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Clinical Application of Exhaled Nitric Oxide Measurements in a Korean Population

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Nitric oxide (NO) is a biologic mediator of various physiologic functions. Recent evidence suggests the clinical utility of fractional exhaled NO (FeNO) as a biomarker for assessing asthma and other respiratory diseases. FeNO methodologies have been recently standardized by international research groups and subsequently validated in several Korean population studies. Normal ranges for FeNO have been reported for various ethnic groups, and the clinical utility has been widely evaluated in asthma and various respiratory diseases. Based on current evidence including most of Korean population data, this position paper aims to introduce the methodological considerations, and provide the guidance for the proper clinical application of FeNO measurements in Korean populations.

Key Words: Exhaled nitric oxide; reference value; guideline; position paper; asthma

INTRODUCTION

Airway inflammation is a key component in asthma and various respiratory diseases.[1] Therefore, the assessment of inflammation can provide important clinical information for patient diagnosis and monitoring, or for predicting treatment responses. Bronchoscopy has been the traditional gold standard method for directly obtaining airway tissues or cells, but its invasiveness has limited its applicability.[2] The induced sputum test is an alternative tool that was standardized during the 1990s as a safer method of assessing airway inflammation.[3,4] However, induced

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sputum analysis is technically challenging, time consuming, and not always feasible.

In this context, exhaled NO measurement has gained substantial clinical and scientific interest. NO is a biologic mediator generated when L-arginine is oxidized by NO synthase (NOS).[5,6] It is involved in various functions of the respiratory system, including physiologic roles as a vasodilator, bronchodilator, neurotransmitter, and immune regulator.[7] Although the specific contributions of NO to the pathophysiology of respiratory diseases remains unclear, patients with asthma exhale high concentrations of NO and show high airway epithelial expression of inducible NOS.[8] Moreover, exhaled NO levels are reduced by corticosteroid therapy in asthma patients.[9] Therefore, exhaled NO (FeNO) has been proposed as a useful biomarker reflecting respiratory eosinophilic inflammation, particularly in asthma.[10,11]

Over the last decade, an expanding literature on the clinical application of exhaled NO measurements has widened the clinical application of this non-invasive, simple, and reproducible measure. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) have jointly published guidelines on the standardization and interpretation of exhaled NO measurement.[10,12] Here, we reviewed current key literature and summarized relevant clinical studies conducted in Korean populations. This position paper aimed to introduce the standardized methods for NO assessment and to suggest its proper clinical applications.

INDICATIONS

FeNO indications[10,13] can be classified into diagnostic and monitoring entities. FeNO is an attractive test as it is completely noninvasive, and provides immediate results. FeNO is a well-established tool in asthma research, with over 2,000 publications on its application. Its measurement adds a new dimension to the traditional clinical tools used in the assessment and management of airways diseases.

FeNO measurements in asthma have been used for the indications listed in Table 1. The current major indications include (1) detecting eosinophilic airway inflammation, (2) determining the likelihood of corticosteroid responsiveness, (3) monitoring airway inflammation to determine the potential need for corticosteroid therapy, and (4) unmasking otherwise unsuspected non-adherence to corticosteroid therapy.[10,13] FeNO is also an effective diagnostic and monitoring tool for chronic cough,[14] acute eosinophilic asthma,[15] sinusitis, nasal polyposis, primary ciliary dyskinesia, chronic obstructive pulmonary disease (COPD), interstitial lung disease, cystic fibrosis, and other pulmonary or extrapulmonary diseases. However, additional research is required to validate its clinical utility. Impediments to the clinical application of FeNO include the paucity of publications on the utility of this marker in predicting exacerbations, improving long-term asthma control,[16-19] or reducing health care costs.

Table 1. Indications for FeNO measurement in asthma

Diagnostic
To assist in assessing the etiology of respiratory symptoms
To support the diagnosis of asthma in situations in which objective evidence is needed
To identify the eosinophilic asthma phenotype
To account for persistent and/or high allergen exposure
To predict the presence of airway hyperresponsiveness
Monitoring
To determine the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possibly due to airway inflammation
To assess potential response or failure to respond to anti-inflammatory agents
To establish a baseline FeNO during clinical stability for subsequent monitoring of chronic persistent asthma
To guide anti-inflammatory medication dosing adjustments: step-down dosing, step-up dosing, or discontinuation of anti-inflammatory medications
To assist in the evaluation of adherence to anti-inflammatory medications
To assess whether airway inflammation is contributing to poor asthma control, particularly in the presence of other contributors (*e.g.*, rhinosinusitis, anxiety, gastro-esophageal reflux, obesity, or continued allergen exposure)

INSTRUMENTS AND MEASUREMENTS

At present, chemiluminescent and electrochemical detection methods have been mainly utilized in Korean population studies. Chemiluminescence is an established, standard technique and was recommended by ATS/ERS in 2005.[12] Chemiluminescence devices measure NO levels by means of light generation from a chemical reaction of FeNO with ozone:[20] $NO + O_3 \rightarrow NO_2 + O_2 + photons$. Light emitted by NO_2 at >600 nm wavelength, which is highly proportional to NO concentration, is then detected by a photomultiplier tube.[20] This technique has high sensitivity, with detection limits at the ppb-level (1.5 ppb for NIOX, Aerocrine, Solna, Sweden; and 0.5 ppb for Sievers NOA 280i, GE Analytical Instruments).[20] However, the devices also have drawbacks such as heavy weight (20-50 kg), a large size and being less user-friendly than other devices. Moreover, there are costs associated with annual maintenance.[20] The ANALYZER CLD 88 sp® (ECO MEDICS, Duernten, Switzerland) is another chemiluminescence device which recently became available for use with infants, children, and adults. This latter analyzer was utilized in a Korean study evaluating healthy newborns.[21]

Electrochemical sensor devices (NIOX MINO®,[22] Aerocrine, Solna, Sweden; NObreath,[23] Bedfont Scientific Ltd, UK) are recently introduced alternatives to chemiluminescence analyzers. These devices have a detection limit of 5 ppb but also the distinct advantages of being small, light-weight (less than 1 kg), easy-to-use, and hand-held. Another strong point is that electrochemical sensors do not require pre-test calibration; rather, they use an electrochemical sensor which needs to be replaced every 100-300 tests.[20] In this regard, the electrochemical analyzers have promising roles in clinical practice. However, despite

lower investment costs than chemiluminescence methods, the electrochemical devices have additional costs for each test and for periodic sensor replacement.

There appears to be a high degree of correlation between these 2 FeNO detection methods.[24,25] However, electrochemical sensor devices generally report 4-10 ppb lower than chemiluminescent detectors.[20,28] Such small differences are generally accepted as being not clinically relevant, but the analyzer device model should be clearly described when reporting the results.

Testing procedure

Prior to initiation procedure

All subjects must refrain from strenuous physical exercise and avoid eating, drinking or smoking for at least 1 hour before the assessment.[26] Caution should be taken, since exhaled NO levels may increase after eating foods containing nitrates.[27] Conversely, smoking causes acute and chronic reductions in NO levels,[28,29] thus short- and long-term, active and passive smoking history should be obtained.[12]

Respiratory tract infections may increase exhaled NO levels in asthma.[30] Therefore, NO assessment tests should be postponed until after recovery if possible. Exhaled NO levels may be decreased by inhaled or systemic corticosteroids,[31] or by leukotriene antagonists.[32] In addition, all patient medication details should be obtained to identify anything that may influence the results. Since circadian rhythms may affect NO levels,[33] serial NO measurements should be performed at approximately the same time of the day.[12]

Finally, FeNO measurement should occur prior to spirometry or bronchial challenge tests. Generally, respiratory maneuvers are considered to transiently reduce FeNO levels.[34-36]

During the procedure

The most important factor to consider during the procedure is to maintain a 'constant flow rate'. In a flow-concentration curve, NO levels vary widely according to the expiratory rate.[20] Accordingly, the ERS/ATS set the standard expiratory flow rate for NO measurement at 50 mL/s.[12] A single-breath method is also used in all cooperative children. However, in uncooperative children, assessment by well-trained and experienced staff with adequate practice time, audiovisual aids, and dynamic flow restrictors is recommended. Alternatively, exhaled NO can be measured during spontaneous tidal breathing, which can be used in preschool children or infants.[37]

Chemiluminescence methods

Subjects are instructed to sit in an upright position, exhale to residual volume, insert a mouth piece, inhale to total lung capacity, and then exhale immediately for 10 seconds at a constant flow rate of 50 mL/s. The investigators select the plateau period, and the plateau concentration is displayed by the instruments. FeNO measurements are repeated until 2 values are obtained that vary by less than 10%. The mean value is then recorded.

Electrochemical sensor methods

Subjects are instructed to sit in the upright position without a nose clip, exhale to residual volume, insert a mouth piece, inhale to total lung capacity through a nitric oxide-free filter connected to the instrument, and then exhale immediately for 10 seconds at a constant pressure guided by a visual cue in order to stabilize expiratory flow rate at 50 mL/s. FeNO levels are assessed along a stable plateau of exhaled NO concentration at least 3 seconds in length.

How to report NO measurements in clinical practice and research

In general, NO measurement protocols should follow the current standard guidelines published by the ERS/ATS in 2005.[12] For reporting, the minimum parameters to include are data, time, age, sex, race, height, weight, smoking status, prior diagnosis (particularly airway diseases), reason for testing, current corticosteroid medication (inhaled or systemic), and analyzer model used in the assessments.

Statements on instruments and measurements

We recommend following the current standardized procedures and validated instruments as stated by the ATS/ERS official documents.[12]

We also recommend that practitioners understand the characteristics of each analyzer and be familiar with the factors that can potentially influence FeNO levels.

INTERPRETATION

Since FeNO levels distribution curves are positively skewed, it is reasonable to use logarithmic transformation for statistical analysis. Geometric means rather than arithmetic means are preferred to describe the skewed values. However, many investigators have used the arithmetic mean and standard deviation to describe FeNO values, and the ATS guidelines do not provide additional recommendations or guidance on this statistical issue. Thus, it should be noted that some of our present data have been provided as being transformed from their original statistical analyses.

Normal ranges in adults

Recent studies have reported normal ranges for adult populations in Korea (Table 2). However, the reported NO level distributions are skewed and show considerable overlap between control subjects and stable asthmatics.[10] Moreover, the suggested 'normal' ranges vary considerably between study populations and analytic instruments used in the study.[38-43] In this regard, ATS guidelines recommend the use of cutoff points rather than reference values based on the specific clinical setting and research question being addressed.[10]

Table 2. Normal ranges of exhaled nitric oxide among healthy Korean adults and children

Reference	Study population	Groups	Ranges	Instruments
Adult studies				
Kim *et al.*[46]	Nonsmoking healthy adults aged 20-68 yr from among employees at medical institutions (n=166, mean age 33 yr, atopy 48.2%)	Atopic male	Mean 37.3 ppb ± SD 12.1	Chemiluminescence analyzer (Sievers NOA280i, GE Analytical Instruments, Boulder, CO, USA)
		Nonatopic male	Mean 33.9 ppb ± SD 14.3	
		Atopic female	Mean 28.6 ppb ± SD 17.7	
		Nonatopic female	Mean 24.1 ppb ± SD 10.6	
Jo *et al.*[45]	Healthy adults from the Ansung cohort (n=570, mean age 60 yr, atopy 23.3%)	Male	Geometric mean (95% CI) 15.5 ppb (14.4-16.8)	Electrochemical sensor analyzer (NIOX MINO, Aerocrine, Sweden)
		Female	Geometric mean (95% CI) 10.1 ppb (9.5-10.8)	
Children studies				
Cho *et al.*[58]	Healthy children from 1 elementary school in Seoul (n=808, mean age 9.26 yr, atopy 38.0%)	Non-atopic	Geometric mean (95% CI) 10.3 ppb (9.9-10.7)	Electrochemical sensor analyzer (NIOX MINO, Aerocrine, Sweden)
		Atopic	Geometric mean (95% CI) 16.6 ppb (15.4-17.8)	
Kim *et al.*[21]	Healthy newborns (n=41) from the nursery of 1 university hospital	Full term (n=31), Preterm (n=10)	Mean 10.0 ppb ± SD 4.9, upper limit of 95% CI 19.8	Chemiluminescence analyzer (CLD 88 exhalyzer) with tidal breathing technique

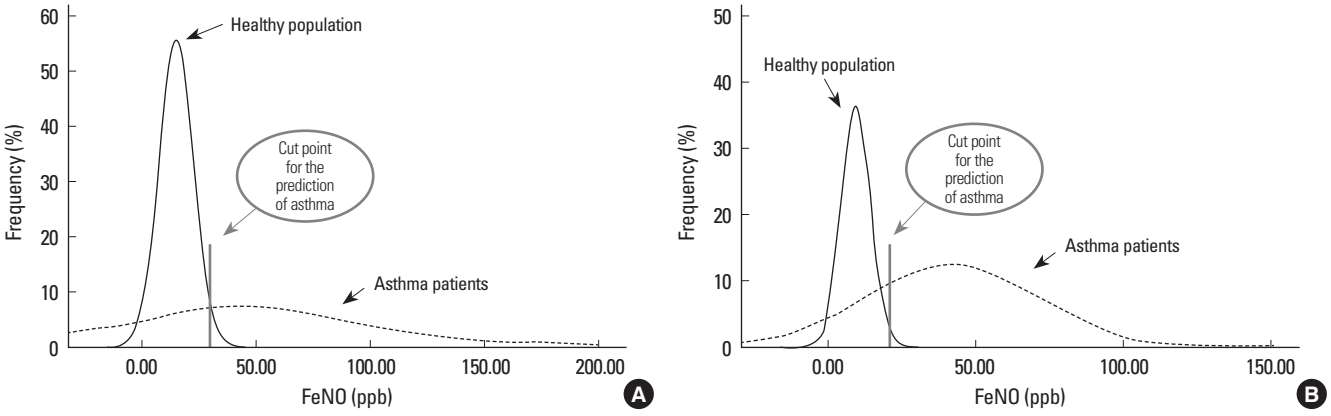

Figure. Schematic presentation of the distribution of fractional exhaled nitric oxide levels in an adult Korean population: (A) males and (B) females. The data were obtained from the studies conducted by Jo *et al*.[45]

The difficulty in determining normal ranges for FeNO may be attributed to several confounding factors. In the literature, race, age, sex, weight, height, smoking, and atopy have all been suggested as potential confounding factors. Amongst them, race, sex, atopy, age, and smoking have been regarded as major factors influencing FeNO measurement in adults. Asians are reported to have higher FeNO levels than other ethnic groups, presumably due to dietary habits or genetic variations in NOS genes.[27,44] Among Korean adults, male sex has been positively associated with higher NO levels (Figure).[45,46] Other population studies also reported sex differences in NO levels.[40,41,47,48] The effects of atopy also have been frequently reported[41,43,46,49,50]; however, a recent study conducted in an unselected Korean older adult population (mean age: 59.9 years) did not confirm previous findings on atopy.[45] The discrepancy in the results on atopy between 2 Korean population studies may be attributed to the effects of age, or also possibly to the analytic devices. Regarding obesity, a small study reported possible associations between FeNO and body mass index (BMI) in healthy non-smoking adults,[51] but these results were not replicated in Koreans.[52] Therefore, the heterogeneity in study design should be considered when interpreting suggested ranges for exhaled NO levels. Overall, both gender and atopy appear to be potentially significant confounding factors impacting FeNO levels in Korean adults.

Normal ranges in children

A few studies have reported normal ranges in healthy children.[53-57] In a recent multicenter study that enrolled 405 healthy children in Europe and the US aged 4 to 16 years, the geometric mean FeNO was 9.7 ppb, and the upper 95% confidence interval (CI) was 25.2 ppb. FeNO levels significantly increased with

Table 3. Individual FeNO values by age in elementary school children

Age (yr)	Non-atopic healthy		Atopic healthy		Total healthy	
	N	GM (95% CI), ppb	N	GM (95% CI), ppb	N	GM (95% CI), ppb
6	65	9.61 (7.62-11.60)	19	13.47 (11.22-15.72)	84	10.38 (8.33-12.43)
7	80	10.40 (8.40-12.40)	58	15.61 (13.44-17.78)	138	12.34 (10.23-14.45)
8	87	10.02 (8.02 -12.02)	53	16.28 (14.15-18.41)	140	12.04 (10.04-14.03)
9	82	9.41 (7.42-11.40)	59	18.80 (16.64-20.96)	141	12.57 (10.39-14.75)
10	85	10.49 (8.52-12.46)	57	15.28 (13.03-17.53)	142	12.20 (10.08-14.32)
11	84	11.27 (9.21-13.33)	44	18.38 (16.24-20.52)	128	13.33 (11.20-15.46)
12	18	13.76 (11.68-15.84)	17	17.77 (15.53-20.01)	35	15.63 (13.51-17.75)

FeNO, fractional concentration of exhaled nitric oxide; GM, geometric mean.

age (15-25 ppb for the upper 95% CI, depending on age), but showed no significant gender difference (geometric mean, 10.0 ppb in boys vs 9.4 ppb in girls; $P=0.27$).[54] The ATS guidelines strongly recommend accounting for age as a factor impacting FeNO levels in children younger than 12 years of age.[10] Another study of 114 healthy, non-atopic children in Finland reported that FeNO levels were significantly associated with age, height, weight, and body surface area. Using a skin prick test, the mean FeNO level for children with atopy was higher than that for children without atopy, irrespective of the presence of respiratory symptoms (10.3 ppb in non-atopics vs 16.1 ppb in symptomatic atopics or 14.6 ppb asymptomatic atopics; $P<0.0001$ and $P=0.005$, respectively).[55] Racial differences of mean FeNO levels in healthy children were reported for Canadian school-aged children. Asian-Canadians had a significantly higher mean FeNO level than whites (12.7 ppb vs 22.8 ppb, $P<0.001$).[56] In a recent study that enrolled children in Taiwan aged 5 to 18 years, the geometric mean FeNO level and the upper 95% CI were 11.2 ppb and 30.2 ppb in children without allergic sensitization. Subjects with allergic sensitization had comparatively elevated FeNO (mean 17.7 ppb, upper 95% CI 74.8 ppb).[57]

In Korea, the geometric mean and upper 95% CI of FeNO in healthy, non-atopic subjects were 10.3 ppb and 10.7 ppb in elementary school children.[58] Healthy atopic children also had higher mean FeNO levels (16.7 ppb) than those of non-atopic children. Individual FeNO values by age were described in Table 3. FeNO measurements in school children was reported as simple and reproducible,[39,54] but its feasibility does depend on age, since measurements can be challenging in preschool children. Age may impact the assessment success rate (from 40% at 4 years and 60% at 5 years to 100% at school age).[54]

Cutoff points for assessing specific disease conditions

Asthma/eosinophilic airway inflammation in adults

The ATS guidelines state that NO levels <25 ppb indicate a decreased likelihood of eosinophilic inflammation or corticosteroid responses, and that levels >50 ppb indicate the eosinophilic or atopic nature of airway inflammation but also the likelihood of a positive response to corticosteroid treatment.[10] However, in patients with intermediate NO levels (25-50 ppb in adults), the interpretation of results should be cautious and made in clinical context.[10]

Among Korean adults, Jo *et al.* found the cutoff points of 30.5 ppb for males and 20.5 ppb for females to be useful for differentiating patients with asthma from controls (sensitivity 0.7 and specificity 0.9 in males, and sensitivity 0.8 and specificity 0.87 in females).[45] No other published studies have evaluated the performance of FeNO cutoff points for identification of asthma in Korean adults. In non-asthmatic patients with chronic cough, Oh *et al.* reported that FeNO measurements have utility in excluding the diagnosis of eosinophilic bronchitis if FeNO levels are <31.7 ppb.[14] For eosinophilic pneumonia, Lee *et al.* analyzed the diagnostic ability of FeNO for differentiating acute eosinophilic pneumonia from non-eosinophilic pneumonia. The authors found that the cutoff value of 23.5 ppb had high diagnostic utility for predicting acute eosinophilic pneumonia among patients with fever and pneumonic infiltrations (positive likelihood ratio, 5.05, and negative likelihood ratio, 0.16) (Table 4).

Asthma/eosinophilic airway inflammation in children

ATS guidelines recommend that for children, FeNO levels <20 ppb can be used to indicate a decreased likelihood of eosinophilic inflammation and corticosteroids response, and that >35 ppb may indicate likely eosinophilic inflammation in symptomatic patients but also responsiveness to corticosteroids.[10] The guidelines also recommend that FeNO levels between 20 ppb and 35 ppb should be interpreted with caution and in line with their clinical context.

In Korean studies, Choi *et al.* reported that children with asthma had higher levels of FeNO than the control group (mean FeNO, 28.3 ppb vs 20 ppb, respectively) and that FeNO levels were negatively correlated with PC20 in a methacholine provocation test.[59] Recently, Oh *et al.* reported that FeNO levels were higher in preschool children with persistent or late-onset wheezing than in children with transient wheezing or non-wheezers. The authors concluded that FeNO measurement may be a bet-

Table 4. Summary of fractional exhaled nitric oxide levels in Koreans with various lung diseases

Reference	Study population	Instrument	Findings	Conclusions
Adult studies				
Oh *et al.*[14]	Chronic cough (>3 weeks), non-smokers (n=211)	Chemiluminescence analyzer (Sievers NOA280i)	31.7 ppb to predict non-asthmatic eosinophilic bronchitis (sensitivity 86% and specificity 76%)	FeNO is useful for excluding non-asthmatic eosinophilic bronchitis
Jo *et al.*[45]	Asthma (n=74) vs population-based controls (n=570)	Electrochemical sensor analyzer (NIOX MINO)	30.5 ppb to predict asthma in males (sensitivity 70% and specificity 90%); 20.5 ppb for asthma in females (sensitivity 79.5% and specificity 86.9%)	FeNO is useful for differentiating asthmatics from controls
Park *et al.*[19]	Asthma (n=90) vs non-asthma (n=71) among patients with respiratory symptoms	Electrochemical sensor analyzer (NIOX MINO)	25.5 ppb to predict asthma among adults with suspected symptoms of asthma (sensitivity 57.1% and specificity 75.7%) 24.5 ppb to predict uncontrolled asthma among asthmatics (sensitivity 76.6% and specificity 80.8%)	FeNO may be useful for diagnosing asthma and for assessing the level of asthma control
Han *et al.*[18]	Controlled asthma (n=34), partly controlled asthma (n=19), and uncontrolled asthma (n=18)	Chemiluminescence analyzer (Sievers NOA280i)	No significant difference in FeNO levels according to the asthma control status, or asthma control test score	FeNO levels are not associated with measures of asthma control in patients treated with inhaled corticosteroids
Lee *et al.*[15]	Acute eosinophilic pneumonia (n=31) vs non-eosinophilic pneumonia (n=29)	Electrochemical sensor analyzer (NIOX MINO)	23.5 ppb to predict acute eosinophilic pneumonia (sensitivity 87% and specificity 83%)	FeNO is useful for differentiating acute eosinophilic pneumonia in patients with fever and pulmonary infiltrates
Kwak *et al.*[99]	Ventilator-associated pneumonia (n=19) vs controls (n=24)	Chemiluminescence analyzer (Sievers NOA280i)	43.5 ppb to predict ventilator-associated pneumonia among adult patients with mechanical ventilation	FeNO may be useful for diagnosing ventilator-associated pneumonia
Children studies				
Oh *et al.*[17]	Transient wheezers (n=67), persistent wheezers (n=23), late onset wheezers (n=29), and non-wheezers (n=282) from general preschool population aged 4 to 6 yr	Electrochemical sensor analyzer (NIOX MINO)	Mean±SD 14.4±9.2 ppb in persistent wheezers, 14.4±9.2 ppb for late-onset wheezers, 11.5±7.0 ppb for transient wheezers, 10.1±5.6 ppb for non-wheezers	FeNO may be a better marker for asthma phenotypes in preschool children than airway hyperresponsiveness or spirometric parameters
Choi *et al.*[59]	Atopic asthma (n=98), non-atopic asthma (n=20), AR (n=79), and controls (n=74), children aged 6 to 15 yr	Chemiluminescence analyzer (CLD 88 exhalyzer)	Mean±SD 48.33±32.28 ppb in atopic asthma, 15.92±5.99 ppb in non-atopic asthma 43.59±29.84 in allergic rhinitis	Patients with atopic asthma had higher FeNO levels than non-atopic asthmatics or controls
Choi *et al.*[100]	Patients with asthma (n=121), and controls (n=81), children aged 5 to 10 yr	Chemiluminescence analyzer (CLD 88 exhalyzer)	Median (interquartile range) 28.3 ppb (15.0-55.7) for asthma, 20.0 (12.3-39.7) for controls	Patients with asthma had higher FeNO values than controls
Seo *et al.*[101]	Asthma (n=55), children aged 7 to 11 yr	Electrochemical sensor analyzer (NIOX MINO)	Geometric means (95% CI) 36.3 ppb (20.9-63.1) before MCT, 25.7 ppb (13.8-47.9) after MCT	FeNO levels may decrease after methacholine-induced bronchoconstriction Repeated spirometry maneuver was determined to have an effect on reducing FeNO levels
Baek *et al.*[102]	Asthma with EIB (n=31), asthma without EIB (n=28), healthy controls (n=42)	Electrochemical sensor analyzer (NIOX MINO)	1) Median (interquartile ranges) 26.0 ppb (15.0-46.0) in asthmatics with EIB, 16.0 ppb (12.5-28.0) in asthmatics without EIB, 12.0 ppb (10.0-15.3) in controls 2) Cutoff value for EIB: 20 ppb (sensitivity 61.3%, specificity 80.0%)	Baseline FeNO levels correlate with the post-exercise decrease in FEV1 FeNO measurement may be a tool for predicting EIB
Kim *et al.*[16]	Atopic asthma (n=126), controls (n=30), children aged 8 to 16 yr	Electrochemical sensor analyzer (NIOX MINO)	Geometric means (95% CI) 16.1 ppb (14.5-17.8) for atopic asthma, 7.5 ppb (7.0-8.1) for controls	FeNO was not related to spirometry values or scores for asthma control
Woo *et al.*[103]	Atopic asthma (n=129), non-atopic asthma (n=38), atopics without asthma (n=60), non-atopics without asthma (n=18), children aged 8 to 16 yr	Electrochemical sensor analyzer (NIOX MINO)	Geometric means (95% CI) 23.4 ppb (20.9-26.2) for asthmatics and 12.6 ppb (10.9-14.5) for non-asthmatics (P<0.001) 22 ppb to predict asthma among children with suspected symptoms of asthma (sensitivity 56.9% and specificity 87.2%)	FeNO value in atopics was higher than that in non-atopics regardless of asthma. In atopic subjects, FeNO value was significantly higher in asthmatics than that in non-asthmatics. In contrast, in non-atopics, there was no difference in FeNO between asthmatics and non-asthmatics

CI, confidence interval; MCT, methacholine challenge test; EIB, exercise-induced bronchoconstriction.

ter marker for identifying preschool wheezing phenotypes than measurement of airway hyperresponsiveness or spirometry.[17] Results from other studies are described in Table 4.

Minor differences

The intra-individual variation in FeNO levels is reported to be 10% (or up to 4 ppb) in healthy subjects[39,60] vs 20% in asthmatics.[39,60,61] Thus, ATS guidelines recommend that in patients with asthma and baseline levels of more than 50 ppb, a change in FeNO of >20% from baseline levels is indicative of a significant change over time or following treatment.[10]

Statement on interpretation of results

We recommend the use of specific FeNO level cutoff points for specific disease conditions or in distinct populations rather than adopting universal reference ranges. The basis for this recommendation includes the effects of various confounders, the methodological heterogeneity in previous studies, and the lack of any large-scale studies presenting nationwide data.

We suggest that FeNO levels have utility in supporting a diagnosis of asthma or eosinophilic inflammation in both adults and children. Despite potential inter-ethnic differences, we determined that the cutoff points suggested by the ATS guidelines are applicable to both Korean adults and children at present. To summarize, FeNO levels >50 ppb in adults or >35 ppb in children indicate a high likelihood of asthma or eosinophilic inflammation. Conversely, FeNO levels <25 ppb in adults (or <20 ppb in children) indicate a decreased likelihood of asthma or eosinophilic inflammation. Intermediate levels (25-50 ppb in adults and 20-35 ppb in children) should be interpreted with caution and consideration for the specific clinical context.

We suggest that a change in FeNO of >20% indicates a significant, clinically relevant change in asthmatics with FeNO levels >50 ppb (>35 ppb in children) at baseline. Therefore, serial measurements can be used to both to monitor clinical disease course and to assess treatment responses in patients with asthma.

SAFETY

FeNO measurement is a straightforward procedure that is easy to perform and well tolerated by subjects. No safety issues have been identified with FeNO assessment methods.[62]

CLINICAL APPLICATIONS

Bronchial asthma

Airway inflammation is an important feature in the development and progression of asthma.[63] FeNO levels are increased in asthmatic patients compared to normal controls as a result of NOS induction by pro-inflammatory cytokines.[64,65] FeNO levels have also been positively correlated with eosinophil concentrations in serum, bronchoalveolar lavage fluid, bronchial biopsies, and induced sputum.[18,19,66-68]

The clinical utility of FeNO is now widely accepted.[11] The diagnostic accuracy for asthma may be superior, or at least similar when compared to conventional diagnostic tools such as spirometry, induced sputum, or peak flow meters.[69] It may also be utilized for predicting exacerbations,[70] or the treatment responses to corticosteroids[71] and leukotriene antagonists.[32] Unlike induced sputum eosinophils, the role of FeNO to tailor the dose of inhaled corticosteroids has not been generally proven at present;[72] however, a recent trial demonstrated the strategy as useful in reducing asthma exacerbations in pregnant asthmatics.[73]

In children, recent Korean studies suggested additional utility of FeNO tests in classifying subtypes of preschool wheezing and predicting the likelihood of wheezing at 8 years. Children with late-onset or persistent preschool wheezing had higher FeNO levels than transient wheezers or non-wheezers.[17] FeNO values in preschool children were also reported to improve the ability of specific IgE measurement to predict asthma symptoms at 8 years.[74]

However, there exist pitfalls in the FeNO interpretations. A proportion of asthmatics do not show elevations in FeNO levels. The discrepancy may be related to several factors.[11] Most of all, the heterogeneity in asthma phenotypes seems to be a major relevant factor, particularly in adults.[75,76] A large proportion of asthmatics may be non-eosinophilic.[77] Despite reports of increased FeNO concentrations in school children with atopic asthma, no significant differences in FeNO were identified in subjects without atopy, irrespective of asthma. Low FeNO values in children may help exclude atopic asthma but high levels may be caused by allergic sensitization in addition to asthma.[36,68,78]

Obesity may be another factor involved in the discrepancy. Consistent data indicate that asthma is closely associated with obesity,[79-83] and obese patients with asthma usually have more severe symptoms than non-obese patients with asthma.[68,84] Now obese asthma is regarded as a unique phenotype characterized by severe symptoms for a given degree of lung function impairment, poor asthma control or quality of life, poor treatment responses to corticosteroids, or lack of eosinophilic inflammation.[68,84,85] Therefore, in an obesity-related subtype of asthma, the diagnostic accuracy of FeNO has not been clearly demonstrated.[86]

Bronchiolitis

Preclinical in vitro and animal data have demonstrated NO involvement in bronchiolitis, but only a few studies have evaluated FeNO levels in children with RSV bronchiolitis.[87,88] In one study, FeNO levels were significantly lower in infants with bronchiolitis than in healthy control infants or in preschool children with recurrent wheezing.[89] However, the same study demonstrated that 3 months after an initial diagnosis of RSV bronchiolitis, FeNO was significantly higher in the affected children than in normal subjects.[89] Future studies are required to investigate

potential relationships between viral infections and subsequent asthma.

Cystic fibrosis

FeNO levels are abnormally low in patients with cystic fibrosis (CF) compared to patients without cystic fibrosis, patients with non-primary ciliary dyskinesia (PCD), or normal controls, but there are no significant differences between CF and PCD.[68,90,91] The low levels of NO in CF are directly related to the absence of NOS2 expression in the airway epithelium, which supports the concept that NOS2 contributes much of the NO that is detectable in exhaled breath.[90,91]

Data on NO levels in children with CF-related bronchiectasis appear conflicting, with one study showing lower NO in CF than in controls, while other authors reported significantly higher NO with CF, but no significant difference in NO compared to healthy children.[66,68,90,91] On the other hand, in children with PCD, very low levels of nasal NO are an as yet only partially explained phenotype, whereas the range of FeNO levels in these subjects show considerable overlap with healthy subjects.[90,91] Until there is consensus on changes in NO in CF, nasal NO levels have not been recommended for use in routine clinical practice.

Interstitial lung disease

In systemic sclerosis, FeNO concentrations are lower in subjects with interstitial lung involvement than in those without lung involvement, whereas patients without pulmonary disease have higher FeNO levels than healthy subjects.[92] However, due to the rareness of diffuse lung disease in children, there are currently no reported studies that evaluated FeNO levels in this population.[93]

In adults, a recent single center study has demonstrated the clinical utility of high FeNO levels (>23.5 ppb) in differentiating acute eosinophilic pneumonia from its non-eosinophilic form.[15]

COPD

Based on some reports, response to corticosteroids is likely to be greater in patients with COPD who have sputum eosinophilia or elevated FeNO.[94] Significant correlations have also been reported between baseline FeNO and FEV1 improvement after 2 months following treatment with inhaled budesonide 800 mg/day.[95] This finding raises the possibility that FeNO measurements might also be used to predict steroid responsiveness in COPD.[94,95]

Chronic cough

In adults with chronic cough, FeNO measurements may be useful in identifying non-asthmatic eosinophilic bronchitis,[14] but have more controversial utility in predicting inhaled corticosteroid responses.[96,97] In a study evaluating Korean children, FeNO levels were not associated with the severity of eosinophilic bronchitis.[98]

Statements on clinical applications

The clinical utility of FeNO measurements is under investigation for various diseases.[11] Its usefulness in asthma is now well accepted, despite several limitations. On the basis of current findings, we encourage the use of FeNO measurements in prospective clinical trials to further validate its utility as an assessment endpoint in various respiratory conditions.

CONCLUSIONS

Measurement of FeNO is an easy, safe, reproducible, and noninvasive method to evaluate airway inflammation in both adults and children. In recent years, FeNO has been widely used to diagnose and manage asthma. FeNO measurement is useful for screening, precise diagnosis, predicting and evaluating treatment response, and predicting exacerbation in asthmatic patients. Age, sex, height, race, smoking, food intake, and atopy may each affect FeNO levels as confounders. FeNO levels increase with age, especially in children younger than 12 years old; however, a relatively low measurement success rate was shown in preschool children.

Evidence-based cutoff points rather than reference ranges are more likely to have diagnostic significance. In asthmatic patients, personal best value and changes from baseline may be more clinically relevant and useful indicators for evaluating patient treatment requirements than the actual FeNO levels themselves. Thus, Individual assessment according to clinical conditions is essential. FeNO measurements in preschool children can help to classify specific wheezing phenotypes and to predict future asthma symptoms at later life. Moving forward, FeNO, as with spirometry, will most likely be used to evaluate airway inflammatory changes during inhalation or an exercise provocation test.

This work will help to improve the routine clinical utilization of FeNO measurements in the field. Large population-based studies need to be conducted, since they will provide essential information on normal FeNO values. For tailored patient management based on the phenotypes of asthma or recurrent wheezing, more detailed study designs and patient classifications are needed.

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