Residual exhaled nitric oxide elevation in asthmatics is associated with eosinophilic chronic rhinosinusitis

Yoshiki Kobayashi, MD, PhD1,2, Mikiya Asako, MD, PhD1, Hisashi Ooka, MD, PhD1, Akira Kanda, MD, PhD1, Koichi Tomoda, MD, PhD1, and Hirotaka Yasuba, MD, PhD2

1Department of Otolaryngology, Kansai Medical University, Osaka, Japan and 2Department of Airway Medicine, Mitsubishi Kyoto Hospital, Kyoto, Japan

Abstract

Objective: Eosinophilic chronic rhinosinusitis (ECRS) is as a subgroup of chronic rhinosinusitis (CRS) with nasal polyps. ECRS is a refractory disease closely related to bronchial asthma. Fractionated exhaled nitric oxide (FeNO) levels were reportedly elevated in some asthmatics with CRS after adequate treatment, suggesting that residual eosinophilic airway inflammation or ECRS might affect FeNO levels. Methods: To investigate the association between asthma with ECRS and FeNO levels, we examined FeNO levels in 133 asthmatics (99 with ECRS and 34 without ECRS) and 13 patients with ECRS without asthma. The severity of asthma was defined by the Global Initiative for Asthma guidelines and that of sinusitis was evaluated by the sinus CT score based on the Lund–Mackay scale. Results and conclusions: FeNO levels were elevated even in well-controlled asthmatics with ECRS, whereas asthmatics without ECRS and ECRS patients without asthma did not have high FeNO levels (>50 ppb). Although FeNO levels were not correlated with asthma severity, they were positively correlated with the sinus CT score. In asthmatics with ECRS, patients with higher FeNO levels had more severe ECRS and asthma. There is a possibility of having comorbid ECRS, particularly in asthmatics with high FeNO levels even after adequate treatment, including ICS, suggesting that asthma and ECRS may be closely associated as one airway disease with eosinophilic inflammation. Continual awareness of the coexistent ECRS is ideally recommended for asthmatics with high FeNO levels.

Keywords

Airway medicine, bronchial asthma, ECRS, exhalation through the nose, FeNO, united airway

Introduction

Eosinophilic chronic rhinosinusitis (ECRS), characterized by a reduction in smell, bilateral eosinophilic polyps, and ethmoid sinus-dominant opacification in computed tomography (CT) findings, is considered as a subgroup of chronic rhinosinusitis (CRS) with nasal polyps in Japan [1]. Moreover, ECRS is closely associated with bronchial asthma, a risk factor of refractory ECRS [2–4]. Fractionated exhaled nitric oxide (FeNO) levels are elevated in patients with conditions with eosinophilic airway inflammation such as bronchial asthma [5]. Most patients with asthma are well-controlled with inhaled corticosteroid (ICS) treatment and have a concomitant reduction in FeNO levels [6]. Recently, several studies have shown higher FeNO levels in asthmatics with rhinosinusitis even after adequate treatment [7,8]. Matsunaga et al. indicated that some patients with severe asthma have higher FeNO levels even after treatments with oral corticosteroids [9]. Although the authors mentioned that 30% of the patients had CRS, it was not clear how they were diagnosed with CRS and which type of CRS (with eosinophil- or neutrophil-predominant inflammation) they had. However, Takeno et al. revealed that FeNO levels in patients with ECRS were higher than those in control patients and patients with non-ECRS [10]. Although, in that study, 18 of 33 patients with ECRS had bronchial asthma, it was not clear whether their asthma can be controlled; therefore, poorly controlled comorbid asthma may have affected the elevation of FeNO levels. Residual FeNO level elevation may be associated with residual eosinophilic airway inflammation in asthmatics with ECRS. However, the involvement of ECRS in well-controlled asthmatics with higher FeNO levels has not been completely elucidated. Therefore, we focused on well-controlled asthmatic and/or ECRS and examined FeNO levels.

Methods

Study patients

To investigate the involvement of ECRS in asthmatics with elevated FeNO levels, we recruited 133 patients with bronchial asthma diagnosed on the basis of a positive response to bronchodilator reversibility test as determined according to the Global Initiative for Asthma (GINA) guidelines [11]. All patients had well-controlled asthma, which was supported by
asthma control test scores (≥20 points) [12], and were undergoing treatment including ICS; the patients were divided into two groups based on the presence of ECRS: 99 asthmatics with ECRS (BA with ECRS) and 34 asthmatics without ECRS (BA w/o ECRS). Patients with uncontrolled allergic rhinitis and/or non-ECRS and patients who had acute exacerbation and had received systemic corticosteroids within 4 weeks before examination were excluded because they could have affected the study outcome. Furthermore, ECRS was diagnosed by clinical characteristics, indicated as a reduced sense of smell and presence of bilateral nasal polyps, and new clinical criteria reported by Sakuma et al. [13]: peripheral blood eosinophils percentage ≥6%, olfactory cleft CT score ≥1 and a posterior sinus CT score ≥1 [CT score was based on Lund–Mackay scale (LMS) [14]]. We also recruited 13 patients with ECRS without asthma as a control group (ECRS w/o BA). The severity of asthma was defined by GINA guidelines [11] and that of sinusitis was evaluated by the sinus CT score based on the LMS, and it was categorized as mild (CT score, ≤7), moderate (CT score, 8–11) or severe (CT score, ≥12) [15]. Current smokers and ex-smokers who had quit smoking within 1 year before measurement were also excluded to prevent any effects on FeNO levels [16,17]. This study was approved by the local ethics committee of Kansai Medical University, and written informed consent was obtained from each patient.

FeNO measurement
FeNO levels were measured for all patients, using NIOX MINO® (Aerocrine AB, Solna, Sweden) and categorized as low (<25 ppb), intermediate (25–50 ppb) or high (>50 ppb), as indicated in the American Thoracic Society (ATS) guidelines [18].

Statistical analysis
Comparisons of three groups of data were performed using the multinominal regression. Spearman’s correlation coefficients were also calculated. A difference was considered statistically significant if p was <0.05. Descriptive statistics were expressed as the mean with 95% confidence interval.

Results
Higher FeNO levels are associated with comorbid ECRS in asthmatics
In asthmatics with ECRS, FeNO levels were significantly higher than those in the other two groups (17.0 ± 8.0 ppb in the BA w/o ECRS group, 50.4 ± 36.0 ppb in the BA with ECRS group and 24.1 ± 11.2 ppb in the ECRS w/o BA group; Figure 1A). Although FeNO levels were not correlated with asthma severity (Supplemental Figure 1A), they were positively correlated with the sinus CT score (r = 0.6199, p < 0.0001; Figure 1B). As with the FeNO levels, the sinus CT score was not correlated with asthma severity (Supplemental Figure 1B). In addition, reflecting eosinophilic inflammation, the number of peripheral blood eosinophils was positively correlated with FeNO levels (r = 0.4195, p < 0.0001) and sinus CT score (r = 0.4441, p < 0.0001).

Discussion
We observed that FeNO levels were still elevated in some well-controlled asthmatics with ECRS even after adequate treatment including ICS, independent of asthma severity, whereas asthmatics without ECRS did not have high FeNO levels.

As shown in the ATS guideline, there are some asthmatics whose FeNO levels remain high (>50 ppb) despite a good
control [18]. This may be because residual eosinophilic airway inflammation, such as ECRS, persists. In the paranasal sinus, particularly ethmoid sinus mucosa, which may be constitutive inducible nitric oxide synthase sources [10], it is difficult to deliver adequate steroids by conventional treatment with ICS and the inhaled nasal steroids. Although Matsunaga et al. reported that 30% of patients with severe asthma and higher FeNO levels had CRS [9], a much higher prevalence of sinusitis may be detected if sinus CT scans were performed for all patients in their study. Hirano et al. showed that changing to an ultra-fine particle ICS from dry powder ICS reduced any persistent elevated FeNO levels concomitant with the improvement in pulmonary function [19]. Recently, we found that ultra-fine particles flow toward the olfactory cleft and middle meatus, where the ethmoid sinus ostium is located during both the inhalation and exhalation phases, and reported a case series in which treatment with an ultra-fine particle ICS inhalation orally, followed by exhalation through the nose (ICS–ETN) improved the disease in asthmatics with ECRS [20]. Although Hirano et al. did not mention the presence of CRS, it has been speculated that inhaled ultra-fine particles may also improve sinusitis as residual eosinophilic inflammation, results in reduced FeNO levels. More importantly, in 26 of 38 study patients with high FeNO (>50 ppb),

Table 1. Characteristics of study patients.

|                  | BA w/o ECRS (n = 34) | BA with ECRS (n = 99) | ECRS w/o BA (n = 13) |
|------------------|----------------------|-----------------------|----------------------|
| Age (years)      | 62.5 (57.6–67.4)     | 60.3 (57.7–62.8)      | 56.2 (47.3–65.0)     |
| Gender (M/F)     | 5/29                 | 46/43                 | 9/4                  |
| Severity of asthma (mild/moderate/severe) | 8/16/10             | 29/44/26              | NA                   |
| NSAIDs intolerance | 28/6                | 12                    | 11/2                 |
| Total IgE (IU/mL) | 278 (66–490)         | 422 (320–524)         | 168 (45–290)         |
| Eosinophils (per μL) | 218 (163–273)**   | 378 (320–436)         | 171 (94–247)*        |
| %FEV1 (%)         | 87.4 (80.1–94.7)     | 81.2 (78.2–84.2)      | 91.6 (84.4–98.9)     |
| %FEF25–75 (%)     | 60.6 (50.2–71.0)     | 52.1 (47.4–56.8)      | 79.9 (66.3–93.4)**   |
| ACT               | 23.9 (23.4–24.5)     | 24.0 (23.8–24.3)      | NA                   |
| LMS Total         | 0.9 (0.5–1.2)**      | 10.4 (9.3–11.5)       | 7.7 (5.9–9.5)        |
| Ethmoid           | 0.3 (0.1–0.5)****    | 4.3 (3.9–4.7)         | 3.5 (2.7–4.2)        |

Treatments

|                  | ICS (L/M/H)         |
|------------------|---------------------|
| BA w/o ECRS (n = 34) | 3/22/9             |
| BA with ECRS (n = 99) | 21/27/51           |
| ECRS w/o BA (n = 13) | 0/0/0              |

BA, bronchial asthma; NSAIDs, non-steroidal anti-inflammatory drugs; FEV1, forced expiratory volume in 1 s; FEF25–75, forced expiratory flow between 25% and 75% of vital capacity; ACT, asthma control test; LMS, Lund–Mackay scale; NA, not applicable; ICS, inhaled corticosteroid (categorized by fluticasone propionate equivalent daily doses (μg): low (L: 100–250), medium (M: >250–500) or high (H: >500); LABA, long-acting β2-agonist; LTRA, leukotrien receptor antagonist; LAMA, long-acting muscarinic receptor antagonist; INS, inhaled nasal steroid; NA, not applicable; *p < 0.05, **p < 0.01 (vs. BA with ECRS).

Figure 2. Association between FeNO levels and disease severities of ECRS and asthma in asthmatics with ECRS. (A) FeNO levels and ECRS severity based on sinus CT score. (B) FeNO levels and asthma severity. Individual values and their means for patients are shown in the lower part of each panel. White, black and gray indicate mild, moderate, and severe ECRS (A) or asthma (B), respectively. 

Figure 2. Association between FeNO levels and disease severities of ECRS and asthma in asthmatics with ECRS. (A) FeNO levels and ECRS severity based on sinus CT score. (B) FeNO levels and asthma severity. Individual values and their means for patients are shown in the lower part of each panel. White, black and gray indicate mild, moderate, and severe ECRS (A) or asthma (B), respectively. 

## p < 0.01 (vs. asthmatics with mild ECRS), #p < 0.05 (vs. mild asthmatics with ECRS).
comorbid ECRS was controlled by treatment, including an ultra-fine particle ICS–ETN with concomitant reduction of FeNO levels (unpublished data). On the basis of our findings that in well-controlled asthmatics, high FeNO levels were linked to more severe ECRS and asthma; the severities of ECRS and asthma could be affected by one another [21,22]. Taken together, comprehensive care is ideally recommended for asthmatics with ECRS, particularly with high FeNO levels.

A limitation of this study is that the subjects are confined exclusively to Japanese patients; hence, several studies for other populations need to be conducted to confirm if our findings are generalizable to them.

**Conclusions**

There is a possibility of having comorbid ECRS, particularly in asthmatics with high FeNO levels even after adequate treatment, including ICS, suggesting that FeNO may be a useful marker for detecting ECRS associated with asthma as one airway disease with eosinophilic inflammation. Therefore, we recommend continual awareness of the coexistent ECRS for asthmatics with high FeNO levels.

**Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. This work was supported by Grants-in-aid for Young Scientists (26860377) from Ministry of Education, Culture, Sports, Science and Technology of Japan and in part by the fund of academic society for research in Otolaryngology, Kansai Medical University.

**References**

1. Ishidoya J, Sakuma Y, Tsukuda M. Eosinophilic chronic rhinosinusitis in Japan. Allergol Int 2010;59:239–245.
2. Yoshimura K, Kawata R, Haruna S, Moriyama H, Hirakawa K, Fujieda S, Masuyama K, et al. Clinical epidemiological study of 553 patients with chronic rhinosinusitis in Japan. Allergol Int 2011; 60:491–496.
3. Tanaka S, Hirota T, Kamijo A, Ishii H, Hatsuhashi K, Fujieda S, Ishii J, et al. Lung functions of Japanese patients with chronic rhinosinusitis who underwent endoscopic sinus surgery. Allergol Int 2014;63:27–35.
4. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, Cohen, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology 2012:50:1–12.
5. Majid H, Kao C. Utility of exhaled nitric oxide in the diagnosis and management of asthma. Curr Opin Pulm Med 2010;16:42–47.
6. Barnes PJ, Dweik RA, Gelb AF, Gibson PG, George SC, Grasemann H, et al. Exhaled nitric oxide in pulmonary diseases: a comprehensive review. Chest 2010;138:682–692.
7. Ishizuka T, Hisada T, Kamide Y, Aoki H, Seki K, Honjo C, Sakai H, et al. The effects of concomitant GERD, dyspepsia, and rhinosinusitis on asthma symptoms and FeNO in asthmatic patients taking controller medications. J Asthma Allergy 2014;7:131–139.
8. Matsunaga K, Yanagisawa S, Hirano T, Ichikawa T, Koarai A, Kamatsu K, Sugiura H, et al. Associated demographics of persistent high FeNO elevation in treated asthmatics. Chest 2014;145:1311–1319.
9. Global Initiative for Asthma (GINA). 2014. From the Global strategy for asthma management and prevention; 2014. Available from: http://www.ginasthma.org/.
12. Jia CE, Zhang HP, Lv Y, Liang R, Jiang YQ, Powell H, Fu JJ, et al. The asthma control test and asthma control questionnaire for assessing asthma control: systematic review and meta-analysis. J Allergy Clin Immunol 2013;131:695–703.
13. Sakuma Y, Ishitoya J, Komatsu M, Shiono O, Hirama M, Yamashita Y, Kaneko T, et al. New clinical diagnostic criteria for eosinophilic chronic rhinosinusitis. Auris Nasus Larynx 2011;38:583–588.
14. Lund VJ, Mackay IS. Staging in rhinosinusitis. Rhinology 1993;31:183–184.
15. Mehta V, Campeau NG, Kita H, Hagan JB. Blood and sputum eosinophil levels in asthma and their relationship to sinus computed tomographic findings. Mayo Clin Proc 2008;83:671–678.
16. Westergaard CG, Porsbjerg C, Backer V. The effect of smoking cessation on airway inflammation in young asthma patients. Clin Exp Allergy 2014;44:353–361.
17. Malinovschi A, Backer V, Harving H, Porsbjerg C. The value of exhaled nitric oxide to identify asthma in smoking patients with asthma-like symptoms. Respir Med 2012;106:794–801.
18. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, Olin AC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011;184:602–615.
19. Hirano T, Matsunaga K, Sugiura H, Minakata Y, Koarai A, Akamatsu K, Ichikawa T, et al. Persistent elevation of exhaled nitric oxide and modification of corticosteroid therapy in asthma. Respir Investig 2013;51:84–91.
20. Kobayashi Y, Asako M, Kanda A, Tomoda K, Yasuba H. A novel therapeutic use of HFA-BDP metereddose inhaler for asthmatic patients with rhinosinusitis: case series. Int J Clin Pharmacol Ther 2014;52:914–919.
21. ten Brinke A, Grootendorst DC, Schmidt JT, De Bruine FT, van Buchem MA, Sterk PJ, Rabe KF, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. J Allergy Clin Immunol 2002;109:621–626.
22. Lin DC, Chandra RK, Tan BK, Zirkle W, Conley DB, Grammer LC, Kern RC, et al. Association between severity of asthma and degree of chronic rhinosinusitis. Am J Rhinol Allergy 2011;25:205–208.

Supplementary material available online
Supplemental Figure 1.