http://dx.doi.org/10.4046/trd.2011.71.2.106
ISSN: 1738-3536(Print)/2005-6184(Online)
Tuberc Respir Dis 2011;71:106-113

Original Article

Relationship between Exhaled Nitric Oxide and Levels of Asthma Control in Asthma Patients Treated with Inhaled Corticosteroid

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Background: While asthma control is defined as the extent to which the various manifestations of asthma are reduced by treatment, current guidelines of asthma recommend assessment of asthma control without consideration of airway inflammation. Our aim was to investigate the relationships between fractional exhaled nitric oxide (FeNO), a reliable marker of airway inflammation, and levels of asthma control in patients treated with inhaled corticosteroids (ICS).

Methods: We enrolled 71 adult patients with asthma who had been treated with ICS for more than four months. FeNO was measured and spirometry was performed at the time of enrollment. Asthma control was assessed (a) by the physician based on the Global Initiative for Asthma guidelines, (b) by the patients, and (c) by using the Asthma Control Test (ACT). Statistical analyses were done to analyze the relationships between (i) FeNO and (ii) measures of asthma control and clinical indices for asthma manifestations.

Results: There was no significant difference in FeNO levels between the three groups according to levels of asthma control (controlled, partly controlled and uncontrolled) as determined by the physician (p=0.81), or by the patients (p=0.81). In addition, FeNO values were not significantly correlated with the ACT scores (r=0.031, p=0.807), while FeNO showed a correlation with peripheral blood eosinophil counts ($p<0.001$).

Conclusion: These findings demonstrate that FeNO levels are not associated with measures of asthma control in patients treated with ICS. Information on airway inflammation from FeNO concentrations seems to be unrelated to levels of asthma control.

Key Words: Nitric Oxide; Asthma; Corticosteroids

Introduction

Guidelines for asthma management say that the purpose of treatments for asthma is its complete control and stepwise treatments of asthma is recommended to be decided by the level of asthma control[1,2]. The strategy of evaluating the control level of asthma and aiming better control has been proved to be effective in achieving complete control in most patients[3]. Asthma control is now defined as the decreased manifestations of various features of asthma such as symptoms, airway obstruction, airway hyperresponsiveness and airway inflammation after treatments. Therefore, there are many markers of asthma and their correlation does not correspond certainly, so each marker should be investigated to evaluate the control level. Global Initiative for Asthma (GINA) suggests the assessment of the level of asthma control by dividing it into three levels - well controlled, partly controlled and uncontrolled ones. In addition, many questionnaires like Asthma Control Test (ACT)[4] and Asthma Control Questionnaire (ACQ)[5] were developed and have been used as scoring systems for

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Received: Jun. 9, 2011
Accepted: Jul. 7, 2011

the evaluation of asthma control. However, the current assessment of asthma control does not include the evaluation of airway inflammation, which is an important aspect of asthma. Therefore, asthma management based on the assessment following the current guidelines or using the current questionnaires such as ACT, can be a limited approach not considering airway inflammation.

Fractional exhaled nitric oxide (FeNO) concentration is useful as an index of airway inflammation in asthma patients[6]. In particular, it is helpful in diagnosing asthma and in predicting and evaluating treatment response and it is invasive and highly reproducible as advantages[7]. Moreover, it is known that the asthma management strategy of regulating inhaled corticosteroid dosage based on FeNO is effective to some degree in reducing the total inhaled corticosteroid dosage[8]. However, guidelines for asthma management including GINA consider pulmonary function or an index of airway obstruction importantly but do not reflect FeNO or an index of airway inflammation, in the assessment of the asthma control which is critical to its management. It is still controversial whether FeNO is significantly related with the asthma control as a concept for comprehensive assessment of asthma[9-15]. This study aims to investigate the correlation between FeNO and the level of asthma control in patients treated for asthma. The authors measured FeNO and assessed the level of asthma control to analyze the correlation between FeNO and the level of asthma control and between FeNO and various asthma markers such as pulmonary function in adults with asthma treated with inhaled corticosteroid.

Materials and Methods

1. Subjects

This study recruited asthma patients aged over 18 years treated by asthma specialists and it prospectively registered patients who had been treated continuously with medications including inhaled corticosteroid for at least four months. Asthma was diagnosed based on the decision of asthma specialists and it was confirmed in the cases of airway hyperresponsiveness observed in methacholine bronchial challenge test (PC_{20} < 16 mg/mL) or response to short acting beta 2 agonist (12%, increase of basal forced expiratory volume in one second [FEV_1] by over 200 mL) along with asthma symptoms. Patients with chronic obstructive pulmonary disease, history of smoking of over 10 pack-years or acute respiratory infection or deterioration of asthma for the last four weeks, were excluded. This study registered the patients who visited Hanyang University Guri Hospital from June 2009 to May 2010, met the inclusion criteria and agreed to participate in this study. The study was conducted after obtaining the approval of Institutional Review Board of Hanyang University Guri Hospital.

2. FeNO measurement

At the date of registration, FeNO was measured by following ATS/ERS recommendations[16]. As mentioned before, the measurement was conducted with Sievers NOA280i (GE Analytical Instruments, Boulder, CO, USA) before pulmonary function test[17]. The subjects did not take any food except water within one hour to the measurement not to influence FeNO and maintained a stable condition with not exercising. In addition, to avoid the effect of high nitric oxide level on the nasal cavity during the measurement, the patients breathed out to the resistance of 10 cm H_2O through a mouthpiece continuously for over six seconds in a sitting posture to block the velophayngeal aperture. Expiratory flow rate was 50 mL/s and the mean of three FeNO concentrations within 10% of the difference among them was calculated to be used as a representative value.

3. Pulmonary function test and skin prick test

FVC and FEV_1 were measured with forced expiration by using a spirometer (Erich Jaeger, Hoechberg, Germany) based on the ATS/ERS recommendations. Among the three values meeting the criteria the highest one was chosen. To evaluate the atopic status of the patients, skin prick test was conducted with 53 common inhalant allergens including house dust mite (Allergopharma, Reinbek, Germany). Wheal and flare reactions were ex-

amined in 15 minutes of skin prick. When the size of wheal was same with or larger than that of histamine, it was decided to be positive. Being positive to one or more antigens was defined as atopy.

4. Assessment of asthma control

The level of asthma control was assessed at the same day of FeNO measurement. The level was determined with 1) physician assessment, 2) self-assessment and 3) ACT-based assessment. Physician assessment classified the control level into 'well-controlled', 'partly controlled' and 'uncontrolled' based on GINA guideline. When physicians evaluated the level of asthma control, they were not allowed to know FeNO concentrations of patients. For self-assessment, the patients answered one of "1) well controlled, 2) partly controlled and 3) not controlled well" to a question, "how do you think your asthma is controlled?" Lastly, the patients filled in Korean-version ACT[18] by themselves and the ACT score was obtained by adding the scores of totally five questions answered with on to five points.

5. Statistical analysis

As FeNO concentrations do not have a normal distribution, they were converted into log values for statistical analysis. The FeNO concentrations by groups by the level of asthma control were compared with Kruskall-Wallis test and the correlation of FeNO with continuous variables such as ACT score, FEV_1, peripheral blood eosinophil count and total serum IgE was analyzed with Pearson's correlation analysis. All statistical analysis was performed with SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) and a p-value of less than 0.05 was considered to be statistically significant.

Results

1. Characteristics of subjects

During the study period, totally 71 asthma patients were registered. All of them were Korean and 35 ones (49.3%) were males. The median age was 49 years (interquartile range, 41～60) (Table 1). Chronic rhinitis was associated in 62 (87.3%) patients and atopy was found in 25 (53.2%) ones. All patients used inhaled corticosteroid and 62 (87.3%) did additional agents for asthma control.

2. Correlation between FeNO and asthma control

In physician assessment of the level of asthma control, 34 (47.9%), 19 (26.8%) and 18 (25.4%) out of the 71 patients were classified as 'well controlled', 'partly controlled' and 'uncontrolled' groups, respectively. The medians of FeNO (interquartile range) of the groups recorded 30.9 (46.2), 32.6 (15.8) and 38.7 (32.1) ppb, respectively. Although the FeNO concentration of the uncontrolled group tended to be higher, the difference among the groups was not significant (Figure 1A). Self-assessment and ACT-based assessment were conducted by 63 (88.7%) patients. The self-assessment found that the level was 'well controlled', 'partly controlled' and 'uncontrolled' in 39 (61.9%), 17 (27.0%) and 7 (11.1%) patients, respectively and the medians of FeNO (interquartile range) of the three groups were not significantly different by recording 31.1 (41.1), 30.4 (20.2) and 31.3 (30.2) ppb, respectively. The correla-

Table 1. Characteristics of the subjects

Variables	Findings (n=71)
Age*, yr	49 (41～60)
Male, n (%)	35 (49.3)
Height, cm	162.8±8.6
Weight, kg	63.0±11.1
Body mass index, kg/m^2	23.7±3.4
Chronic rhinitis, n (%)	62 (87.3)
Smoking, n (%)	
Never smoker	38 (65.5)
Ex-smoker	14 (24.1)
Current smoker	6 (10.3)
Skin prick test positivity, n (%)	25 (53.2)
Serum total IgE, IU/U	455.8±538.5
FEV_1, % predicted value	90.6±20.7
FEV_1/FVC, %	70.0±11.9

Values are presented as mean±SD unless otherwise indicated.
*Values in parenthesis are interquartile range.
SD: standard deviation; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

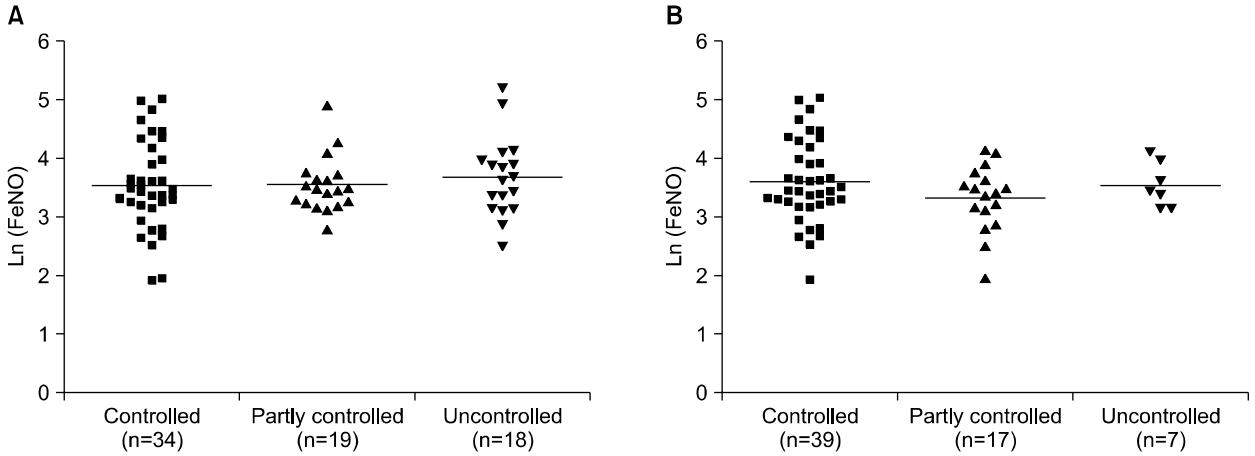

Figure 1. FeNO concentrations according to the level of asthma control. (A) Physician-assessed asthma control based on GINA guideline. (B) Self assessment of asthma control by the patients with asthma. FeNO: fractional exhaled nitric oxide; GINA: global initiative for asthma.

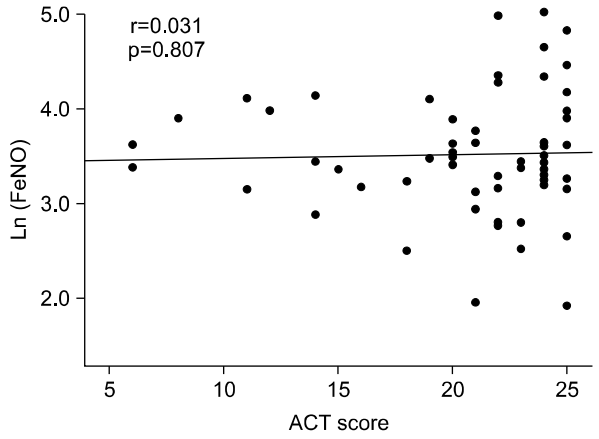

Figure 2. Correlation between ACT score and FeNO. ACT: asthma control test; FeNO: fractional exhaled nitric oxide.

tion between ACT score and FeNO also was not significant (r=0.031, p=0.807) (Figure 2).

3. Correlation between FeNO and various asthma markers

It was investigated whether FeNO, an index of airway inflammation, is related with markers of asthma such as atopy, the degree of airway obstruction and eosinophilie inflammation. The FeNO concentration of atopy patients was significantly higher than those of nonatopic subjects (median, 37.2 ppb vs. 29.2 ppb; p=0.042). Although FeNO did not show any correlation with FEV_1% value (r=0.038, p=0.754) (Figure 3A), its correlation with peripheral blood eosinophil count reflecting eosinophilic airway inflammation was significant (r=0.428, $p<0.001$) (Figure 3B).

Discussion

Asthma is presented in various manifestations including symptoms, airway obstruction, airway hyperresponsiveness, airway inflammation, limitations of daily activities, and acute exacerbation. Treatments for asthma aim to decrease all of these clinical manifestations. In asthma management, the assessment of the level of asthma control is very important to achieve this purpose and it provides critical basis to decide therapeutic steps for asthma[19]. However, the assessment suggested by the current guidelines for asthma management[1,2] examines various aspects at a same time, so it is complex and the correlation among asthma markers is not consistent. In addition, it does not reflect the degree of airway inflammation, which is an important characteristic of asthma. This study investigated the correlation between FeNO, an index of airway inflammation, and the level of asthma control and found that the level of asthma in physician assessment based on GINA, self-assessment of patients and ACT-based assessment was not related with FeNO. As FeNO showed a significant correlation

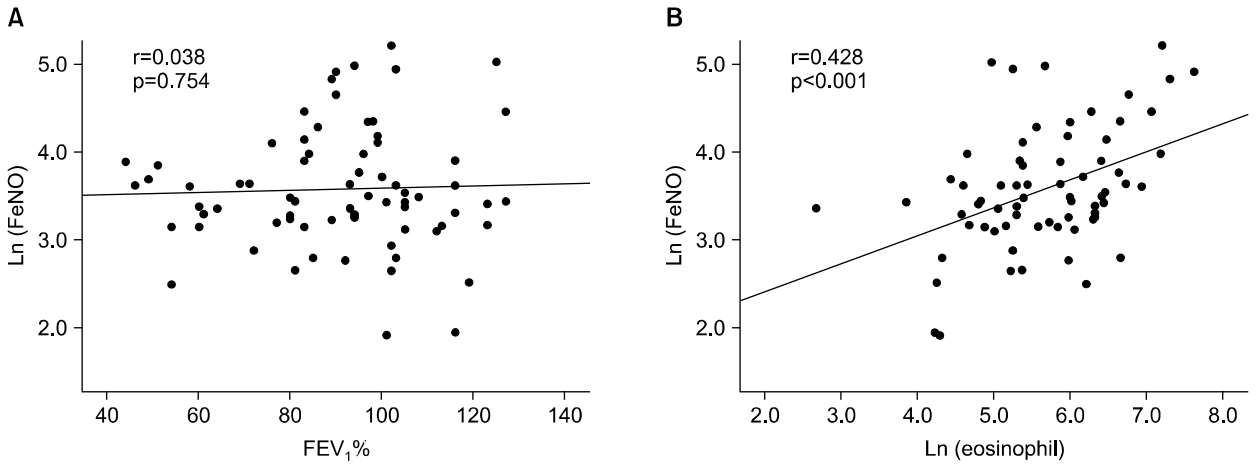

Figure 3. Correlation between FeNO and various markers of asthma manifestations. (A) FeNO and FEV_1. (B) FeNO and peripheral blood eosinophil count. FeNO: fractional exhaled nitric oxide; FEV_1; forced expiratory volume in one second.

with peripheral blood eosinophil count reflecting eosinophilic airway inflammation, it is considered to be a sensitive index of inflammation. But, its correlation with FEV_1 or an index of airway obstruction was not significant suggesting poor correlation of FeNO with lung function. These results mean that the overall condition of the asthma control cannot be determined only with FeNO concentration and that the level of asthma control cannot predict the degree of eosinophilic airway inflammation. That implies that indexes reflecting airway inflammation such as FeNO should be considered along with the current markers of the asthma control to assess the control including various aspects of asthma and to decide a phase of therapy.

Although some studies investigated the correlation of FeNO with the overall asthma control, the correlation has not been determined[9-15]. Sippel et al.[9] insisted that FeNO was related with asthma symptoms, the frequency of use of short acting bronchodilators and the response to bronchodilator in 100 children and adults with asthma, to reflect the asthma control but they did not confirm its correlation with the overall level of asthma control. Senna et al.[10] analyzed the correlation of FeNO with FEV_1, severity and ACT score in 27 patients aged 16～57 years newly diagnosed as asthma and found a significant correlation of FeNO with ACT and severity (r=0.69, p=0.001). However, the study included a small number of subjects and did not investigate the asthmatics on treatment but the patients who have not been diagnosed or treated, so it was technically hard to apply ACT to them. Moreover, it is difficult to evaluate the asthma control in the strict sense in patients having not been treated. Because the concept of the asthma control means the decrease of asthma manifestations following treatments, the asthma manifestations before treatments should be presented as severity rather than control[20]. ACT contains five questions answered with one to five points to record 5～25 points totally and it has been recognized as a useful and highly reproducible test to evaluate the asthma control[4]. Although the items of ACT include day time and night time symptoms of asthma, limits on activities of daily living, the frequency of use of short acting inhalants and self-assessment of the asthma control, it does not reflect pulmonary function, the degree of airway inflammation and the frequency of exacerbation. So, it has critical limitations to be considered as an index containing various aspects of asthma. Shirai et al.[11] reported that the correlation between FeNO and ACT score was statistically significant but the significance was weak in 105 adults with asthma using inhaled corticosteroid (r=−0.310, p=0.003).

However, current reports have revealed no correlation between FeNO and the level of asthma control. According to a study performed with 100 children and

adults with asthma aged 6～86 years in the U.S., FeNO did not show any significant correlation with scores of tests to evaluate the asthma control like ACT and ACQ and with markers to assess the asthma control based on the classification of guidelines such as GINA and EPR3[12]. The level of asthma control classified with other asthma control assessment tool or ACQ had no significant correlation with FeNO[13,14]. A recent study on adults with asthma in the U.S. and Spain, found that the correlation between ACT score and FeNO was significant in asthma patients without the experience of using inhaled corticosteroid in Spain but the significant correlation was not observed in patients with the experience in Spain and patients in the U.S.[15]. This difference was considered to be because the severity of the patients in the U.S. was higher than that of those in Spain and more patients utilized inhaled corticosteroid in the U.S populations. From all of these results, the possibility of no correlation between ACT and FeNO is likely to be large in patients treated with inhaled corticosteroid and previous inconsistent results are considered to be caused by the inclusion of both of patients before treatment and on treatment. To avoid these different effects of subjects, this study included only patients undergoing treatments whose asthma control could be assessed, by excluding patients before treatments. In this study, the asthma control was divided into three groups to analyze its correlation with FeNO and the level of asthma control in all of physician assessment based on GINA, self-assessment of patients and ACT-based assessment was not related with FeNO consistently. These results show that the indexes of the asthma control do not reflect airway inflammation or an important aspect of asthma fully and imply that additional FeNO measurement as well as the current asthma control evaluation can provide more information for asthma management.

A strategy evaluating the asthma control with markers such as asthma symptoms, pulmonary function and the frequency of exacerbation and changing the treatment steps based on the control level have been found to be effective in many clinical studies and they have been reflected in the current guidelines for asthma management, but some insist that the strategy is simplified to some degree and is limited because the current assessment of asthma control does not reflect airway inflammation[21]. Asthma is a heterogeneous disease with various clinical features and it can be classified by numerous phenotypes[22]. In particular, asthma can be divided by inflammatory cells of eosinophilic, neutrophilic and mixed inflammation and patients of each group show different clinical features and courses. Haldar et al.[23] described that asthma patients could be classified into group with significantly differentiated characteristics by the degree of symptoms and the degree of eosinophilic inflammation through cluster analysis. In cluster analysis with severe asthma patients included by a study of Severe Asthma Research Program (SARP), eosinophilic and neutrophilic inflammation was significant different in the five classified groups[24]. In addition, a treatment strategy guided by FeNO[25] and sputum eosinophilie[26,27] was proven to be effective in declining exacerbation and the use of steroid. Mepolizumab or an anti-IL-5 antibody, which is being studied in a clinical trial as a medication for asthma, did not produce a significant effect on asthma overall, but it was found to be effective in decreasing exacerbation and improving quality of life in severe asthma patients with eosinophilic inflammation[28,29]. This finding suggests that the evaluation of eosinophilic inflammation is useful in treating asthma patients and the assessment of airway inflammation should be added to the assessment of asthma control based on the current guidelines for asthma management. As an index of eosinophilic inflammation, FeNO measurement is non-invasive, highly reproducible and easy to measure and it is expected to be useful in not only selecting drugs for asthma and but also evaluating treatment response in the future.

In conclusion, FeNO, an index of eosinophilic airway inflammation, was not significantly related with the level of asthma control in adults with asthma treated with inhaled corticosteroid. This finding suggests that the current assessment of asthma control does not reflect the degree of airway inflammation and that measurement

to evaluate airway inflammation is needed in addition to the current assessment. Moreover, our findings imply that airway inflammation should be considered in the overall assessment of asthma control for treatment and management of asthma patients. In the future, prospective studies to determine the usefulness of the strategy evaluating both of the asthma control and the airway inflammation are needed.

Acknowledgements

This study was supported by a grant of the Korea Healthcare technology R&D Project, Ministry of Health and Welfare, Republic of Korea (A102065).

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