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Persistently high exhaled nitric oxide and loss of lung function in controlled asthma

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ACT, Asthma Control Test;
BDR, bronchodilator response;
FeNO, exhaled nitric oxide fraction;
FEV1, forced expiratory volume in 1 second;
FVC, forced vital capacity; NO, nitric oxide;
NOS, nitric oxide synthase; RNSs, reactive nitrogen species

ABSTRACT

Backgrounds: It remains unclear whether a persistently high exhaled nitric oxide fraction (FeNO) in patients with controlled asthma is associated with the progressive loss of lung function.
Methods: This was a 3-year prospective study. We examined the changes in pre- and post-bronchodilator forced expiratory volume in 1 s (FEV1) and FeNO in 140 patients with controlled asthma. We initially determined the FeNO cut-off point for identifying patients with a rapid decline in FEV1 (>40 mL/yr). Next, a total of 122 patients who maintained high or non-high FeNO were selected, and the associations between the FeNO trend and changes in FEV1 and bronchodilator response (BDR) were investigated.
Results: A FeNO level >40.3 ppb yielded 43% sensitivity and 86% specificity for identifying patients with a rapid decline in FEV1. Patients with persistently high FeNO had higher rates of decline in FEV1 (42.7 ± 37.5 mL/yr) than patients with non-high FeNO (16.7 ± 31.5 mL/yr) ($p < 0.0005$). The changes in BDR from baseline to the end of the study, in patients who had high or non-high levels of FeNO were −0.8% and 0.1%, respectively ($p < 0.01$). In a multivariate analysis adjusted by age, body mass index, asthma control, blood eosinophil numbers, and FEV1% of predicted, a FeNO level of ≥40 ppb was independently associated with an accelerated decline in FEV1 ($p < 0.05$).
Conclusions: This study suggests that FeNO is potentially valuable tool for identifying individuals who are at risk of a progressive loss of lung function among patients with controlled asthma.

Introduction

Nitric oxide (NO), a gaseous signaling molecule generated by NO synthase (NOS), is enhanced by inflammatory stimuli.[1] The exhaled nitric oxide fraction (FeNO) has been proposed as a marker of airway inflammation and a guide for anti-inflammatory therapy in asthma.[1–3] However, a persistently high FeNO is occasionally observed despite steroid therapy in some patients.[4,5] Excessive NO synthesis is well documented in severe asthma[6,7] and a European multicenter study suggested that the FeNO levels of patients with severe asthma, who are refractory to conventional treatments may not be suppressed by corticosteroids.[8] Importantly, this large study showed that the mean FeNO levels of patients with severe asthma are similar to those of patients with non-severe asthma.[8] Also, the analysis of data from a Severe Asthma Research Program demonstrated that 40% of the study subjects had FeNO levels of >35 ppb regardless of the severity of asthma.[4] The grouping of asthma by FeNO has now been proposed to provide an independent classification of the asthma severity.[4]

Recent evidence suggests that airway inflammation may play an important role in the progression of airflow limitation in asthma.[9–13] Cross-sectional studies that targeted patients with severe asthma have shown associations between persistent airflow limitation and eosinophilia in blood,[9] sputum,[10] and bronchial tissues.[11] Also, some longitudinal studies reported that the baseline sputum eosinophil numbers and FeNO could predict a decline in forced expiratory volume in 1 s (FEV1) in asthmatic patients with fixed airflow limitation.[12,13] To identify patients who are at risk of a

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rapid loss of lung function at an early stage of asthma is important. However, it remains unclear whether a persistently high FeNO in patients with controlled asthma is associated with the progressive loss of lung function.

In a 3-year prospective cohort study, we recently reported that the annual rate of change in FEV1 among patients with well-controlled asthma was highly variable and the rapid decliners were more likely to have higher levels of FeNO at baseline.[14] In this subsequent analysis, we first determined the FeNO cut-off point for identifying patients with an accelerated decline in FEV1. Next, the patients who maintained high or non-high FeNO were selected, and the associations between the FeNO trend and changes in FEV1 and bronchodilator response (BDR) were investigated.

Methods

Study design and patients

This was a stratified analysis of a prospective cohort study. The study subjects were followed with Asthma Control Test (ACT), spirometry, and FeNO every 3 month over a 3-year period. The use of asthma controllers within 24 h before an examination was prohibited for all study visits. Blood eosinophil numbers and serum specific immunoglobulin E (IgE) for common inhaled allergens (house dust mite, cedar, ragweed, cocksfoot, dog, and cat) were examined. Positive specific IgE to at least one allergen was assumed to confirm the presence of atopy. The study was approved by the Ethics Committee of Wakayama Medical University (IRB #526) and registered with the University Hospital Medical Information Network (UMIN 000012105).

250 Adults with stable asthma following treatment with inhaled corticosteroids (ICS) with or without long-acting β2-agonist, leukotriene modifier, or theophylline for more than 4 years were recruited from the outpatient clinic of Wakayama Medical University Hospital. Current smokers and patients with >10 pack-year smoking history were excluded from the study. Also, patients with poor adherence to therapy (defined as <80% adherence calculated by dividing the number of days supplied for a medication by the number of days between the visits) or with other pulmonary diseases such as COPD were not included. All patients had a history of episodic dyspnea, wheezing, and documented significant airway reversibility and/or airway hyperresponsiveness. The changes in FEV1 before and 15 min after inhalation of 400 μg of salbutamol were measured to assess BDR. Airway reversibility is regarded as significant when FEV1 is increased by ≥12% and ≥200 mL of the absolute volume. Airway responsiveness to methacholine was measured using a device (Astograph; Chest, Tokyo, Japan) that displays respiratory resistance measured via the forced oscillation method. Airway hyperresponsiveness was defined as the cumulative provocative dose of methacholine causing a 100% increase in the baseline respiratory resistance of less than 25 mg/mL. In this analysis, 140 patients with controlled asthma aged over 25 years old were selected based on the GINA guidelines (twice or less/week daytime symptoms, no nocturnal symptoms, no limitation of daily activities, twice or less/week need for reliever, normal lung function (≥70% FEV1/FVC ratio and ≥80% FEV1% of predicted), no exacerbation in the previous one year).[1] The flow diagram of the study is shown in Figure 1. Informed written consent was obtained from each participant.

Study assessments

The FVC and FEV1 values were measured using a dry rolling seal spirometer. The post-bronchodilator FEV1 was selected to reflect loss of lung function as in other studies following lung function in patients with asthma.[14,15] The mean annual rates of changes in FEV1 and BDR over a 3-year period were estimated for each subject by fitting a least-square regression line. The random slope was based on time of FEV1 assessment. In total, 3168 FEV1 measurements were analyzed excluding lung function data during periods of worsening asthma (4 weeks before and 4 weeks after the start of a severe exacerbation, defined as worsening asthma requiring at least 3 days treatment with systemic corticosteroids or as a hospitalization due to asthma).[16] Based on the magnitude of change in FEV1 over a 3-year period, we labeled those of less than the 25th percentile as rapid decliners. All rapid decliners had an estimated rate of decline in FEV1 of more than 40 mL/yr. The FeNO was measured by an online NO analyzer (NIOX MINO; Aerocrine, Solna, Sweden). Repeated exhalations were performed to obtain two acceptable measurements that agreed within 10% deviation, and the average of these two values was registered.[1,17]

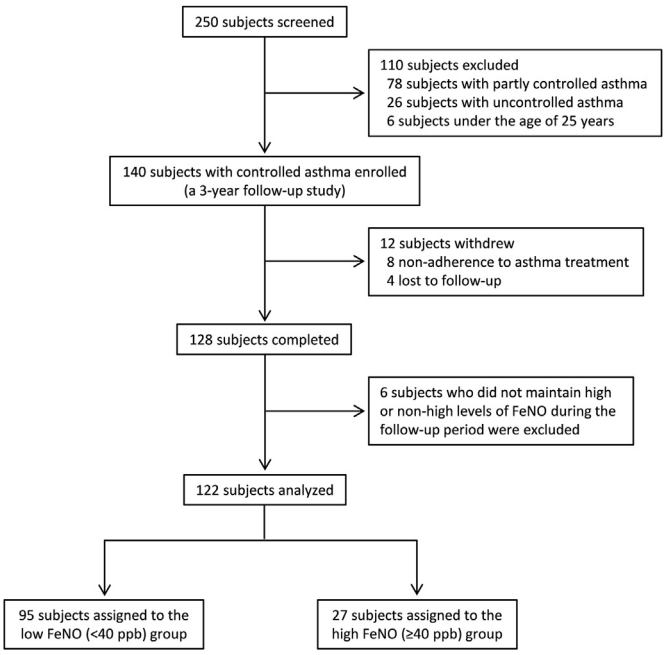

Fig. 1. Disposition of the study patient population.

Statistical analyses

We dichotomized the subjects into two groups based on the FeNO levels. The receiver operating characteristic (ROC) analysis was used to find a cut-off value for FeNO that would identify patients with a rapid decline in FEV1. The clinical characteristics were compared using the Chi-squared test for categorical variables, and unpaired *t*-tests or Mann–Whitney *U* tests as appropriate for continuous variables. Chi-squared test and multivariate logistic regression analysis were used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for rapid loss of FEV1. The variables with *p* values <0.20 in the univariate analysis were included in the multivariate model. All data were expressed as mean values ± standard deviation for continuous variables. For categorical variables, the numbers of observations were given in each category. A *p* value of <0.05 was considered statistically significant.

Results

The 3-year follow-up study was completed in 128 patients (Fig. 1). A FeNO level >40.3 ppb yielded 43% sensitivity and 86%