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ORIGINAL ARTICLE

Measurements of Nasal Fractional Exhaled Nitric Oxide with a Hand-held Device in Patients with Allergic Rhinitis: Relation to Cedar Pollen Dispersion and Laser Surgery

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ABSTRACT

Background: There has been an increasing interest in monitoring the fractional concentrations of exhaled NO (FeNO) levels in allergic rhinitis (AR) patients. In the present study, we examined whether the nasal FeNO measurement might reflect the degree of local allergic inflammation as well as subjective symptoms.

Methods: The FeNO measurement was performed using a handheld electrochemical analyzer (NObreath®) with a nose adaptor. In the cross-sectional study, 56 patients with perennial AR patients, 18 AR patients with bronchial asthma (BA), 12 patients with vasomotor rhinitis, and 30 normal subjects were enrolled. For the follow-up study, 12 seasonal allergic rhinitis (SAR) patients against Japanese cedar and 10 perennial AR patients who underwent laser surgery were examined.

Results: The AR patients and vasomotor rhinitis patients showed significantly higher oral FeNO levels as compared with the normal subjects. The nasal FeNO levels were significantly higher in the perennial AR patients with or without BA than in the normal subjects and vasomotor rhinitis patients. There were positive correlations between the nasal symptom scores and FeNO levels. The SAR patients showed a significant decrease in the nasal FeNO level after the pollen dispersion season. In addition, the therapeutic effects of laser surgery in the AR patients accompanied a significant reduction in the nasal FeNO levels one month after treatment.

Conclusions: The nasal FeNO measurement by NObreath® is easy to perform and suitable for monitoring AR patients in various treatment modalities. Furthermore, it may have potential usefulness as a tool to improve daily clinical care.

KEY WORDS

allergic rhinitis, cedar pollen, electrochemical analyzer, exhaled, laser surgery, nitric oxide

ABBREVIATIONS

AR, Allergic rhinitis; BA, Bronchial asthma; FeNO, Fractional concentrations of exhaled nitric oxide; HDM, house dust mites; NO, Nitric oxide; NOS, nitric oxide synthase; ppb, Parts per billion; SAR, Seasonal allergic rhinitis.

INTRODUCTION

Nitric oxide (NO) is abundantly produced in human airways by the activation of NO synthase. The fractional concentration of exhaled NO (FeNO) has been shown to be increased in inflammatory airway diseases, including bronchial asthma (BA),[1,2] allergic rhinitis (AR),[3-5] and chronic rhinosinusitis.[6,7] There

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has been rapidly increasing interest in monitoring the FeNO levels. Recently, a new hand-held device with an electrochemical sensor (NObreath®; Bedfont Scientific Ltd., Rochester, UK) has been developed and is available in Japan.[8,9] These devices have been clinically tested and were shown to provide values in good agreement with those obtained by the standard chemiluminescence analyzer.[10-12] Allergic rhinitis has been considered to be associated with increased FeNO levels, although there is still a divergence of opinion about whether local inflammation is responsible for increased levels of FeNO in the disease. Nasal NO is not routinely measured in daily clinical practice. One reason may be the heterogeneous results found in previous studies and the lack of consensus concerning the most suitable measurement technique.

In the present study, we measured the FeNO levels both trans-orally and trans-nasally in a population of normal subjects, perennial AR patients against house dust mites (HDM) with or without BA, and patients with vasomotor rhinitis using a handheld NO analyzer. The relationship between the FeNO levels and degree of subjective allergic symptoms was examined. We also evaluated changes in the FeNO levels in a group of seasonal allergic rhinitis (SAR) patients against Japanese cedar during and after the pollen season, and in a group of perennial AR patients who underwent laser surgery of the inferior turbinate. We found that the assessment of nasal FeNO described here is noninvasive, quickly performed, and may directly reflect the degree of allergic inflammatory conditions neighboring the surface mucosa of the inferior turbinate.

METHODS

SUBJECTS

One-hundred and sixteen subjects were included in the cross-sectional study. They are 56 patients with perennial HDM allergic rhinitis without BA (33 males and 23 females with a mean age of 32), 18 patients with perennial HDM allergic rhinitis and BA (11 males and 7 females with a mean age of 31.5), 12 patients with vasomotor rhinitis (7 males and 5 females with a mean age of 75.3), and 30 normal volunteers without nasal symptoms (17 males and 13 females with a mean age of 34.9). For the follow-up study of cedar pollinosis, 12 SAR patients against Japanese cedar (6 males and 6 females with a mean age of 33.3) were enrolled. Measurements were performed during the pollen dispersion season (March to April in 2010), when patients demonstrated allergic nasal symptoms, and 2 to 3 months after the season. For the follow-up study of laser surgery, 10 patients with perennial HDM allergic rhinitis who had chronic nasal obstruction (6 males and 4 females with a mean age of 27.7) were enrolled. The surgical procedure was performed on an outpatient basis and described in detail elsewhere.[13] Briefly, the whole septal surface of the inferior turbinates was vaporized bilaterally using a carbon dioxide laser (LESAC CO2-25, LESAC Co., Funabashi, Japan) equipped with a 45° reflected handpiece.

Diagnosis of allergic rhinitis was based on clinical history and a positive serum allergen-specific IgE score of 2 or greater on the CAP-RAST against HDM (Dermatophagoides farinae) or Japanese cedar (*Cryptomeria japonica*). The diagnosis of asthma was confirmed by clinical history of respiratory symptoms based on the Japanese guidelines for the diagnosis and treatment of allergic diseases 2010. Vasomotor rhinitis was clinically diagnosed by sporadic or persistent nasal symptoms with the predominant symptom being rhinorrhea and nasal itching. They were considered to be non-allergic with normal eosinophil proportion and negative IgE scores against any examined inhalant allergens. Patients who had been treated with any allergen-specific immunotherapy were excluded and did not receive any anti-allergic medication in the 14 days before the study.

The patients' subjective symptoms were recorded at the time of the NO measurement. Symptom scores were obtained using the following criteria based on a modified Okuda classification.[14] They include the daily number of sneezes, the frequency of rhinorrhea, and the degree of nasal congestion. Each symptom was scored on a scale of 0 to 4 (0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe). The study protocol was approved by the Institutional Review Board at the Hiroshima University School of Medicine, and informed consent was obtained from each subject.

MEASUREMENTS OF NITRIC OXIDE

Measurements of the FeNO level were obtained according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines using a handheld electrochemical analyzer (NObreath®).[15] For the oral FeNO measurements, the subjects first inhaled ambient air to near total lung capacity and then exhaled for 16 s at a constant flow rate of 50 mL/s through a disposable mouthpiece into the device.[8] For the nasal FeNO measurements, the subjects were advised to blow up their cheeks with mouth closed and to exhale transnasally with a nose adaptor attached to the mouthpiece.[16] The flow rate and duration were the same as for the oral FeNO measurement (Fig. 1). Each measurement was performed in triplicate and the mean value was used for analysis. After a brief period of training, all patients succeeded in performing acceptable nasal FeNO measurements. The detection limit of the device was 1 part per billion (ppb) and the measurement range was 5 to 256 ppb.

DATA ANALYSIS

Group data were expressed as means ± SD. For mul-

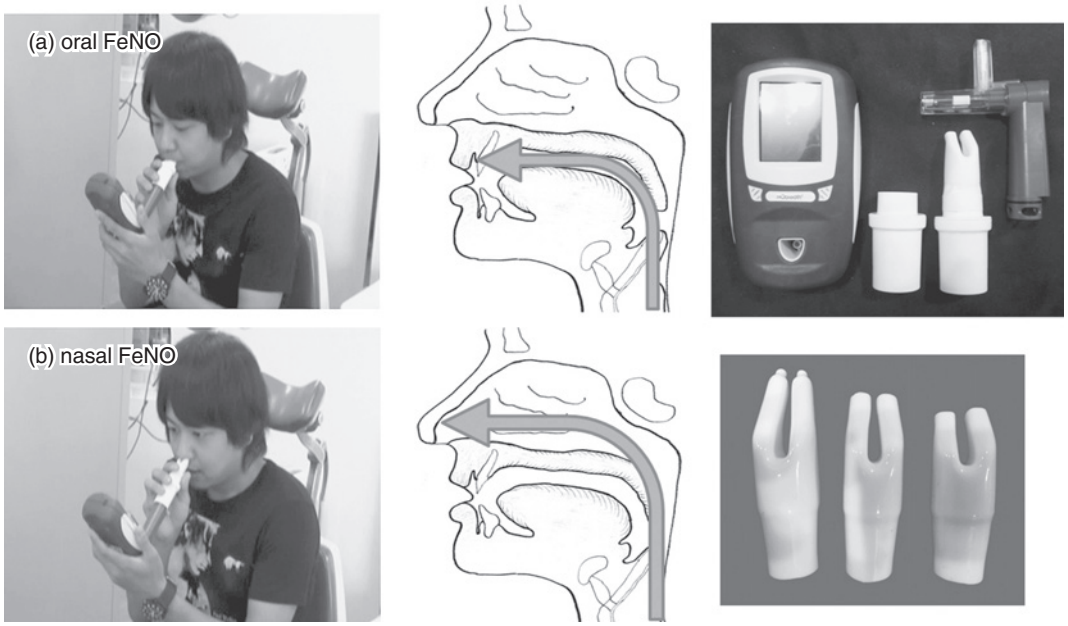

Fig. 1 A normal subject is exhaling against the disposable (**a**) mouthpiece and (**b**) nosepiece connected to the handheld analyzer (NObreath®). The nosepiece consists of a nasal olive connected to the mouthpiece. Different sizes of nasal olives are prepared to adjust nasal valve areas.

tiple comparisons, screening of data for differences was first carried out using the Kruskal-Wallis test. If the analysis gave a significant result, further comparison was done by the Mann-Whitney U test for between-group analysis. The comparison between each visit was assessed with the Wilcoxon rank sum test. Correlation coefficients were calculated by the Spearman method. Statistical analysis was carried out with STATISTICA for Windows (StatSoft Inc., Tulsa, OK, USA). A p value < 0.05 was considered significant.

RESULTS

FeNO LEVELS IN ALLERGIC PATIENTS

Figure 2 shows the values of oral and nasal FeNO in each group. The mean oral FeNO levels were 9.9 ± 8.0 ppb in normal subjects, 21.1 ± 11.6 ppb in vasomotor rhinitis patients, 17.3 ± 11.8 ppb in HDM allergic patients without BA [AR(+)BA(-)], and 96.3 ± 33.6 ppb in HDM allergic patients with BA [AR(+)BA(+)]. Compared with the normal group, the patients in the other three groups showed significantly higher oral FeNO levels. In addition, the AR(+)BA(+) patients showed significantly higher oral FeNO levels compared to the patients in the other two groups. The mean nasal FeNO levels were 48.6 ± 20.0 ppb in normal subjects, 46 ± 14.9 ppb in vasomotor rhinitis patients, 76.9 ± 30.2 ppb in AR(+)BA(-) patients, and 102.7 ± 47.0 ppb in AR(+)BA(+) patients. Compared with the normal group and vasomotor rhinitis group, both the AR(+)BA(-) and AR(+)BA(+) patients showed significantly higher nasal FeNO levels. In addition, the mean nasal FeNO level of the AR(+)BA(+) group was significantly higher than that of the AR(+)BA(-) group. Figure 3 shows the correlation between the nasal symptom scores and oral or nasal FeNO levels in patients of the AR(+)BA(-) and AR(+)BA(+) groups. We found weak but positive correlations between the nasal symptom scores and FeNO levels, with the coefficient being higher for nasal FeNO than oral FeNO (r = 0.356 vs. r = 0.303).

CHANGES IN FeNO LEVELS AFTER POLLEN SEASON

The release of pollen from *C. japonica* was first observed on February 11 in 2010 and pollen dispersion lasted for about 60 days. The total pollen counts in the season were 1286 per cm2. As shown in Figure 4, the mean oral FeNO levels in the SAR patients were 12.8 ± 9.5 ppb during the season and 12 ± 7.9 ppb after the season, and the difference was not significant. The mean nasal FeNO levels in the same patients were 62.1 ± 21.2 ppb during the season and 43.5 ± 17.4 ppb after the season. All the SAR patients showed a reduction in the nasal FeNO level at postseason, and the difference was significant. In addition, there was no significant difference in the mean nasal FeNO level between the SAR patients during the season and the HDM patients in the AR(+)BA(-) group (p = 0.134).

CHANGES IN FeNO LEVELS AFTER LASER SURGERY

After laser surgery, all the patients reported a better

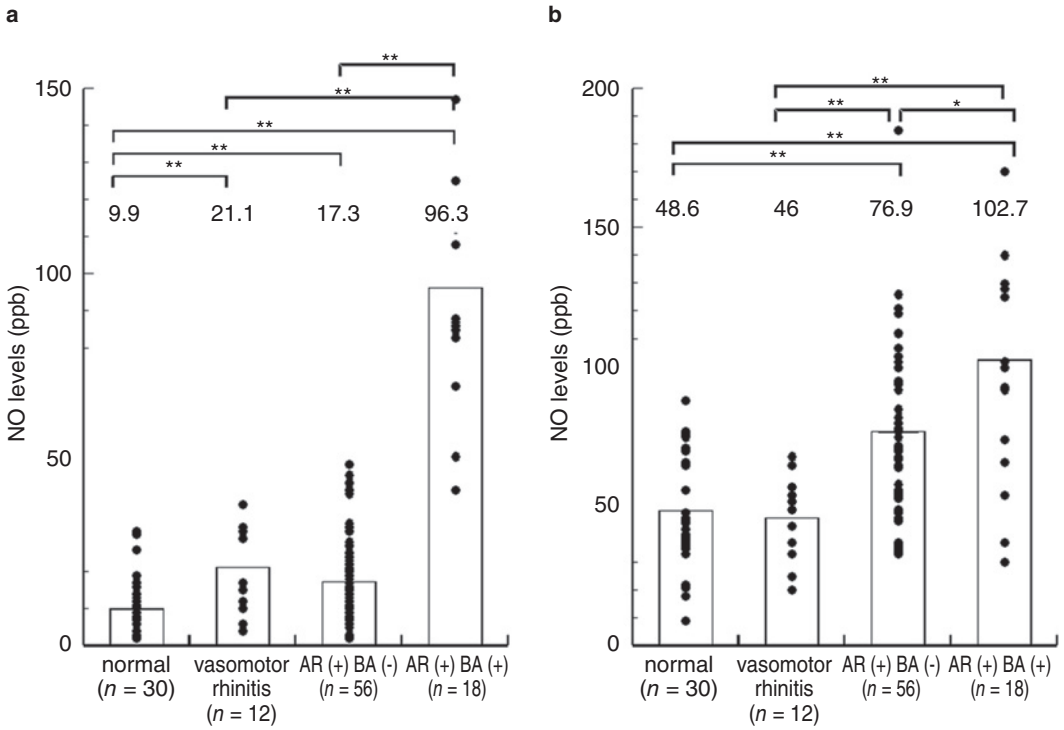

Fig. 2 (**a**) Oral FeNO and (**b**) nasal FeNO levels in normal subjects, in patients with vasomotor rhinitis, HDM allergic patients without BA [AR(+)BA(-)], and HDM allergic patients with BA [AR(+)BA(+)]. *P < .05; **P < .01; FeNO, fractional exhaled nitric oxide.

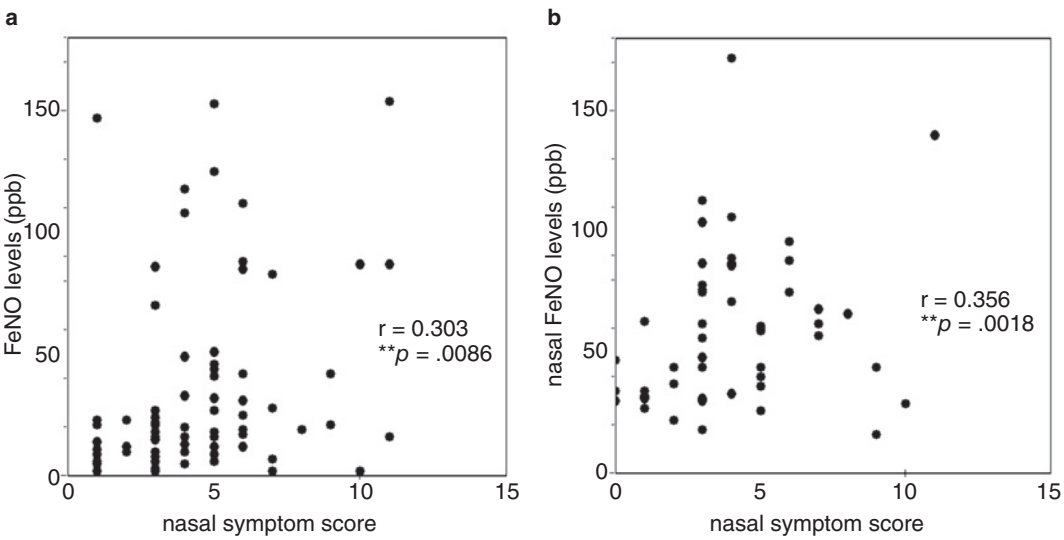

Fig. 3 Correlation between nasal symptom scores and (**a**) oral FeNO levels and (**b**) nasal FeNO levels in patients with HDM allergic patients (n = 74).

quality of life with improvement of nasal symptoms. The therapeutic effects generally appeared within 2 weeks with formation of scar tissue in the mucosal layer of the inferior turbinates. As shown in Figure 5, the mean oral FeNO levels in the patients were 36.7 ± 30.3 ppb before surgery and 35 ± 37 ppb one month after surgery, and the difference was not significant. However, the mean nasal FeNO levels in the same patients were 108.8 ± 42.9 ppb before surgery and 68.2 ± 54.7 ppb after surgery. The difference was significant and 9 out of 10 patients showed a reduction in the nasal FeNO level.

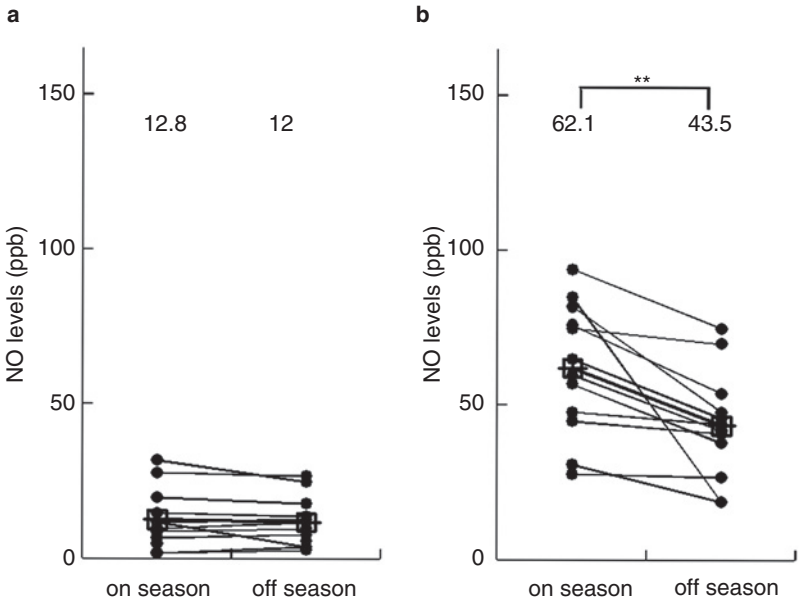

Fig. 4 Changes in the level of (**a**) oral FeNO and (**b**) nasal FeNO during the pollen season and after the season. $^{**}P < .01$.

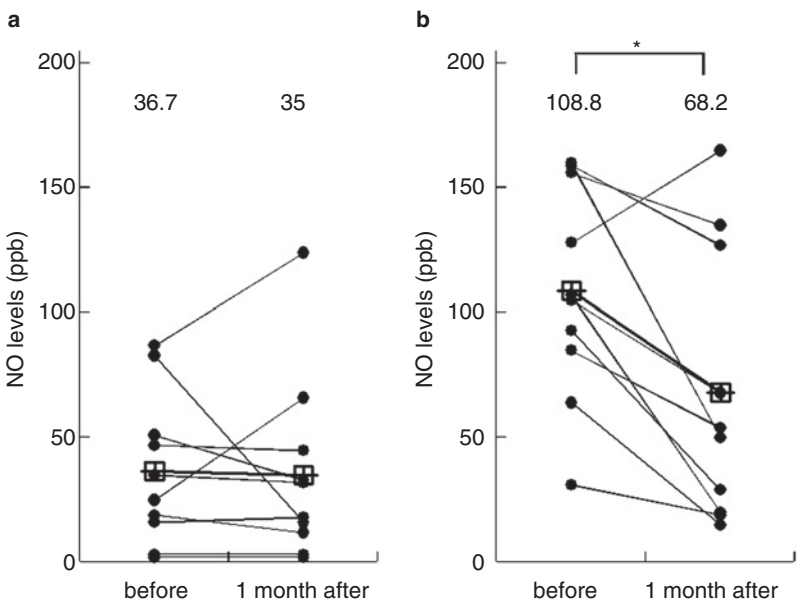

Fig. 5 Changes in the level of (**a**) oral FeNO and (**b**) nasal FeNO before laser surgery and one month after surgery. $^{*}P < .05$.

DISCUSSION

The measurement of FeNO has become a reliable and noninvasive marker of inflammation in human airways, reflecting the growing interest in this area.[1,2,6,8,9,12] In the present study, we measured the oral and nasal FeNO levels in normal and allergic subjects of the Japanese population by using the NObreath®. In this method, both the upper and lower airway FeNO levels can be easily measured with the same NO analyzer sequentially in a short period of time. We observed good agreement with those obtained by previously validated instruments.

Two different methods are recommended by the American Thoracic Society to assess the NO level in the nasal cavity, i.e., nasal NO and nasal FeNO.[3,5,15] Measurement of nasal NO is performed by aspirating air from the nasal cavity with a target airflow rate while the velum is closed during breath hold.[17] To measure nasal FeNO, the subject exhales trans-

nasally with a fixed flow while the mouth is closed. Nasal FeNO is considered to represent a fraction of endogenous NO with contaminated air passing through the nose with a relatively high flow rate.[3] Although measurement of nasal FeNO is easier and suitable for daily clinical use, it should be kept in mind that the concentrations depend on several factors. First, no normative data for a very large population including Japanese have so far been published. Second, the nasal NO output in normal subjects are usually high relative to the lower respiratory tract, with the contribution of a reservoir of abundant NO sources in the paranasal sinuses. Evaluation of the nasal FeNO measurement using a handheld analyzer was carried out in previous studies.[2,18] During the exhalation process, different flow rates may occur as a result of changes in the airflow physics caused by inter-individual differences in the anatomical structure of the nose. However, Djupesland *et al*. reported that interpretation of nasal NO levels was relatively constant and reliable when trans-nasal flow rates remained in a range between 0.25 and 3 L/min.[19] We also consider that the reproducibility of this measurement technique with NObreath® is acceptable from a clinical point of view and the intraindividual variability within each measure is usually minor in a cooperative and trained subject.[20]

Allergic rhinitis has been considered to be associated with increased FeNO levels mainly by the increased expression of inducible nitric oxide synthase (iNOS).[21-25] Several authors have reported increased nasal NO levels in symptomatic AR patients.[4,26-29] In these patients, an overexpression of iNOS as well as an increase in nitrites and nitrates, NO-derived metabolites, was observed in sampled specimens,[21] the breath condensate,[4] and nasal lavage fluid.[30] Kharitonov *et al*. reported that during the pollen season, the nasal NO levels, but not the FeNO concentrations, increased in SAR patients.[26] Conversely, some studies revealed no significant differences between rhinitis patients and control subjects.[31,32] Palm *et al*. reported increased levels of orally exhaled NO in SAR patients with a larger interindividual spread, whereas there were no changes in the nasal NO levels.[32] In the present study, significant increase in oral and nasal FeNO levels was observed in both AR(+)BA(-) and AR(+)BA(+) patients. Allergic diathesis is generally associated with increased NO production, although there is a divergence of opinions whether allergic rhinitis alone is responsible for increased exhaled NO levels detected from oral breathing. These seemingly conflicting results on the NO levels in AR patients may also reflect the difference in the selection of the patients studied and their disease backgrounds. Recently, Maniscalco *et al*. reported a slightly higher nasal FeNO level in AR patients compared with healthy subjects (59.0 vs. 49.1 ppb). The results were obtained by using another portable electrochemical analyzer (NIOX MINO®) from a single nasally exhaled breath maneuver.[20] The data are compatible with the present cross-sectional study. We also found significant differences in the nasal FeNO levels between perennial AR patients and normal controls (76.9 vs. 48.6 ppb).

The presence of bronchial asthma in AR patients was associated with higher nasal FeNO levels (mean 102.7 ppb). This represents a larger production of endogenous NO derived from both the upper and lower airways in this group because all patients uniformly revealed oral FeNO levels more than the cut-off level. It should be noted that nasal FeNO levels are more variable and susceptible to the lower airway condition as compared to nasal NO. Further studies including direct NO measures inside the nasal cavity are required to assess exact contribution of nasal NO production under the high background levels of oral FeNO in these patients.

We found increased oral FeNO levels in patients with vasomotor rhinitis as compared with control subjects, whereas there was no change in nasal FeNO levels. The mechanisms underlying vasomotor rhinitis are considered to be different from allergic rhinitis. Generally, vasomotor rhinitis arises from an imbalance of autonomic input into the nasal mucosa and enhanced parasympathetic responses, which results in increased plasma excretion and glandular secretion.[33,34] Previous reports observed histological damage to the surface epithelium with impaired mucociliary clearance as well as increased NADPH diaphorase activity in these patients.[35,36] Possible influence of age should be considered on FeNO measurement because the mean age of this group is higher than the other groups. It has been reported that respiratory NO does not appear to be age-dependent in normal adults and in children after the age of 11 years.[37,38] Little information has been available to date on the FeNO levels of vasomotor rhinitis patients. We suppose that the difference in the FeNO levels reflects pathological backgrounds characteristic of the disease and FeNO monitoring can be applied to differentiate vasomotor rhinitis from perennial AR patients.

There is still some inconsistency as for relation between nasal FeNO levels and the degree of nasal symptoms in perennial and seasonal AR patients. The present follow-up study indicates that nasal FeNO can be used as a good marker to evaluate inflammatory conditions of the diseased inferior turbinate in designated AR patients during the pollen season or after laser surgery. An increasing level of nasal FeNO during the pollen season and a moderate decrease in the off-season have been observed in SAR patients.[5,39] On the other hand, Bozek *et al*. failed to find a positive correlation with nasal symptom scores and nasal FeNO in any of the SAR patients during and after the pollen season.[5] One possible explanation for the di-

vergence is that low NO levels can be seen in certain conditions such as severe nasal blockage, watery nasal polyps, and nasal hypersecretion. Also, high background levels of NO from constitutive sources, such as paranasal sinuses, may blunt smaller increases in nasal NO output.[40,41]

To date there is little information available on changes in the FeNO levels after turbinate surgery in AR patients. Laser surgery has become one of the most popular methods among ENT surgeons to alleviate chronic nasal symptoms in perennial AR patients because of the improved results and simplicity of the procedure.[42] Rational backgrounds regarding the efficacy of laser surgery are mainly based on the degenerative process of the surface epithelium and scar tissue formation, which is preferable for interruption of allergic reactions.[43] In the present study, we found significant reduction in the nasal FeNO levels after laser surgery, whereas the oral FeNO levels remained unchanged. The result clearly indicates that attenuation of local allergic inflammation is responsible for decreased nasal FeNO in these patients.

In summary, nasal FeNO measurements obtained by NObreath®, a portable FeNO analyzer, are easy to use and suitable for monitoring AR patients in various treatment modalities as well as for basic research studies. Furthermore, the measurement may have potential usefulness as an additional tool to improve daily clinical care for these patients.

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REFERENCES

1. Kharitonov SA, Barnes PJ. Exhaled biomarkers. *Chest* 2006;**130**:1541-6.
2. Barnes PJ, Dweik RA, Gelb AF *et al*. Exhaled nitric oxide in pulmonary diseases: a comprehensive review. *Chest* 2010;**138**:682-92.
3. Maniscalco M, Sofia M, Pelaia G. Nitric oxide in upper airways inflammatory diseases. *Inflamm Res* 2007;**56**:58-69.
4. Gratziou C, Rovina N, Makris M, Simoes DC, Papapetropoulos A, Roussos C. Breath markers of oxidative stress and airway inflammation in seasonal allergic rhinitis. *Int J Immunopathol Pharmacol* 2008;**21**:949-57.
5. Bozek A, Krajewska J, Jarzab J. Nasal nitric oxide and other diagnostic procedures in seasonal allergic rhinitis: elderly vs juvenile patients. *Am J Otolaryngol* 2011;**32**:105-8.
6. Rolla G, Guida G, Heffler E *et al*. Diagnostic classification of persistent rhinitis and its relationship to exhaled nitric oxide and asthma: a clinical study of a consecutive series of patients. *Chest* 2007;**131**:1345-52.
7. Guida G, Rolla G, Badiu I *et al*. Determinants of exhaled nitric oxide in chronic rhinosinusitis. *Chest* 2010;**137**:658-64.
8. Antus B, Horvath I, Barta I. Assessment of exhaled nitric oxide by a new hand-held device. *Respir Med* 2010;**104**:1377-80.
9. Pisi R, Aiello M, Tzani P, Marangio E, Olivieri D, Chetta A. Measurement of fractional exhaled nitric oxide by a new portable device: comparison with the standard technique. *J Asthma* 2010;**47**:805-9.
10. Alving K, Janson C, Nordvall L. Performance of a new hand-held device for exhaled nitric oxide measurement in adults and children. *Respir Res* 2006;**7**:67.
11. Menzies D, Nair A, Lipworth BJ. Portable exhaled nitric oxide measurement: comparison with the "gold standard" technique. *Chest* 2007;**131**:410-4.
12. Pizzimenti S, Bugiani M, Piccioni P *et al*. Exhaled nitric oxide measurements: correction equation to compare hand-held device to stationary analyzer. *Respir Med* 2008;**102**:1272-5.
13. Takeno S, Osada R, Ishino T, Yajin K. Laser surgery of the inferior turbinate for allergic rhinitis with seasonal exacerbation: An acoustic rhinometry study. *Ann Otol Rhinol Laryngol* 2003;**112**:455-60.
14. Okuda M. Grading the severity of allergic rhinitis for treatment strategy and drug study purposes. *Curr Allergy Asthma Rep* 2001;**1**:235-41.
15. American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;**171**:912-30.
16. Profita M, La Grutta S, Carpagnano E *et al*. Noninvasive methods for the detection of upper and lower airway inflammation in atopic children. *J Allergy Clin Immunol* 2006;**118**:1068-74.
17. ATS Workshop Proceedings. Exhaled nitric oxide and nitric oxide oxidative metabolism in exhaled breath condensate: Executive summary. *Am J Respir Crit Care Med* 2006;**173**:811-3.
18. Weschta M, Deutschle T, Riechelmann H. Nasal fractional exhaled nitric oxide analysis with a novel hand-held device. *Rhinology* 2008;**46**:23-7.
19. Djupesland PG, Chatkin JM, Qian W *et al*. Aerodynamic influences on nasal nitric oxide output measurements. *Acta Otolaryngol* 1999;**119**:479-85.
20. Maniscalco M, de Laurentiis G, Weitzberg E, Lundberg JO, Sofia M. Validation study of nasal nitiric oxide measurements using a hand-held electrochemical analyzer. *Eur J Clin Invest* 2008;**38**:197-200.
21. Kawamoto H, Takeno S, Yajin K. Increased expression of inducible nitric oxide synthase in nasal epithelial cells in patients with allergic rhinitis. *Laryngoscope* 1999;**109**:2015-20.
22. Takeno S, Osada R, Furukido K, Chen JH, Yajin K. Increased nitric oxide production in nasal epithelial cells from allergic patients - RT-PCR analysis and direct imaging by a fluorescence indicator: DAF-2 DA. *Clin Exp Allergy* 2001;**31**:881-8.
23. Gratziou C, Lignos M, Dassiou M, Roussos C. Influence of atopy on exhaled nitric oxide in patients with stable asthma and rhinitis. *Eur Respir J* 1999;**14**:897-901.
24. Jouaville LF, Annesi-Maesano I, Nguyen LT, Bocage AS, Bedu M, Caillaud D. Interrelationships among asthma, atopy, rhinitis and exhaled nitric oxide in a population-based sample of children. *Clin Exp Allergy* 2003;**33**:1506-11.

25. Yuksel H, Kirmaz C, Yilmaz O *et al*. Nasal mucosal expression of nitric oxide synthases in patients with allergic rhinitis and its relation to asthma. *Ann Allergy Asthma Immunol* 2008;**100**:12-6.

26. Kharitonov SA, Rajakulasingam K, O'Connor B, Durham SR, Barnes PJ. Nasal nitric oxide is increased in patients with asthma and allergic rhinitis and may be modulated by nasal glucocorticoids. *J Allergy Clin Immunol* 1997;**99**: 58-64.

27. Henriksen AH, Sue-Chu M, Holmen TL, Langhammer A, Bjermer L. Exhaled and nasal NO levels in allergic rhinitis: relation to sensitization, pollen season and bronchial hyperresponsiveness. *Eur Respir J* 1999;**13**:301-6.

28. Martin U, Bryden K, Devoy M, Howarth P. Increased levels of exhaled nitric oxide during nasal and oral breathing in subjects with seasonal rhinitis. *J Allergy Clin Immunol* 1996;**97**:768-72.

29. Arnal JF, Didier A, Rami J *et al*. Nasal nitric oxide is increased in allergic rhinitis. *Clin Exp Allergy* 1997;**27**:358-62.

30. Sato M, Fukuyama N, Sakai M, Nakazawa H. Increased nitric oxide in nasal lavage fluid and nitrotyrosine formation in nasal mucosa—indices for severe perennial nasal allergy. *Clin Exp Allergy* 1998;**28**:597-605.

31. Maniscalco M, Sofia M, Carratù L, Higenbottam T. Effect of nitric oxide inhibition on nasal airway resistance after nasal allergen challenge in allergic rhinitis. *Eur J Clin Invest* 2001;**31**:462-6.

32. Palm JP, Alving K, Lundberg JO. Characterization of airway nitric oxide in allergic rhinitis: the effect of intranasal administration of L-NAME. *Allergy* 2003;**58**:885-92.

33. Jaradeh SS, Smith TL, Torrico L *et al*. Autonomic nervous system evaluation of patients with vasomotor rhinitis. *Laryngoscope* 2000;**110**:1828-31.

34. Loehrl TA, Smith TL, Darling RJ *et al*. Autonomic dysfunction, vasomotor rhinitis, and extraesophageal manifestations of gastroesophageal reflux. *Otolaryngol Head Neck Surg* 2002;**126**:382-7.

35. Ruffoli R, Fattori B, Giambelluca MA, Soldani P, Giannessi F. Ultracytochemical localization of the NADPH-d activity in the human nasal respiratory mucosa in vasomotor rhinitis. *Laryngoscope* 2000;**110**:1361-5.

36. Giannessi F, Fattori B, Ursino F *et al*. Ultrastructural and ultracytochemical study of human nasal respiratory epithelium in vasomotor rhinitis. *Acta Otolaryngol* 2003;**123**: 943-9.

37. Dotsch J, Demirakca S, Terbrack HG, Huls G, Rascher W, Kuhl PG. Airway nitric oxide in asthmatic children and patients with cystic fibrosis. *Eur Respir J* 1996;**9**:2537-40.

38. Bartley J, Fergusson W, Moody A, Wells AU, Kolbe J. Normal adult values, diurnal variation, and repeatability of nasal nitric oxide measurement. *Am J Rhinol* 1999;**13**: 401-5.

39. Vural C, Gungor A. Variations of nasal nitric oxide in a subject with allergic rhinitis: a longitudinal study. *Am J Otolaryngol* 2002;**23**:191-5.

40. Haight JS, Djupesland PG, Qjan W *et al*. Does nasal nitric oxide come from the sinuses? *J Otolaryngol* 1999;**28**:197-204.

41. Scadding G. Nitric oxide in the airways. *Curr Opin Otolaryngol Head Neck Surg* 2007;**15**:258-63.

42. Takeno S, Hirakawa K, Ishino T, Goh K. Surgical treatment of the inferior turbinate for allergic rhinitis: clinical evaluation and therapeutic mechanisms of the different techniques. *Clin Exp Allergy Rev* 2009;**9**:80-5.

43. Takeno S, Osada R, Furukido K, Yajin K. Analysis of local cytokine gene expression in patients with allergic rhinitis treated with carbon dioxide laser surgery. *Laryngoscope* 2000;**110**:1968-74.