Is fractional exhaled nitric oxide (FeNO) associated with asthma control in children?

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Summary

Introduction: **The most important way to achieve and maintain asthma control is to reduce airway inflammation. Fractional exhaled nitric oxide (FeNO) levels have been used as a marker of airway inflammation.**

Objectives: **To evaluate the association between FeNO levels and the asthma control status in children.**

Methods: **This was a cross-sectional clinical trial in children with atopic asthma aged ≥ 7 years. The levels of asthma control were assessed by using the criteria from the GINA Guideline. FeNO levels and spirometry were measured. Asthma medications were recorded. The association between FeNO levels and asthma control status and the usage of asthma medications were analyzed.**

Results: **One hundred and fourteen asthmatic children aged 12.1 ± 3.5 years were recruited into the study. Most of the patients had mild persistent asthma (79.8%). The administration of inhaled corticosteroid (ICS) was reported in 82.4% of cases. According to the GINA Guideline, 34.2% of cases were controlled, 44.7% were partly controlled and 21.1% were uncontrolled. We found that there was no significant difference in the median FeNO levels in the controlled, partly controlled and uncontrolled groups [19.2 (95% CI 5.1-108.9), 24.9 (2.2-85.7), and 39.2 (2.4-192.3) ppb, respectively (p = 0.24)]. However, in 20 cases who did not receive ICS treatment, the median FeNO levels showed a significant difference among controlled, partly controlled and uncontrolled groups [31.8 (95% CI 11.1-108.9), 34.1 (5.3-81.8), 92.0 (46.3-192.3) ppb, respectively; p <0.05].**

Conclusions: **FeNO levels were increased in ICS-treated asthmatic patients with less asthma control, albeit with no statistically significance. However, FeNO levels correlated with poor asthma control status in ICS untreated cases.** ***(Asian Pac J Allergy Immunol 2014;32:218-25)***

Key words: *FeNO, asthma, airway inflammation, asthma control, spirometer*

Abbreviations

ACT = Asthma control test
FeNO = Fractional exhaled nitric oxide
GINA = Global initiative for asthma
ICS = Inhaled corticosteroids
LTRA = Leukotriene receptor antagonist

Introduction

Asthma is a chronic inflammatory airway disease characterized by recurrent bronchospasm, bronchial hyper-responsiveness and reversible airway obstruction. According to the global initiative for asthma (GINA) guideline[1] there are 3 levels of asthma control (controlled, partly controlled and uncontrolled asthma) classified by clinical characteristics (symptoms and exacerbation), limitation of activities and reduction in lung function test results. The gold standard for asthma treatment is to achieve and maintain asthma control, which requires the suppression of airway inflammation by inhaled corticosteroids.

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Recently, several self-administered questionnaires have been developed for the assessment of asthma control status in clinical practice by patients and/or parents. The asthma control test (ACT) for patients ≥ 12 years old includes 5 questions related to the frequency of asthma symptoms and the need for rescue medication use during the previous 4 weeks and is widely used for assessing asthma control in adults.[2] More recently, the pediatric (childhood) asthma control test (PACT) was developed.[3] These questionnaires have been validated in Thailand.[4]

Nitric oxide (NO) is pathologically synthesized by inducible nitric oxide synthase (NOS) in inflamed airway epithelial cells and eosinophils which are present in the airways of asthmatics. The endogenous nitric oxide in exhaled air was first demonstrated by chemiluminescence.[5] Fractional exhaled nitric oxide (FeNO) is increased in asthmatic patients.[6] Previous studies have demonstrated that there is a positive correlation between FeNO and the degree of eosinophilia in blood, sputum, bronchoalveolar lavage specimens, or bronchial mucosa.[7,8] Therefore, FeNO levels reflect eosinophilic airway inflammation and might be used for monitoring airway inflammation in asthma. In addition, a number of studies have suggested that FeNO levels might be beneficial as a test for diagnosing asthma,[9] predicting an exacerbation,[10] and adjusting maintenance doses of inhaled corticosteroids (ICS) in asthmatic patients.[7,11-12]

FeNO measurement is non-invasive, simple, repeatable, reproducible and safe. If the levels correlate well with clinical control of asthma, we could use it as guidance for adjusting treatment of childhood asthmatics. The data with regard to the association between FeNO levels and asthma control status has not been well described in Thai childhood asthmatics.

The aim of this study was to determine the correlation between FeNO levels and asthma control status, as defined by GINA guideline and ACT scores.

Methods

Study Design

This was a cross-sectional, clinical trial approved by the Siriraj Institutional Ethics Committee. The study was carried out during February to December 2010. Informed consent was obtained from all patients before enrollment into the study. On the day of inclusion, the demographic data of the patients, asthma severity, asthma control status, skin prick test positivity, environmental control data, previous medications usage and medications adherence were recorded on the case record form. Adequate environmental control and adequate inhalation technique were defined according to the GINA guideline.[1] The inhaled corticosteroid usage was divided into low, medium and high dose (compatible with Budesonide 200-400, >400-800 and >800-1600 micrograms respectively).[13] In females of reproductive age, a urine pregnancy test was done before performing the other procedures.

The patients were classified according to their different levels of asthma control (controlled, partly controlled and uncontrolled) according to GINA 2008.[13] ACT (asthma control test for patients ≥ 12 years old) or PACT (pediatric asthma control test for patients < 12 years old), FeNO and spirometry were performed.

Subjects

Male or female patients ≥ 7 years of age who were diagnosed with atopic asthma by clinical manifestations and positivity at least to one aeroallergen on skin prick testing (SPT) or the presence of specific IgE were enrolled. The allergic sensitization test was done using SPT for common aeroallergens (ALK, Port Washington, New York). Histamine dihydrochloride (10 mg/ml) and 0.9% saline solution were used as positive and negative controls, respectively. The test was considered positive if the wheal measured at 15 minutes was ≥ 3 mm. in diameter when compared with the reaction from negative control. Patients were excluded if they had a history of smoking, other serious systemic or chronic diseases, a respiratory tract infection within 6 weeks, pregnancy, systemic corticosteroid usage within 8 weeks, ethanol ingestion in the previous 48 hours or caffeine beverages ingestion during the day of enrollment.

Devices

FeNO was measured by means of an electrochemical technique (ECO medics, CLD 88 sp, chemiluminescence NO-analyzer with optional ultrasonic flow meter). This procedure, which was carried out according to the manufacturer's and American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations,[14] requires a single-breath on-line measurement with the mouthpiece in place. Subsequently spirometry was performed using the standard method.[15] The baseline and post-bronchodilator FEV_1 and FEV_1/FVC were expressed as absolute values and % of predicted values.

Statistical analysis

Qualitative variables data were expressed as percentages. Quantitative variables were expressed as means and standard deviations (SD) for parametric data and as median and minimum-maximum values for non-parametric data.

For comparison among groups with different statuses of asthma control and FeNO levels, ANOVA was used for log FeNO levels (parametric data) and the Kruskal Wallis test was used for absolute FeNO levels (non-parametric data). Multivariate regression analysis (Post-hoc tests) was also done (2 by 2 comparison). Student's T-test and the Mann-Whitney U test were used to compare FeNO levels and univariate factors between the groups as appropriate. Linear correlation between ACT scores and levels of FeNO were assessed with the Pearson coefficient for log FeNO level (parametric data) and the Spearmann coefficient for FeNO levels (non-parametric data). P values less than 0.05 were considered significant. The statistical analysis was performed using the SPSS version 16 software package for Windows (release 16.0; SPSS Inc., Chicago, IL, USA).

Results

One hundred and fourteen patients with mean age of 12.1 $\pm$ 3.5 years and 61.4% male participated in the study. Most of the patients had mild persistent asthma (79.8%) followed by moderate to severe persistent asthma (14.9%) and mild intermittent asthma (5.3%). According to the GINA guideline for asthma control status, 39 cases (34.2%) were controlled, 51 (44.7%) were partly controlled and 24 (21.1%) were uncontrolled. Fifty eight patients (50.9 %) were $\geq$ 12 years old. The demographic data of the 114 asthmatic children studied, categorized accordingt to the level of asthma control, are shown in Table 1. The median ACT scores in patients $\geq$ 12 years old was 22 (minimum 15, maximum 25) and < 12 years old was 25 (minimum 15, maximum 28). Most of the subjects were classified in the partly controlled group according to ACT scores.

The majority of the patients had a history of allergic rhinitis (AR, 99.1%). The prevalence of allergic conjunctivitis was significantly higher in those with uncontrolled asthma than the remaining groups (p =0.029). The number of cases of uncontrolled asthma with AR symptom presentations (95.5%) was also significantly greater than that in the two other groups (p =0.011). There were no significant differences in sex, age, duration and onset of asthma, body mass index and prevalence of atopic dermatitis, food allergy and drug allergy among those with different asthma control statuses.

The number of patients with positive skin prick tests (SPT) to *Dermatophagoides pteronyssinus (Dp)* and *Dermatophagodes farina*e *(Df)* in the uncontrolled group was statistically significantly higher than in the other groups (p value=0.029). However, we found no significant differences in SPTs for other allergen extracts from pets (cat, dog), American cockroach, German cockroach, grass *(Bermuda* grass, *Johnson* grass), mold (*Cladosporium*, *Alternaria*) and food (cow's milk, egg white, egg yolk, wheat, and seafood) among the groups. Subjects in the uncontrolled asthma group had significantly lower FEV_1 and PEFR (% predicted, pre-bronchodilator) results than those in the other groups ($p < 0.001$ for FEV_1 and =0.015 for PEFR).

Most of the patients (82.5%) had received inhaled corticosteroids prior to enrollment. Administered ICS dose (micrograms equivalent to budesonide)/day in the uncontrolled group was significantly greater than the partly controlled and controlled groups (p = 0.002). There was no significant difference in the types of ICS device (MDI, MDI with spacer, DPI) among the 3 groups (p = 0.417). Other concomitant medications were antihistamine (94.7%), intranasal corticosteroids (84.2%), leukotriene receptor antagonist (LTRA) (11.4%) doxophylline (2.6%) and allergen immunotherapy (7%).

There were statistically significant differences in environmental control (p <0.001) and inhalation technique (p = 0.032) among the 3 groups. The controlled asthma group had a higher percentage of adequate environmental control than the partly controlled group and the partly controlled group had a higher percentage of adequate environmental control than the uncontrolled group (p <0.001). The controlled and partly controlled groups tended to have more compliance to controller medications than the uncontrolled group (p = 0.057). The uncontrolled group needed more demonstration time to master the correct inhalation technique and gain understanding of appropriate environmental control.

Fractional exhaled nitric oxide and asthma control status

The FeNO levels and log FeNO in patients with different asthma control status as defined in GINA guideline are shown in Figure 1. The median FeNO level in the uncontrolled group was 39.15 (2.40-192.30) ppb, which was higher than the partly controlled group [24.90 (2.20-85.70) ppb], and the

Table 1. The demographic data for 114 asthmatic children categorized by the level of asthma control according to the Global Initiative for asthma (GINA) Guideline.

	Total N=114	Controlled N=39 (34.2%)	Partly controlled N=51 (44.7%)	Uncontrolled N=24 (21.1%)	*P* value
- Age *(yr)	12.13±3.50	12.62± 4.05	11.89± 2.93	11.86± 3.72	0.568
- BW*(kg)	44.65±16.20	44.57± 17.99	45.57± 15.70	42.85±14.60	0.797
- Height*(cm)	146.31±15.52	145.30± 15.50	148.42±15.73	143.51± 15.14	0.393
- BMI*(kg/m^2)	20.21±4.65	20.35± 5.46	20.09± 4.17	20.26 ±4.36	0.393
Sex; n (%)					
- Male	70 (61.4)	27 (69.2)	33 (64.7)	10 (41.7)	0.075
- Female	44 (38.6)	12 (30.8)	18 (35.3)	14 (58.3)	
Age group; n (%)					
- < 12 yrs	58 (50.9)	20 (51.3)	24 (47.1)	12 (50)	0.920
- ≥ 12 yrs	56 (49.1)	19 (48.7)	27 (52.9)	12 (50)	
Caregiver; n (%)					
- Mother	97 (85.1)	34 (87.2)	46 (90.2)	17 (70.8)	
- Father	10 (8.8)	4 (10.3)	3 (5.9)	3 (12.5)	0.123
- Other	7 (6.1)	1 (2.6)	2 (3.9)	4 (16.7)	
Other allergic history; n (%)					
- Allergic rhinitis	113 (99.1)	39 (100)	50 (98)	24 (100)	0.536
- Food allergy	12 (10.5)	5 (12.8)	4 (7.8)	3 (12.5)	0.702
- Atopic dermatitis	8 (7)	1 (2.6)	4 (7.8)	3 (12.5)	0.536
- Allergic conjunctivitis	46 (40.4)	9 (23.1)	20 (39.2)	17 (70.8)	0.029
- Drug allergy	9 (7.9)	2 (5.1)	4 (7.8)	3 (12.5)	0.538
Presentation of AR symptoms; n (%)	73/102 (71.6)	20 (58.8)	32 (69.6)	21 (95.5)	0.011
Environmental control; n (%)					
- Adequate	45 (39.5)	25 (64.1)	16 (31.4)	4 (16.7)	<0.001
- Inadequate	69 (60.5)	14 (35.9)	35 (68.6)	20 (83.3)	
Inhalation technique n; (%)					
- Adequate	91 (79.8)	35 (89.7)	41 (80.4)	15 (62.5)	0.032
- Inadequate	23 (20.2)	4 (10.3)	10 (19.6)	9 (37.5)	
Compliance; n (%)					
- ≥ 80%	71 (62.3)	30 (76.9)	29 (56.9)	12 (50)	0.057
- < 80%	43 (37.7)	9 (23.1)	22 (43.1)	12 (50)	
Inhaled corticosteroid usage; n (%)					
-yes					
-no	94 (82.5)	30 (76.9)	43 (84.3)	21 (87.5)	>0.05
	20 (17.5)	9 (23.1)	8 (15.7)	3 (12.5)	
Asthma information					
- Duration of asthma* (yr)	8.47± 3.47	9.16± 3.66	7.97± 2.94	8.42± 4.12	0.273
- Onset of asthma** (yr)	3.00 (0.25, 12.00)	3.00 (0.34,10.00)	3.00 (0.25, 12.00)	3.00 (0.36, 10.00)	0.840
- FEV1*(% pre-bronchodilator)	82.23± 11.11	87.90± 10.91	80.06± 10.80	80.06 ±10.8	<0.001
- PEFR*(%pre-bronchodilator)	85.82±18.15	91.08± 14.73	80.47± 19.53	80.47±19.53	0.015
- ICS dose** (µg equivalent to budesonide)/day	200 (0, 1200)	100 (0,400)	200 (0,800)	260 (0,1200)	0.002

* Mean±SD

** Median (minimum, maximum)

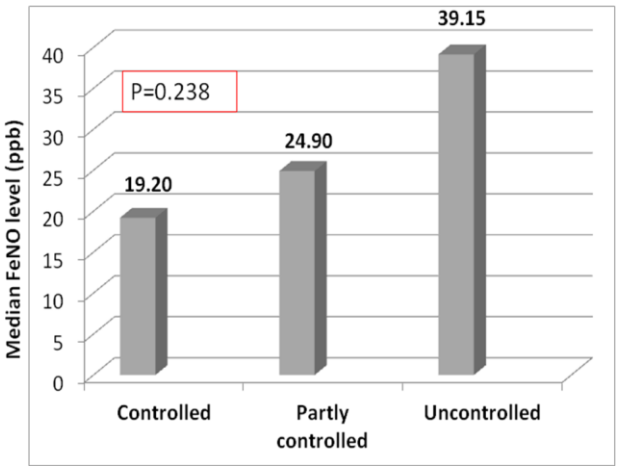

Figure 1. The median fractional exhaled nitric oxide (FeNO) levels in patients with different asthma control status according to GINA guideline

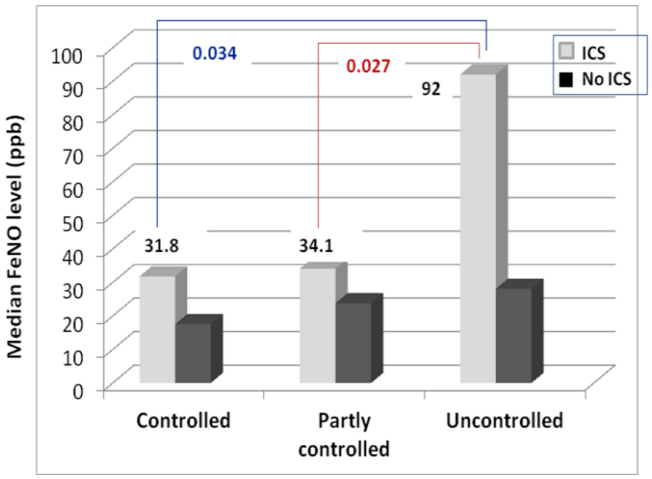

Figure 2. Fractional exhaled nitric oxide (FeNO) levels and the usage of inhaled corticosteroid (ICS) in different asthma control status according to GINA guideline

controlled group [19.20 (5.10-108.90) ppb], albeit without statistical significance (p = 0.238). Similarly, the mean±SD of Log FeNo was 1.295±0.31 in controlled group, 1.298±0.41 in partly controlled group and 1.417±0.49 in uncontrolled group, all of which differences were not statistically significant (p =0.458).

When we performed a subgroup analysis of the patients who were not treated with ICS, we found 20 cases who had never been treated with ICS (9 in controlled, 8 in partly controlled and 3 in uncontrolled groups). There was a significant difference in median FeNO level in uncontrolled group compared with controlled and partly controlled groups [92 (46.30-192.30) ppb *vs* 31.8 ppb (11.10- 108.90), p = 0.034; 92 (46.30-192.30) ppb *vs* 34.1 ppb (5.30-81.80), p = 0.027, respectively] (Figure 2). By contrast, in ICS-treated patients, there was no significant difference in the median FeNO levels in uncontrolled group compared with controlled and partly controlled groups (28.10 ppb (2.40-92.60) *vs* 17.55 ppb (5.10-88.20) and *vs* 23.80 ppb (2.20-85.70), p = 0.145 for multiple comparison).

We also found no significant correlation both between FeNO levels and ACT scores in both groups (≥ 12 and < 12 years old groups) and between FeNO levels and pulmonary function parameters. By contrast, FeNO levels inversely correlated with ICS dose (r = - 0.186 and p = 0.048). In both groups of patients treated with ICS and untreated with ICS, the median FeNO levels were not significantly different among different asthma control statuses, as defined by ACT (p = 0.163 and 0.921 respectively).

The median FeNO levels were 20.70 ppb (4-88.2) in the group using low dose ICS, 24.90 ppb (5.10-85.70) in medium dose ICS and 12.10 ppb (2.20-92.60) in high doses ICS. These differences are not no statistically significant (p = 0.362).

By univariate analysis, factors that significantly affected FeNO levels (Table 2) included nasal swelling, allergic rhinitis symptoms, compliance with controller medications, using ICS or montelukast as controller and types of ICS devices. Patients treated with ICS via metered dose inhaler (MDI) with a spacer had lower median FeNO levels (9.40 ppb) than those treated with ICS via MDI without a spacer (26.45 ppb). Multiple regression analysis demonstrated that FeNO levels were affected by LTRA, ICS via MDI with a spacer and the use of a dry powder inhaler (DPI); (p =0.042, <0.001 and 0.032, respectively).

Discussion

The present study demonstrates that there is no significant difference in FeNO levels between childhood asthmatic patients with different asthma control status during ICS treatment, although FeNO levels in uncontrolled asthmatic children are higher than those with controlled and partly controlled asthma.

Airway inflammation is a hallmark of asthma. Objective measurements of airway inflammation, such as FeNO as inflammometer, may lead to

Table 2. Factors that affected fractional exhaled nitric oxide (FeNO) levels (univariate analysis)

Factors		FeNo (ppb) Median (Min, Max)	P value	Log FeNO (ppb) Mean (SD)	*P* value
Swelling of nose					
- Mild		19.10 (2.20, 108.90)	0.036	1.25 (0.41)	0.029
- Marked		26.20 (2.40, 192.30)		1.42 (0.35)	
Symptoms of AR					
- Yes		26.10 (2.40, 192.30)	0.041	1.37 (0.38)	0.046
- No		17.20 (2.20, 108.90)		1.20 (0.41)	
Compliance with controller					
- ≥ 80%		17.90 (2.20, 92.60)	0.004	1.23 (0.39)	0.002
- < 80%		28.10 (5.30, 192.30)		1.47 (0.37)	
Controller medication					
-ICS*	Yes	19.90 (2.20, 92.60)	0.004	1.27 (0.39)	0.003
	No	37.90 (5.30, 192.30)		1.56 (0.37)	
-LTRA**	Yes	12.90 (3.00, 92.60)	0.039	1.10 (0.44)	0.035
	No	25.30 (2.20, 192.30)		1.35 (0.39)	
Number of different controller medications used					
- 0		46.30 (5.30, 192.30)	0.007	1.60 (0.38)	0.006
- 1		20.45 (2.20, 88.20)		1.29 (0.38)	
- ≥2		17.60 (3.00, 92.60)		1.21 (0.43)	
Device ICS					
- Not use		41.20 (5.30, 192.30)	<0.001	1.59 (0.36)	<0.0001
- Metered dose inhaler		26.45 (6.00, 88.20)		1.40 (0.37)	
- Metered dose inhaler with spacer		9.40 (2.20, 63.90)		1.02 (0.39)	
- Dried powder inhaler		24.40 (2.40, 92.60)		1.34 (0.35)	

*ICS = Inhaled corticosteroids
** LTRA = Leukotriene receptor antagonist

improved management of the disease. FeNO is particularly attractive for usage in children and daily clinical practice because it is noninvasive, reproducible, provides real-time results and has a standardized method for its use.[7] FeNO measurement has shown potential promise as a noninvasive tool for use in prediction of persistent wheezing[15] and the diagnosis of asthma in preschool children.[16] Measurement of FeNO has also shown potential utility in guiding anti-inflammatory therapy in both adults[12] and children with asthma.[11]

Many studies that investigated the role of FeNO in guiding treatment in asthma found that there was no reduction in the frequency of exacerbations based on the use of this parameter.[11-12,17] Moreover, there are conflicting data on whether the daily dose of ICS could be reduced when using FeNO as a tool for guiding asthma therapy.[12,17] Thus, although FeNO certainly has shown some promise as a biomarker in asthma diagnosis and therapy, many questions remain, especially the association with asthma control and its role in daily clinical practice.

When we subcategorized the patients according to the use of ICS, we found statistically significant difference between controlled and uncontrolled groups and between partly controlled and uncontrolled groups. So FeNO level can be an inflammatory marker to assess control status in asthmatic children who had never used ICS before. A previous study showed that ICS dramatically reduced FeNO levels in asthmatic patients.[18] The majority of our subjects were on ICS, which might explain why FeNO was not useful for predicting asthma control in our study. This was supported by a previous study in unselected non-smoking asthmatic patients.[19] The study showed that a single measurement of FeNO was not a good reflection of asthma control, particularly in patients on medium to high dose corticosteroids.[19] FeNO levels was not significantly correlated with the level of control as

assessed by ACT, both with or without ICS usage. This was supported by previous studies that showed no significant association between FeNO levels and ACT scores.[20-21] These studies also showed that the authors preferred clinical scores to FeNO level in predicting a change in asthma therapy when assessing asthma control.[21-22]

The study by Khailii, et al.[20] showed that up to 38% of patients with appropriately controlled asthma had FeNO > 35 ppb. These cases could have persistent subclinical inflammation of the airways that could subsequently cause problems.

Many factors were found to correlate with FeNO levels such as atopy[23] and age.[24] Levels of FeNO in childhood are also known to increase with age.[24] The factors that influenced FeNO levels in our study were swelling of the nose, symptoms of allergic rhinitis, compliance with controller medications, ICS usage, montelukast usage and the device used to deliver ICS. These findings are supported by previous studies which showed that ethnicity, previous treatment with ICS[23] and other controllers (eg. LTRA),[25] diet, and co-morbidities (allergic rhinitis, eczema, atopic status)[26] influenced FeNO levels. These factors could also modify the relationship between the FeNO measurement and asthma control status, ACT scores and pulmonary function test results.

Our study showed that the patients who used MDI with a spacer had lower FeNO values than those using MDI alone. The effect of device used to deliver ICS could be explained by the dose of ICS that patients received. This finding demonstrates that MDI with a spacer is the most appropriate device for children being treated with ICS. FeNO levels also tended to be lower in the patients with good treatment compliance who used ICS properly.

A recent study has shown that longitudinal changes in FeNO could be a reliable marker of asthma control in unselected asthmatic patients, especially in those patients treated with low doses of ICS.[19] It would be of interest to assess the longitudinal changes of FeNO in predicting the adjustment of asthma therapy and change of control status over time.

Our study showed weak correlation between PACT scores and FeNO levels ($r = 0.22$, $p = 0.871$) and no correlation between ACT scores and FeNO levels ($r = -0.17$, $p = 0.211$). These findings are supported by those of previous studies.[20] A previous study showed that FeNO levels correlate with ACT scores (in ACT for $\geq$ 12 years old) and post hoc analysis showed significant differences in FeNO value between patients whose ACT scores were $\leq$18 and $\geq$ 21.[22] The author of that study concluded that ACT showed a good relationship with therapeutic decisions made by specialists, even higher than those of functional tests or FeNO. There was a discrepancy between ACT scores and physician assessment when evaluating asthma control in their study and it was thought to be due to hypo-perception of patients symptoms.

The reference value of FeNO has been reported in children and adults in western country but not in Asia. [27] In addition, whether FeNO is of value in monitoring asthma in Asians is currently unknown. Previous studies in a paediatric Chinese population found that the FeNO values were higher than those of Caucasians.[28] In Thailand, there is also lack of good reference data for FeNO values, both in adults and in the pediatric population. Further research is needed to assess whether the Thai population also has higher FeNO values than Caucasians or not.

Asthma has different phenotype expressions. Each phenotype expression may have different control parameters. FeNO may be useful in evaluation of patients with eosinophilic airway inflammation but may not be useful in the patients with neutrophilic airway inflammation and in those with a mixed type. It is necessary to combine many measurements (functional, bronchial hyper-reactivity, FeNO level and clinical questionnaire results) for a complete assessment of the asthma control status in each patient, since asthma is a multifaceted disease. Individual baseline FeNO with longitudinal levels may provide much more valuable infromation than single measurements in the evaluation of asthma control status.

Conclusion

FeNO levels were increased in ICS-treated asthmatic patients with less asthma control, albeit without statistically significance. However, FeNO levels correlated with poor asthma control status in ICS untreated cases.

Acknowledgements

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Conflicts of interest

The authors have no conflicts of interest.

References

1. Koshak EA. Classification of asthma according to revised 2006 GINA: evolution from severity to control. Ann Thorac Med. 2007;2:45-6.
2. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus PH, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004;113:59-65.
3. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol. 2007;119:817-25.
4. Saejong R, Dejsomritrutai W. Validity and reliability assessment of the Siriraj Asthma Control Questionnaire. J Med Assoc Thai. 2011;94:S72-6.
5. Gustafsson LE, Leone AM, Persson MG, Wiklund NP, Moncada S. Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. Biochem Biophys Res Commun. 1991;181:852-7.
6. Alving K, Weitzberg E, Lundberg JM. Increased amount of nitric oxide in exhaled air of asthmatics. Eur Respir J. 1993;6:1368-70.
7. Strunk RC, Szefler SJ, Phillips BR, Zeiger RS, Chinchill VM, Larsen G, et al. Relationship of exhaled nitric oxide to clinical and inflammatory markers of persistent asthma in children. J Allergy Clin Immunol. 2003;112:883-92.
8. Payne DNR, Adcock IM, Wilson NM, Oates T, Scallan M, Bush A. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. Am J Respir Crit Care Med. 2001;164:1376-81.
9. Pijnenburg MW, De Jongste JC. Exhaled nitric oxide in childhood asthma: a review. Clinical and Experimental Allergy. 2007;38:246-59.
10. Pijnenburg MW, Hofhuis W, Hop WC, De Jongste JC. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. Thorax. 2005;60:215-8.
11. Pijnenburg MW, Bakker EM, Hop WC, De Jongste JC. Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial. Am J Respir Crit Care Med. 2005;172:831-6.
12. Shaw DE, Berry MA, Thomas M, Green RH, Brightling CE, Wardlaw AJ, et al. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. Am J Respir Crit Care Med. 2007;176:231-7.
13. Bateman ED, Hurd SS, Barnes PJ, Bousque J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008;31:143–78.
14. American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med. 2005;171:912-30.
15. Moeller A, Diefenbacher C, Lehmann A, Rochat M, Brooks-Wildhaber J, Hall GL, et al. Exhaled nitric oxide distinguishes between subgroups of preschool children with respiratory symptoms. J Allergy Clin Immunol. 2008;121:705-9.
16. Malmberg LP, Pelkonen AS, Haahtela T, Turpeinen M. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. Thorax. 2003;58:494-9.
17. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Eng J Med. 2005;352:2163-73.
18. Kharitonov SA, Yates DH, Barnes PJ. Inhaled glucocorticoids decrease nitric oxide in exhaled air of asthmatic patients. Am J Respir Crit Care Med. 1996;153:454-7.
19. Michils A, Baldassarre S, Van Muylem A. Exhaled nitric oxide and asthma control: a longitudinal study in unselected patients. Eur Respir J. 2008;31:539-46.
20. Khalili B, Boggs PB, Shi R, Bahna SL. Discrepancy between clinical asthma control assessment tools and fractional exhaled nitric oxide. Ann Allergy Asthma Immunol. 2008;101:124-9.
21. Calhoun WJ, Ameredes BT, King TS, Icitovic N, Bleecker ER, Castro M, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. JAMA. 2012;308:987-97.
22. Ko FW, Leung TF, Hui DS, Chu HY, Wong GW, Wong E, et al. Asthma control test correlates well with the treatment decisions made by asthma specialists. Respirology. 2009;14:559-66.
23. Brussee JE, Smit HA, Kerkhof M, Koopman LP, Wijga AH, Postma DS, et al. Exhaled nitric oxide in 4-year-old children: relationship with asthma and atopy. Eur Respir J. 2005;25:455-61.
24. Ko FW, Leung TF, Wong GW, Chu JH, Sy HY, Hui DS. Determinants and reference equation of exhaled nitric oxide in the Chinese population. Eur Respir J. 2013;42:767-75.
25. Ghiro L, Zanconato S, Rampon O, Piovan V, Pasquale MF, Baraldi E. Effect of montelukast added to inhaled corticosteroids on fractional exhaled nitric oxide in asthmatic children. Eur Respir J. 2002;20:630-34.
26. Jackson DJ, Virnig CM, Gangnon RE, Evans MD, Roberg KA, Anderson EL, et al. Fractional exhaled nitric oxide measurements are most closely associated with allergic sensitization in school-age children. J Allergy Clin Immunol. 2009;124:949-53.
27. Buchvald F, Baraldi E, Carraro S, Gaston B, De Jongste J, Pijnenburg MW, et al. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. J Allergy Clin Immunol. 2005;115:1130-6.
28. Wong GW, Liu EK, Leung TF, Yung E, Ko FW, Hui DS, et al. High levels and gender difference of exhaled nitric oxide in Chinese schoolchildren. Clin Exp Allergy. 2005;35:889-93.