

Exhaled nitric oxide identifies the persistent eosinophilic phenotype in severe refractory asthma

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Background: The fractional concentration of exhaled nitric oxide (FE_{NO}) is increased in asthma, correlates with eosinophilic inflammation, and decreases after steroid therapy. **Objective:** We sought to examine whether persistent eosinophilia would be accompanied by an increased FE_{NO} level despite steroid therapy in patients with severe refractory asthma (SRA) as manifestations of steroid resistance. **Methods:** Subjects with SRA, subjects with mild-moderate asthma, and healthy control subjects had FE_{NO} measured, followed by endobronchial biopsy and bronchoalveolar lavage. Tissue and bronchoalveolar lavage inflammatory cells were assessed for all subjects, and eosinophil status (EOS^+/EOS^-) was determined for subjects with SRA. **Results:** Twenty-four subjects with SRA, 15 subjects with moderate-mild asthma, and 17 healthy control subjects were studied. Subjects with EOS^+ SRA had significantly higher median FE_{NO} levels compared with levels in subjects with EOS^- SRA ($P = .0084$) and all other groups. In subjects with SRA, FE_{NO} levels correlated with tissue eosinophils ($r_s = 0.54$, $P = .007$), lymphocytes ($r_s = 0.40$, $P = .003$), and mast cells ($r_s = 0.44$, $P = .05$). FE_{NO} levels of greater than 72.9 ppb were associated with a sensitivity of 0.56 and a specificity of 1.0 for EOS^+ status in subjects with SRA. **Conclusion:** FE_{NO} measurement identified the subgroup of subjects with SRA with persistent eosinophilia despite steroid therapy. Further studies are needed on the use of FE_{NO} to monitor response to therapy over time in subjects with SRA. (*J Allergy Clin Immunol* 2005;116:1249-55.)

Key words: asthma, exhaled nitric oxide, eosinophils, airway, inflammation

Asthmatic patients with refractory asthma pose a major health and economic concern, using a disproportionate amount of the health care expenditure.¹ Airway inflammation is the underlying factor driving asthma, involving complex interactions between inflammatory cells, including mast cells, eosinophils, macrophages, neutrophils, and lymphocytes, and the respiratory epithelium itself.² Free

Abbreviations used

AUC: Area under the curve
BAL: Bronchoalveolar lavage
EBBX: Endobronchial biopsy
 EOS^+ : Eosinophil-positive phenotype
 EOS^- : Eosinophil-negative phenotype
 FE_{NO} : Fractional concentration of exhaled nitric oxide
ICS: Inhaled corticosteroid
iNOS: Inducible nitric oxide synthase
NO: Nitric oxide
ROC: Receiver operator characteristic
SRA: Severe refractory asthma

radicals, including nitric oxide (NO) and its derivatives, are produced during the course of inflammation, causing oxidative damage that might amplify the inflammatory process.

Several phenotypes of severe refractory asthma (SRA) have been proposed, including those subjects who, despite steroid therapy, have persistent eosinophilic infiltration of the airways (EOS^+) and those without it (EOS^-).³ In addition, there is evidence to support a neutrophilic asthmatic phenotype.⁴ Some evidence exists for prognostic differences according to phenotype. For example, one study demonstrated that subjects with EOS^+ SRA had more intubations than subjects with EOS^- SRA.³ Furthermore, there is evidence that neutrophilic subjects could be less responsive to corticosteroids.⁵ Therefore identification of inflammatory phenotypes might be of importance in assessing risk and tailoring asthma therapy according to phenotype.

To identify asthma phenotypes, bronchoscopy remains the gold standard for assessing airway inflammation.⁶ However, this is an invasive and costly technique and considered unsuitable for routine clinical use. Sputum induction and analysis, although less invasive than bronchoscopy, might induce bronchospasm and is time consuming and costly, detracting from its widespread clinical application.

Since the discovery that NO is an important biologic mediator,⁷ the measurement of the fractional concentration of exhaled NO (FE_{NO}) has gained prominence as a noninvasive marker of airway inflammation in asthma.⁸ In contrast to bronchoscopy and sputum induction, the measurement of FE_{NO} is entirely noninvasive, simple, and quick. Exhaled NO is increased in non-steroid-treated

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asthma,⁹ decreased within several days after treatment with inhaled or oral corticosteroids, and increases equally rapidly after steroid withdrawal,¹⁰ in part because of modulation of epithelial inducible NO synthase (iNOS) by steroids.¹¹ There is a moderate correlation between FE_{NO} and sputum eosinophils in non-steroid-treated asthma¹² and a positive correlation between FE_{NO} and airway tissue eosinophilic inflammation.^{13,14} In light of the correlation between FE_{NO} and eosinophilic inflammation and the observed rapid increase in FE_{NO} levels in response to corticosteroid therapy, we determined whether FE_{NO} had utility in predicting the persistence of lung eosinophils in subjects with SRA treated with high-dose inhaled and oral steroids.

METHODS

Study design

This was a cross-sectional study at a single time point looking at the relationship between exhaled NO and bronchoscopic parameters of inflammation.

Subjects

Subjects with asthma of various severities who were referred to National Jewish Medical and Research Center for evaluation were recruited together with healthy control subjects. They underwent history and physical examination, lung function testing (short-acting bronchodilators and long-acting bronchodilators were held for 4 hours and 12 hours, respectively, before spirometry), and FE_{NO} measurement, followed by bronchoscopy within 0 to 2 days. All participants were not currently smoking and had a history of less than 5 pack-years. Subjects with other significant general medical or other respiratory diseases were excluded.

Asthma was graded on the basis of severity, as previously reported.³ Patients with SRA were referred to our clinic for evaluation by external specialists. Known significant nonadherence was an exclusion criteria for participation. Subjects with mild-moderate asthma and healthy control subjects were recruited from National Jewish or by advertisement. For the purposes of this study, SRA was defined as follows: (1) FEV_1 less than 70% of predicted value; (2) at least 10 mg/d oral prednisone or equivalent for at least 50% of the previous year with high-dose inhaled corticosteroids (ICSs); and (3) at least 2 urgent care visits for asthma in the previous year. Moderate asthma was defined as an FEV_1 of less than 80% of predicted value with 400 to 1000 mg of ICSs or equivalent and β_2 -agonists and without a history of urgent care visits or systemic steroid use in the prior year. Mild asthma was defined as an FEV_1 of greater than 80% of predicted value with β_2 -agonists alone. Healthy control subjects had normal pulmonary function, no bronchodilator response, and no chronic illness, but mild atopy was allowed. The study was approved by the institutional review board, and all subjects provided informed consent.

Bronchoscopy

Bronchoscopies were performed as outpatient procedures, and endobronchial biopsy (EBBX) tissue samples were processed as previously described.³ Tissue sections were immunostained for markers of eosinophils (eosinophil major basic protein, clone BMK-13; Accurate Chemical & Scientific Corp, Westbury, NY), lymphocytes (CD3), and neutrophils (neutrophil elastase; both from Dako, Carpinteria, Calif). The cell counts were normalized per tissue

area and expressed as cells per square millimeter of airway submucosa. Tissue analysis was performed by a single observer who was blinded to the subjects' identity and status. The coefficient of variation in cell counts for the same section was less than 7%. Bronchoalveolar lavage (BAL) was performed in subsegments of the lingula or right middle lobe by using four 60-mL aliquots of warm sterile saline. BAL fluid was pooled and centrifuged at 600g for 10 minutes to separate fluid from cells, and cell differentials were determined from cytospin preparations.

Subgrouping by eosinophils

Patients with SRA were divided into those with eosinophilia (EOS^+) and those without eosinophilia (EOS^-) on the basis of EBBX eosinophil counts, eosinophil percentages, or both in BAL fluid as follows: EOS^+ subjects had greater than 22 eosinophils/mm² of tissue ($>mean + 2$ SD of the number of eosinophils per square millimeter in the healthy control group), 2% or greater BAL fluid eosinophils, or both, as previously reported.¹⁵

Measurement of exhaled NO

FE_{NO} was measured with a single-breath technique according to American Thoracic Society recommendations at an exhalation flow rate of 50 mL/s with an Ionics-Sievers NOA 280 analyzer (Boulder, Colo).¹⁶

Statistical analysis

The Kruskal-Wallis test was used to compare severity groups for each inflammatory variable. Two sets of groups were analyzed separately: (1) healthy control subjects, subjects with mild-moderate asthma, and subjects with severe asthma and (2) healthy control subjects, subjects with mild-moderate asthma, subjects with EOS^+ SRA, and subjects with EOS^- SRA. Intergroup comparisons were performed for a particular variable and group set by using Wilcoxon rank sum tests if significant differences were observed with the Kruskal-Wallis test. Spearman correlations (r_s) were used to determine the strength of relationships between FE_{NO} and BAL/EBBX variables. The ability of FE_{NO} to diagnose the SRA EOS^+ phenotype was examined by constructing receiver operator characteristic (ROC) curves, which are plots of sensitivity by $(1 - \text{specificity})$. The area under the ROC curve (AUC) is a common index used to summarize the value of a diagnostic test, where AUC is 1.0 for a perfect test.

RESULTS

Subject characteristics

Twenty-four subjects with SRA, 4 subjects with moderate asthma, 11 subjects with mild asthma, and 17 healthy control subjects were studied. This article reports only subjects with both FE_{NO} measurement and a bronchoscopy: for EOS^+ SRA, 8 of 10 underwent BAL, and 8 of 10 underwent EBBX (different missing subjects); for EOS^- SRA, 14 of 14 underwent BAL, and 12 of 14 underwent EBBX. All 14 subjects with mild-moderate asthma and all control subjects underwent both procedures. Eleven of 14 subjects with EOS^- SRA and 5 of 10 subjects with EOS^+ SRA were taking oral steroids at the time of the bronchoscopy, with no significant difference in mean oral steroid dose between the groups. Morning cortisol levels were available for 12 of 24 subjects with SRA; only 1 subject taking oral steroids had a morning cortisol level of greater than 5 μ g/dL. Six of 10 subjects

TABLE I. Subject characteristics

Group	n	Age (y)	White/African American or Hispanic	M/F	Mean oral steroid (mg/d)	FEV ₁ (%)
SRA combined	24	37 ± 3	17/7	12/12	20 ± 4	57 ± 4
SRA EOS ⁺	10	37 ± 4	6/4	5/5	22 ± 8	68 ± 6*
SRA EOS ⁻	14	37 ± 4	11/3	7/7	20 ± 4	49 ± 4*
Mild-moderate asthma	15	32 ± 2	15/0	9/6	0	84 ± 3
healthy control subjects	17	32 ± 2	16/1	5/12	0	105 ± 3

All Values are expressed as means ± SEM.

**P* = .01.

with EOS⁺ SRA, 7 of 14 subjects with EOS⁻ SRA, and 11 of 13 subjects with mild-moderate asthma were atopic. Because of small numbers, subjects with mild and moderate asthma were analyzed together.

Demographic details and lung function are summarized in Table I. FEV₁ percent predicted was significantly higher in the SRA EOS⁺ group compared with that in the SRA EOS⁻ group (*P* = .01).

Exhaled NO

For SRA when disregarding EOS status, there were no significant differences between the severity groups (*P* = .17, Fig 1) for FE_{NO}. However, when classifying SRA by EOS status, the EOS⁺ SRA group had significantly higher median FE_{NO} levels compared with the EOS⁻ SRA group (67.3 vs 20.4 ppb, *P* = .0084), the subjects with mild-moderate asthma (*P* = .01), and the healthy control subjects (*P* = .001, Fig 1 and Table II).

Correlations between FE_{NO} and BAL/EBBX inflammatory cells

FE_{NO} levels were positively correlated with tissue BMK⁺ eosinophils for SRA (*r_s* = 0.54, *P* = .007) but not for subjects with mild-moderate asthma (*r_s* = -0.03, *P* = .91) or control subjects (*r_s* = 0.37, *P* = .19, Fig 2). FE_{NO} levels also correlated with tissue lymphocytes (*r_s* = 0.40, *P* = .003) and with tissue mast cells (*r_s* = 0.44, *P* = .05) in SRA alone. There was a trend toward significance between FE_{NO} levels and the percentage of eosinophils in BAL fluid for all groups combined (*r_s* = 0.26, *P* = .06).

ROC analysis

Exhaled NO was an excellent surrogate marker for the EOS⁺ phenotype in the SRA group (n = 24), with an area under the ROC curve (AUC) of 0.83; a FE_{NO} level of greater than 72.9 ppb was associated with a sensitivity of 0.56 and a specificity of 1.0 for the identification of EOS⁺ status in subjects with SRA (Fig 3).

Inflammatory cells

Tables II and III show medians and quartiles for BAL and EBBX inflammatory cells by asthma severity. When analyzing SRA while disregarding EOS status, tissue mast cells were significantly greater in healthy subjects compared with those in subjects with SRA (*P* = .0001), and there were significantly less BAL macrophages in

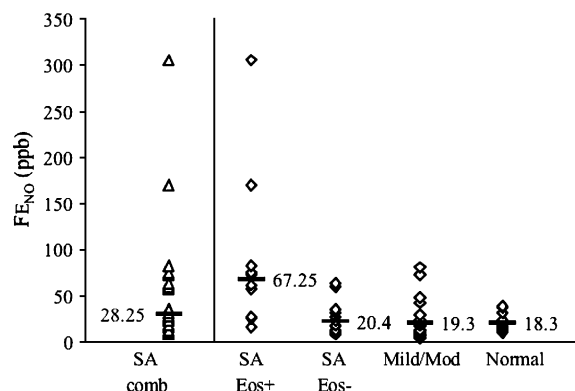


FIG 1. FE_{NO} versus asthma severity for SRA as a whole and classified by SRA EOS status. Dashed lines indicate medians. FE_{NO} distributions were not significantly different between the 3 asthma severity groups for SRA as a whole, but when classifying SRA by EOS status, the subjects with EOS⁺ SRA had significantly higher median FE_{NO} levels than the subjects with EOS⁻ SRA (*P* = .0084), the subjects with mild-moderate asthma (*P* = .01), and the control subjects (*P* = .001).

subjects with SRA when compared with subjects with mild-moderate asthma (*P* = .023).

However, when separating SRA by EOS status, overall differences were detected among the 4 severity groups. The EOS⁺ SRA group had higher EBBX eosinophil counts compared with those in the EOS⁻ SRA group (by definition) but also compared with those in the mild-moderate asthma and healthy control subject groups (*P* < .001 and *P* < .0001, respectively). In addition, the EOS⁻ SRA group had lower EBBX eosinophil counts compared with those in the mild-moderate asthma group (*P* = .0056). The subjects with EOS⁺ SRA had significantly higher tissue mast cell counts (*P* = .02) compared with those in the EOS⁻ SRA group. The EOS⁺ SRA group had significantly lower BAL fluid percentage macrophages compared with that in the mild-moderate asthma group (*P* = .002) and the healthy control subjects (*P* = .014). The distribution of neutrophils and lymphocytes in tissue was similar among the groups (overall *P* = .11 and .39, respectively).

The percentage of eosinophils in BAL fluid was increased in the subjects with EOS⁺ SRA compared with the subjects with mild-moderate asthma and the control subjects (*P* < .01). All other BAL variables were not significantly different among the groups (Table III).

TABLE II. BAL inflammatory cells and exhaled NO

Group	n	Median (25th-75th percentile)					BAL % macrophages*†
		BAL % eosinophils*	BAL % neutrophils	BAL % lymphocytes	BAL cells/mL	FE _{NO} (ppb)*	
SA combined	24	0.2 (0-1.2)	1.4 (0.7-3.2)	11.3 (3.9-21.4)	16.2 (10.9-26.6)	28.3 (16.2-62.8)	77.7 (65.2-90.7)
SA EOS ⁺	10	2.1 (0.6-4.1)	1.2 (0.7-9.4)	12.0 (7.9-14.5)	14.1 (8.1-36.3)	67.3 (25.6-102.9)	72.4 (64.7-82.6)
SA EOS ⁻	14	0.05 (0-0.3)	1.5 (0.4-3.2)	5.7 (3.4-32.0)	17.2 (10.9-26.6)	20.4 (10.5-34.1)	82.9 (62.3-94.6)
Mild- moderate	15	0.05 (0-0.25)	0.7 (0.4-0.9)	6.0 (2.8-11.8)	14.0 (10.5-19.8)	19.3 (9.4-40.9)	90.0 (84.2-92.8)
Control subjects	17	0.1 (0-0.25)	1.0 (0.5-1.6)	16.0 (2.9-13.1)	16.0 (11.3-23.9)	18.3 (13.3-31.2)	89.8 (81.4-95.4)

SA, Severe asthma.

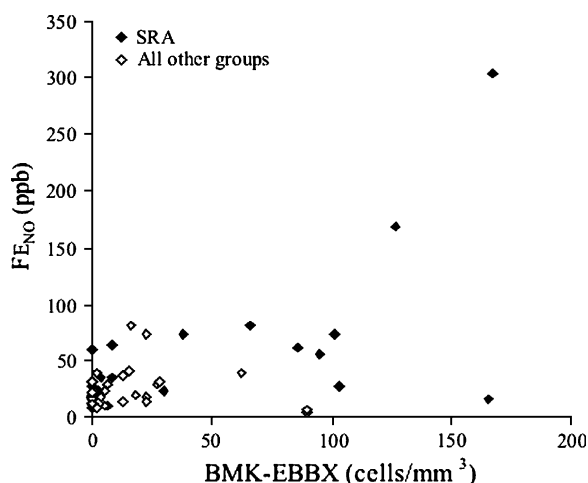
* $P \leq .05$ when all severity groups were compared (subjects with severe asthma were separated into EOS⁺/EOS⁻ groups).† $P \leq .05$ when all severity groups were compared (subjects with severe asthma were combined).

FIG 2. Correlation between FE_{NO} levels and tissue eosinophil counts in all subjects. There was a significant correlation between FE_{NO} level and tissue eosinophils in SRA alone ($r_s = 0.54$, $P = .007$).

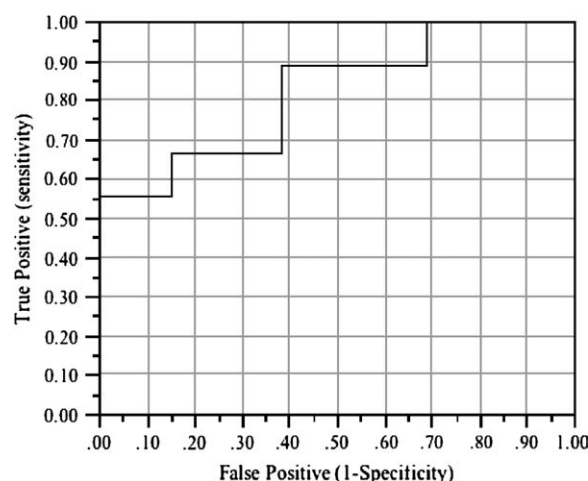


FIG 3. ROC curve for FE_{NO} for the identification of the EOS⁺ phenotype in SRA. AUC was 0.83; FE_{NO} levels of greater than 72.9 ppb were associated with a sensitivity of 0.56 and a specificity of 1.0 for the identification of EOS⁺ status in subjects with SRA.

DISCUSSION

In this study FE_{NO} measurement identified the persistent eosinophilic phenotype in subjects with SRA despite therapy with inhaled and systemic steroids. Correspondingly, FE_{NO} levels correlated with eosinophilic inflammation in the SRA group but not in the subjects with mild-moderate asthma, probably because of more significant suppression of both eosinophilia and exhaled NO by ICSs. Exhaled NO levels also correlated with tissue lymphocyte and mast cell counts in SRA, with no significant relationship to tissue or BAL fluid neutrophil counts. Finally, FE_{NO} levels did not correlate with asthma severity, as defined in this study, but this might be due to the relatively small number of subjects in the individual groups. This study suggests that increases in FE_{NO} levels are primarily associated with eosinophilic airway inflammation but also lymphocyte and mast cell numbers in steroid-dependent refractory asthma.

Disregarding the EOS status of the SRA group, there was no significant difference in FE_{NO} levels between the severity groups. However, the EOS⁺ SRA group had significantly higher FE_{NO} levels than the EOS⁻ SRA group,

the mild-moderate asthma group, or the healthy control subjects. Exhaled NO levels correlated with tissue eosinophils, mast cells, and lymphocytes but showed no significant relationship with neutrophils in subjects with SRA.

Our study is in agreement with others that show a link between FE_{NO} levels and eosinophilic inflammation.^{12,17-19} However, it demonstrates for the first time that FE_{NO} levels might be predictive of eosinophilic inflammation, even in steroid-dependent SRA. The persistent eosinophilia and increased FE_{NO} levels might both be manifestations of relative steroid resistance in subjects with SRA.

Hamid et al²⁰ first showed that iNOS was overexpressed in the airway epithelium in asthma. Later, it was shown that both the increase in iNOS expression and FE_{NO} levels decreased significantly after 2 weeks of inhaled budesonide.¹¹ Van Den Toorn et al¹⁹ reported a correlation between FE_{NO} levels and eosinophil activation in bronchial biopsy specimens in both subjects with active asthma and in subjects whose asthma had remitted. Lim et al,²¹ however, could find no relationship between FE_{NO} levels and mucosal eosinophilic inflammation in subjects with mild-to-moderate asthma. Despite this, our study

TABLE III. Tissue inflammatory cells

Group	n	Median (25th-75th percentile)				
		Eosinophils, cells/mm ² *	Neutrophils, cells/mm ²	Lymphocytes, cells/mm ²	Mast cells, cells/mm ² *†	Macrophages, cells/mm ²
SA (all)	24	8.0 (0-95.0)	43.0 (14.0-116.0)	38.0 (11.5-76.3)	28.0 (7.0-45.5)	43.0 (28.3-99.0)
SA EOS ⁺	10	98.0 (59-136.8)	42.5 (13.0-71.8)	64.0 (27.5-115.0)	40.5 (33.5-62.8)	41.0 (28.3-120.0)
SA EOS ⁻	14	0 (0-5.0)	60.0 (18.0-128.0)	31.0 (6.0-57.5)	12.0 (1.0-39.0)	43.5 (24.3-92.5)
Mild-moderate asthma	15	15.5 (1.8-24.0)	36.5 (16.8-101.0)	11.0 (7.8-63.5)	73.5 (10.5-122.5)	27.0 (13.8-47.3)
Healthy control subjects	17	3.0 (0-15.5)	53.0 (33.0-148.0)	40.0 (17.0-112.0)	88.0 (42.0-102.0)	36.0 (26.0-48.0)

SA, Severe asthma.

* $P \leq .05$ when all severity groups were compared (subjects with severe asthma were separated into EOS⁺/EOS⁻ groups).

† $P \leq .05$ when all severity groups were compared (subjects with severe asthma were combined).

further supports the concept that FE_{NO} levels directly reflect eosinophilic inflammation in subjects receiving oral steroid therapy, ICS therapy, or both. Furthermore, ROC curve analysis showed that FE_{NO} measurement can accurately identify the EOS⁺ phenotype in subjects with SRA (AUC = 0.83).

The reason for the close relationship between eosinophilic inflammation and exhaled NO in asthma deserves scrutiny. First, it is known that human eosinophils can express messenger RNA for iNOS, and eosinophils could therefore be one of the sources of the increased NO production.²² This expression could be driven by inflammatory cytokines present in the asthmatic airway. Indeed, in the rat, cytokines such as IL-4 induce iNOS expression in eosinophils.²³ Second, NO production might be involved in facilitating the migration of eosinophils.^{24,25} Third, it is also known that NO, perhaps produced by the respiratory epithelium, might be a chemoattractant for eosinophils.²⁶ The observation that mast cell numbers correlate with FE_{NO} levels could be due to mast cell NO production, as recently described.²⁷

This study found no correlation between FE_{NO} levels and overall asthma severity, as defined here, which is in agreement with another report.²⁸ Although FE_{NO} levels decrease and pulmonary function improves after treatment, there is little evidence for a correlation between pulmonary function, a determinant of severity, and FE_{NO} levels, although there is a correlation with bronchodilator response.²⁹ In fact, this study showed that subjects with EOS⁺ SRA and higher FE_{NO} levels had better lung function when compared with the EOS⁻ group, despite the evidence that this group generally has more symptoms, exacerbations, and intubations.³ Others have, however, reported that fixed airflow obstruction was associated with EOS⁺ SRA.³⁰ It is possible that the high airway levels of NO in the EOS⁺ SRA group reflect higher airway wall NO levels that improve lung function as NO is a bronchodilator.

This study confirms earlier observations that a significant proportion of patients with steroid-dependent asthma have persistent eosinophilia despite high-dose ICS therapy, chronic oral steroid therapy, or both.^{3,15} The identification of specific asthma phenotypes, particularly the EOS⁺ phenotype, might have both clinical application

and prognostic implication. For example, it has been shown that treatment aimed at reducing sputum eosinophil counts reduces asthma exacerbations and hospital admissions,³¹ and changes in sputum eosinophil counts might predict deterioration of asthma control.³² Thus appropriate management of SRA likely involves varying strategies, depending on the phenotype. Furthermore, the persistence of eosinophilia despite systemic steroids reflects steroid resistance, although a recent study in subjects with SRA taking high-dose inhaled prednisone, oral prednisone, or both suggested that persistent sputum eosinophilia can be cleared by very high-dose parenteral steroids, with improvement in lung function and symptoms.³³

In addition to differences in eosinophil numbers, other physiologic and biologic characteristics differentiate EOS⁺ and EOS⁻ SRA. Wenzel et al³ demonstrated that subjects with EOS⁺ SRA had higher numbers of tissue lymphocytes, macrophages, and mast cells; a thicker basement membrane; and a history of significantly more intubations when compared with subjects with EOS⁻ SRA. In our study subjects with EOS⁺ SRA had significantly higher tissue mast cell and lymphocyte numbers than subjects with EOS⁻ SRA. The higher number of mast cells in healthy control subjects compared with those seen in subjects with asthma has been described previously.³⁴

Direct assessment of the inflammatory component in asthma is gaining popularity because of an associated improvement in asthma outcomes,^{31,35} especially when such measurement complements conventional methods of asthma monitoring, such as lung function. The gold standard for assessing airway inflammation remains bronchoscopy, yet this technique is invasive and carries significant risk. Induced sputum has been widely applied in research but has limitations for clinical application because of time and cost.

Exhaled NO measurement, however, is simple, fast and noninvasive and is now used in clinical settings. FE_{NO} is an excellent diagnostic test for asthma³⁶ and correlates with clinical parameters, such as reactivity,³⁷ steroid responsiveness,^{38,39} and bronchodilator responsiveness.⁴⁰ In 2000, Sipple et al²⁸ demonstrated that FE_{NO} levels correspond to measures of disease control, including symptoms within the last 2 weeks, dyspnea score, and daily use of rescue medication. Recently, FE_{NO} levels have

also been shown to predict future asthma exacerbation^{41,42} and to aid in strategies of inhaled steroid reduction.⁴³

Because subjects with EOS⁺ SRA are likely to have more exacerbations and intubations, use of FE_{NO} as a predictor of asthma worsening, particularly in this group, might be highly beneficial. It could indicate that when FE_{NO} levels are high, further increases in anti-inflammatory therapy with corticosteroids or other agents might be required. Alternatively, if FE_{NO} levels are low, further increasing steroids could be less beneficial.

In conclusion, this study suggests that FE_{NO} measurement identifies the SRA phenotype with persistent eosinophilia in a manner that is noninvasive and simple. Further studies are needed to determine whether FE_{NO} measurement can be used to monitor SRA over time, to guide therapy, and to alter the prognosis in subjects with SRA.

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