	.604	.125
	0.5000	.451	.062
	1.0000	.361	.027
	1.5000	.251	.016
	2.0000	.169	.012
	2.5000	.086	.008
	3.0000	.031	.004
R_ch	-3.0000	1.000	1.000
	-2.5000	1.000	.996
	-2.0000	.996	.981
	-1.5000	.886	.160
	-1.0000	.796	.058
	-0.5000	.635	.047
	0.0000	.467	.027
	0.5000	.306	.008
	1.0000	.141	.004
	1.5000	.047	.000
	2.0000	.031	.000
Itch_ch	-4.0000	1.000	1.000
	-3.5000	.996	1.000
	-3.0000	.996	.996
	-2.5000	.839	.128
	-2.0000	.714	.051
	-1.5000	.561	.035
	-1.0000	.451	.031
	-0.5000	.365	.008
	0.0000	.255	.008
	0.5000	.169	.004
	1.0000	.082	.000

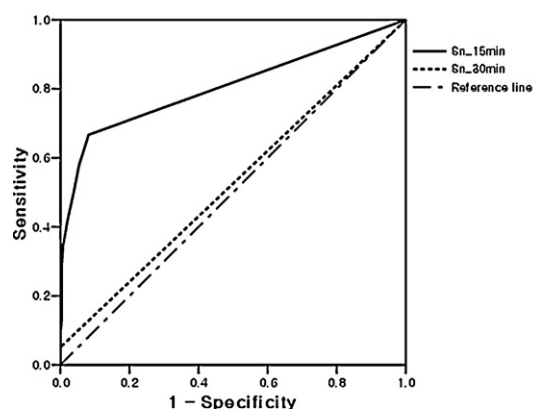
Fig. 5. The ROC curve, sensitivity and specificity of each of the nasal symptoms (NO_ch: change of nasal obstruction, R_ch: change of rhinorrhea, It_ch: change of itching).

anaphylactic reaction. But it is relatively easy and requires no special skill.

There are subjective and objective nasal provocation test methods. In the subjective one, the researchers evaluate patients' symptoms such as nasal obstruction, rhinorrhea, sneezing and itching using VAS. One of the objective studies is rhinomanometry. It is a dynamic study measuring the resistance of airflow during exhalation [15]. The resistance of airflow could reflect all factors that could influence the

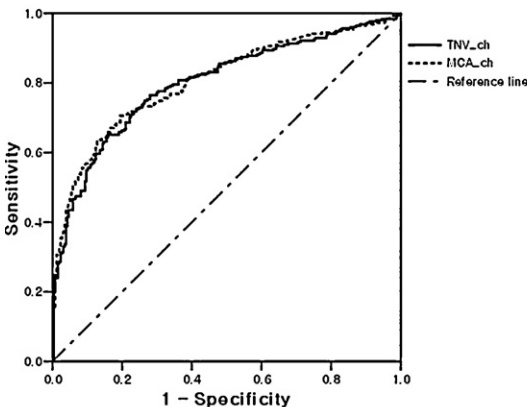
resistance of nasal cavity. The result of rhinomanometry is influenced by the change in the cross-sectional area of the nasal cavity [16]. Factors that could influence nasal airflow are the length of nasal cavity, its cross-sectional area and the characteristics of air stream. Factors such as temperature, humidity, density and viscosity of airstream are negligible.

Rhinomanometry is a highly sensitive study and the researchers were able to identify the influence of both nasal valves. But there is no clear cut-off between normal and



	Positive if Greater Than or Equals To(a)*	Sensitivity	1 - Specificity
Sn_15min	-1.0000	1.000	1.000
	-0.5000	.667	.082
	0.0000	.580	.054
	0.5000	.502	.039
	1.0000	.412	.019
	1.5000	.345	.008
	2.0000	.278	.004
	2.5000	.243	.004
	3.0000	.180	.004
	3.5000	.145	.004
	4.0000	.129	.004
	4.5000	.086	.000
	5.0000	.075	.000
	5.5000	.051	.000
	6.0000	.039	.000
	6.5000	.031	.000
Sn_30min	-1.0000	1.000	1.000
	-0.5000	.051	.000
	0.0000	.031	.000
	0.5000	.027	.000
	1.0000	.016	.000
	1.5000	.008	.000
	2.0000	.004	.000
	2.5000	.000	.000

Fig. 6. The ROC curve, sensitivity and specificity of the number of sneezes. (Sn_15 min: the number of sneezes until 15 min after provocation, Sn_30 min: the number of sneezes until 30 min after provocation).



	Positive if Greater Than or Equal To(a)	Sensitivity	1 - Specificity
TNV_ch	24,0182	.714	.233
	24,2029	.710	.233
	24,3451	.710	.230
	24,5175	.710	.226
	24,6313	.706	.226
	24,6805	.702	.226
	24,7291	.702	.222
	24,7800	.698	.222
	24,8574	.694	.222
	24,9724	.690	.222
	25,1272	.686	.222
	25,2612	.686	.218
	25,3228	.686	.214
	25,3860	.686	.210
	25,4931	.682	.210
	25,6360	.678	.210
	25,7578	.675	.210
	25,8144	.671	.210
	25,8425	.667	.210
	25,9577	.667	.206
MCA_ch	26,1764	.663	.206
	18,6773	.714	.222
	18,7500	.714	.218
	18,8194	.710	.218
	18,9683	.710	.214
	19,1129	.710	.206
	19,2044	.710	.202
	19,4515	.706	.202
	19,7126	.706	.198
	19,8765	.706	.195
	20,1449	.702	.195
	20,3600	.698	.195
	20,6047	.694	.195
	20,8896	.690	.195
	21,2143	.686	.195
	21,4835	.686	.191
	21,6026	.682	.191
	21,9444	.682	.187
	22,3787	.682	.183
	22,6312	.678	.183
	22,7671	.678	.179
	22,8618	.675	.179
	22,9337	.675	.175
	23,1421	.671	.175
	23,3333	.671	.171

Fig. 7. The ROC curve, sensitivity and specificity of the change of the TNV and MCA as the diagnostic criteria. (TNV_ch: change of the total nasal volume, MCA_ch: change of the minimal cross-sectional area).

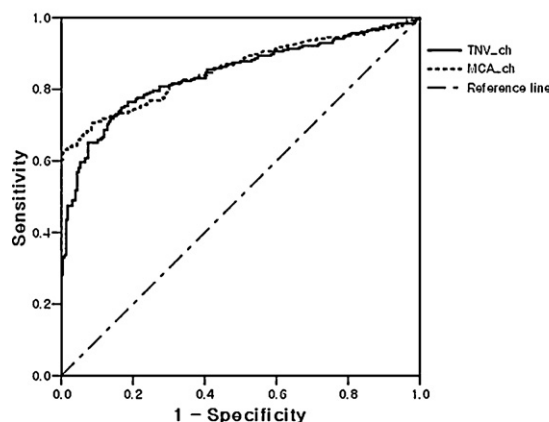
abnormal. The problem could not be identified for the patients with high resistance. The positive predictive value is low and special equipment along with the patient's active cooperation is required. Finally, it is very time consuming [16]. The endoscopic evaluation of nasal congestion, edema and rhinorrhea has high positive predictive value and requires no special equipment. It requires only a little time [10,11]. But it does require the patient's cooperation and an experienced examiner. There are other tests such as carbon elimination test, plethysmography and measuring the number of eosinophils in the nasal secretion. However, there is still no simple, accurate and standardized method.

Acoustic rhinometry is superior to other tests in that it requires very little time and no specific equipment or patient's cooperation. It is also highly reproducible and could evaluate several factors such as stenosis, nasal polyp and intranasal tumor as well as the nasal mucosal factor [4,7,13]. The most widely accepted threshold for positive result is more than 29% decrease in cross sectional area from the basal value after allergen challenge [1]. Ludmila and researchers suggested that there may normally be 10–15% decrease [12]. Terrien and researchers defined the threshold as more than 30% decrease from the basal value [13].

In Korea, Min and researchers reported that the MCA of symptom free adult was 0.53 cm [2,3]. However, there is no study defining the threshold of acoustic rhinometry in allergic

rhinitis patients. The number of patients and the normal control group is small in existing studies, commonly fewer than 100 persons. Moreover, since healthy volunteers as well as patients with chronic hypertrophic rhinitis are in the same control group, it is not homogeneous. In our study, the patient and control group is more than 200 people each, and each group is more homogeneous in that the clinical symptoms are similar and the result of MAST is either 4+ or 0+. We excluded patients with nonspecific hyper-response, paradoxical response and localized allergy pattern prior to the statistical analysis to improve the statistical significance. Surely it would be more reasonable to set control group as healthy volunteers without any nasal symptoms. But because of retrograde nature of our study, the authors selected non-allergic perennial rhinitis patients as control group. However, we could guess that the symptom change and MCA change of symptomless healthy volunteer would be even smaller than non-allergic perennial rhinitis patients. Therefore the authors decided that this diagnostic standard would be rational.

In our study, the allergic rhinitis patients had smaller TNV, MCA and length of MCA compared with the control group. We could explain these results according to the theory of Lenders, namely, allergic rhinitis patients show 'Descending W pattern' while normal individuals show 'Ascending W pattern'; MCA moves to C-notch instead of I-notch; TNV, MCA decrease and the length of MCA



	Positive if Greater Than or Equal To	Sensitivity	1 - Specificity
TNV_ch	22,6246	.733	.159
	22,6376	.729	.159
	22,6890	.729	.155
	22,7776	.729	.150
	22,9598	.725	.150
	23,1031	.725	.146
	23,2051	.722	.146
	23,4910	.718	.146
	23,7741	.718	.142
	23,8860	.718	.137
	24,0182	.714	.137
	24,2029	.710	.137
	24,4430	.710	.133
	24,6313	.706	.133
	24,6805	.702	.133
	24,7291	.702	.128
	24,7800	.698	.128
	24,8574	.694	.128
	24,9724	.690	.128
	25,1272	.686	.128
	25,2612	.686	.124
	25,3768	.686	.119
	25,4931	.682	.119
	25,6360	.678	.119
MCA_ch	17,4415	.725	.137
	17,8441	.722	.137
	17,9296	.722	.133
	18,0653	.722	.128
	18,2458	.718	.128
	18,3386	.718	.124
	18,4429	.718	.119
	18,5616	.718	.115
	18,6773	.714	.115
	18,7500	.714	.111
	18,8194	.710	.111
	18,9683	.710	.106
	19,1129	.710	.097
	19,2044	.710	.093
	19,4515	.706	.093
	19,7126	.706	.088
	19,8765	.706	.084
	20,1449	.702	.084
	20,3600	.698	.084
	20,6047	.694	.084
	20,8896	.690	.084
	21,2143	.686	.084
	21,4835	.686	.080
	21,6026	.682	.080
	21,9444	.682	.075
	22,3787	.682	.071
	22,6312	.678	.071
	22,7671	.678	.066
	22,8618	.675	.066
	22,9337	.675	.062
	23,1421	.671	.062

Fig. 8. The ROC curve, sensitivity and specificity of the change of the TNV and MCA, with excluding the 31 patients with localized mucosal allergy. (TNV_ch: change of the total nasal volume, MCA_ch: change of the minimal cross-sectional area).

moves posterior [14]. The changes in TNV, MCA, and the length of MCA were also greater in allergic rhinitis patients. To the best of our knowledge, it is the first study that has proposed a more objective diagnostic standard of nasal provocation using statistical methods such as ROC curve analysis. According to our results, the authors set the diagnostic criteria of nasal provocation as follows: (1) symptom change: more than 2 points in the case of nasal obstruction and more than 1 point in the case of rhinorrhea or itching, (2) more than 24.5% of TNV change, and (3) more than 20% of MCA change. The number of sneezes was excluded because of low sensitivity.

In designing our study, we used Allergopharma D.P. antigen diluted at 1:10. It is generally considered sufficient concentration for provocation [16]. However, it is acceptable to use challenges of greater concentration to ensure that the challenge is not below the threshold for provocation. This may be considered a drawback of our study. In fact, Krouse and researchers used progressively diluted concentration of timothy extract to avoid misdiagnosing patients with

provoked response at higher concentration as non-response group [17]. Krouse and researchers also used progressively diluted concentration of alternaria for the same reason [18]. Despite these limitations, our study has the benefit of the large size of patients and a detailed documentation of the variable nature of acoustic rhinometry.

We selected house dust mite for the provocative antigen because it is a very common causative antigen in Korea. Surely other antigen such as Japan Cedar pollen is more common in Japan, for example. Researchers in Japan could design a similar study using other antigen such as Japan Cedar pollen to establish a new diagnostic standard, which is best, suited for Japanese patients.

While interpreting the result of acoustic rhinometry, the clinical practitioner should also consider the patient's clinical picture and the result of other tests such as MAST. And he or she should keep in mind that the whole pattern as well as the absolute value of TNV and MCA is important.

According to above discussions, the authors could conclude that nasal provocation test with acoustic rhino-

metry is suitable as the diagnostic tool of allergic rhinitis in that it is the direct method of nasal mucosal provocation, and in that it has a diagnostic standard of high sensitivity and specificity. With these standards in mind, the authors would try to evaluate the therapeutic effect of various anti-allergic medication, surgical management or immunotherapeutic agents in the nearby future.

5. Conclusions

The symptom change and change of MCA value was significantly different between allergic patients and control group. Therefore, the authors were able to propose a new diagnostic standard, which could be a useful cut-off value for diagnosing nasal hyper-reactivity and for predicting prognosis. Although it is helpful in diagnosing allergic rhinitis, the practitioner should also take into account the clinical picture and other test results.

Acknowledgements

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