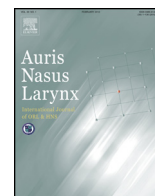




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The role of nasal fractional exhaled nitric oxide as an objective parameter independent of nasal airflow resistance in the diagnosis of allergic rhinitis

Sachio Takeno*, Yutaka Okabayashi, Takashi Kohno,
Kouhei Yumii, Katsuhiro Hirakawa

Department of Otolaryngology, Head and Neck Surgery, Division of Clinical Medical Science, Programs for Applied Biomedicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

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ABSTRACT

Objective: Patients with allergic rhinitis (AR) show augmented activity of nitric oxide (NO) metabolism, similar to those in bronchial asthma (BA). We hypothesized that measurements of nasal fractional exhaled NO (FeNO) could be used as an objective marker to detect the presence of AR. Our objective was to clarify the influence of nasal airflow resistance (NAR) on nasal FeNO levels through an exhalation maneuver in symptomatic AR patients. We also examined the diagnostic test validity of the mean nasal FeNO level for disease discrimination by means of a receiver operating characteristic (ROC) curve analysis.

Methods: Fifty-nine untreated perennial AR patients without BA and 60 healthy controls were enrolled in this retrospective cross-sectional study. The subjective symptoms were recorded and the disease severity was classified according to the Japanese guideline for AR. The oral and nasal FeNO measurements were carried out using a handheld electrochemical analyzer according to the ATS/ERS guidelines. NAR was measured using a rhinomanometer by the anterior method.

Results: The patients in the moderate-to-most severe AR group showed significantly higher levels of oral FeNO compared to the controls. The AR patients in both the mild ($n = 25$) and the moderate-to-most severe ($n = 34$) groups showed significantly higher levels of nasal FeNO compared to the controls (44.1 ppb, 54.5 ppb, and 26.5 ppb, respectively). There was no significant difference in total NAR between the AR patients and the controls. The results of our comparison of nasal FeNO and NAR values of the ipsilateral nasal cavity for each individual indicated no significant correlation between the two-paired parameters. The optimal cut-off point of the mean nasal FeNO level was calculated as 38.5 ppb (with 71% sensitivity and 86% specificity) to discriminate the presence of AR.

Conclusion: Nasal FeNO measurements can be an objective parameter for the diagnosis and classification of perennial AR in Japanese individuals. Nasal FeNO and NAR appear to be two independent measures that can be used to objectively evaluate nasal functions.

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* Corresponding author at: Department of Otolaryngology, Hiroshima University School of Medicine, Kasumi 1-2-3, Minami-ku, Hiroshima 734-8551, Japan. Fax: +81 82 257 5254.

E-mail address: takeno@hiroshima-u.ac.jp (S. Takeno).

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1. Introduction

The metabolism of nitric oxide (NO), also known as the nitrate–nitrite–NO pathway, has drawn growing interest in the study of human airways. The human nose and paranasal sinuses

serve as a physiological reservoir of intrinsic NO production, in which NO plays pivotal roles in both defense mechanisms and the mediation of inflammatory conditions [1]. In addition, the standardization of measuring techniques by the American Thoracic Society/European Respiratory Society (ATS/ERS) has opened the way for the monitoring of fractional exhaled NO (FeNO) for the diagnosis and management of airway diseases [2,3].

Patients with allergic rhinitis (AR) show higher levels of nasal NO caused by the increased expression of inducible nitric oxide synthase (iNOS) in the inferior turbinate mucosa [4,5]. The regulatory mechanisms of the nitrate–nitrite–NO pathway in AR patients are compatible with those in patients with bronchial asthma (BA), in whom increased NO has several pathophysiologic consequences in common with AR, including vasodilation, modification of nerve endings, and the accumulation of activated eosinophils [6,7].

Here we examined the oral and nasal FeNO levels and nasal airflow resistance (NAR) in a population of healthy subjects and patients with perennial AR. NAR evaluated by rhinomanometry is a commonly used measure that provides an objective and quantitative assessment of nasal patency based on anatomical features [8]. Nasal obstruction is one of the major symptoms in AR, but no data have been available regarding the influence of nasal patency on the exhalation maneuver for nasal FeNO measurements. We hypothesized that nasal NO might reflect the degree of ongoing allergic inflammation apart from that of airway patency in the nasal cavity, and thus that measurements of the nasal FeNO level can be used to detect the presence of AR as a valid and objective marker that is independent of NAR measurement. To test our hypothesis, we obtained nasal FeNO levels by measuring the right and left nasal cavities separately for a direct comparison of these two-paired parameters (i.e., the nasal FeNO level and NAR values).

To the best of our knowledge, this is the first study to validate the role of FeNO measurements as an objective parameter for the diagnosis of AR independent of nasal airway patency. We observed that the AR patients showed increased levels of nasal FeNO that were high enough for the use of a receiver operating characteristic (ROC) curve analysis, with the optimal cut-off points of 38.5 ppb being set to discriminate the AR patients from the healthy subjects with moderate accuracy.

2. Methods

2.1. Study design

This was a retrospective cross-sectional study conducted at the Department of Otorhinolaryngology–Head and Neck Surgery, Hiroshima University Hospital, Hiroshima, Japan between July 2013 and June 2016. Clinical records were obtained from 59 patients with perennial AR without bronchial asthma (41 males and 18 females; mean age 27.6 years) from hospital outpatient clinics, and from 60 healthy control subjects without nasal symptoms (43 males and 17 females; mean age 27.1 years). The diagnosis of AR was based on the patient's clinical history, the presence of nasal symptoms together with positive nasal eosinophil tests, and positive allergen-specific

IgE antibody or skin tests against house dust mites. The patients' subjective symptoms were recorded and classified according to the Japanese guideline for allergic rhinitis [9]. The symptoms include the average number of paroxysmal sneezing, episodes of nose-blowing, and the degree of nasal blockage. The severity of the AR was then determined as mild, moderate, severe, or most severe based on the guideline.

Patients who had clinical evidence of airway infection or chronic sinusitis were excluded from the study. We also excluded patients with previous nasal surgery, and those who were treated with allergen-specific immunotherapy or medication that could influence the congestive state of the nasal mucosa (i.e., antihistamines, antileukotrienes, topical or oral corticosteroids). The study protocol was approved by the ethical committee overseeing epidemiological research at Hiroshima University (No. E-356).

2.2. Measurements of NAR and FeNO

Nasal airflow resistance (NAR) was measured using a rhinomanometer (model HI-801, CHEST, Tokyo) by the anterior method. Unilateral measurements were performed for each side in a sitting position at rest. NAR was determined by the calculated value at an inspiratory reference pressure of ΔP 100 Pa and expressed as Pa/cm³/s in accord with the Japanese Guidelines for Rhinomanometry proposed by Japan Rhinologic Society [10]. Total NAR was also calculated according to Ohm's law.

Measurements of the FeNO level were obtained using a handheld electrochemical analyzer (NObreath[®], Bedfont Scientific, Rochester, UK) according to the ATS/ERS guidelines [3]. For the oral FeNO measurements, the subject exhaled at a flow rate of 50 mL/s through a mouthpiece according to the instructions supplied by the manufacturer. For the nasal FeNO measurements, the subjects were instructed to exhale transnasally with their mouth closed into a nose adaptor (NE-C10-10, OMRON Health Care, Kyoto, Japan) at the same flow rate as described [11]. Each measurement was performed in triplicate, and the mean value was used for analysis. We modified the nasal FeNO measurements for the right and left nasal cavities separately, with the other nostril held closed by the subject in turn (Fig. 1). The unilateral evaluation enabled us to examine the correlation between nasal FeNO and NAR as a corresponding pair for each side of the nose.

2.3. Data analysis

For multiple comparisons, we first carried out a screening of the data for differences, using the Kruskal–Wallis test. If the analysis gave a significant result, a further comparison was done by the Mann–Whitney *U*-test for the between-group analysis. We used Spearman correlation coefficients to analyze the relationship between the nasal FeNO levels and the NAR values. We also carried out a study of the diagnostic test validity of the nasal FeNO level for AR patients. We conducted a receiver operating characteristic (ROC) curve analysis to calculate the area under the curve (AUC) as an indicator to discriminate AR patients from non-AR subjects. The optimal

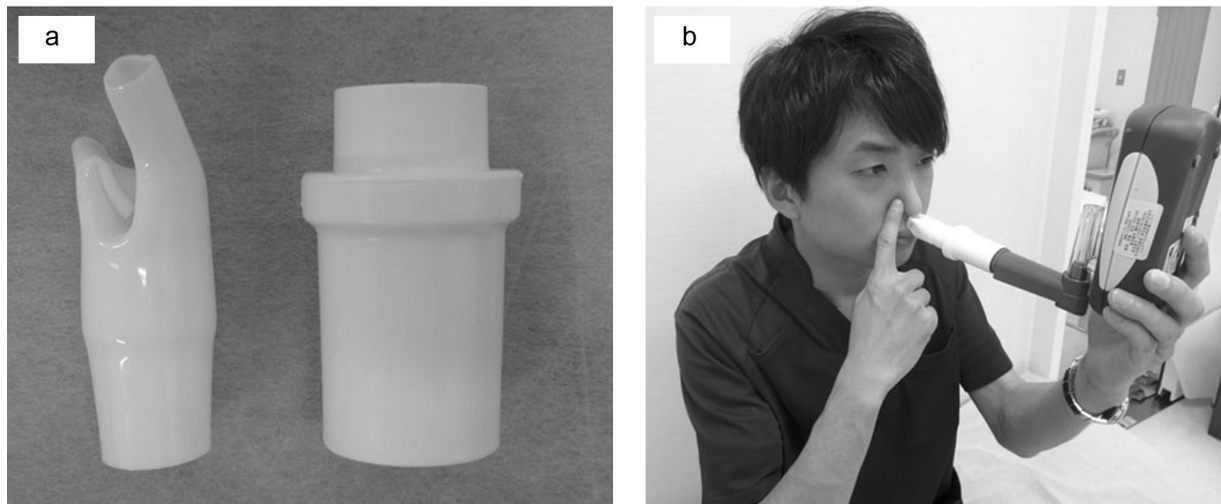


Fig. 1. (a) The disposable nosepiece (left) and mouthpiece (right) for the NObreath[®]. (b) Nasal FeNO measurement in a healthy control with the nosepiece connected to the NObreath[®]. The subject was advised to exhale through the one nasal cavity at a time, with the other nostril sealed.

Table 1

Demographics and clinical background of the AR patients and healthy controls.

	Control subjects	AR patients	
		Mild group	Moderate/severe/most severe group
Number (male/female)	60 (43/17)	25 (15/10)	34 (26/8)
Age	27.1 (7.8)	26.7 (7.8)	28.2 (9.3)
<i>Subjective symptom score</i>			
Sneezing	–	0.48 (0.51)	1.52 (1.02)
Nose blowing	–	0.76 (0.43)	1.91 (1.11)
Nasal blockage	–	0.76 (0.43)	2.26 (1.02)
Total score	–	2 (0.64)	5.71 (2.43)

Data are shown as mean with standard deviations in parenthesis.

cut-off value was then determined by using the Youden index based on the ROC to jointly maximize the sensitivity and specificity. p -Values <0.05 were considered significant.

3. Results

The demographic characteristics and clinical features of the AR patients and controls are summarized in Table 1. We divided the 59 AR patients into two groups based on disease severity: the mild group ($n = 25$) and the moderate-to-most severe group ($n = 34$). No significant difference was found among the three groups in the baseline data of age or gender distribution.

Fig. 2 shows the distribution of total NAR and oral and nasal FeNO values in each group. Technically adequate nasal FeNO readings were obtained for all participants, and none of them reported adverse effects after the procedure. The average of the right and left nasal cavities was used for the nasal FeNO level of each individual. The mean values of total NAR were 0.31 Pa/cm³/s in the control group, 0.36 Pa/cm³/s in the mild AR group, and 0.35 Pa/cm³/s in the moderate-to-most severe AR group. The AR patients tended to show higher NAR values, but the difference was not significant between the AR patients and the controls, or between the AR subgroups. Compared to the control

subjects, the patients in the mild and moderate-to-most severe AR groups showed significantly higher levels of oral FeNO. There was no significant difference in oral FeNO levels between the mild and the moderate-to-most severe AR group. The AR patients in both groups showed significantly higher levels of nasal FeNO compared to the healthy controls. The mean nasal FeNO levels were 26.5 ppb in the control group, 44.1 ppb in the mild AR group, and 54.5 ppb in the moderate-to-most severe AR group, with the significance being more prominent compared to that of oral FeNO in both AR groups ($p < 0.0001$ vs. $p < 0.05$).

The correlations between the nasal FeNO levels and the NAR values of the ipsilateral nasal cavity are shown in Fig. 3. No significant correlation was found between the paired parameters in the healthy controls or the two AR subgroups. Fig. 4 shows the ROC curves for nasal FeNO that were used to differentiate all AR patients and the moderate-to-most severe AR patients from the healthy controls. The area under the ROC curve (AUC) values calculated for the presence of AR were 0.853 for all patients and 0.873 for the moderate-to-most severe patients. An AUC of 1 indicates a perfect classification, and an AUC of 0.5 indicates that the ability to correctly classify is no better than happenstance. The optimal diagnostic cut-off points of nasal FeNO levels were 38.5 ppb (with 71.2% sensitivity and

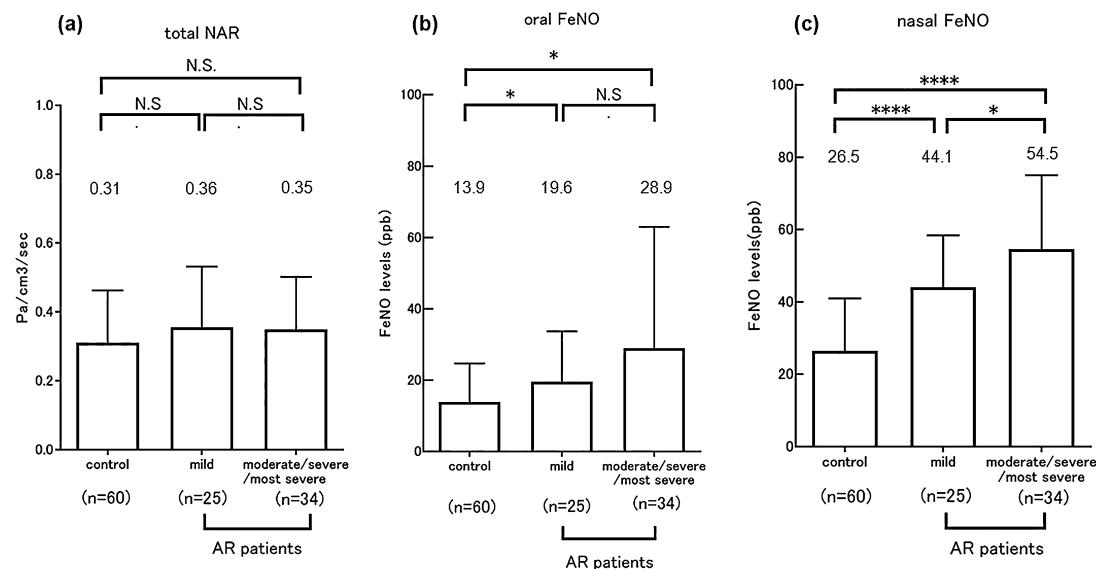


Fig. 2. Total NAR (a), oral FeNO (b), and nasal FeNO levels (c) in the healthy control subjects ($n = 60$), the patients in the AR mild group ($n = 25$), and the patients in the moderate-to-most severe AR group ($n = 34$). Error bars indicate mean values and SD. * $p < 0.05$; **** $p < 0.0001$; N.S., no significance.

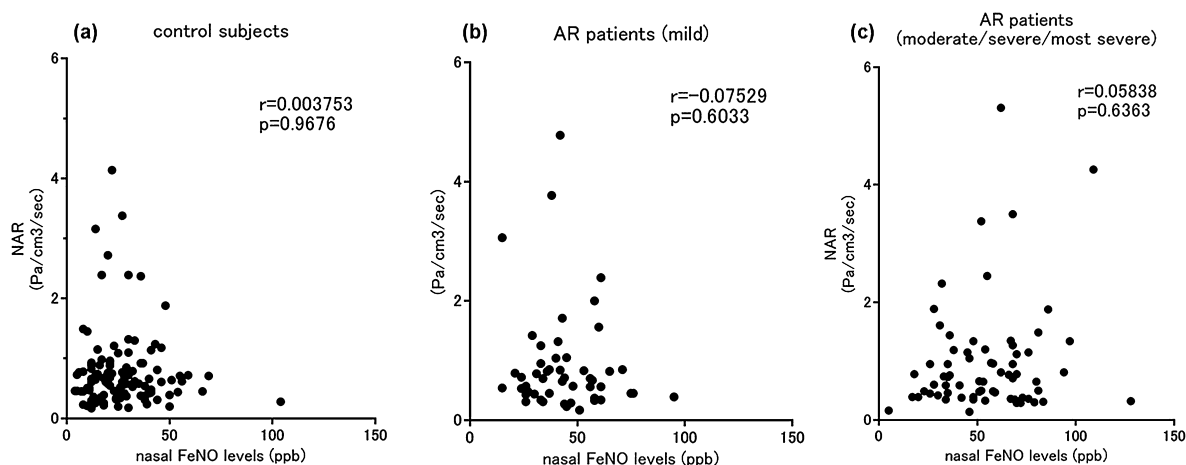


Fig. 3. Correlation between nasal FeNO levels and NAR in the control group (a), the mild AR group (b), and the moderate-to-most severe AR group (c). Each dot corresponds to a pair value of the two parameters for each side of the nasal cavity.

86.7% specificity) to discriminate the presence of AR and 40.3 ppb (with 76.5% sensitivity and 90% specificity) to discriminate the presence of moderate-to-most severe AR. Because the patients in the mild and moderate-to-most severe AR groups showed higher levels of oral FeNO, we also plotted the ROC curves for oral FeNO and compared the differentiation power between the two measures. The AUC values for oral FeNO calculated for the presence of AR were much lower with less sensitivity and specificity for all patients and for the moderate-to-most severe patients (0.6463 and 0.6426, respectively) (Fig. 5).

4. Discussion

Allergic rhinitis is commonly associated with substantial morbidity that is manifested as reduced quality of life and productivity. Nasal symptom scores derived from subjective questionnaires provide the basis of most outcome variables in studies of AR [9]. In the current stream of evidence-based

medicine, the assessment of allergic symptoms based on both subjective and reliable objective measures is expected. It is therefore of great use to set up reliable and valid objective markers of disease severity in AR patients. In this study we investigated nasal FeNO diagnostic modalities to assess symptomatic AR patients in relation to their NAR values. To our knowledge, no such study has been conducted, and thus it would be beneficial to accumulate data on two different parameters for an evidence-based diagnostic schema for AR.

In patients with untreated AR, augmented activity of the nitrate-nitrite-NO pathway has been reported to be due to enhanced iNOS expression in the nasal epithelium of the inferior turbinate [4,12]. It is therefore reasonable to assume that the nasal NO concentration can be used as a valid marker of local allergic inflammation. In fact, a majority of prior studies have reported increased nasal NO levels in AR patients (symptomatic or asymptomatic) [13–17]. However, the development of standardized techniques for nasal NO measurement and the establishment of guidelines with standard

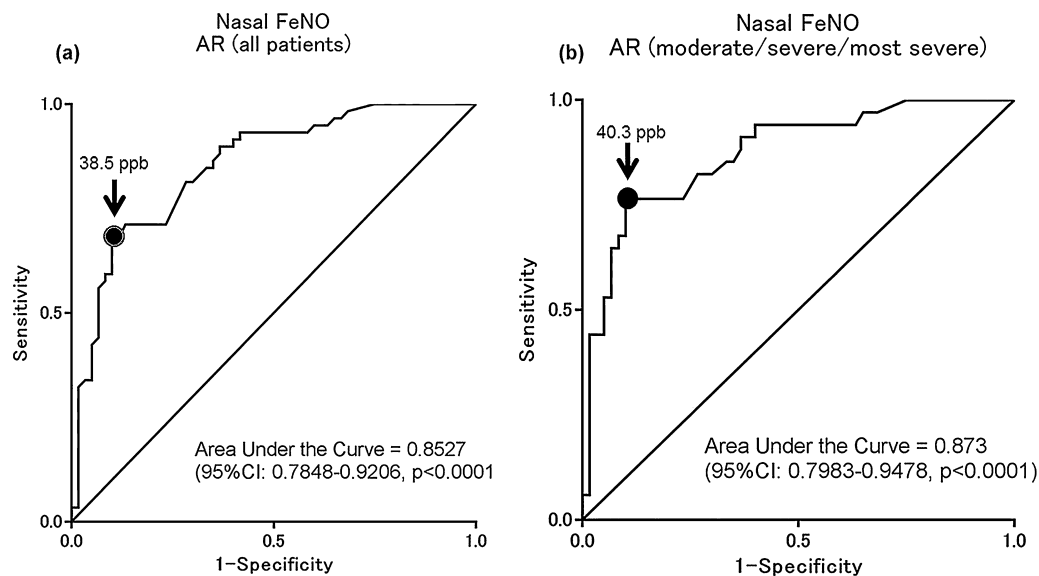


Fig. 4. ROC curve analysis for predictive values of mean nasal FeNO in all AR patients (a) and the AR patients with moderate-to-most severe symptoms (b). The black circles show the point for optimal cut-off values by using the Youden index. Nasal FeNO was 38.5 ppb with 71.2% sensitivity and 86.7% specificity in (a) and 40.3 ppb with 76.5% sensitivity and 90% specificity in (b).

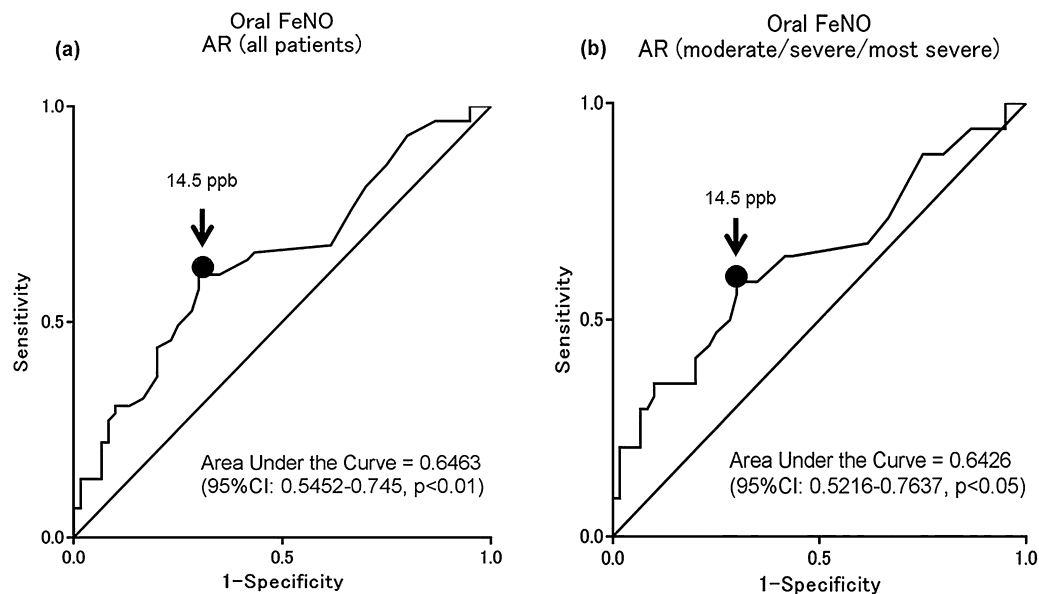


Fig. 5. ROC curve analysis for the predictive values of oral FeNO in all AR patients (a) and the AR patients with moderate-to-most severe symptoms (b). The black circles show the point for optimal cut-off values. Oral FeNO was 14.5 ppb with 61.2% sensitivity and 70% specificity in (a) and 14.5 ppb with 58.8% sensitivity and 70% specificity in (b).

cut-off values for the diagnosis of AR are still hampered by the functional complexity of NO in the human nose [6]. For example, Moody et al. reported that nasal NO levels were not elevated in a cohort of patients with perennial AR compared with nonatopic subjects [18]. They encountered relatively poor reproducibility of their weekly nasal NO measurements for each participant. Alexanderson et al. reported, in a survey of 357 Swedish subjects, that nasal NO was significantly increased among the subjects with high levels of IgE against cats, but no significant relation was observed between the nasal NO and subjective rhinitis symptoms [19]. These results imply a need to develop methods for measuring nasal NO that minimize contamination from the sinuses with fair reproducibility.

Nasal FeNO measurement is a simple and brief procedure, and it is ideal for immediate clinical assessments in outpatient settings [2]. Nasal FeNO represents a fraction of endogenous NO with contaminated air passing through the nose at a relatively high flow rate. In the present study, the AR patients showed significantly higher levels of nasal FeNO compared to the healthy subjects, with the difference being more prominent in the moderate-to-most severe AR group. This finding is compatible with our previous study and other studies based on several different approaches that have been proposed [11,13,15,16]. We measured nasal FeNO levels in essentially the same way as previously described, i.e., by having the subject exhale transnasally into a nose adaptor at a constant

flow rate as recommended by the ATS [2,11]. We modified this method so that the participants carried out a unilateral exhalation for each nasal cavity in turn, and the average was used for the evaluation of each individual. We found that compared to bilateral exhalation, the unilateral measurements were easier for the participants to get accustomed to, and they had fair reproducibility. However, further studies are required to investigate the contribution of other factors outside the nose that may influence nasal FeNO levels, e.g., the lower airways or paranasal sinuses. Because patients with bronchial asthma or chronic sinusitis were excluded in this study population, our analysis was based on the assumption that the contribution of gaseous NO that is diffused from either component should be identical.

Because nasal FeNO measurements may be influenced by the airflow physics based on anatomical variations of the nasal cavity, it is useful to assess the relationship between nasal FeNO and other objective parameters that reflect nasal airflow patterns, looking toward additional future applications. In the present study, we examined the relationship between nasal FeNO levels and NAR measured by rhinomanometry. Anterior rhinomanometry is an established device that provides an objective and quantitative assessment of nasal patency [8]. The Japanese Guidelines for Rhinomanometry propose reference values for total NAR in healthy Japanese adults as $0.25 \text{ Pa/cm}^3/\text{s}$ (SD 0.10) [10,20]. The AR patients enrolled in this study tended to show higher resistance, but no significant difference was detected in the mean values between the healthy controls and the AR groups. Although nasal obstruction is considered one of the key symptoms of allergic rhinitis, it appears that this subjective sensation is not directly related to a decrease in total nasal airflow.

Previous studies also reported the dissociation between the recordings from rhinomanometry and the reported nasal symptoms [21–23]. Several hypotheses have been proposed to explain the discrepancy, including problems in the nasal valve region, effects of the nasal cycle, and congestion in other areas of the nasal cavity such as the middle meatus [24]. An analysis in a sizable number of AR patients who reported the sensation of nasal obstruction showed that total inspiratory NAR was less influenced by the presence of seasonal or perennial AR than by the degree of nasal septal deviation [25]. These results, taken together, indicate that nasal FeNO and NAR are two distinctly independent modalities, with the former being suitable for the diagnosis of AR. This is substantiated by our observation of no relationship between the nasal FeNO level and the NAR of the same nasal cavity for each individual in both the control and AR groups.

We hypothesized that nasal FeNO can be used as a feasible detector for the presence of AR. The ROC curve analysis for the discriminating capacity had an AUC of 0.853 (95% CI 0.78–0.92), which was significantly different from happenstance. The AUC value for oral FeNO was much lower (0.6463) with far less sensitivity and specificity than that for nasal FeNO. These results clearly indicate the superiority of measuring nasal FeNO. The optimal cutoff values of nasal FeNO to discriminate the presence of AR and that of moderate-to-most severe AR were 38.5 ppb and 40.3 ppb, respectively. To the best of our

knowledge, this study is the first attempt to obtain the predictive values of nasal FeNO for distinguishing AR from healthy subjects in a Japanese population. In the management of asthmatic patients with eosinophilia, the 2011 ATS/ERS clinical practice guidelines recommend the use of cutoff points rather than reference values when interpreting oral FeNO levels [3,5,26]. In BA, the predictive values for oral FeNO (usually at the cutoff point $>25 \text{ ppb}$) have been shown to be sufficiently robust for oral FeNO to be used for the diagnosis of BA. In addition, oral FeNO $>50 \text{ ppb}$ in adults can be considered to indicate that eosinophilic inflammation and responsiveness to corticosteroids are likely in symptomatic patients [3]. Our present findings suggest that NO release from the nasal cavity is also practically detectable at levels of inflammation in the turbinate mucosa corresponding to the threshold for clinical manifestations. In this sense, NO release does not need to correlate in a cross-sectional manner with NAR, but it could provide an additional objective outcome when assessed prospectively [8].

There are several limitations in this study. Its cross-sectional design prevents any conclusions about causal relationships between the before and after successful treatment values. The number of subjects was relatively small. A large population-based study is needed to assess the applicability of nasal FeNO. Moreover, a general consensus about the optimal settings to standardize nasal FeNO measurements has yet to be reached.

In conclusion, the present study validates the role of FeNO measurements as an objective parameter for the diagnosis and classification of perennial AR in Japanese. The ROC curve analysis indicated that the optimal cut-off points of mean nasal FeNO levels is 38.5 ppb for the discrimination of the presence of AR, with sufficient sensitivity and specificity. Further, no significant correlation was found between nasal FeNO and NAR, indicating that these are two independent measures that can be used to evaluate nasal function. It will be necessary to achieve a consensus regarding the standardization of reliable AR measurement techniques and the possibility of using nasal FeNO to monitor the therapeutic effects of AR treatments.

Conflicts of interest

None of the authors have any conflict of interest to declare in relation to this study.

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