

ORIGINAL ARTICLE

Repeated Measurement of Fractional Exhaled Nitric Oxide Is Not Essential for Asthma Screening

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■ Abstract

Background: Older guidelines recommend that fractional exhaled nitric oxide (FeNO) should be checked more than twice during the same session to confirm an asthma diagnosis. Recent studies show the excellent reproducibility of FeNO measurements.

Objective: We aimed to determine whether repeated FeNO measurements during the same session are necessary for asthma screening.

Methods: We retrospectively reviewed the electronic medical records of adult outpatients who visited the respiratory medicine department for diagnosis of asthma and assessed FeNO measurements obtained from June 2016 to July 2017.

Results: Of the 132 patients enrolled, 79 (59.8%) were diagnosed with asthma. Repeated FeNO measurements taken during the same session showed high reproducibility (intraclass correlation coefficient >0.9 ; $P<.001$) and a strong correlation (Pearson coefficient >0.9 ; $P<.001$), although reproducibility and correlation were slightly weaker in patients with low FeNO values. The value of repeated measurement was not significant; however, the second FeNO measurement was significantly higher than the first measurement in patients with the worst and best lung function. The predictive power of the first measurement of FeNO (sensitivity, 80.5%; specificity, 85.1%) was not inferior to the second (sensitivity, 76.6%; specificity 85.1%). The same was true of the geometric mean of the two.

Conclusion: Repeated FeNO measurement during the same session is not essential for asthma screening in cases where the first acceptable FeNO measurement is performed using the proper method.

Key words: Asthma. Fractional exhaled nitric oxide. Repeated measurements.

■ Resumen

Introducción: Aunque las guías más antiguas recomiendan que el óxido nítrico exhalado (FeNO) se determine más de dos veces en la misma sesión para el diagnóstico de asma, algunos estudios recientes han demostrado la excelente reproducibilidad de las mediciones de FeNO.

Objetivo: Nuestro objetivo fue determinar si las mediciones repetidas de FeNO durante la misma sesión son necesarias para el cribado del asma.

Métodos: Revisamos retrospectivamente los registros médicos electrónicos de pacientes adultos ambulatorios que visitaron el departamento de neumología para confirmar un diagnóstico de asma durante los meses de junio de 2016 a julio de 2017, y se evaluaron las mediciones de FeNO obtenidas.

Resultados: De un total de 132 pacientes estudiados, 79 pacientes (59,8%) fueron diagnosticados con asma. Las mediciones repetidas de FeNO tomadas durante la misma sesión mostraron una alta reproducibilidad (coeficiente de correlación intraclass $> 0,9$; $p < 0,001$) y una fuerte correlación (coeficiente de Pearson $> 0,9$; $p < 0,001$); sin embargo, la reproducibilidad y la correlación fueron ligeramente más débiles en sujetos con valores bajos de FeNO. El valor de la medición repetida no fue significativamente diferente entre sí en general; sin embargo, la segunda medición de FeNO fue significativamente más alta que la primera medición en sujetos con valores de la función pulmonar más bajos y más altos. El poder predictivo de FeNO para el diagnóstico de asma medido la primera vez (sensibilidad, 80,5%; especificidad, 85,1%) no fue inferior al medido la segunda vez (sensibilidad, 76,6%; especificidad 85,1%) o la media geométrica uniforme de los dos.

Conclusión: La medición repetida de FeNO durante la misma sesión no es esencial para el cribado del asma en los casos en que la primera medición de FeNO es aceptable y se realiza con el método adecuado.

Palabras clave: Asma. Óxido nítrico exhalado fraccional. Mediciones repetidas.

Introduction

Fractional exhaled nitric oxide (FeNO) reflects eosinophilic airway inflammation and is easily measured. The utility of FeNO was recently demonstrated for the diagnosis and monitoring of asthma [1,2]. However, specific patient characteristics and environmental factors are known to influence FeNO levels [3-6]. In addition, to obtain a reliable FeNO level, the operator must be sufficiently skilled to maintain a constant expiratory flow rate during the test. The 2005 American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines recommend performing FeNO measurements twice to obtain 2 values; the mean of the 2 values should then be used to interpret the test [7]. However, there has been no definite evidence to support this protocol. The reproducibility of FeNO measurements was recently shown to be excellent, and it was suggested that repeated FeNO measurements during the same session are unnecessary [8,9]. The utility of multiple FeNO measurements for diagnosis of asthma has never been studied.

This study aimed to determine whether repeated FeNO measurements obtained during the same session are necessary for confirmation of a diagnosis of asthma.

Methods

Patients and Study Design

We retrospectively reviewed the electronic medical records of adult outpatients aged ≥ 18 years who visited the Respiratory Medicine Department of Gangnam Severance Hospital, Seoul, Korea. The patients were referred for measurement of FeNO between June 2016 and July 2017 to diagnose suspected asthma. To assess repeatability, a subset of the participants underwent paired FeNO measurements during the same visit. We examined the medical records of the patients enrolled and assessed baseline characteristics to define significant factors for FeNO level.

FeNO Measurements

FeNO was measured using a handheld device (NObreath FeNO Monitor, Bedfont Scientific Ltd) during scheduled study visits according to ATS/ERS guidelines [7]. The device uses an electrochemical sensor to detect exhaled NO levels and provides measurements from 5 ppb to 300 ppb in whole numbers. We requested that all patients avoid eating, drinking, smoking, and performing strenuous exercise for 2 hours before the FeNO measurements to rule out bias. Moreover, the use of asthma drugs was forbidden unless the patient's physician had instructed otherwise.

Patients exhaled fully while seated, then inhaled over 2 to 3 seconds to total lung capacity through a filter, and finally exhaled with an upper airway pressure of 5 to 20 cmH₂O. Two successive FeNO measurements were performed with an interval of 4-5 minutes between them. All patients exhaled against an airflow resistor for 10 seconds at a flow rate of 50 mL/s, and the FeNO values were monitored on the screen of the device. Measurements were taken before performing spirometry. The detection limit of the NObreath device is 5 ppb.

Lung Function Test and Bronchodilator Response Test

Spirometry was carried out on the first study day after the FeNO measurements. Lung function tests were performed with a spirometer (Vmax, SensorMedics) in accordance with ATS/ERS recommendations [10]. Forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), and the FEV₁/FVC ratio were obtained from the best reproducible forced expiratory maneuvers. A significant improvement in lung function resulting from bronchodilator use was defined as an improvement in prebronchodilator FEV₁ of $\geq 12\%$ and 200 mL after administration of salbutamol (200 μ g).

Methacholine Challenge Test

The methacholine challenge test was carried out using the standard 5-breath dosimeter method recommended by the ATS [11]. Methacholine dilutions of 1, 4, 8, and 16 mg/mL were used. Spirometry was performed 30 seconds and 90 seconds after each inhalation. The test was finished when the FEV₁ value decreased by more than 20% from baseline. Positivity was defined as a provocative concentration < 16 mg/mL that resulted in a 20% decrease in FEV₁.

Asthma Diagnosis

Asthma was diagnosed by clinicians based on the symptoms, physical examination, and the results of the bronchodilator test and methacholine test in all patients according to the Global Initiative for Asthma standard [12].

Definition of a Large Gap and Positivity in FeNO Measurements

The upper quartile of patients with a larger gap between the first and second individual measurement values formed the large gap group. Moreover, a large gap was defined as a $> 17.5\%$ difference in FeNO values between the 2 measurements. Although there are some concerns about the cut-off value for FeNO, we adopted 30 ppb based on findings from previous studies, including a Korean study [13,14].

Statistics

All data analyses were performed using SPSS (SPSS Inc). As the FeNO values appeared to be log-normally distributed, we used the geometric mean. The chi-square test and *t* test were used to assess differences in characteristics between patients with and without a large gap. The intraclass correlation coefficient (ICC) and Pearson correlation were used to assess the reproducibility and correlation between the first and second FeNO measurements. The significance of the difference in FeNO values between the first and second measurements was assessed using the paired *t* test. Agreement between FeNO positivity and a diagnosis of asthma diagnosis was calculated. Univariate and multivariate regression analyses showed that sex, age, height, weight, body mass index (BMI), pulmonary function variables, and asthma history were significantly associated with FeNO level. After adjustment for significant factors (absolute FVC and FEV₁), the ability to predict asthma was based on a receiver operating

characteristic analysis to obtain the area under the curve, the sensitivity and specificity of the first and second FeNO measurements, the geometric mean, the larger of the 2 values, and the smaller of the 2 values. A *P* value less than .05 was considered statistically significant.

Ethics

This study was exempt from approval by the Institutional Review Board of the Gangnam Severance Hospital, Yonsei University Health System.

Results

Clinical Characteristics of the Patients

Of the 132 patients enrolled (mean age, 42.8 [16.0] years; men, 50.0%), 79 (59.8%) were diagnosed with asthma. The geometric mean values of the first and second FeNO measurements were 32.5 ppb and 33.4 ppb, respectively; there was no statistically significant difference between the 2 values (Table 1).

Determinants of a Large Gap in FeNO Measurements

When we used 17.5% as the threshold for a large gap between FeNO measurements, 33 patients (25.0%) were classified as belonging to the large gap group. Sex, age, height, weight, and lung function were not significantly different between patients with and without a large gap. Patients with a large gap had significantly higher BMI values than those without a large gap (*P*=.015). Asthma was significantly more prevalent in patients without a large gap (66.7%) than in those

with a large gap (39.4%; *P*=.005). Patients with large gaps showed significantly lower FeNO values than those without large gaps (Table 1).

Reliability, Correlation, and Comparison of FeNO Measurements

In general, repeated FeNO measurements showed high reproducibility (ICC>0.9; *P*<.001) and strong correlations (Pearson coefficient >0.9; *P*<.001); however, in patients with low FeNO levels (<52.8 ppb), the values for reliability and correlation were slightly weaker (ICC, 0.772-0.886; Pearson coefficient, 0.681-0.774) (Table 2; Figure, A).

The first FeNO levels measured (32.5 [2.3] ppb) were not significantly different from the second FeNO levels (33.4 [2.3] ppb) (Figure, B). However, the second values were significantly higher than the first values in patients with the poorest lung function (44.36 ppb vs 40.60 ppb in patients with the lowest FVC values, *P*=.024) (Table 2). This trend was also observed in patients with the best lung function (30.74 ppb vs 28.79 ppb in patients with the highest FVC values, *P*=.004; 34.34 ppb vs 32.50 ppb in patients with the highest FEV₁ values, *P*=.014).

Predictability of FeNO Measurements for Asthma Diagnosis Using the Agreement Rate

When FeNO positivity was defined as ≥ 30 ppb, the predictive power of the FeNO measurement for asthma was excellent. Overall, the first measured FeNO value was not inferior to the second measurement for prediction of asthma in all subgroups (total agreement rate, 79.5% vs 78.0%). Moreover, the total agreement rate for asthma using the first value was not inferior to that using the numerical mean of the 2

Table 1. Clinical Characteristics, Lung Function Test, and Geometric Mean of FeNO According to Group

Variables	Total (N=132)	Patients Without Large Gap ^a (n=99)	Patients With Large Gap ^a (n=33)	<i>P</i> Value
Sex (Male)	50.0%	51.5%	45.5%	.546
Age, y	42.8 (16.0)	41.9 (15.2)	45.5 (18.2)	.307
Height, cm	165.7 (9.2)	166.5 (9.4)	163.1 (7.9)	.079
Weight, kg	66.6 (13.1)	66.1 (14.0)	67.9 (10.1)	.535
BMI, kg/m ²	24.2 (3.7)	23.7 (3.5)	25.6 (3.9)	.015 ^b
Absolute FVC, L	3.8 (1.0)	3.9 (1.0)	3.6 (1.0)	.094
Predicted FVC, %	97.3 (13.0)	97.9 (13.1)	95.7 (12.8)	.419
Absolute FEV ₁ , L	3.0 (0.8)	3.0 (0.8)	2.8 (0.9)	.226
Predicted FEV ₁ , %	99.1 (16.3)	99.1 (16.2)	99.1 (16.8)	.998
Asthma	59.8%	66.7%	39.4%	.005 ^b
Geometric mean of FeNO, ppb				
First measurement	32.5 (2.3)	37.7 (2.4)	20.9 (1.8)	<.001 ^b
Second measurement	33.4 (2.3)	38.5 (2.4)	21.8 (1.8)	.001 ^b

Abbreviations: BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

^aA large gap was defined as a >17.5% difference in FeNO between the first and second measurements.

^bSignificant factors (independent samples *t*-test).

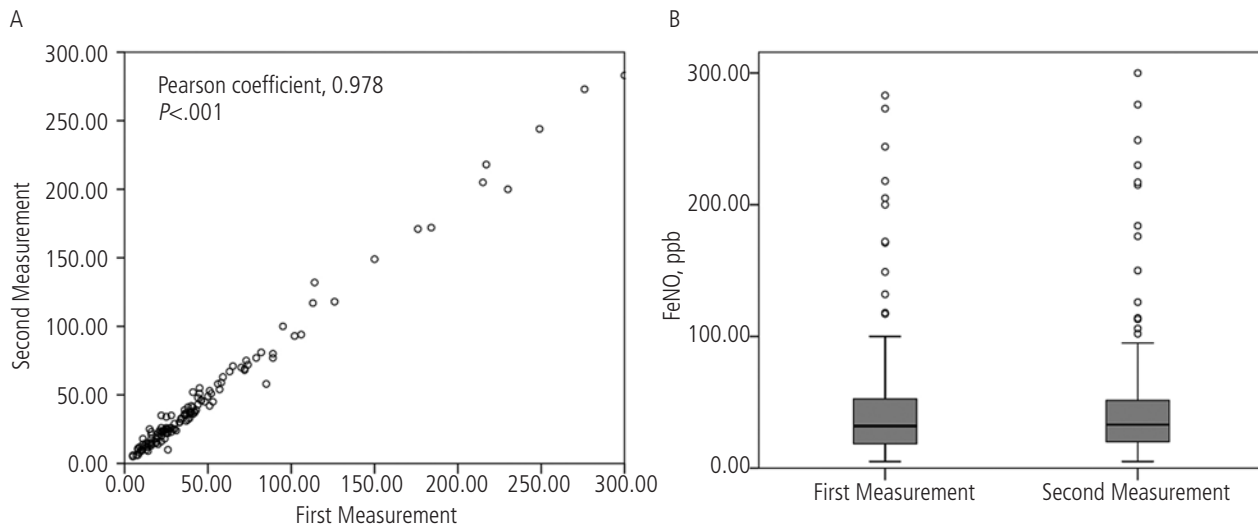


Figure. Correlation (A) and comparison (B) between the first and second FeNO measurements.

Table 2. Reliability, Correlation, and Comparison of FeNO Measurements

Variables	Patients, No.	Intraclass Correlation		Pearson correlation		Paired t Test		
		Coefficient	P Value	Coefficient	P Value	First Measurement	Second Measurement	P Value
Sex								
Male	66	0.988	<.001	0.977	<.001	33.28	33.62	.584
Female	66	0.989	<.001	0.979	<.001	31.83	33.20	.095
Age								
<65	115	0.991	<.001	0.983	<.001	32.26	32.83	.236
≥65	17	0.929	<.001	0.952	<.001	34.56	37.61	.233
BMI								
<18.5	6	>0.999	<.001	0.999	<.001	40.17	39.75	.428
18.5-23	40	0.986	<.001	0.973	<.001	28.17	29.32	.222
23-25	29	0.989	<.001	0.979	<.001	34.85	36.34	.210
>25	40	0.983	<.001	0.967	<.001	29.84	29.86	.984
FVC								
<25% (<3.12 L)	31	0.989	<.001	0.980	<.001	40.60	44.36	.024 ^a
25-50% (3.12-3.71 L)	32	0.988	<.001	0.979	<.001	31.11	30.42	.507
20-75% (3.71-4.65 L)	30	0.988	<.001	0.976	<.001	32.59	32.66	.944
>75% (>4.65 L)	31	0.995	<.001	0.991	<.001	28.79	30.74	.004 ^a
FEV₁								
<25% (<2.46 L)	31	0.989	<.001	0.979	<.001	48.59	52.00	.088
25-50% (2.46-3.00 L)	33	0.978	<.001	0.958	<.001	30.77	31.47	.466
20-75% (3.00-3.58 L)	29	0.989	<.001	0.978	<.001	23.97	23.60	.642
>75% (>3.58 L)	31	0.995	<.001	0.991	<.001	32.50	34.34	.014 ^a
FeNO								
<25% (<18.25)	33	0.866	<.001	0.774	<.001	11.76	12.67	.117 ^b
25-50% (18.25-32.00)	34	0.772	<.001	0.715	<.001	24.40	24.74	.613 ^b
50-75% (32.00-52.75)	32	0.780	<.001	0.681	<.001	40.04	39.77	.783 ^b
>75% (>52.75)	33	0.991	<.001	0.983	<.001	99.14	101.38	.204
Total	132	0.989	<.001	0.978	<.001	32.55	33.40	.094

Abbreviations: BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

^aP value <.05 obtained by paired t test.

^bSlightly decreased reliability and correlation of FeNO between first and second measurements.

Table 3. Agreement Rate Between FeNO Positivity (≥ 30 ppb) and Asthma

Variables	First Measurement	Second Measurement	Numerical Mean of 2 Above	Larger one Selection Between 2 Above	Smaller one Selection Between 2 Above
FVC					
<25% (<3.12 L)	87.1% ^a	83.9%	87.1% ^a	83.9%	87.1% ^a
25-50% (3.12-3.71 L)	84.4% ^a	75.0%	78.1%	81.3%	78.1%
20-75% (3.71-4.65 L)	70.0%	73.3% ^a	70.0%	73.3% ^a	70.0%
>75% (>4.65 L)	77.4% ^a	77.4% ^a	77.4% ^a	77.4% ^a	77.4% ^a
FEV₁					
<25% (<2.46 L)	90.3% ^a	87.1%	90.3% ^a	87.1%	90.3% ^a
25-50% (2.46-3.00 L)	75.8% ^a	69.7%	69.7%	75.8% ^a	69.7%
20-75% (3.00-3.58 L)	69.0% ^a	69.0% ^a	69.0% ^a	69.0% ^a	69.0% ^a
>75% (>3.58 L)	83.9% ^a	83.9% ^a	83.9% ^a	83.9% ^a	83.9% ^a
FeNO, ppb					
<25% (<18.25)	70.0% ^a	70.0% ^a	70.0% ^a	70.0% ^a	70.0% ^a
25-50% (18.25-32.00)	70.6% ^a	67.6%	70.6% ^a	67.6%	70.6% ^a
50-75% (32.00-52.75)	81.3% ^a	78.1%	75.0%	81.3% ^a	78.1%
>75% (> 52.75)	97.0% ^a	97.0% ^a	97.0% ^a	97.0% ^a	97.0% ^a
Total	79.5%^a	78.0%	78.0%	78.8%	78.8%

Abbreviations: FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

^aHighest agreement rate in the subgroup.

Table 4. Significant Factors in the Determination of the FeNO Value

	Univariate Analysis			Multivariate Analysis		
	Coefficients	Standard Error	P Value	Coefficients	Standard Error	P Value
Gender	-0.045	0.147	.763			
Age	0.009	0.005	.050	0.003	0.006	.637
Height	-0.004	0.008	.596			
Weight	-0.006	0.006	.284			
BMI	-0.021	0.021	.311			
Absolute FVC	-0.195 ^a	0.092 ^a	.035 ^a	0.361 ^a	0.174 ^a	.041 ^a
Predicted FVC	-0.009	0.005	.045	-0.001	0.007	.846
Absolute FEV ₁	-12.740 ^a	5.669 ^a	.026 ^a	-0.532 ^a	0.219 ^a	.017 ^a
Predicted FEV ₁	<0.001	0.006	.996			

Abbreviations: BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

^aSignificant factors for first FeNO measurement by multivariate linear regression analysis.

values, the larger of the first and second values, or the smaller of the first and second values (Table 3).

Significant Determinants of the FeNO Value

In the univariate linear regression analysis, sex, height, weight, and BMI were not significantly associated with

the FeNO value. Age showed borderline significance ($P=.050$). The absolute FVC, predicted FVC, and absolute FEV₁ were significant factors for FeNO. The multivariate linear regression analysis showed that absolute FVC and absolute FEV₁ were significantly associated with FeNO levels (Table 4).

Table 5. Predictive Power of FeNO Measurements for Asthma Diagnosis Using a Multiple Regression Analysis^a

Variables	AUC	95% CI	P Value	Sensitivity	Specificity
First measurement	0.859 ^a	0.794-0.924 ^a	<.001 ^a	80.5% ^a	85.1% ^a
Second measurement	0.850	0.785-0.916	<.001	76.6%	83.0%
Geometric mean of the previous two	0.856	0.792-0.922	<.001	81.8%	83.0%
Larger of the previous two	0.857	0.793-0.922	<.001	79.2%	85.1%
Smaller of the previous two	0.859	0.795-0.923	<.001	81.8%	80.9%

Abbreviations: AUC, area under the curve; FeNO, fractional exhaled nitric oxide.

^aAll data are obtained by logistic regression after adjustment with absolute FVC and FEV₁.

^aBest results among the variables.

Predictive Power of FeNO Measurements for Diagnosis of Asthma Using a Multiple Regression Analysis

After adjustment for lung function (FVC and FEV₁, based on the results of Table 4), the first FeNO value measured (AUC, 0.859; 95%CI, 0.794-0.924; $P < .001$; sensitivity, 80.5%; specificity, 85.1% with a cut-off of 30.0 ppb) was not significantly inferior to the second measured value (AUC, 0.850; 95%CI, 0.785-0.916; $P < .001$; sensitivity, 76.6%; specificity 85.1% with a cut-off of 29.0 ppb) (comparison of the ROC curves between the first FeNO value and second FeNO value, $P = .694$), the geometric mean of the 2 measurements (AUC, 0.856; 95%CI, 0.792-0.922; $P < .001$; sensitivity, 81.8%; specificity, 83.0%) (comparison of ROC curves between first FeNO value and geometric mean FeNO value, $P = .923$), the larger of the 2 values (AUC, 0.857; 95%CI, 0.793-0.922; $P < .001$; sensitivity, 79.2%; specificity, 85.1%) (comparison of ROC curves between first FeNO value and larger one, $P > .999$), or the smaller of the 2 values (AUC, 0.859; 95%CI, 0.795-0.923; $P < .001$; sensitivity, 81.8%; specificity, 80.9%) (comparison of ROC curves between the first FeNO value and the smaller one, $P = .848$) (Table 5).

Discussion

We demonstrated that repeated FeNO measurements during the same session are not essential for diagnosis of asthma. The FeNO value was highly reproducible. In addition, the predictive value of the first FeNO measurement for asthma was not inferior to that measured the second time [15], the mean of the 2 values, the larger value, or the smaller value. Various institutions currently use the protocol recommended in the 2005 ATS/ERS guidelines, which state that the FeNO level should be measured twice and the mean value should be applied [7]. However, this recommendation is not supported by sufficient scientific evidence. Recent studies showed the excellent reproducibility and repeatability of FeNO measurements [8,9]. However, whether an asthma diagnosis can be made with only 1 FeNO measurement has not been studied. We suggest that the time and effort required to repeat the FeNO measurement could be saved, because a single FeNO measurement is sufficient to diagnose asthma.

Although we proved the excellent predictive value of a single FeNO measurement for diagnosis of asthma, some patients showed a significant gap in FeNO levels between the first and second measurements. Patients with normal-to-low FeNO values (in the bottom 75%) showed modest agreement between the first and second FeNO values measured. The groups with the best lung function (in the top 25%) and worst lung function (in the bottom 25%) showed significantly higher FeNO values for the second measurement than for the first measurement. Therefore, we need to pay attention when measuring FeNO levels in these subgroups, where more than 1 measurement of the FeNO level may be necessary to obtain a definitive value. However, repeating the measurement may not affect the diagnosis of asthma.

Lung function played a significant role in the measurement of FeNO, whereas age, sex, and height did not. Several studies have demonstrated that age, sex, height, atopy, smoking status, and lung function can influence the level of FeNO [16]; however, no consensus has been reached [3-6,10,13,17,18]. We attempted to establish significant associations between these factors. Given that our study included a relatively small number of patients compared with previous studies, we could not be sure that age, sex, and height were not significantly associated. We reconfirmed that lung function was negatively correlated with FeNO values, consistent with previous data from a group in Korea [10]. A possible explanation for this finding could be that patients with severe eosinophilic inflammation might have high levels of FeNO and poor lung function [19].

Asthma is a chronic inflammatory airway disease that can be diagnosed and monitored using various tests [20]. The classic tests include lung function, a questionnaire, and induced sputum. Data were recently reported for FeNO and periostin, and interest in potential biomarkers such as IgE, ykl-40, and CD93 has grown [21-24]. In the clinic, the FeNO level is easily measured before the performance of the lung function test. The utility of FeNO values has been widely demonstrated [25,26]; therefore, FeNO will be used more extensively in the future. Our study showed that repeated measurements of FeNO were unnecessary; consequently, the convenience and ease of a single FeNO measurement will enhance the utility of this approach.

Our study is subject to a series of limitations. First, it was performed at a single institution with a small number of

patients. Our results should be confirmed in a larger study. Second, despite having a highly skilled and well-trained practitioner (which ensures excellent reproducibility), we are unsure whether a single FeNO measurement would be sufficient at institutions without skilled trainers. Third, we should interpret the results carefully, because we might have included patients with noneosinophilic asthma. Lastly, atopy, which is known to be significantly associated with FeNO level, was not included in the analysis because of missing data.

In conclusion, a single FeNO measurement was sufficient for asthma screening in cases where the first acceptable FeNO measurement was made using the appropriate method. A second measurement would be helpful in cases where the first acceptable measurement is much lower or higher than the clinician expected and in cases where lung function is extremely good or poor.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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