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Association of longitudinal fractional exhaled nitric oxide measurements with asthma control in atopic children

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Summary
Objectives: We sought to determine whether longitudinal measurements of FeNO are informative for future loss of asthma control in children with atopic asthma.
Methods: One hundred seventy-eight patients aged 8–16 years with atopic asthma were enrolled. FeNO and lung functions were serially monitored 10 times or more over 2 years when subjects were not receiving controller medications. After completion of monitoring, 1-year observation on the occurrence of loss of asthma control was performed and associations of loss of asthma control with spirometric and FeNO measurements were analyzed.
Results: Loss of asthma control occurred during observation periods in 110 (76%) of 145 patients who completed the study. Of all monitored parameters including airway reactivity, the highest FeNO of serial measurements (H-FeNO) (adjusted odds ratio (aOR), 1.21; 95% CI, 1.08–1.36) and the rate of FeNO levels higher than 21 ppb (R_{21}FeNO) (aOR, 1.06; 95% CI, 1.01–1.11) were the only independent predictors of upcoming control loss in the multiple logistic regression analysis. In receiver-operator characteristic curve analysis, H-FeNO $>$ 37 ppb and R_{21}FeNO $>$ 20% demonstrated 91% and 88% sensitivity for a future loss of asthma control at the cost of low specificity (60% and 65%, respectively). In contrast, H-FeNO $>$ 47 ppb and R_{21}FeNO $>$ 41% gave 96% and 88% specificity, but these sacrificed sensitivity to 70% and 72%, respectively.
Conclusions: Our data show that both amount and frequency of a FeNO increase during longitudinal monitoring are helpful in predicting asthma control status.

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Introduction

Asthma is the most common chronic disease during childhood and its exacerbation is one of the most distressing events [1]. Identification of at-risk children for deteriorating asthma is important for personalized managements leading to reduced asthma morbidity. To assess asthma severity or the level of asthma control, careful history and lung function measurements are usually required [2,3]. In addition, monitoring of biomarkers is needed for a multidimensional approach that incorporates various asthma outcomes [4].

Fractional exhaled nitric oxide (FeNO) has been extensively investigated as a noninvasive marker of airway inflammation in asthma. High FeNO values above certain cut-point may indicate active eosinophilic airway inflammation and the likelihood of deteriorations in asthma control [5]. FeNO measurements have also shown potential utility in guiding anti-inflammatory therapy in asthmatic patients [6–8]. However, the clinical value of FeNO measurements may be questioned because FeNO levels were increased even in mild and asymptomatic conditions [9,10].

Prior investigations have raised several important features that should be considered in the evaluation of FeNO utility for asthma monitoring. First, FeNO has been observed to be increased primarily in atopic asthma, which presents a contrast to normal or near-normal FeNO in nonatopic asthma [11–13]. Second, FeNO measurements have been shown to be more predictive of asthma relapse in subjects who were taken off inhaled corticosteroids (ICS) than those who are still on ICS [14,15]. Lastly, various factors including allergen exposure influence FeNO levels, resulting in fluctuations and inconsistency of this biomarker [16–18]. Therefore, single FeNO values are not predictive of asthma exacerbations and at least several data points for a certain period of time are required to detect an upcoming exacerbation [19]. These features of FeNO measurements might be at least partially responsible for the inconsistency among previous studies regarding the utility of FeNO as a predictor of deteriorations of asthma control or the association between asthma control status and FeNO level [6,16,20,21].

In this current study, we explored whether longitudinal measurements of FeNO are informative for a future loss of asthma control in atopic asthmatic children. For this purpose, we serially monitored asthmatic patients over 2 years using FeNO measurements along with spirometric lung function tests when they were not receiving controller medications. After completion of this monitoring, we regularly followed up these patients to observe the occurrence of the loss of asthma control for 1 year and examined the association between the loss of asthma control and longitudinal FeNO measurements.

Material and methods

Subjects and study design

We enrolled 178 child patients aged 8–16 years with atopic asthma, who had been receiving care at the outpatient clinic of the Chungbuk National University Hospital, Cheongju, Republic of Korea. All participants were found to be sensitized to more than one aeroallergen and previously diagnosed to have asthma based on the documentation of airway hyperresponsiveness (methacholine $PC_{20} \leq 8$ mg/mL) and/or reversible airflow obstruction ($\geq$12% improvement in FEV_1 in response to inhaled short-acting β_2-agonist). All enrolled individuals had a history of one or two asthma control loss during the previous 1 year. They had no other clinically significant conditions. The Ethics Committee of Chungbuk National University Hospital Institutional Review Board approved the study and written informed consent was obtained from the parents of all subjects.

The study protocol took place between May, 2008, and February, 2013, and was divided into 2 periods: an initial monitoring period over 2-year and a 1-year observation period. During monitoring periods, all participants had been serially monitored with spirometric lung function tests including bronchodilator responses and FeNO measurements at least 10 times. They did not receive inhaled short-acting β_2-agonists in the 8 h prior to the measurements and were also not receiving a regular treatment with controller medications for 1 month or more before evaluation of FeNO and lung function. The minimal interval between each monitoring was 1 month. In addition, participants had received annual methacholine provocation challenge tests as well. Loss of asthma control was defined as daytime symptoms more than twice per week, reliever medication use more than twice per week, any nocturnal awakening due to asthma symptoms, limitation of daily activities and exercise, and FEV_1 of less than 80% predicted. During the course of monitoring period, participants who maintained asthma control did not receive any medication even though their FeNO was found to be increased. However, participants whose asthma was uncontrolled received twice daily treatment with 200–400 μg of budesonide for at least 3 months and were taken off their inhaled corticosteroid (ICS) therapy when asthma control was maintained. Individuals were excluded from the study if their asthma remained uncontrolled requiring does escalation, they developed severe asthma exacerbations requiring use of systemic corticosteroids, or they experienced deteriorations of asthma control more than twice per year. Reliever medication was to be taken whenever patients judged that it was needed.

After completion of serial monitoring for more than 2 years, the lowest value of the percent predicted forced vital capacity (L-%FVC), the lowest value of the percent predicted forced expiratory volume in the first second (L-%FEV_1), the lowest value of FEV_1/FVC (L-FEV_1/FVC), the lowest value of the percent predicted forced expiratory flow between 25% and 75% of vital capacity (L-%FEF_{25-75}), the rate of %FEV_1 lower than 80% (R_{80}%FEV_1), the rate of %FEV_1/FVC lower than 80% ($R_{80}FEV_1$/FVC), the rate of %FEF_{25-75} lower than 60% (R_{60}%FEF_{25-75}), the highest value of bronchodilator response (H-BDR), the rate of BDR higher than 12% (R_{12}BDR), the highest value of FeNO (H-FeNO), the rate of FeNO higher than 21 ppb (R_{21}FeNO), and the lowest value of natural log-transformed PC_{20} (L-lnPC_{20}) were determined and kept unknown to investigators who determined a loss of asthma control. During an observation period, clinic visits were performed every 2 months for a

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