

Usefulness of Impulse Oscillometry and Fractional Exhaled Nitric Oxide in Children With Eosinophilic Bronchitis

Yoon Hee Kim, MD,¹ Kyung Won Kim, MD, PhD,¹ Jiyoung Baek, MD,¹ Hyun Bin Park, MD,¹
Hyemi Kim, BSc,² Kyung-Joo Song, BSc,² Jae Myun Lee, MD, PhD,²
Myung Hyun Sohn, MD, PhD,^{1*} and Kyu-Earn Kim, MD, PhD¹

Summary. Background: Eosinophilic bronchitis (EB) is a common cause of chronic cough. Although EB shares many immunopathologic features with asthma, it does not show airway hyperresponsiveness or reversible airway obstruction by spirometry. Objective: Compared to healthy children without pulmonary disease, we hypothesized that EB patients would demonstrate abnormal pulmonary function and inflammation with impulse oscillometry (IOS) and fractional exhaled nitric oxide (FeNO), which are more sensitive tests of these parameters than spirometry. Methods: A total of 232 children with asthma, 109 with EB, and 115 control subjects were enrolled. We compared pulmonary function parameters and FeNO levels among the three groups. Additionally, we designated a screening cutoff value of FeNO combined with IOS parameters to distinguish EB from the control group, and identify which children with EB have more asthmatic characteristics. Results: By IOS, the bronchodilator response of the EB and asthma groups increased significantly compared to controls for both reactance at 5 Hz (ΔX_5) and reactance area (ΔAX) ($P < 0.0001$). Cutoff values to distinguish EB from controls were a ΔX_5 of -20% (sensitivity, 77.5%; specificity, 49.6%), and ΔAX of -30% (sensitivity, 75.0%; specificity, 46.0%), when the FeNO is 20 ppb. Conclusions: Reversible airway obstruction in IOS and elevated FeNO levels can be detected in children with EB. This would support that EB in children shows airway characteristics similar to those of asthma, and that a continuum exists between asthma and EB. **Pediatr Pulmonol.** © 2012 Wiley Periodicals, Inc.

Key words: Asthma; bronchitis; bronchodilator effect; child; nitric oxide.

Funding source: Korea Health Industry Development Institute, Number: A110379.

INTRODUCTION

Eosinophilic bronchitis (EB) and asthma are common causes of chronic cough associated with eosinophil inflammation. Symptoms of EB are relieved by inhaled corticosteroids,¹ and the condition shares many immunopathological features with asthma, including similar degrees of eosinophilia and cytokines in sputum,^{2–4} bronchoalveolar lavage,² and bronchial biopsy.² Reticular basement membrane thickening, a typical feature of airway remodeling in asthma, is also shown in EB.² However, EB does not demonstrate airway hyperresponsiveness or reversible airway obstruction by spirometry.⁵

Although many studies focused on the correlation between EB and asthma, it has not been clarified whether EB is a precursor of asthma, an asthma variant, or an entirely different disease entity. Additionally, some studies have suggested the possibility that EB may progress to asthma or chronic obstructive pulmonary disease (COPD), which have abnormal pulmonary functions.^{6–8}

Additional supporting information may be found in the online version of this article.

¹Department of Pediatrics and Institute of Allergy, Severance Biomedical Science Institute, Brain Korea 21 Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea.

²Department of Microbiology, Brain Korea 21 Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea.

The authors declare that they have no competing interests.

Yoon Hee Kim and Kyung Won Kim contributed equally to this study.

*Correspondence to: Prof. Myung Hyun Sohn, MD, PhD, Department of Pediatrics, Institute of Allergy, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea.
E-mail: mhsohn@yuhs.ac

Received 19 December 2011; Accepted 8 June 2012.

DOI 10.1002/ppul.22631
Published online in Wiley Online Library
(wileyonlinelibrary.com).

Impulse oscillometry (IOS) has emerged as a powerful tool for the evaluation of pulmonary function in children who are unable to undergo a forced expiration, and for a more sensitive detection of small changes in pulmonary function.^{9,10} Fractional exhaled nitric oxide (FeNO) has also been studied as a good guideline for the diagnosis and treatment of asthma by detecting airway inflammation.¹¹ However, there are few studies concerning FeNO in EB, especially with regard to the pediatric population.¹²

We hypothesized that EB shows abnormal pulmonary function, which previously could not be detected by spirometry alone. We evaluated pulmonary function by IOS and airway inflammation by FeNO and compared findings among children with EB, asthma, and healthy controls. We also assessed FeNO combined with IOS to distinguish EB in children from the control and identifying which children with EB have more asthmatic characteristics.

METHODS

Subjects

We evaluated 456 children who visited Severance Children's Hospital from January 2006 to March 2011. Among the 456 children, 232 were diagnosed with asthma, which was defined as an increased forced expiratory volume in 1 sec (FEV₁) $\geq 12\%$ in response to a short-acting bronchodilator, or bronchial hyperreactivity in a methacholine challenge test (PC₂₀ ≤ 16 mg/ml) accompanied by any typical asthmatic symptom such as cough or dyspnea.¹³ Additionally, 109 children were diagnosed with EB based on the following criteria: chronic cough over 4 weeks without any clinical symptom related to reversible airway obstruction, such as recurrent wheezing or dyspnea; no reversible airway obstruction that could be demonstrated by a negative response to a short-acting bronchodilator (change in FEV₁ $< 12\%$); absence of bronchial hyperreactivity in a methacholine challenge test (PC₂₀ > 16 mg/ml); sputum eosinophilia $> 3\%$; and no lung parenchymal abnormality seen on a simple chest radiograph.^{1,14} The control group consisted of 115 children who had no history of respiratory disease, normal spirometry, and the absence of bronchial hyperreactivity, bronchial reversibility, sputum eosinophilia, and lung parenchymal abnormality. No subject had a history of respiratory infection for at least a 6-week period preceding the evaluations. We excluded subjects who had taken inhaled or systemic corticosteroids or leukotriene antagonists within 8 weeks prior to the study. All subjects were instructed to discontinue their β_2 -agonist medications for at least 3 days before the pulmonary function and challenge tests.

Total serum immunoglobulin E (IgE) levels, peripheral blood eosinophil count, and eosinophil cationic

protein (ECP) levels were determined at the initiation of the evaluations. Total and specific IgE levels were measured using the Pharmacia CAP assay (Uppsala, Sweden). A specific IgE test was performed with six allergens common in Korea: *Dermatophagoides pteronyssinus*, *Dermatophagoides farina*, egg whites, cow milk, German cockroach, and *Alternaria alternata*. Atopy was defined as more than 0.7 KUa/L specific IgE to more than one allergen, or 150 IU/ml total IgE. Atopy was also defined as more than one positive skin test result of 12 common aeroallergens, including two types of house dust mites, cat and dog epithelium, as well as mold and pollen antigens. A saline solution was used as a negative control, and a 0.5% histamine HCl solution was used as a positive control. Wheal diameters were measured after 15 min, and a positive reaction was defined as a wheal diameter > 3 mm.¹⁵

The sputum eosinophil count was also determined at the initial visit of the evaluations. IOS and spirometry were then performed at the second visit. IOS was performed prior to spirometry to avoid any influence of forced expiratory maneuvers on airway function during resting breathing. Finally, FeNO was measured and a methacholine challenge test was performed at the third visit.

This study was approved by the Institution Review Board of Severance Hospital (Seoul, Korea). Written consent for participation was obtained from parents, with verbal assent from children.

Sputum Induction and Processing

Sputum induction and processing were performed as previously described by Yoshikawa et al.¹⁶ All children were instructed to wash their mouths thoroughly with water. They then inhaled a 3% saline solution nebulized in an ultrasonic nebulizer (NE-U12; Omron Co., Tokyo, Japan) at maximum output at room temperature. The children were encouraged to cough deeply at 3-min intervals thereafter. After sputum induction, spirometry was repeated. If FEV₁ had fallen, the child was required to wait until it returned to baseline values. Sputum samples were kept at 4°C for no more than 2 hr before further processing. A portion of the samples was diluted with a phosphate-buffered saline solution containing 10 mmol/L of dithiothreitol (WAKO Pure Chemical Industries Ltd, Osaka, Japan) for cell count and was gently vortexed at room temperature for 20 min. After centrifugation at 400g for 10 min, the cell pellet was resuspended. We performed a sputum viability determination with the trypan blue exclusion method to ensure adequate viability. Total cell counts were performed with a haemocytometer, and slides were prepared with cytospin (Cytospin3; Shandon, Tokyo, Japan) and stained with May-Grünwald-Giemsa stain

for differential cell counts. Differential cell counts were performed by two observers who were blind to clinical details and who counted 400 nonsquamous cells.

Spirometry and Methacholine Challenge Test

Spirometry (VIASYS Healthcare, Inc., Conshohocken, PA) was performed, and flow-volume curves were obtained according to American Thoracic Society guidelines before and after bronchodilator (BD) inhalation.¹⁷ A methacholine challenge test was performed according to standardized procedures.¹³ Each child inhaled increasing concentrations of methacholine (0.075, 0.15, 0.31, 0.62, 1.25, 2.5, 5, 10, 25, and 50 mg/ml) nebulized by a dosimeter (MB3; Mefar, Brescia, Italy) until FEV₁ reduced by 20% from a post-nebulized saline solution value. The bronchial response was expressed as a provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀; measured in milligrams per milliliter) and was calculated by linear interpolation of the log dose response curve.

FeNO Measurement

Fractional exhaled nitric oxide was measured using CLD 88 (Eco Medics, Duernten, Switzerland; measurement at a constant 50 ml/sec expiratory flow rate). Measurements were performed according to the ERS/ATS guidelines.¹⁸ All children refrained from eating nitrate-rich foods for 24 hr before FeNO measurement for the ingestion of nitrate-rich foods could affect the levels of FeNO.¹⁹ We accepted the mean value of three measurements.

Impulse Oscillometry

A Jaeger MasterScreen IOS system (Jaeger Co., Wurzburg, Germany) was used to measure impulse oscillometry. The system was calibrated through a single volume of air (3 L) at different rates (flow) and also with a reference device (0.2 kPa/L/sec) per the manufacturer. The machine was also calibrated for air temperature and pressure of saturated gas. An impulse generator produced brief pressure pulses at intervals of 0.2 sec. In this study, mean resistance (R) values were calculated over a measurement period of 60 sec at the frequencies 5 and 10 Hz, while reactance (X) values were measured at 5 Hz. Also recorded was the reactance area (AX), an integrated response index for reactance developed by Goldman²⁰ reflecting the integral of the negative values of reactance from 5 Hz to the resonant frequency.

During IOS measurements, the children were sitting upright with their heads resting against the back of the chair. The children used nose clips, and they were instructed to breath quietly through a mouthpiece. To

decrease the shunt compliance of the cheeks, the investigator stood behind the patient and supported both the cheeks and the chin with their hands. The observations did not have artifacts caused by coughing, breath holding, swallowing, or vocalization. Three correct measurements were averaged at each time point. We used acceptable coherence values which are 0.8 or greater at 10 Hz.¹⁰

Statistical Analysis

Values in the text and tables that were parametrically distributed are expressed as mean $\pm$ standard deviation. Values that were nonparametrically distributed are expressed as median with interquartile ranges. The association among the patients' characteristics, spirometry, FeNO, and IOS were analyzed with analysis of variance and chi-square tests if the data were parametrically distributed, and the Kruskal-Wallis and Mann-Whitney tests if the data were nonparametrically distributed. We analyzed again the relation among three groups based on atopy. Receiver operating characteristic (ROC) curves were generated with combined IOS parameters and FeNO tests to establish screening values to distinguish EB from the control group and identify which children with EB have more asthmatic characteristics.

A P -value < 0.05 was considered statistically significant. Statistical software (SAS version 9.2, SAS Institute, Inc., Cary, NC) was used for all analyses.

RESULTS

Clinical Characteristics

The clinical characteristics of the children in this study are shown in Table 1. The groups did not differ according to age, sex, and height. Compared with the control group, the prevalence of atopic subjects and serum total IgE levels were significantly higher in the EB and asthma groups ($P < 0.0001$). Similarly, sputum eosinophil percentage, blood eosinophil count, and serum ECP were also significantly higher in the EB and asthma groups than in the control group ($P < 0.0001$). Sputum eosinophil percentage was significantly higher in the EB group than in the asthma group ($P < 0.0001$), but blood eosinophil count tended to be lower in the EB group than in the asthma groups ($P = 0.930$).

Spirometry

Indices of pulmonary function of the EB, asthma, and control groups are shown in Table 2, as determined by spirometry. The forced vital capacity (FVC) and the FEV₁ in the three groups were over 90%. FEV₁/FVC and the forced expiratory flow between 25% and 75%

TABLE 1—Subjects' Characteristics

	Asthma (n = 232)	EB (n = 109)	Control (n = 115)
Age (years)	9.1 ± 2.7	9.5 ± 2.5	9.8 ± 2.8
Male sex, no. (%)	147 (63)	83 (76)	90 (78)
Height (cm)	134.4 ± 16.4	136.9 ± 15.7	138.2 ± 16.3
Atopy, no. (%)	204 (88)*	91 (85)*	72 (63)
Total IgE, IU/ml	343 (156–722)*	229 (104–548)*	87 (34–241)
Sputum eosinophil, %	4 (1–15)*,**	13 (5–30)*	0 (0–0)
Blood eosinophil, μl^{-1}	430 (218–673)*	380 (230–610)*	190 (100–355)
Serum ECP, $\mu\text{g/L}$	26.9 (14.1–49.1)*	31.5 (15.9–51.4)*	14.6 (6.7–29.1)

Data expressed as number (percentage), mean ± SD or median (interquartile range).

EB, eosinophilic bronchitis; ECP, eosinophil cationic protein.

* $P < 0.05$ versus control.

** $P < 0.05$ versus EB.

(FEF_{25–75}) were significantly lower in the asthma group than in the EB and the control group ($P < 0.0001$). The maximal bronchodilator response and the percentage change in FEV₁ (Δ FEV₁) increased significantly more in the asthma group than in the others ($P < 0.0001$).

Fractional Exhaled Nitric Oxide

The median (interquartile range) of FeNO was 40.10 (19.85–70.95) ppb in the asthma group, 32.42 (18.35–63.80) ppb in the EB group, and 21.57 (11.73–35.24) ppb in the control group. FeNO levels in the EB group as well as in the asthma group were significantly higher than those in the control group ($P < 0.0001$; Fig. 1). When we compared each group according to atopy status, we found that only atopic subjects in the EB and asthma groups had higher levels of FeNO compared with controls ($P < 0.05$), and that there were no differences among the non-atopic subset (E-Table 1).

Impulse Oscillometry

The percentage of predicted R5 (R5) and the percentage of predicted X5 (X5) were higher in the asthma group than in the EB and control groups ($P < 0.0001$). The bronchodilator response in resistance at 5 Hz (Δ

R5) increased more in the asthma group than in the others ($P = 0.005$). However, the percentage of predicted R10 (R10) and the percentage change in resistance at 10 Hz (Δ R10) were significantly different only between the asthma group and the control group ($P = 0.007$ and $P = 0.044$, respectively; Table 3).

The bronchodilator response of the EB and asthma groups increased significantly compared to controls for both reactance at 5 Hz (Δ X5) and reactance area (Δ AX) ($P < 0.0001$; Table 3). When the groups were again compared according to atopy status, the parameters that showed a significant difference between EB and controls were Δ X5 and Δ AX in the atopic subset, and Δ X5 in the non-atopic subset ($P < 0.05$; E-Table 1).

Fractional Exhaled Nitric Oxide Combined With Δ AX and Δ X5

We tested the evaluation function of FeNO, Δ X5, and Δ AX for EB, which showed significant differences compared to those for the control group. The areas under the ROC (AUCs) for describing the relationships between sensitivity and specificity of FeNO, Δ X5, and Δ AX to distinguish EB from the control group were

TABLE 2—Spirometry in Children With Asthma, Eosinophilic Bronchitis, and Control

	Asthma (n = 232)	EB (n = 109)	Control (n = 115)
FEV ₁ , % predicted	93.8 (84.2–103.6)*,**	99.7 (90.6–108.4)*	104.9 (96.3–114.4)
FVC, % predicted	95.6 ± 15.7	96.1 ± 14.2	99.7 ± 13.5
FEV ₁ /FVC, %	84.0 (77.2–90.4)*,**	90.6 (84.8–97.9)	90.1 (85.8–95.8)
FEF _{25–75} , % predicted	74.3 ± 27.1***	95.3 ± 21.9	100.3 ± 22.9
Maximal BD response, % change in FEV ₁	9.1 (3.6–14.3)*,**	3.6 (0.9–6.6)	2.5 (0.2–4.4)

Data expressed as mean ± SD or median (interquartile range).

EB, eosinophilic bronchitis; FEV₁, forced expiratory volume in 1 sec; FVC, forced vital capacity; BD, bronchodilator response.

* $P < 0.05$ versus control.

** $P < 0.05$ versus EB.

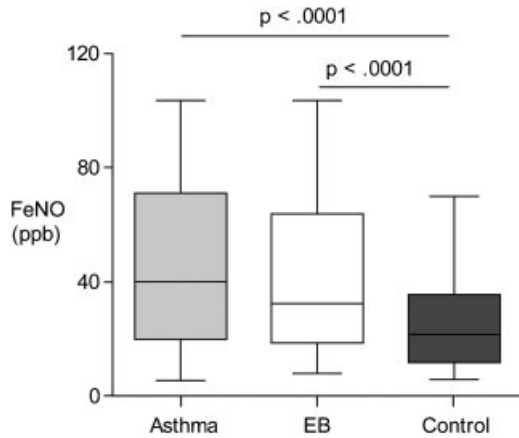


Fig. 1. Fractional exhaled nitric oxide (FeNO) in asthma, eosinophilic bronchitis (EB), and control. FeNO levels in the EB group as well as in the asthma group were significantly higher than those in the control group ($P < 0.0001$). Box-and-whisker plots represent the 25th and 75th percentiles, with the median line and the error bars representing the 10th and 90th percentiles.

0.66, 0.64, and 0.65, respectively. On the other hand, the AUCs of the other parameters in IOS such as R5, R10, X5, Δ R5, Δ R10 were below 0.60. We also assessed the AUC of FeNO combined with Δ X5 (area, 0.71) and Δ AX (area, 0.71; Fig. 2). Cut-off values of Δ X5 and Δ AX combined with FeNO were a Δ X5 of -20% (sensitivity, 77.5%; specificity, 49.6%), and a Δ AX of -30% (sensitivity, 75.0%; specificity, 46.0%) when the FeNO is 20 ppb (Table 4).

DISCUSSION

Our study compared three subject groups: EB, asthma, and healthy controls. We showed, for the first time, that the bronchodilator response parameters determined by IOS (Δ X5 and Δ AX) can detect mild reversible airway obstruction in children with EB, which cannot

be detected by spirometry. We also showed an elevated level of FeNO in EB. Based on spirometry, pulmonary function and bronchodilator responses of the EB group were within the normal range, as were those of the healthy control group.⁵ However, the elevated bronchodilator response detected by IOS and increased airway inflammation based on FeNO were characteristics of both EB and asthma, which suggests that EB has airway characteristics similar to those of asthma.

Although there are many studies concerning the relationship among T-lymphocyte cytokines, eosinophilic inflammation, airway dysfunction, and airway remodeling in asthma, the concrete relationship among them is not clarified yet.³ Moreover, eosinophilic airway inflammation cannot reflect directly eosinophilic systemic inflammation such as blood eosinophil count as shown in Table 1.²¹ EB is one way of clarifying the pathophysiology of airway dysfunction in asthma because EB does not show airway hyperresponsiveness or reversible airway obstruction, although EB does share similarities to asthma, such as the presence of T-lymphocyte cytokines and eosinophilic inflammation.^{3,12}

In clinical studies focused on the natural course of EB, asthma and fixed airflow obstruction developed in some patients.^{7,8} As such, it has been suggested that EB may be either a precursor or the very mildest form of symptomatic asthma.²² Recently, the major difference in the airway pathophysiology of asthma and EB has been characterized by whether or not mast cell infiltration and activation are within airway smooth muscle.^{6,23} This is because mast cells in asthma act in deeper airway epithelium, whereas those in EB act in more superficial areas.²³ As it were, EB is not completely different from asthma, and EB may indeed have mild airway hyperresponsiveness or reversible airway obstruction that cannot be detected by methacholine challenge tests or spirometry. In this study, we verified reversible airway obstruction in EB by the bronchodilator response parameters of IOS, those being Δ X5 and Δ AX.

TABLE 3—Impulse Oscillometry in Children With Asthma, Eosinophilic Bronchitis, and Control

	Asthma (n = 232)	EB (n = 109)	Control (n = 115)
R5, % predicted	102.5 (81.6/123.7)*,**	90.9 (79.0/114.3)	88.2 (72.1/109.2)
R10, % predicted	88.9 (73.3/107.1)*	85.0 (66.2/106.1)	81.2 (65.7/101.9)
X5, % predicted	133.3 (105.9/174.5)*,**	114.0 (91.3/150.7)	106.7 (79.7/134.7)
Maximal BD response			
% change in R5	$-16.1 \pm 17.2^{*,**}$	-11.2 ± 14.9	-11.2 ± 14.7
% change in R10	$-10.7 (-21.2/-1.8)^*$	$-9.2 (-16.7/1.3)$	$-9.4 (-16.6/1.2)$
% change in X5	$-28.2 (-44.0/-12.8)^*$	$-25.1 (-38.6/-11.1)^*$	$-14.3 (-27.0/2.4)$
% change in AX	$-37.4 (-52.9/-20.7)^*$	$-31.8 (-52.5/-17.4)^*$	$-27.2 (-40.7/-6.7)$

Data expressed as mean $\pm$ SD or median (interquartile range).

EB, eosinophilic bronchitis; BD, bronchodilator response.

* $P < 0.05$ versus control.

** $P < 0.05$ versus EB.

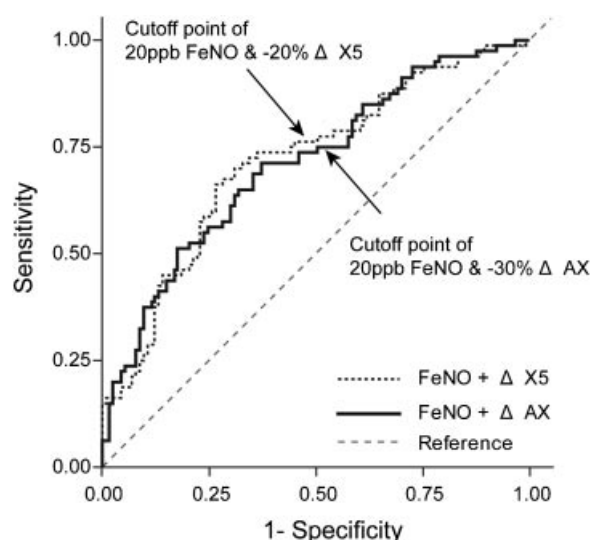


Fig. 2. Receiver operating curves for fractional exhaled nitric oxide (FeNO) combined with the bronchodilator response in reactance at 5 Hz (Δ X5) and the bronchodilator response in reactance area (Δ AX). The area under the curves are 0.71 in both FeNO + Δ X5 and FeNO + Δ AX.

IOS systems are finding increased use in the clinical diagnostic testing of airway obstruction and bronchodilator responsiveness.^{9,10,24} Reactance at 5 Hz (X5) reflects the elastic recoil properties of peripheral airway tissue, and the AX reflects a composite index for reactance.¹⁰ These parameters are useful for detecting airway obstruction and changes in pulmonary function more sensitively than can spirometry,^{25,26} which is also supported by our study. Our cut-off values are -20% and -30% for Δ X5 and Δ AX, respectively which are lower than those in other studies about comparison between subjects with asthma and those without asthma.^{10,20} The lower cut-off values may be caused by the different disease entity, EB instead of asthma, and our more atopic control

subjects than general population. Although FEF₂₅₋₇₅ has also emerged as a good predictor for mild airway hyperresponsiveness or variable airway obstruction,²⁷ it could not distinguish EB from control subjects in our study.

FeNO is markedly high in EB, which means that it can be used as an evaluating measure for EB as well as for asthma. However, FeNO should be used with caution because it can also be elevated in allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis.²⁸ In this study, we designated the IOS parameters Δ AX and Δ X5 according to FeNO to distinguish EB from the control group with more accuracy. We chose the cut-off value of FeNO as 20 ppb, which is a similar level for asthma in other studies.^{29,30}

We found that EB demonstrates an atopic tendency in children similar to that of asthma. However, this is different from EB in adults, which has a similar atopic tendency as that of the general population.¹² This is important because an atopic tendency can exaggerate asthmatic airway characteristics of EB, which we showed in our analysis based on atopy. We also found reversible airway obstruction in children with EB, which is also an asthmatic characteristic. Interestingly, other studies have reported that adults with EB developed fixed airway obstruction, which is more characteristic of COPD.^{7,8}

A close follow-up evaluation for EB can be ignored by both patients and clinicians, particularly as inhaled corticosteroids improve symptoms of EB and as sputum eosinophil counts decrease significantly.^{8,31} However, EB can progress to asthma or COPD, and some studies even report the possibility of airway remodeling in EB.^{32,33} For these reasons it is important to understand EB at young ages and provide early detection and intervention. Additionally, cough variant asthma is another frontier that can progress to typical asthma,³⁴ which has been known to be rare in children because the majority of children with isolated cough do not have asthma.¹⁴ Nonetheless, future studies of asthma, cough variant asthma, and EB with IOS and FeNO may reveal additional useful clinical implications.

In conclusion, EB in children has mild reversible airway obstruction detected with IOS, in addition to elevated airway inflammation given elevated levels of FeNO. If the bronchodilator response in reactance at 5 Hz (Δ X5) increased more than 20% , or the bronchodilator response in reactance area (Δ AX) increase more than 30% when FeNO was over 20 ppb in EB, we considered this representative of a mild reversible airway obstruction with accompanying airway inflammation. These findings support that EB in children has airway characteristics similar to those found in asthma, and that a continuum exists between asthma and EB.

TABLE 4—Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value to Distinguish EB From Control

Parameters	Cut off value	Sensitivity	Specificity	PPV	NPV
Maximal BD response					
% change in X5	-20%	59.6	60.0	58.6	61.1
% change in AX	-30%	57.8	55.7	55.3	58.2
FeNO	20 ppb	71.3	47.8	49.1	70.1
FeNO 20 ppb+					
% change in X5	-20%	77.5	49.6	52.1	75.7
% change in AX	-30%	75.0	46.0	49.6	72.2

PPV, positive predictive value; NPV, negative predictive value; EB, eosinophilic bronchitis; FeNO, fractional exhaled nitric oxide.

ACKNOWLEDGMENTS

We would like to thank Hana Kim for her statistical assistance (Department of Biostatistics, College of Medicine, Yonsei University) and also Anthony Thomas Milliken for English editing (English Support Division, College of Medicine, Yonsei University).

REFERENCES

- Brightling CE. Chronic cough due to nonasthmatic eosinophilic bronchitis: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129:116S–121S.
- Brightling CE, Symon FA, Birring SS, Bradding P, Wardlaw AJ, Pavord ID. Comparison of airway immunopathology of eosinophilic bronchitis and asthma. *Thorax* 2003;58:528–532.
- Brightling CE, Ward R, Woltmann G, Bradding P, Sheller JR, Dworski R, Pavord ID. Induced sputum inflammatory mediator concentrations in eosinophilic bronchitis and asthma. *Am J Respir Crit Care Med* 2000;162:878–882.
- Kim KW, Jee HM, Park YH, Choi BS, Sohn MH, Kim KE. Relationship between amphiregulin and airway inflammation in children with asthma and eosinophilic bronchitis. *Chest* 2009;136: 805–810.
- Brightling CE, Ward R, Goh KL, Wardlaw AJ, Pavord ID. Eosinophilic bronchitis is an important cause of chronic cough. *Am J Respir Crit Care Med* 1999;160:406–410.
- Siddiqui S, Mistry V, Doe C, Roach K, Morgan A, Wardlaw A, Pavord I, Bradding P, Brightling C. Airway hyperresponsiveness is dissociated from airway wall structural remodeling. *J Allergy Clin Immunol* 2008;122:335–341, e331–e333.
- Berry MA, Hargadon B, McKenna S, Shaw D, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. Observational study of the natural history of eosinophilic bronchitis. *Clin Exp Allergy* 2005;35: 598–601.
- Brightling CE, Woltmann G, Wardlaw AJ, Pavord ID. Development of irreversible airflow obstruction in a patient with eosinophilic bronchitis without asthma. *Eur Respir J* 1999;14:1228–1230.
- Song TW, Kim KW, Kim ES, Park JW, Sohn MH, Kim KE. Utility of impulse oscillometry in young children with asthma. *Pediatr Allergy Immunol* 2008;19:763–768.
- Komarow HD, Myles IA, Uzzaman A, Metcalfe DD. Impulse oscillometry in the evaluation of diseases of the airways in children. *Ann Allergy Asthma Immunol* 2011;106:191–199.
- Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005;352:2163–2173.
- Brightling CE. Cough due to asthma and nonasthmatic eosinophilic bronchitis. *Lung* 2010;188:S13–S17.
- Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS, Anderson SD, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000;161:309–329.
- Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129:260S–283S.
- Brown WG, Halonen MJ, Kaltenborn WT, Barbee RA. The relationship of respiratory allergy, skin test reactivity, and serum IgE in a community population sample. *J Allergy Clin Immunol* 1979;63:328–335.
- Yoshikawa T, Shoji S, Fujii T, Kanazawa H, Kudoh S, Hirata K, Yoshikawa J. Severity of exercise-induced bronchoconstriction is related to airway eosinophilic inflammation in patients with asthma. *Eur Respir J* 1998;12:879–884.
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, et al. Standardisation of spirometry. *Eur Respir J* 2005;26: 319–338.
- American Thoracic 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;171:912–930.
- Vints AM, Oostveen E, Eeckhout G, Smolders M, De Backer WA. Time-dependent effect of nitrate-rich meals on exhaled nitric oxide in healthy subjects. *Chest* 2005;128:2465–2470.
- Goldman MD. Clinical application of forced oscillation. *Pulm Pharmacol Ther* 2001;14:341–350.
- Baigelman W, Chodosh S, Pizzuto D, Cupples LA. Sputum and blood eosinophils during corticosteroid treatment of acute exacerbations of asthma. *Am J Med* 1983;75:929–936.
- Cockcroft DW. Eosinophilic bronchitis as a cause of cough. *Chest* 2000;118:277.
- Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID. Mast-cell infiltration of airway smooth muscle in asthma. *N Engl J Med* 2002;346:1699–1705.
- Song TW, Kim KW, Kim ES, Kim KE, Sohn MH. Correlation between spirometry and impulse oscillometry in children with asthma. *Acta Paediatr* 2008;97:51–54.
- Lee JH, Lee YW, Shin YS, Jung YH, Hong CS, Park JW. Exercise-induced airway obstruction in young asthmatics measured by impulse oscillometry. *J Investig Allergol Clin Immunol* 2010;20:575–581.
- Komarow HD, Skinner J, Young M, Gaskins D, Nelson C, Gergen PJ, Metcalfe DD. A study of the use of impulse oscillometry in the evaluation of children with asthma: analysis of lung parameters, order effect, and utility compared with spirometry. *Pediatr Pulmonol* 2012;47:18–26.
- Simon MR, Chinchilli VM, Phillips BR, Sorkness CA, Lemanske RF, Jr., Szefer SJ, Taussig L, Bacharier LB, Morgan W. Forced expiratory flow between 25% and 75% of vital capacity and FEV1/forced vital capacity ratio in relation to clinical and physiological parameters in asthmatic children with normal FEV1 values. *J Allergy Clin Immunol* 2010;126:527–534, e521–e528.
- Kovesi T, Dales R. Exhaled nitric oxide and respiratory symptoms in a community sample of school aged children. *Pediatr Pulmonol* 2008;43:1198–1205.
- Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, Taylor DR. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. *Am J Respir Crit Care Med* 2004;169:473–478.
- Fritsch M, Uxa S, Horak F Jr, Putschoegl B, Dehlink E, Szepfalusi Z, Frischer T. Exhaled nitric oxide in the management of childhood asthma: a prospective 6-months study. *Pediatr Pulmonol* 2006;41:855–862.
- Brightling CE, Ward R, Wardlaw AJ, Pavord ID. Airway inflammation, airway responsiveness and cough before and after inhaled budesonide in patients with eosinophilic bronchitis. *Eur Respir J* 2000;15:682–686.
- Siddiqui S, Sutcliffe A, Shikotra A, Woodman L, Doe C, McKenna S, Wardlaw A, Bradding P, Pavord I, Brightling C. Vascular remodeling is a feature of asthma and nonasthmatic eosinophilic bronchitis. *J Allergy Clin Immunol* 2007;120:813–819.
- Siddiqui S, Gupta S, Cruse G, Halder P, Entwistle J, McDonald S, Whithers PJ, Hainsworth SV, Coxson HO, Brightling C. Airway wall geometry in asthma and nonasthmatic eosinophilic bronchitis. *Allergy* 2009;64:951–958.
- Dicpinigaitis PV. Chronic cough due to asthma: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129:75S–79S.

E-table 1–Impulse Oscillometry and Fractional exhaled Nitric Oxide in Children with Asthma, Eosinophilic Bronchitis, and Control according to atopy.

	Atopic (n=367)			Non-atopic (n=89)		
	Asthma (n=204)	EB (n=91)	control (n=72)	Asthma (n=28)	EB (n=18)	control (n=43)
R5, % predicted	100.9 (81.3/118.8) *	92.5 (80.7/116.0)	87.6 (72.3/108.1)	106.7 (85.0/128.9) *,**	85.8 (66.5/115.0)	90.3 (70.8/115.6)
R10, % predicted	87.3 (72.5/103.1)	85.0 (67.3/106.5)	80.1 (67.8/100.9)	91.9 (75.2/111.3)	85.6 (63.6/100.4)	85.1 (62.3/103.4)
X5, % predicted	130.8 (105.3/172.2) *	119.2 (98.5/154.9)	107.1 (78.8/133.4)	137.6 (107.8/182.5) *,**	102.9 (66.4/131.0)	106.7 (84.5/135.8)
Maximal BD response						
% change in R5	-15.9 ± 16.4	-11.2 ± 15.4	-11.8 ± 14.9	-17.7 ± 22.8	-11.3 ± 12.8	-10.3 ± 14.4
% change in R10	-11.5 ± 14.4	-8.1 ± 14.8	-7.8 ± 15.8	-13.0 ± 21.5	-7.5 ± 14.0	-4.9 ± 17.7
% change in X5	-28.2 (-44.1/-13.2) *	-23.5 (-38.3/-11.0) *	-12.7 (-25.3/3.9)	-28.6 (-43.4/4.2)	-31.1 (-42.7/-14.8) *	-16.4 (-29.5/-1.2)
% change in AX	-37.4 (-52.9/-21.4) *	-31.3 (-52.1/-17.8) *	-28.2 (-39.9/-6.9)	-34.7 (-56.8/-6.9)	-35.8 (-67.7/-14.1)	-25.7 (-44.0/-8.7)
FeNO (ppb)	46.7 (23.5/76.2) *	34.3 (22.2/77.2) *	28.6 (14.2/41.2)	17.0 (10.9/27.6)	14.6 (10.4/40.9)	13.1 (9.7/24.0)

EB, eosinophilic bronchitis; BD, bronchodilator response.

Data expressed as mean ± SD or median (interquartile range).

* $P < 0.05$ vs. control; ** $P < 0.05$ vs. EB.