

Lower Airway Inflammation in Eosinophilic Chronic Rhinosinusitis as Determined by Exhaled Nitric Oxide

Rumi Kambara^a Takafumi Minami^b Hitoshi Akazawa^c Fumio Tsuji^b
Takanobu Sasaki^d Hidenori Inohara^c Arata Horii^d

Departments of ^aOtolaryngology and ^bRespiratory Medicine, Suita Municipal Hospital, and ^cDepartment of Otorhinolaryngology, Head and Neck Surgery, Osaka University Graduate School of Medicine, Suita, and ^dDepartment of Otolaryngology, Head and Neck Surgery, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Keywords

Eosinophilic chronic rhinosinusitis · Nitric oxide · Endoscopic sinus surgery · Asthma

Abstract

Background: Chronic rhinosinusitis (CRS) is classified into eosinophilic CRS (ECRS) and non-ECRS. The objectives of this study were to evaluate lower airway inflammation by measuring the fractional concentration of exhaled nitric oxide (FeNO) and to examine the effects of endoscopic sinus surgery (ESS) on FeNO in patients with ECRS compared to non-ECRS. **Methods:** CRS patients with nasal polyps (23 with ECRS and 22 with non-ECRS) were enrolled into this study. ECRS was diagnosed based on the definition proposed by the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) study group. Several clinical markers including blood eosinophil counts, percent of eosinophils in white blood cells (WBC), number of eosinophils in nasal polyps, JESREC scores, total IgE, FeNO, and Lund-Mackay paranasal sinus CT scores were compared between ECRS and non-ECRS. These markers were also tested before

and 2 months after ESS. **Results:** FeNO was significantly higher in patients with ECRS than in non-ECRS patients. When all CRS patients were tested, a significant correlation was found between FeNO and eosinophilic markers including blood eosinophil counts, percent of eosinophils in WBC, number of eosinophils in nasal polyps, and JESREC scores. FeNO showed a significant correlation with Lund-Mackay scores only in ECRS patients. Blood eosinophil counts, percent of eosinophils in WBC, and FeNO decreased after ESS only in ECRS patients. **Conclusions:** ECRS patients had lower airway inflammation as revealed by an elevated FeNO, which was parallel to the Lund-Mackay CT scores. ESS decreased the blood eosinophils and FeNO, leading to an improvement of the occult pulmonary dysfunction in ECRS patients.

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Introduction

Chronic rhinosinusitis (CRS) is classified into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSSNP) [1]. In Western countries, patients with

CRSsNP have a good prognosis, whereas CRSwNP is usually intractable. However, in Japan and East Asia, there are 2 types of CRSwNP patients: one is well controlled with endoscopic sinus surgery (ESS) and the other is more intractable and often has a recurrence shortly after ESS. To differentiate these 2 groups before surgery, the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) study group conducted a multicenter retrospective study on 1,716 CRS patients treated with ESS and proposed a subdivision of CRS into eosinophilic CRS (ECRS) and non-ECRS [2]. This is not a new but rather an old concept [3]; however, this group identified a cut-off point to differentiate ECRS from non-ECRS, which statistically correlates with the treatment outcome after ESS [2]. It was demonstrated that ECRS patients who had a JESREC score of 11 or more (Table 1), calculated on the basis of laterality (unilateral or bilateral disease), the presence or absence of nasal polyps, ethmoid or maxillary sinus dominance, and blood eosinophil counts, showed significant refractoriness to ESS compared to non-ECRS patients with JESREC scores ≤ 10 [2]. The latter group may represent the traditional neutrophil infiltration-dominant CRS, whereas the main pathology of the former group is eosinophilic inflammation. This study has established the definition of ECRS, which correlates with a poor outcome, and therefore ECRS has been designated as an intractable disease by the Ministry of Health, Labor, and Welfare of Japan. As a result, medical expenses for ECRS are now subsidized by the government of Japan (<http://www.mhlw.go.jp/english/wp/wp-hw9/dl/02e.pdf>, pp. 80–81).

The fractional concentration of exhaled nitric oxide (FeNO) is a noninvasive and reliable marker of lower airway inflammation, which is especially useful to evaluate the clinical status of asthma and to predict the responsiveness of asthmatic patients to steroids [4, 5]. The concept of “one airway, one disease” means that upper and lower airway diseases could be recognized as being a continuum of inflammation within one common airway [6]. This idea was initially stated in relation to atopic asthma and allergic rhinitis in the lower and upper airways, respectively [6, 7]; however, recent studies have suggested eosinophilic inflammation as an important pathophysiological mechanism of both asthma [8, 9] and CRS [3]. Therefore, we hypothesized that the lower airway in ECRS patients may be involved in eosinophilic inflammation, which would result in the increase in FeNO. In the present study, we measured FeNO in patients with CRSwNP before and after ESS and examined its correlation with diagnosis (ECRS or non-ECRS) and treatment outcome.

Table 1. JESREC score criteria for the diagnosis of eosinophilic chronic rhinosinusitis

Factor	Score
Disease side: both	3
Nasal polyp	2
CT shadow: ethmoid greater than or equal to maxillary	2
Eosinophils in peripheral blood	
>2% but $\leq 5\%$	4
>5% but $\leq 10\%$	8
>10%	10
Diagnosis	JESREC score
ECRS	≥ 11
Non-ECRS	≤ 10

JESREC, Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis; ECRS, eosinophilic Chronic rhinosinusitis.

Materials and Methods

This study was conducted in accordance with Declaration of Helsinki and it was approved by the IRB of Suita Municipal Hospital (No. 2016-KEN-36). This study is registered in the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR) (No. T000005486), which is approved by the International Committee of Medical Journal Editors (ICMJE).

A total of 45 patients with CRSwNP were enrolled into this study. ECRS was diagnosed based on a definition slightly modified from that proposed by the JESREC study group [2]. An eosinophil count of 70 or more in nasal polyps in a high-power field ($\times 400$) was added to the criterion of a JESREC score ≥ 11 (Table 1). This combination criterion was adopted by the Ministry of Health, Welfare, and Labor of Japan, according to which if CRS patients are deemed to have ECRS then their medical expenses are to be subsidized by the government of Japan. Twenty-three patients fulfilled the criteria for ECRS, whereas the other 22 patients were diagnosed as having non-ECRS. Thirteen and 3 patients had comorbid asthma in the former and latter groups, respectively. The diagnosis of asthma was based on the definition of the Global Initiative for Asthma (GINA), updated in 2015. All of the non-ECRS and ECRS patients had nasal polyps (the presence of nasal polyps was one of the markers used to determine the indication for surgical treatment). The exclusion criteria were as follows: an asthma attack during the 2 months prior to or the 2 months after surgery, oral or intravenous administration of steroids, a prior surgery for CRS, and a history of other eosinophilic diseases including eosinophilic granulomatosis with polyangitis, eosinophilic pneumonia, and hypereosinophilic syndrome. Inhaled steroids were not restricted. Table 2 shows the demographic and clinical data of the patients.

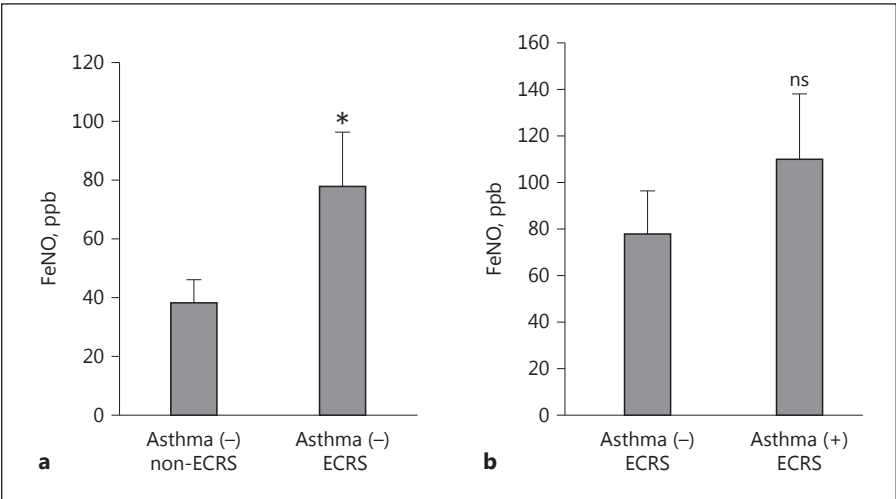
FeNO was measured at a single expiratory flow rate of 50 mL/s according to American Thoracic Society/European Respiratory

Table 2. Demographic and clinical data on the patients

	Non-ECRS	ECRS	<i>p</i> value
Patients, <i>n</i>	22	23	ns
Male/female ratio	16/6	18/5	
Age, years	50.3±16.8	53.9±12.2	ns
Comorbid asthma, <i>n</i> (%)	3 (13.6)	13 (56.5)**	0.007087
FeNO, ppb	40.3±32.6	107.0±89.6**	0.005146
Blood eosinophil count	185.7±28.2	529.3±47.9**	7.71×10 ⁻⁶
Eosinophils in WBC, %	3.3±2.3	8.6±2.9**	6.96×10 ⁻⁷
Eosinophils in polyps	11.9±12.4	198.8±104.7**	4.83×10 ⁻⁹
JESREC score	8.5±2.8	14.9±2.0**	3.24×10 ⁻⁸
Total IgE	247.6±368.6	415.4±601.1*	0.018874
%VC	108.2±16.3	114.1±13.9	ns
%FEV ₁	95.2±4.2	92.8±3.5	ns
V50/V25	3.7±1.3	4.3±3.3	ns

Data are presented as means ± standard error unless otherwise stated. ECRS, eosinophilic chronic rhinosinusitis; FeNO, fractional concentration of exhaled nitric oxide; WBC, white blood cells; JESREC, Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis; ns, nonsignificant. * *p* < 0.05, ** *p* < 0.01 vs. non-ECRS.

Fig. 1. Fractional concentration of exhaled nitric oxide (FeNO) in patients with chronic rhinosinusitis with nasal polyps without asthma (**a**) and patients with eosinophilic chronic rhinosinusitis (ECRS) with or without asthma (**b**). **a** FeNO was significantly higher in patients with ECRS than in those with non-ECRS among patients with chronic rhinosinusitis with nasal polyps and no asthma (* *p* < 0.05). **b** There were no differences in FeNO between ECRS patients with asthma and those without asthma. Data are means ± standard error. ns, nonsignificant.



Society guidelines [5, 10] using a Sievers nitric oxide analyzer (NOA 280i; GE Analytical Instruments, USA). Eosinophil infiltration into biopsy specimens of nasal polyps was determined before ESS under a microscope (×400). The severity of the CT findings on paranasal sinuses was scored according to the Lund-Mackay system, which ranges from 0 (none) to 24 (most severe) [11]. FeNO, Lund-Mackay CT score, number of eosinophils in nasal polyps, blood eosinophil counts, percent of eosinophils in white blood cells (WBC), total IgE, JESREC score, and spirometric tests (%VC, %FEV₁, and V50/V25) were compared between ECRS and non-ECRS. All patients were treated with conventional ESS, by which all nasal polyps were removed and all paranasal sinuses opened. Systemic or topical steroids were not administered either before ESS or 2 months after ESS when postoperative data were collected. FeNO, spirometric, and laboratory data from before and 2 months after ESS were compared. This time point was se-

lected because the patients had already recovered from the postoperative status but the disease had not yet recurred. Among 45 patients, 10 non-ECRS and 6 ECRS patients were lost to follow-up for unknown reasons and thus postoperative data was available for 12 non-ECRS and 17 ECRS patients. To evaluate the diagnostic capability, receiver operating characteristic (ROC) curves for percent of eosinophils in WBC, FeNO, and total IgE to diagnose ECRS were created.

The Mann-Whitney U test or a χ^2 test was used to test the differences between the 2 groups. Spearman's rank correlation coefficient was used to test the correlation between FeNO and blood eosinophil counts, percent of eosinophils in WBC, number of eosinophils in nasal polyps, or JESREC score. Differences between preoperative and postoperative values were tested using Wilcoxon's signed-rank test. *p* < 0.05 was considered statistically significant.

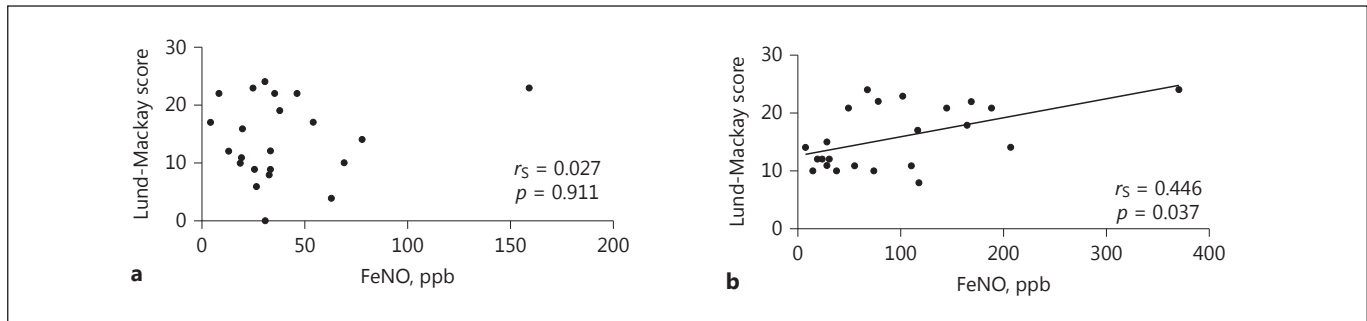


Fig. 2. Fractional concentration of exhaled nitric oxide (FeNO) with CT findings (Lund-Mackay scores) in patients with noneosinophilic chronic rhinosinusitis (**a**) and eosinophilic chronic rhinosinusitis (**b**). **a** There was no correlation between FeNO and Lund-Mackay CT scores in non-ECRS patients. **b** FeNO showed a significant correlation with Lund-Mackay CT scores in eosinophilic chronic rhinosinusitis patients.

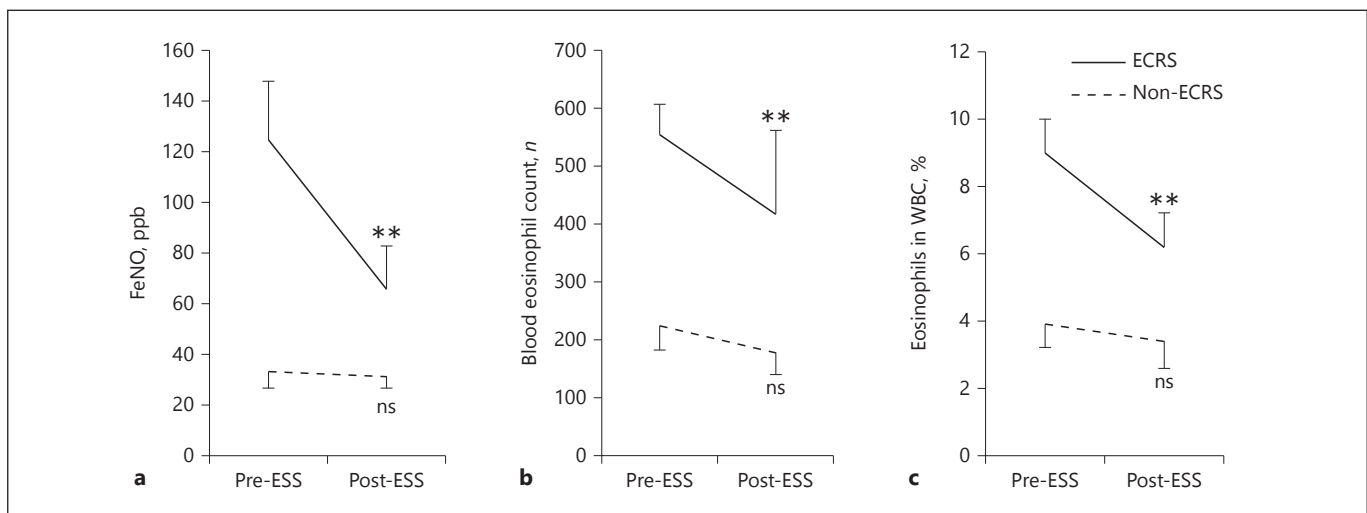


Fig. 3. Fractional concentration of exhaled nitric oxide (FeNO) (**a**), blood eosinophil counts (**b**), and percent of eosinophils in white blood cells (WBC) (**c**) measured before and after endoscopic sinus surgery (ESS). FeNO (**a**), blood eosinophil counts (**b**), and percent of eosinophils in WBC (**c**) were decreased 2 months after ESS in patients with eosinophilic chronic rhinosinusitis (ECRS) (** $p < 0.01$) but not in those with non-ECRS. Data are means $\pm$ standard error. ns, nonsignificant.

Results

Table 2 shows the demographic and clinical data of the patients. There were no significant differences in gender or age between non-ECRS and ECRS. Asthma was more frequently seen in ECRS patients than in non-ECRS patients. FeNO, blood eosinophil counts, percent of eosinophils in WBC, number of eosinophils in nasal polyps, JESREC score, and total IgE were all higher in ECRS patients than in non-ECRS patients. There were no differences in pulmonary function tests, including %VC, %FEV₁, and V50/V25, between non-ECRS and ECRS patients.

Figure 1 shows the FeNO values in CRSwNP (non-ECRS or ECRS) patients without asthma (Fig. 1a) and in ECRS patients with or without asthma (Fig. 1b). As shown in Figure 1a, ECRS patients without asthma showed significantly higher FeNO values than non-ECRS patients without asthma (Mann-Whitney U test, $p < 0.05$). As shown in Figure 1b, there was no significant difference in FeNO between asthma (–) ECRS patients and asthma (+) ECRS patients.

Figure 2 shows the correlation between FeNO and Lund-Mackay CT scores in patients with non-ECRS (Fig. 2a) and ECRS (Fig. 2b). Lund-Mackay scores showed a significant correlation with FeNO in patients with ECRS

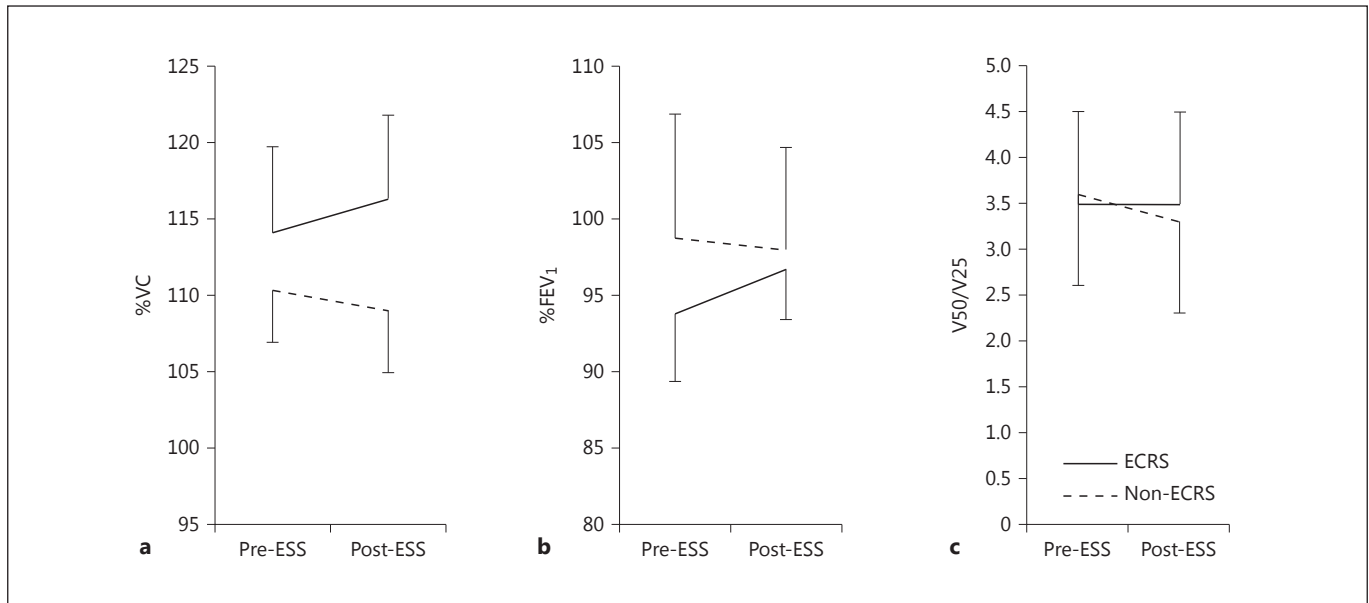


Fig. 4. Pulmonary function measured before and after endoscopic sinus surgery (ESS). There were no differences in %VC (a), %FEV₁ (b), or V50/V25 (c) before and after ESS in either eosinophilic chronic rhinosinusitis (ECRS) or non-ECRS patients. Data are means $\pm$ standard error.

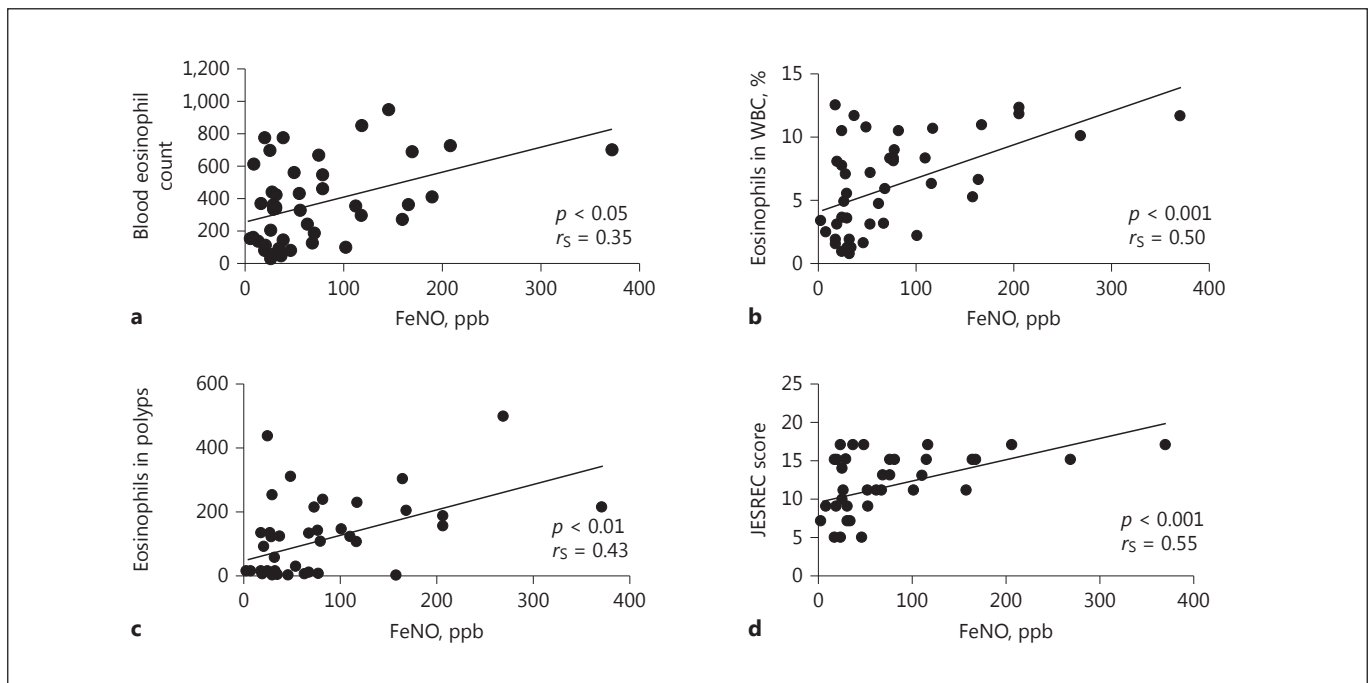


Fig. 5. Correlation of fractional concentration of exhaled nitric oxide (FeNO) with eosinophilic markers in patients with chronic rhinosinusitis with nasal polyps. Blood eosinophil counts (a), percent of eosinophils in white blood cells (WBC) (b), number of eosinophils in nasal polyps (c), and Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) score (d) were significantly correlated with FeNO.

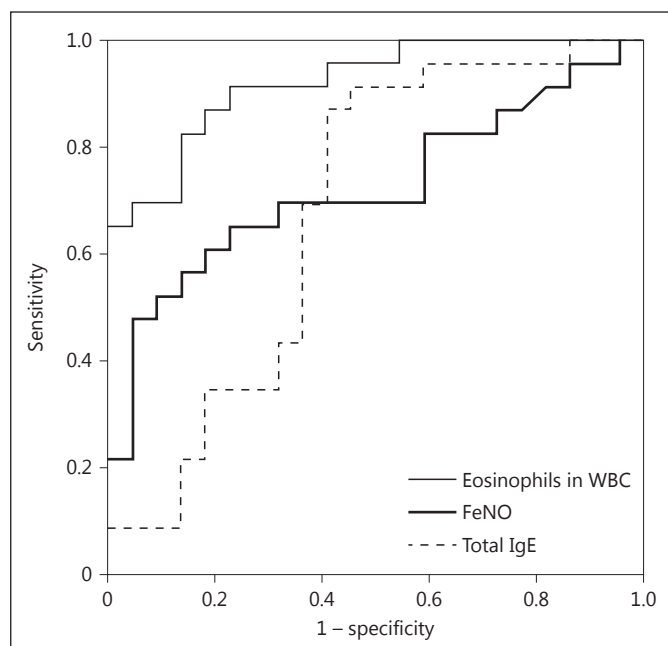


Fig. 6. Receiver operating characteristic curves for percent of eosinophils in white blood cells (WBC), fractional concentration of exhaled nitric oxide (FeNO), and total IgE to diagnose eosinophilic chronic rhinosinusitis. The area under the curve for FeNO was the middle point between the percent of eosinophils in WBC and total IgE (0.921 for % of eosinophils in WBC, 0.736 for FeNO, and 0.682 for total IgE).

(Fig. 2b) (Spearman's rank correlation coefficient, $p < 0.05$, $r_s = 0.446$) but not in patients with non-ECRS (Fig. 2a).

Figure 3 shows the pre- and postoperative FeNO (Fig. 3a), blood eosinophil counts (Fig. 3b), and percent of eosinophils in WBC (Fig. 3c) in CRSwNP patients. FeNO, blood eosinophil counts, and percent of eosinophils in WBC measured 2 months after ESS were significantly lower than those before ESS only in ECRS patients (Wilcoxon's signed-rank test, $p < 0.01$). These did not change after ESS in non-ECRS patients.

Figure 4 shows the results of pulmonary function tests including %VC (Fig. 4a), %FEV₁ (Fig. 4b), and V50/V25 (Fig. 4c) before and 2 months after ESS in CRSwNP patients. There were no changes in pulmonary function data before and after ESS in either ECRS or non-ECRS patients.

Figure 5 shows the correlation of FeNO with several markers of eosinophilic inflammation in CRSwNP patients. There were significant correlations between FeNO and blood eosinophil counts (Fig. 5a), percent of eosinophils in WBC (Fig. 5b), number of eosinophils in nasal polyps (Fig. 5c), and JESREC score (Fig. 5d). p values and coefficients of correlation are presented in Figures 5 and 6.

Figure 6 shows the ROC curves for percent of eosinophils in WBC, FeNO, and total IgE to diagnose ECRS. The area under the curve for percent of eosinophils in WBC (thin line), FeNO (thick line), and total IgE (dashed line) was 0.921, 0.736, and 0.682, respectively.

Discussion

Lower Airway Inflammation in ECRS

FeNO, a marker of lower airway inflammation, was above the normal range (<25 ppb) and significantly higher in patients with ECRS than in those with non-ECRS (Table 2), suggesting that the lower airway is involved in inflammation in patients with ECRS, an upper airway disease. There remains a possibility that the increase in FeNO in ECRS patients might be due to comorbid asthma. However, even if only patients without asthma had been tested, FeNO was significantly higher in patients with ECRS than in patients with non-ECRS (Fig. 1a). In addition, FeNO values for ECRS patients without asthma were as high as 78.4 ± 18.4 ppb, which is above the normal range (<25 ppb), and there were no differences in FeNO between ECRS patients with asthma and those without asthma (Fig. 1b). Therefore, ECRS patients had lower airway inflammation irrespective of the comorbidity of asthma. Moreover, the severity of the CT findings as evaluated by the Lund-Mackay system showed a significant correlation with FeNO in patients with ECRS but not in those with non-ECRS (Fig. 2), suggesting that the progress of upper airway disease was parallel to the lower airway inflammation specifically in ECRS patients. Eosinophil counts of sputum were higher in ECRS patients than in non-ECRS patients when only patients without asthma were tested (data not shown). Consistent with previous reports [12, 13], all of these findings suggest that ECRS but not non-ECRS patients had lower airway inflammation.

Effects of ESS on Lower Airway Inflammation

Inconsistent results on the effects of ESS on asthma and pulmonary function in CRSwNP patients have been reported [14–16]. Regarding the FeNO before and after nasal surgery, Galli et al. [17] reported that endoscopic surgical removal of polyps reduced the FeNO in patients with CRSwNP. A decrease in oral NO and an increase in nasal NO were reported after ESS in ECRS patients, but they were not measured in non-ECRS patients [18]. In the study by Galli et al. [17], patients were not classified into ECRS and non-ECRS categories, and the type of surgery was not specified (just removal of polyps or opening of

the paranasal sinus). The extent of the surgery was not described. In the present study, FeNO, blood eosinophil counts, and percent of eosinophils in WBC were significantly decreased 2 months after ESS in patients with ECRS but not in those with non-ECRS (Fig. 3). The present study demonstrated for the first time that ESS, a treatment for upper airway inflammation, can potentially affect the systemic eosinophilia and thus lessen lower airway inflammation specifically in ECRS patients. Spirometric tests including %VC, %FEV₁, and V50/V25 were not changed after ESS even in patients with ECRS (Fig. 4). This is probably because FeNO may be more sensitive in terms of detection of lower airway inflammation than spirometric markers especially in mild diseases [4, 5]. These results suggest that upper airway inflammation (i.e., ECRS) may be upstream of lower airway inflammation (i.e., asthma) in the concept of “one airway, one disease” [6] and that effective treatment of ECRS including ESS may lessen lower airway inflammation and thus prevent the future development of asthma in ECRS patients who do not yet have comorbid asthma.

Regarding the biological mechanisms underlying the sinonasal influences on lower airway inflammation, it has been reported that the production and maturation of eosinophilic precursors in bone marrow are accelerated by Th2 cytokines such as IL-5, which is released via local inflammation in the nose [19]. Therefore, anti-inflammatory effects due to ESS decreased blood eosinophils (Fig. 3b) and thus showed beneficial effects on lower airway inflammation as revealed by a decrease in FeNO (Fig. 3a). As another explanation for the nasal effects on the lower airway, it has been reported in ECRS patients with asthma that the cysteinyl leukotriene (Cys-LT) concentration is increased in nasal polyps and that urinary LT4 is decreased after ESS [20]. Because Cys-LT plays an essential role in eosinophilic inflammation including eosinophil adhesion to vessels, Cys-LT produced by nasal polyps would enter the systemic circulation and then cause eosinophilic inflammation in the lower airway.

Eosinophilic Inflammation in ECRS

Not only eosinophilic markers but also total IgE, a marker for type I allergy, was significantly higher in ECRS patients than in non-ECRS patients perhaps due to the comorbid nasal allergy (Table 2). To confirm the eosinophilic but not the allergic nature of ECRS, we created ROC curves for FeNO and total IgE to diagnose ECRS on the same plot. As a more direct marker for eosinophilic inflammation, an ROC curve for the percent of eosinophils in WBC to diagnose ECRS was also plotted. As

shown in Figure 6, the area under the curve for FeNO was the middle point between the percent of eosinophils in WBC and total IgE, indicating that the more eosinophilic markers, the greater the area under the curve (% of eosinophils in WBC > FeNO > total IgE), whereas all 3 of these markers were significantly higher in ECRS patients than in non-ECRS patients (Table 2). Moreover, blood eosinophil counts and the percent of eosinophils in WBC were significantly decreased after ESS in patients with ECRS but not in those with non-ECRS (Fig. 3b, c) and Lund-Mackay CT scores were parallel to FeNO, an eosinophilic inflammation marker. All of these findings suggest that the nature of ECRS is exactly eosinophilic inflammation rather than type I allergy.

Several markers for eosinophilic inflammation including blood eosinophil counts, percent of eosinophils in WBC, number of eosinophils in nasal polyps, and JES-REC score were all higher in ECRS patients than in non-ECRS patients (Table 2). As shown in Figure 5, FeNO showed a significant correlation with these eosinophilic markers, suggesting that FeNO is a noninvasive and easily measurable marker of eosinophilic inflammation. Eosinophil counts of biopsy specimens are required in order to diagnose ECRS according to the current definition by the Ministry of Health, Welfare, and Labor of Japan. FeNO could be added to the JESREC scoring system as a possible marker for lower airway inflammation and/or to replace invasive measurements such as eosinophil counts of biopsy specimens.

In terms of limitations of this study, the long-term effects of ESS on FeNO were not investigated. Because ECRS can often recur after surgery, combination therapy with ESS and medical treatment including steroids and immunotherapy should be considered to prevent recurrence [21, 22]. Therefore, it is difficult to assess the long-term effects of pure surgical treatment (ESS) on FeNO without medical treatment. Given that Lund-Mackay CT scores were parallel to FeNO in ECRS patients (Fig. 2), FeNO may be a noninvasive and nonradiological marker for the early detection of recurrence.

In conclusion, ECRS patients had occult lower airway inflammation as indicated by the elevated FeNO, which was parallel to the Lund-Mackay CT scores. ESS reduced not only blood eosinophils but also the FeNO and thus could potentially lessen lower airway inflammation in ECRS patients.

Disclosure Statement

All authors have no conflict of interests to declare.

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