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Study of the role of exhaled nitric oxide (NO) in predicting controlled or uncontrolled asthma in asthmatic children

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ABSTRACT

Background: Exhaled nitric oxide (NO), especially fractional concentration of exhaled NO ($F\text{E}_{\text{NO}}$) has been used to predict the responsiveness to inhaled corticosteroid (ICS) in children with asthma. However, the use of exhaled NO for predicting asthma control in children is still controversial.
Methods: This was a perspective observational study. Asthmatic children who were naïve to inhaled corticosteroid (ICS) were included in the present study. The measurements of $F\text{E}_{\text{NO}}$ and $C\text{A}_{\text{NO}}$ (concentration of NO in the gas phase of the alveolar), spirometry, blood eosinophil counts (BEC), and total IgE levels were done for each asthmatic child. All study subjects started proper asthma treatment after the enrollment.
Results: Ninety three asthmatic children (9±3 years) with moderate (63.4%) to severe (36.6%) asthma were included and finished the 3-month study. The levels of $F\text{E}_{\text{NO}}$ and $C\text{A}_{\text{NO}}$ at inclusion were 37±11 ppb and 5.8±1.4 ppb, respectively; the mean of BEC was 617±258 cells/µL; the level of total IgE was 1563±576 UI/mL; 89% of subjects were positive for at least one respiratory allergen. The percentage of severe asthma was reduced significantly after 3 months (P<0.001). Well controlled asthma subjects at 3 months had higher levels of $F\text{E}_{\text{NO}}$ and lower levels of $C\text{A}_{\text{NO}}$ at inclusion (P<0.05 and P<0.05). $F\text{E}_{\text{NO}}$<20 ppb or $C\text{A}_{\text{NO}}$>5ppb had a risk of uncontrolled asthma at 3 months (OR: 1.7, CI 95% [(0.8) - (3.3)], P<0.05; OR: 1.9, CI 95% [(0.9) - (2.7)], P<0.05; respectively). $F\text{E}_{\text{NO}}$>35 ppb at inclusion had a positive predictive value for asthma control at 3 months (OR: 3.5, CI 95% [2.2 - 5.9], P<0.01).
Conclusions: Exhaled NO is a biomarker of asthma which may have a potential role to predict the control of asthma in short-term follow up in asthmatic children.

Key words: Asthma; asthma control; exhaled NO; FE_{NO}; $C\text{A}_{\text{NO}}$.

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Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate: The study was realized in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Lam Dong Medical College Institutional Review Board. All study subjects had signed Informed Consent approved by Institutional Review Board (IRB) of Lam Dong Medical College. Children's parents/guardians signed an Institutional Review Board-Approved consent form on the patient’s behalf.

Consent for publication: Not applicable.

Introduction

Asthma is a very common chronic respiratory disease in children [1]. It remains a leading cause of emergency department visits, hospitalization, and unscheduled school absences due to asthma exacerbations [2,3]. In Vietnam, the prevalence of school-age children with asthma has been varied from 5.1% up to 12.1% [4,5]. Although many advancements have been discovered in the last decades over asthma management, obtaining well-controlled asthma in children is still a big challenge for physicians in practice. As with adults, the control of asthma in children is dependent mainly on their treatment responsiveness and adherence [1]. Moreover, it is challenging for pediatric physicians to predict the different levels of asthma control in short-term follow up of their asthmatic patients. This problem is due to the heterogeneity of asthma symptoms and phenotypes, especially in young children. Currently, the control of asthma is measured by symptoms during the day and at night, during physical activities, and associated with the use of rescue treatment to relieve symptoms with short acting beta 2 agonist (SABA). However, in asthmatic children with moderate to severe asthma, the choice of predictive factors for asthma control remains an important issue for asthma management.

Currently, the use of GINA (Global Initiative for Asthma) recommendations for asthma control is often used in practice with three different control levels, including controlled (or totally controlled), partially controlled, and uncontrolled asthma [1]. In addition to GINA recommendations, the use of ACT (Asthma Control Test) and especially Childhood Asthma Control Test (cACT), useful for youngest children, have been equally available to evaluate the control of asthma [1,6]. In Vietnam, the local version of ACT for asthmatic children is also available for pediatric physicians and it has been considered as a useful additional tool for childhood asthma control [7,8]. According to that, different biomarkers have been studied and used to evaluate the level of asthma control in short-term follow up such as blood or sputum eosinophil count, periostin, and exhaled nitric oxide (NO) [9-12]. In asthmatic adults, previous studies suggest that $F\mathrm{E}_{\mathrm{NO}}$ (fractional concentration of exhaled NO) might be used to predict the persistence of asthma control in asymptomatic patients and can be used in asthma management [13-15]. Actually, the association between $F\mathrm{E}_{\mathrm{NO}}$ and current asthma control in adults is much more complex, with a clear correlation in patients who are naïve to ICS (inhaled corticosteroids) and very weak correlation when patients are properly treated; while $F\mathrm{E}_{\mathrm{NO}}$ seems to be useful in predicting future risk of losing asthma control [16,17]. $F\mathrm{E}_{\mathrm{NO}}$ can be measured by portable devices for evaluating the airway inflammation in asthmatic patients [18]. The use of exhaled NO for predicting asthma control in children is still controversial. However, NICE guidelines recommend to consider $F\mathrm{E}_{\mathrm{NO}}$ test in children and young people in case of uncertainty in the diagnosis (with a cut-off 35 ppb) [19].

In addition, the use of NO concentration in the gas phase of the alveolar ($C\mathrm{A}_{\mathrm{NO}}$) as an inflammatory biomarker of small airways in patients with asthma has been demonstrated [20-22]. It has been suggested that the increase of $C\mathrm{A}_{\mathrm{NO}}$ level might reflect a severe or persistent asthma and the increase of $C\mathrm{A}_{\mathrm{NO}}$ might reflect the allergic inflammation (Type 2 asthma) in distal airways [23,24]. Therefore, the present study aimed to clarify a predictive role of exhaled NO ($F\mathrm{E}_{\mathrm{NO}}$ and $C\mathrm{A}_{\mathrm{NO}}$) in the control of asthma in children in short-term follow up.

Methods

Patients

Asthmatic children who presented to the Clinical Research Center of Lamdong Medical College (Dalat, Vietnam) from June 2018 to June 2019 were eligible for the present study after their parents/guardians signed an Institutional Review Board-Approved consent form on the patient's behalf. This study was approved by the Ethic Council of Lamdong Medical College (04.18/LMC-TTYSH-YD, approved in March 2018). The parents/guardians and patients also had been informed that they could withdraw of the study without the impact on asthma management.

Inclusion criteria

Asthmatic children over 6 years old who were newly diagnosed with asthma according to GINA [1] beginning of the study or who were previously diagnosed with asthma and did not take any daily treatment over one month were included in the present study. The included subjects were able to perform spirometry, exhaled NO measurements ($F\mathrm{E}_{\mathrm{NO}}$, $C\mathrm{A}_{\mathrm{NO}}$ and $F\mathrm{n}_{\mathrm{NO}}$ [fractional concentration of nasally aspirated NO]), blood tests, and skin prick test (SPT). Every subject had been followed and finished the study after three months.

Exclusion criteria

Patients who had one of the following criteria were excluded from the present study: being unable to perform spirometry or exhaled NO measurements; having other acute or chronic diseases such as congenital heart disease, hepatobiliary disorders, nephritic syndrome or chronic glomerulonephritis, acute respiratory infection, or psychological problems; being unable to obtain consent or absent during follow up; having acute asthma exacerbations (AAE) at the beginning.

Study design

This was a prospective observational study. Patients with uncontrolled asthma who met the inclusion criteria were included and treated as recommended by GINA [1] and followed up for three months. All the data concerning medical history, exposure to tobacco smoke, disease severity, laboratory tests including peripheral blood eosinophil counts (BEC), total IgE, skin prick test (SPT) with standard respiratory allergens, exhaled NO measurement ($F\mathrm{E}_{\mathrm{NO}}$, $C\mathrm{A}_{\mathrm{NO}}$, and nNO), and lung function testing were recorded for analysis.

The severity of asthma was defined by daytime symptoms, symptoms at night, asthma crisis, and airflow limitation measured by FEV_1. Fluticasone propionate was used as ICS with moderate or high doses depending on asthma severity and combined with long acting beta agonist (LABA; salmeterol); short acting beta 2 agonist (SABA; albuterol) was used as a rescue treatment. All subjects had clinic visits after one month and three months for the assessment of asthma severity, asthma control by GINA and ACT (Asthma Control Test) in Vietnamese version for children of 4-11 years and >11 years, frequency of SABA use, lung function testing, and exhaled NO measurement ($F\mathrm{E}_{\mathrm{NO}}$, $C\mathrm{A}_{\mathrm{NO}}$, and $F\mathrm{n}_{\mathrm{NO}}$). The adherence of asthmatic children was evaluated by the percentage of patients who did regularly their daily treatment during follow up.

Laboratory techniques

Blood Eosinophil Count (BEC) and total IgE concentration quantifying. Blood samples of all study patients were collected through venipuncture and used for counting eosinophils and measuring total IgE. BEC in peripheral blood was analyzed by automatic machine. IgE concentration in peripheral blood was quantified by chemical luminescence technique (COBASC 501; Hitachi, Japan). The increases of eosinophil and total IgE in peripheral blood were defined by local Biology Lab (eosinophilils 6%; total IgE >214 UI/mL) and as described previously [8].

Skin prick test (SPT). SPT was done for all study patients with standardized respiratory allergens (Stallergenes; London, UK) including *Dermatophagoides Pteronyssius (Dp), Dermatophagoides Farinae (Df), Blomia tropicalis (Blo), Phoenix dactylisera, Alternaria spp,* mixed pollens (*Dactylus glomerata, Phleum pratense, Lolium perenne*), dog hairs, cat hairs, and cockroaches. Negative control with 0.9% saline solution and positive control with 1 mg/mL of histamine was done for each SPT. The test was positive when the wheal size exceeded the negative control ≥3 mm.

Lung Function Testing (LFT). LFT (spirometry) was done by Blue Spiro (Medisoft; Sorinnes, Belgium). The reversibility of airway obstruction was measured by forced expiratory volume in one second (FEV_1) after 15 min using 200 mcg albuterol. The reversibility test was defined as positive when there was an increase of FEV_1 ≥12% and >200 mL as described previously [8,24]. The reference values and used equations were defined by integrated Expair Software (Medisoft; Sorinnes, Belgium) with race correction for Asian people. The level of obstruction was defined as mild obstruction (FEV_1 ≥ 80% predicted, moderate obstruction (FEV_1 of 60-79% predicted), and severe obstruction (FEV_1 < 59% predicted). LFT was done routinely after the measurement of exhaled nitric oxide.

Exhaled nitric oxide (NO) measurements. FE_{NO}, CA_{NO} and Fn_{NO} were done by Hypair FE_{NO}^+ Device (Medisoft; Sorinnes, Belgium) according to manufacturer's instructions as described previously with expiratory air flows of 50 mL/sec for FE_{NO} and with multiple flows for CA_{NO} [8]. CA_{NO} was done by machine's integrated Expair Software using a linear equation of y = ax + b (x: flow rate [4 flow rates of 50/100/150/350 mL/s]; b: *J*awNO 115 [maximal bronchial production of NO in the airways]; a: CA_{NO}). CA_{NO} and *J*awNO have been corrected according to the Condorelli equation [25]. The mean value of two correct measurements was used for analysis. FE_{NO}, CA_{NO} and Fn_{NO} levels were classified as recommended by the ATS (American Thoracic Society) / ERS (European Respiratory Society) and previous publications [16,24,26].

Statistical analysis

The statistical analysis was performed with SPSS software 22.0 (Chicago, IL, USA) for all recorded data. Categorical variables were presented absolute and relative frequencies (n and %) and continuous variables were described by mean and standard deviation (mean ± SD). Normal distribution was evaluated by using Skewness-Kurtosis test. The pair-comparison of mean was done by Mann-Whitney U test or by Kruskal-Wallis test for more than two groups. Odds ratios (OR) with 95% confidence interval (CI) was used to measure the association between clinical and functional parameters at inclusion with controlled or uncontrolled asthma after 3 months. P<0.05 was considered as statistically significant.

Results

Clinical and functional characteristic of study patients at inclusion

From June 2018 to June 2019, 93 asthmatic children more than 6 years of age who met the inclusion criteria and followed up during 3 months were included in the study (Figure 1). The mean age of patients was 9 ± 3 years; 62.4% male; and asthma onset age of 3.5 ± 2.5 years (Table 1). There were 54.8% passive smokers (exposed to second-hand smoke), 87.1% personal allergic history, and 62.3% had family history of allergies (Table 1). The percentage of moderate and severe asthma was respectively 63.4% and 36.6%. 8.6%, 59.1% and 32.3% of subjects were never treated, discontinued treatment or unregularly treated with an asthma preventive drug, respectively (Table 1).

The result of spirometry showed study subjects had a moderate

Table 1. Clinical and functional characteristics of patients at the beginning of study.

Characteristics (N=93)	Mean ± SD or Percentage % (N)
Age, years	9 ± 3
Gender	
Male	62.4 (58
Female	47.6 (35)
Age of asthma onset, years	3.5 ± 2.5
BMI, kg/m^2	17.5 ± 1.5
Passive smokers, %	54.8 (51)
Atopy	
Personal allergic history	87.1 (81)
Familiar allergic history	62.3 (58)
Asthma severity, %	
Moderate asthma	63.4 (59)
Severe asthma	36.6 (34)
AAE with hospitalization, times/year	2.4 ± 1.6
Asthma preventive treatment	
Never treated with preventive drugs	8.6 (8)
Discontinued treatment	59.1 (55)
Unregularly treated	32.3 (22)
ACT, scores	8 ± 4
Comorbidity	
Allergic rhinitis	83.8 (78)
Eczema	31.2 (29)
Spirometry	
FEV_1, % of predicted	64 ± 18
FVC, % of predicted	73 ± 12
FEV_1/FVC, % of predicted	67 ± 11
FEF_{25-75}, % of predicted	48 ± 19
PEFR, % of predicted	58 ± 15
Reversibility*, % (N)	76.3 (71)
Exhaled NO	
FE_{NO}, ppb	37 ± 11
CA_{NO}, ppb	5.8 ± 1.4
Jaw_{NO}, nL/min	77 ± 22
Fn_{NO}, ppb	1826 ± 379
Total IgE, UI/mL	1563 ± 576
BEC, % (cells/μL)	6.3 ± 3.5 (617 ± 258)
SPT (+)§	89

BMI, body mass index; AAE, acute asthma exacerbation; ACT, asthma control test; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow at 25-75% of time; PEFR, peak expiratory flow rate; NO, nitric oxide; FE_{NO}, fractional concentration of exhaled nitric oxide; CA_{NO}, concentration of nitric oxide in the gas phase of the alveolar; Jaw_{NO}, total flux of NO in the conducting airway compartment; Fn_{NO}, fractional concentration of nasally aspirated nitric oxide; ppb: part per billion; BEC, blood eosinophil count; SPT, skin prick test; *defined by increase of FEV_1>12% and 200 mL; §positive at least with one allergen on skin prick test.

to severe reduction of FEV_1 and PEFR with mean values of 64±18% and 58±15%, respectively (Table 1). The levels of FE_{NO}, CA_{NO}, Jaw_{NO}, and Fn_{NO} were 37±11 ppb, 5.8±1.4 ppb, 77±22 nL/min, and 1,826±379 ppb, respectively. The mean of BEC was 617±258 cells/µL or 6.3±3.5% of total white blood cells; the level of total IgE was 1,563±576 UI/mL (Table 1). 89% of study subjects were positive with at least one respiratory allergen confirmed by SPT.

Clinical and functional characteristics of study patients after asthma management

The results after one month of asthma treatment showed the percentage of passive smokers, moderate or severe asthma, and asthma treatment with high or moderate dose of ICS plus LABA were not significant different in comparison to those at the beginning of study in study subjects (47.3%, 72.1%, 27.9%, 27.9%, and 72.1% *vs* 54.8%, 63.4%, 36.6%, 36.6%, and 63.4%; P>0.05; Table 2, Figure 2). The daily use of SABA and ACT scores were significantly improved after one month compared to that at inclusion in study patients (3.5±1.7 and 15±6 *vs* 6.2±3.4 and 8±4; P<0.05 and P<0.01, respectively; Table 2). The percentage of uncontrolled asthma was significantly reduced after one month in comparison to that at inclusion (49.5% *vs* 100%; P<0.001; Table 2, Figure 2). After one month of asthma treatment, there was significant improvement of spirometric parameters (Table 2). The levels of FE_{NO}, CA_{NO}, Jaw_{NO}, and Fn_{NO} were significant reduced after one month in compared to those at inclusion (25±12 ppb, 4.9±2.1 ppb, 41±16 nL/min, and 1432±561 ppb *vs* 37±11 ppb, 5.8±1.4 ppb and 1826±379 ppb; P<0.01, P<0.05 and P<0.05, respectively; Table 2).

The results after 3 months of asthma treatment showed there were significant reductions of severe asthma, weekly use of SABA, high dose of ICS + LABA, LTRA treatment, and uncontrolled asthma in comparison to those at inclusion and after one month of treatment (13.9%, 2.6±1.5 times, 13.9%, and 66.5% *vs* 36.6% and 27.9%, 6.2±3.4 and 3.5±1.7 times, 36.6% and 27.9%,

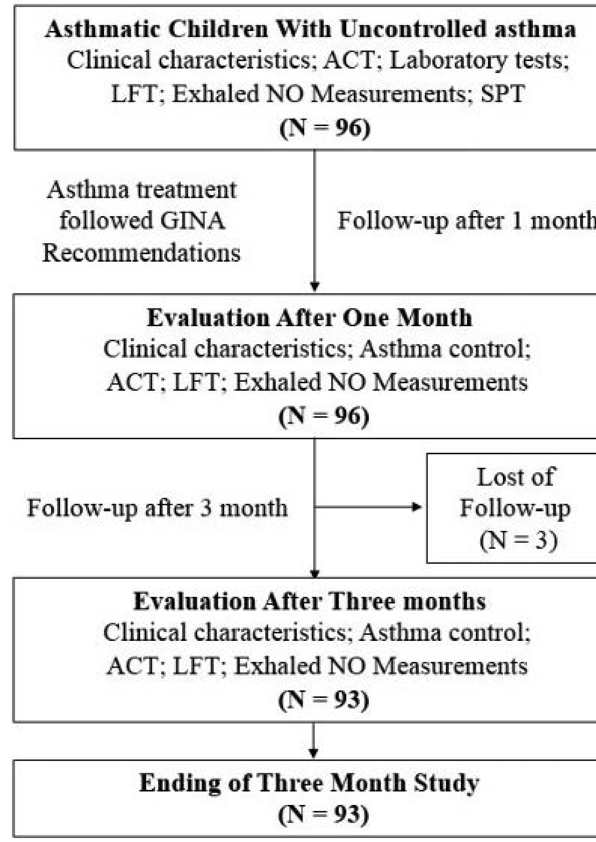

Figure 1. Flow chart of study with asthmatic children after three months followed-up. ACT, Asthma Control Test; LFT, lung function test; NO, nitric oxide; SPT, skin prick test.

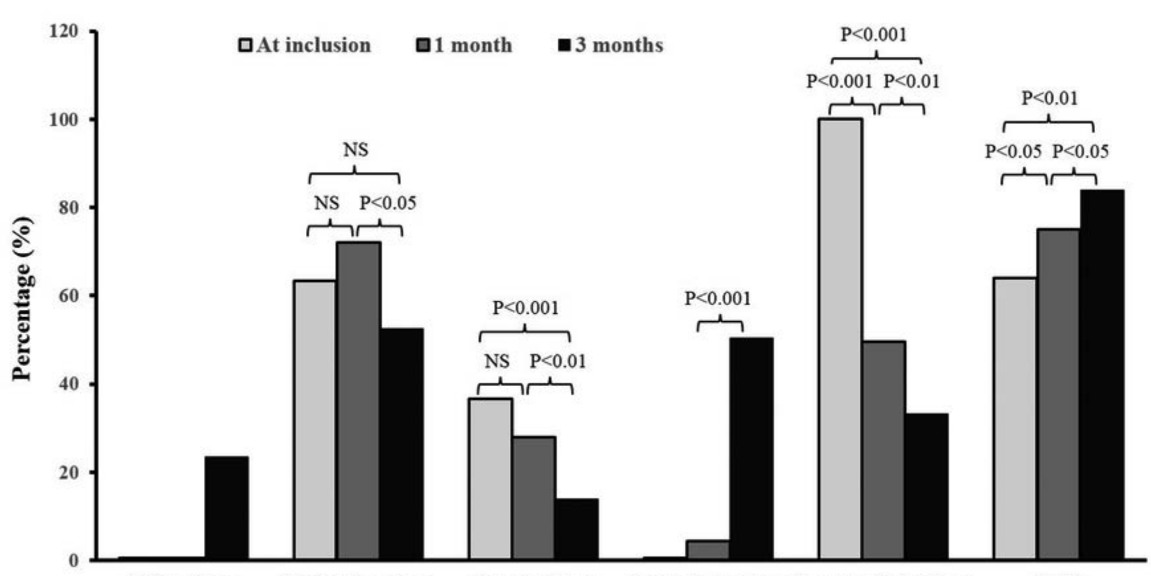

Figure 2. Significant modification of clinical and functional characteristics of study patients after 1 month and 3 months. FEV_1, forced expiratory volume in 1 second; NS, not significant difference.

and 100% and 100%; P<0.001 and P<0.01, P<0.01 and P<0.05, P<0.001 and P<0.01, and P<0.001 and P<0.001, respectively; Table 2, Figure 2). The ACT scores and percentage of controlled asthma were also significantly increased after 3 months of treatment in comparison to those at inclusion and after one month of treatment (19±5 *vs* 8±4 and 15±6; 50.5% *vs* 0% and 4.3%; P<0.001 and P<0.05; P<0.001, respectively; Table 2, Figure 2). There was the significant improvement of FEV_1 and PEFR after 3 months of treatment compared to the values at inclusion (P<0.01 and P<0.01, respectively; Table 2). The levels of FE_{NO}, CA_{NO}, and Fn_{NO} were also significantly reduced after 3 months of treatment in comparison to those at inclusion and after one month of treatment (16±9 ppb *vs* 37±11 and 25±12 ppb, 3.7±1.8 ppb *vs* 5.8±1.4 and 4.9±2.1 ppb, and 978±425 *vs* 1,826±379 and 1,432±561 ppb; P<0.001 and P<0.01, P<0.01 and P<0.05, and P<0.001 and P<0.01, respectively; Table 2).

Comparison of clinical and functional characteristics at inclusion between uncontrolled and controlled asthmatic patients at 3 months

The results of the present study showed there was no significant difference between controlled and uncontrolled asthmatic patients classified at 3 months for age, gender, BMI, and atopy measured at inclusion (9±2 *vs* 8±3, 29% *vs* 20%, 17.3±1.4 *vs* 17.9±1.6 kg/m², 87.2% *vs* 80.6%; P>0.05, P>0.05, P>0.05, and P>0.05, respectively; Table 3). Controlled asthmatic patients were older and had moderate asthma severity at inclusion than uncontrolled asthmatic patients (5.5±2.0 *vs* 2.5±1.5 and 80.8% *vs* 25.8%; P<0.01 and P<0.001, respectively; Table 3, Figure 3).

In comparison to uncontrolled asthmatic patients, study patients with controlled asthma at 3 months had higher FEV_1, PEFR, and FE_{NO} levels at inclusion than those with uncontrolled asthma (78±19% *vs* 52±16%, 69±17% *vs* 46±12%, and 45±14 ppb *vs* 29±8 ppb; P<0.05, P<0.05, and P<0.05, respectively; Table 3, Figure 3). Controlled asthma also had a higher reversibility rate than uncontrolled asthma (91.4% *vs* 54.8%, P<0.01; Table 3). Uncontrolled asthmatic patients at 3 months had a higher level of CA_{NO}, n_{NO}, total IgE, and BEC at inclusion than controlled asthmatic patients (6.9±1.9 ppb *vs* 4.7±0.8 ppb, 2,341±487 ppb *vs* 1,322±256 ppb, 2,154±785 UI/mL *vs* 1,143±437 UI/mL, and 823±367 cells/µL *vs* 451±184 cells/µL; P<0.05, P<0.01, P<0.01, and P<0.05, respectively; Table 3).

Odds ratios and 95% confidence intervals for the predictive factors at inclusion on controlled and uncontrolled asthma at 3 months

The severity of asthma evaluated at inclusion had a significant odds ratio (OR) for the control of asthma defined by GINA or ACT

Table 2. Comparison of clinical and functional characteristics at the beginning of study vs after 1 month and 3 months.

Characteristics	At inclusion (N=93)	1 month (N=93)	3 months (N=93)	P
Passive smokers, % (N)	54.8 (51)	47.3 (44)	44.1 (41)	NS#,§,°
Asthma severity, %				
Mild asthma	0 (0)	0	23.5 (31)	n/a#,§,°
Moderate asthma	63.4 (59)	72.1 (67)	52.6 (49)	NS#,§; <0.05
Severe asthma	36.6 (34)	27.9 (26)	13.9 (13)	NS#; <0.001§; <0.01°
Use of SABA, times/week	6.2 ±3.4	3.5 ± 1.7	2.6 ± 1.5	<0.05#; <0.01§; <0.05°
Asthma treatment*				
High dose of ICS+LABA	36.6 (34)	27.9 (26)	13.9 (13)	NS#; <0.001§; <0.01°
Moderate dose of ICS+LABA	63.4 (59)	72.1 (67)	52.6 (49)	NS#,§; <0.01°
LTRA	100 (93)	100 (93)	66.5 (62)	NS#; <0.001§; <0.001°
Moderate dose of ICS	0 (0)	0 (0)	23.5 (31)	n/a#,§,°
ACT, scores	8 ± 4	15 ± 6	19 ± 5	<0.01#; <0.001§; <0.05°
Control of asthma				
Uncontrolled, %	100 (93)	49.5 (46)	33.3 (31)	<0.001#; <0.001§; <0.01°
Partially controlled, %	0 (0)	46.2 (43)	16.1 (15)	n/a#,§; <0.001°
Total controlled, %	0 (0)	4.3 (4)	50.5 (47)	n/a#,§; <0.001°
Treatment adherence				
Good	0 (0)	87.1 (81)	100 (93)	n/a#,§; <0.001°
Poor	100 (93)	12.9 (12)	0 (0)	<0.001#; n/a§,°
Spirometry, % of predicted				
FEV_1	64 ± 18	75 ± 12	84 ± 14	<0.05#; <0.01§; <0.05°
FVC	73 ± 12	81 ± 14	88 ± 11	<0.05#; <0.05§; NS°
FEV_1/FVC	67 ± 11	78 ± 8	81 ± 12	<0.05#; <0.01§; NS°
FEF_{25-75}	48 ± 19	59 ± 15	64 ± 12	<0.05#; <0.05§; NS°
PEFR	58 ± 15	77 ± 12	81 ± 11	<0.01#; <0.01§; NS°
Exhaled NO				
FE_{NO}, ppb	37 ± 11	25 ± 12	16 ± 9	<0.01#; <0.001§; 0.01°
CA_{NO}, ppb	5.8 ± 1.4	4.9 ± 2.1	3.7 ± 1.8	<0.05#; <0.01§; 0.05°
Jaw_{NO}, nL/min	77 ± 22	41 ± 16	38 ± 13	<0.01#; <0.001§; NS°
Fn_{NO}, ppb	1826 ± 379	1432 ± 561	978 ± 425	<0.05#; <0.001§; 0.01°

SABA, short acting beta 2 agonist; ICS, inhaled corticosteroid; LABA, long acting beta 2 agonist; LTRA, leukotriene receptor antagonist; ACT, asthma control test; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow at 25-75% of time; PEFR, peak expiratory flow rate; NO, nitric oxide; FE_{NO}, fractional exhaled nitric oxide; CA_{NO}, concentration of nitric oxide in the gas phase of the alveolar; Jaw_{NO}, total flux of NO in the conducting airway compartment; Fn_{NO}, fractional concentration of nasally aspirated nitric oxide; ppb: part per billion; *treatment started at the beginning of study; #at the beginning *vs* 1 month; §at the beginning *vs* 3 months; °3 months *vs* 1 month.

scores >20 (Table 4, Figure 4). The medical history of hospitalization due to asthma exacerbation in previous year had significant and negative OR for uncontrolled asthma defined by GINA at 3 months (OR = 1.9 and P<0.05; Table 4, Figure 4). Asthmatic patients who had allergic rhinitis also had significant OR for asthma control defined by ACT scores (OR = 1.4 and P<0.05). FEV_1 <60% of predicted value at inclusion had a risk of uncontrolled asthma in study subjects (OR = 1.8 and P<0.05). FEV_1 ≥80% of predicted value at inclusion had a good agreement of OR for asthma control defined by both criteria of GINA and ACT scores (OR = 1.6 and P<0.05; OR = 1.5 and P<0.05, respectively; Table 4, Figure 4). FE_{NO} <20 ppb had a risk of uncontrolled asthma at 3 months in study patients (OR = 1.7 and 1.5; P<0.05 and P<0.05; Table 4, Figure 4). However, FE_{NO} >35 ppb had a good agreement for asthma control defined by GINA (OR = 3.5 and P<0.01) whereas CA_{NO} >5 ppb had a risk of asthma control defined by GINA and ACT scores at 3 months (Table 4, Figure 4).

Discussion

The results of this study showed that i) the cut-off of FE_{NO} <20 ppb or CA_{NO} >5 ppb demonstrated a risk of uncontrolled asthma at 3 months in study patients; ii) the level of FE_{NO} and CA_{NO}, percentage of uncontrolled asthma, daily use of SABA were significantly reduced after one and three months of asthmatic treatment; 3) the controlled asthmatic subjects evaluated at three months had higher levels of FE_{NO} and CA_{NO} and lower percentages of severe asthma and hospitalization frequency in previous year measured at inclusion than uncontrolled asthmatic subjects.

The asthmatic children in this study had the general characteristics of asthma in childhood with early asthma onset (<5 years-old) and medical history of allergy and atopy (Table 1). The percentage of second-hand smoke exposure in asthmatic subjects was very high (54.8%; Table 1); however, there was no significant difference of FE_{NO} level in subjects with or without passive smoking (36±10 ppb *vs* 38±11 ppb; data not shown). Bobrowska-Korzeniowska *et al.* have suggested that FE_{NO} measurement could be interpreted in the context of environmental tobacco smoke exposure in asthmatic children [27]. Second-hand smoke exposure is a significant and complicating factor for asthma management in children in emerging countries such as Vietnam where the prevalence of adult smokers is high [28]. Asthmatic children exposed to tobacco smoke (passive smoking / second-hand smokers) are at higher risk for uncontrolled asthma with more severe asthma symptoms and exacerbations [29,30]. Therefore, cigarette smoking avoidance in childhood asthma education should be highly emphasized.

The present study showed that at inclusion, the majority of subjects had moderate asthma and their asthma treatment was discontinued or irregular; and especially, they had high levels of FE_{NO}, CA_{NO}, and Fn_{NO} (Table 1, Figure 3). Although the use of FE_{NO} in diagnosis and treatment of Type 2 asthma has been recommended previously [1,7,31], its role in predicting the control of asthma in children in short-term follow up has not been well demonstrated. In asthmatic patients, the level of airway inflammation measured by FE_{NO} may be used to step-up (with increased FE_{NO}) or step-down (with decreased FE_{NO}) the dose of ICS treatment [8,18,26,32]. A recent study of ours showed that the use of FE_{NO} in combination with GINA recommendations may help to reduce the dose of ICS *vs* using GINA alone in asthmatic children [8]. In the present study, the level of FE_{NO} and CA_{NO} has been reduced after asthma treatment at one month and three months (Table 2). Interestingly, our study found that a reduction of FE_{NO} and CA_{NO} was associated with an increased percentage of subjects with controlled asthma (Table 2). Therefore, the reduction of FE_{NO} and CA_{NO} level might predict the responsiveness of asthma treatment in patients who are naïve to ICS. However, the results of our study showed that Jaw_{NO} level was significantly reduced after one month but not after three months and especially there was no significant difference of Jaw_{NO} level between controlled asthma vs uncontrolled asthma at inclusion (Tables 2 and 3) Although the use of

Table 3. Comparison of clinical and functional characteristics at the beginning of study between controlled and uncontrolled asthma patients classified at 3 months.

Characteristics	Uncontrolled asthma (N=31)	Total controlled asthma (N=47)	P
Age, years	8 ± 3	9 ± 2	NS
Gender			
Male	20	29	NS
Female	11	18	NS
Age of asthma onset, years	2.5 ± 1.5	5.5 ± 2.0	<0.01
BMI, kg/m²	17.9 ± 1.6	17.3 ± 1.4	NS
Passive smokers, %	61.3 (19)	38.2 (18)	<0.05
Atopy			
Personal allergic history	80.6 (25)	87.2 (41)	NS
Familiar allergic history	58.1 (18)	61.7 (29)	NS
Asthma severity, %			
Moderate asthma	25.8 (8)	80.8 (38)	<0.001
Severe asthma	74.2 (23)	19.2 (9)	<0.001
AAE with hospitalization, times/year	3.2±1.8	1.8±0.9	<0.05
Asthma treatment*			
High dose of ICS+LABA	74.2 (23)	19.2 (9)	<0.001
Moderate dose of ICS+LABA	25.8 (8)	80.8 (38)	<0.001
LTRA	100 (31)	100 (47)	NS
Moderate dose of ICS	0 (0)	0 (0)	n/a
Use of SABA, times/week	8.5 ± 2.6	2.4 ± 1.3	<0.001
Comorbidity			
Allergic rhinitis	90.3 (28)	65.9 (31)	<0.01
Eczema	29.0 (9)	31.9 (15)	NS
Spirometry			
FEV_1, % of predicted	52 ± 16	78 ± 19	<0.05
FVC, % of predicted	69 ± 11	79 ± 14	NS
FEV_1/FVC, % of predicted	66 ± 9	69 ± 12	NS
FEF_{25-75}, % of predicted	46 ± 17	51 ± 21	NS
PEFR, % of predicted	46 ± 12	69 ± 17	<0.05
Reversibility§, %(N)	54.8 (17)	91.4 (43)	<0.01
Exhaled NO, ppb			
FE_{NO}, ppb	29 ± 8	45 ± 14	<0.05
CA_{NO}, ppb	6.9 ± 1.9	4.7 ± 0.8	<0.05
Jaw_{NO}, nL/min	79 ± 23	75 ± 21	NS
Fn_{NO}, ppb	2341 ± 487	1322 ± 256	<0.01
Total IgE, UI/mL	2154 ± 785	1143 ± 437	<0.01
Blood eosinophil count, cells/µL	823 ± 367	451 ± 184	<0.05
Skin prick test (+)°	83.9 (26)	80.8 (38)	NS

BMI, body mass index; AAE, acute asthma exacerbation; SABA, short acting beta 2 agonist; ICS: inhaled corticosteroid; LABA, long acting beta 2 agonist; LTRA, leukotriene receptor antagonist; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow at 25-75% of time; PEFR, peak expiratory flow rate; NO, nitric oxide; *F*ENO, fractional exhaled nitric oxide; CA_{NO}, concentration of nitric oxide in the gas phase of the alveolar; Jaw_{NO}, total flux of NO in the conducting airway compartment; Fn_{NO}, fractional concentration of nasally aspirated nitric oxide; ppb: part per billion; BEC, blood eosinophil count; SPT, skin prick test; *treatment started at inclusion; §defined by increase of FEV_1>12% and 200mL; °positive at least with one allergen on skin prick test; NS, not significant difference.

FE_{NO} in patients with asthma, especially in severe asthma, has been considered currently as biomarker of ICS and biologic therapy [33], the use of CA_{NO} in asthma is still controversial. The results of recent studies suggest CA_{NO} might be used as a biomarker of distal airways in asthmatic patients [33-35]. Therefore, CA_{NO} has been considered as an additional tool to categorize asthmatic children who have atopy and are sensitive to ICS [33]. A previous study demonstrated the level of CA_{NO} was higher in asthmatic children than that in healthy subjects and it was related to asthma control and depended on alveolar inflammation [35]. It has been suggested that an increase of CA_{NO} level could reflect a severe or persistent asthma [21,23]. Until now, the phenotype of asthmatic children with high level of CA_{NO} has not been well clarified. Increased CA_{NO} in exhaled breath might reflect the allergic inflammation in small airways in patients with asthma, whereas it has been reduced in patients with lung fibrosis or pulmonary hypertension [36]. In adults, the increase of CA_{NO} level could reflect a severe or persistent asthma during asthma follow up [7,30]. Thus, the reduction of CA_{NO} may be used as a predictive biomarker of the responsiveness of ICS treatment in asthmatic children with increased exhaled NO.

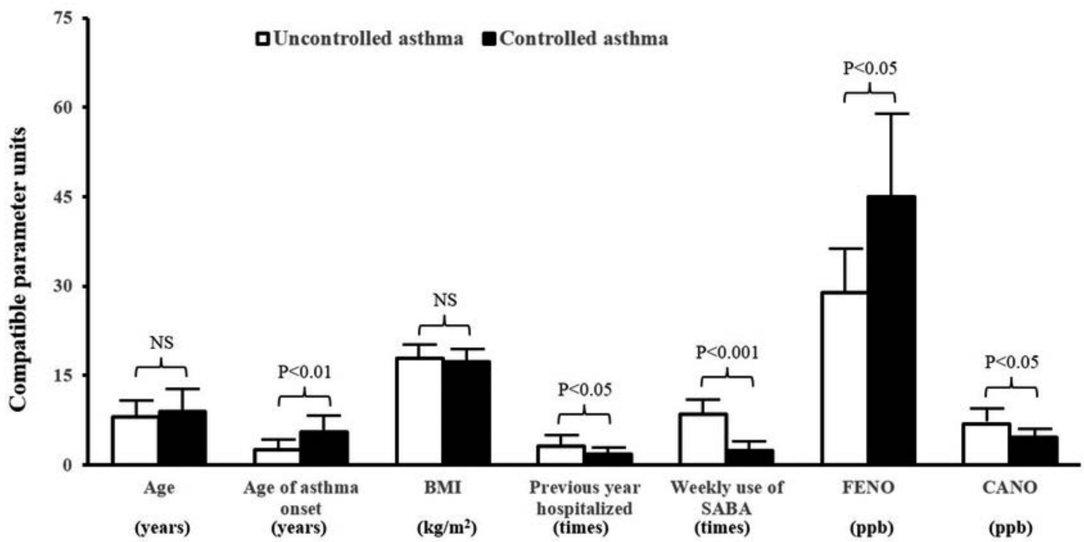

Figure 3. **Comparison of clinical and functional characteristics measured at inclusion of controlled and uncontrolled asthma at 3 months. BMI, body mass index; FE_{NO}, fractional exhaled nitric oxide; CA_{NO}, concentration of alveolar nitric oxide; NS, not significant difference.**

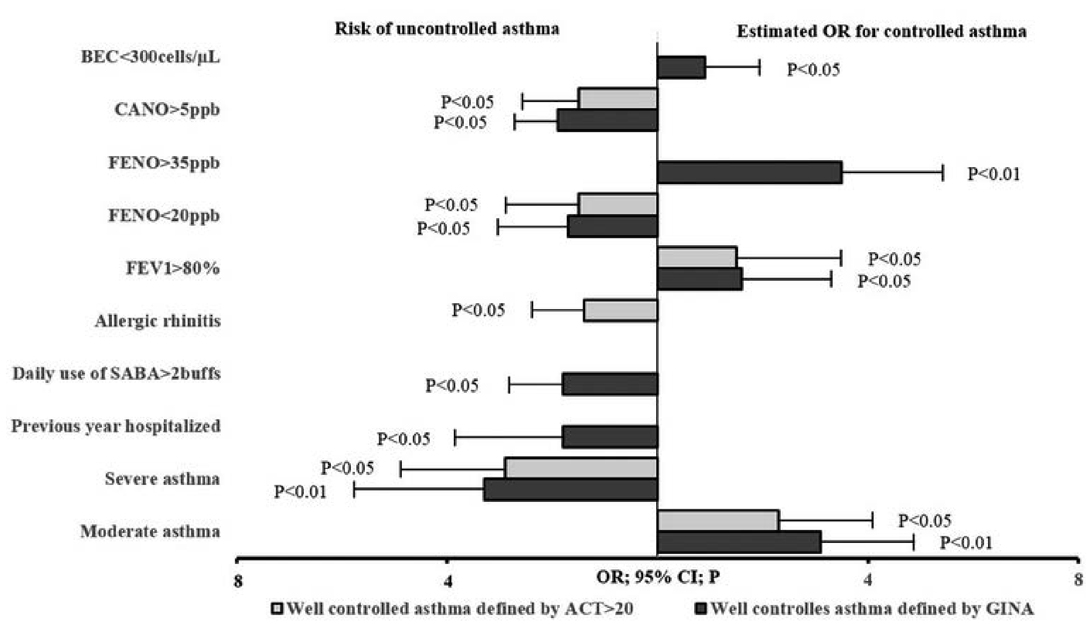

Figure 4. **Odds ratios (OR) and 95% confidence intervals (CI) for the predictive factors at inclusion on controlled and uncontrolled asthma at 3 months. BEC, blood eosinophil count; FE_{NO}, fractional exhaled nitric oxide; CA_{NO}, concentration of alveolar nitric oxide; FEV_1, forced expiratory volume in one second; SABA, short acting beta 2 agonist.**

Table 4. **Odds ratios (OR) and 95% confidence intervals for the predictive factors at inclusion on controlled and uncontrolled asthma at 3 months.**

Parameters		Well controlled asthma					
		Defined by GINA			Defined by ACT scores ≥ 20		
		OR (min/max)	CI 95%	P	OR	CI 95%	P
Clinical characteristics*							
Asthma onset >5 years (+)		1.3	0.5 / 1.8	NS	1.5	0.8 / 1.9	NS
Passive smoker (-)		1.4	0.7 / 2.1	NS	1.3	0.7 / 1.8	NS
Asthma severity	Moderate (+)	3.1	1.8 / 5.3	<0.01	2.3	1.6 / 4.1	<0.05
	Severe (-)	3.3	1.7 / 5.9	<0.01	2.9	1.4 / 4.8	<0.05
AAE hospitalized in previous year ≥2 times (-)		1.9	0.9 / 2.9	<0.05	1.7	0.6 / 3.1	NS
Daily used SABA ≥2 buffs§ (-)		1.8	0.8 / 2.7	<0.05	1.5	0.7 / 2.7	NS
Allergic rhinitis (-)		1.5	0.7 / 2.9	NS	1.4	0.7 / 2.4	<0.05
Functional characteristics*							
FEV_1, %	<60 (-)	1.8	0.1 / 4.1	<0.05	1.4	0.9 / 3.9	NS
	60 – 80 (+)	0.9	0.5 / 2.1	NS	0.7	0.2 / 1.9	NS
	≥ 80 (+)	1.6	0.9 / 3.2	<0.05	1.5	0.7 / 3.8	<0.05
nNO, ppb	>500 (-)	1.4	0.7 / 3.5	NS	1.3	0.6 / 3.1	NS
	500 - 1000 (-)	1.5	0.5 / 3.1	NS	1.4	0.8 / 2.4	NS
	>1000 (-)	1.3	0.7 / 3.1	NS	0.9	0.4 / 2.7	NS
$F\mathrm{E}_{NO}$, ppb	<20 (-)	1.7	0.8 / 3.3	<0.05	1.5	0.9 / 3.1	<0.05
	20 – 35 (+)	1.3	0.3 / 3.4	NS	0.9	0.4 / 2.9	NS
	>35 (+)	3.5	2.2 / 5.9	<0.01	2.9	1.4 / 4.9	NS
$C\mathrm{A}_{NO}$, ppb	>5 (-)	1.9	0.9 / 2.7	<0.05	1.5	0.8 / 2.6	<0.05
	≤5 (+)	0.8	0.2 / 1.7	NS	0.7	0.3 / 1.9	NS
	<300 (+)	0.9	0.3 / 2.1	<0.05	0.7	0.2 / 1.8	NS
BEC, cells/μL	300-600 (+)	1.6	0.8 / 3.5	NS	1.4	0.7 / 2.9	NS
	≥600 (-)	1.3	0.6 / 2.3	NS	1.2	0.5 / 2.1	NS

AAE, acute asthma exacerbation; SABA, short acting beta 2 agonist; FEV_1, forced expiratory volume in 1 s; $F\mathrm{E}_{NO}$, fractional exhaled nitric oxide; CA_{NO}, concentration of nitric oxide in the gas phase of the alveolar; $F\mathrm{n}_{NO}$, fractional concentration of nasally aspirated nitric oxide; ppb, part per billion; BEC, blood eosinophil count; NS, not significant difference; *measured at inclusion; §measured at 1 month; (-), risk of uncontrolled asthma; (+), positive agreement of controlled asthma.

In the management of asthma, especially in asthmatic children, the other important issue is how to predict the success of asthma management in order to recommend the appropriate asthma action plan. The results of this study showed that some clinical characteristics of subjects at inclusion had the significant predictive factors of asthma control at 3 months, evaluated by OR. These predictive factors included age of asthma onset, frequency of hospitalization in previous year, and asthma severity with airflow limitation (Table 4, Figure 4). For asthmatic children with low level of $F\mathrm{E}_{NO}$ at inclusion, there was a risk of uncontrolled asthma at 3 months, whereas for whom with high level of $F\mathrm{E}_{NO}$ at inclusion there was a good agreement for asthma control (Table 4, Figure 4). Interestingly, high level of $C\mathrm{A}_{NO}$ had a risk of uncontrolled asthma defined by GINA and ACT scores at 3 months (Table 4, Figure 4). These results suggest that the measurement of exhaled NO ($F\mathrm{E}_{NO}$ and $C\mathrm{A}_{NO}$) might be used to predict the control of asthma in children who are naïve with ICS.

Until now, the studies on the role of $C\mathrm{A}_{NO}$ in asthmatic children are limited. The present study suggests a new approach in the control of asthma by measuring $C\mathrm{A}_{NO}$ concomitant with $F\mathrm{E}_{NO}$ in asthmatic children. However, the present study still has some limitations relating to the small number of study subjects and lack of long-term follow up. In addition, the measurement of $C\mathrm{A}_{NO}$ needs the multiple flow device which is costlier and has not been extensively equipped in all asthma care centers. Thus, more studies on the role of exhaled NO as predictive biomarkers of asthma control in children should be undertaken to clarify its benefits and cost-effectiveness.

Conclusions

Children with asthma who are naïve with ICS usually have high levels of exhaled NO. High levels of $F\mathrm{E}_{NO}$ in asthmatic children might have a predictive value for controlled asthma. However, low levels of $F\mathrm{E}_{NO}$ and high levels of CA_{NO} can predict uncontrolled asthma in children. The measurement of exhaled NO, especially CA_{NO}, is still a new area in the field of asthma management; therefore, more studies in this field should be done in the future.

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List of abbreviations

AAE	acute asthma exacerbation;
ACT	asthma control test;
BEC	blood eosinophil count;
BMI	body mass index;
CA_{NO}	concentration of alveolar nitric oxide;
FEF_{25-75}	forced expiratory flow at 25-75% of time;
FEV_1	forced expiratory volume in 1 second;
FE_{NO}	fractional exhaled nitric oxide;
Fn_{NO}	nasal nitric oxide;
FVC	forced vital capacity;
ICS	inhaled corticosteroid;
LABA	long acting beta 2 agonist;
LTRA	leukotriene receptor antagonist;
NO	nitric oxide;
PEFR	peak expiratory flow rate;
Ppb	part per billion;
SABA	short acting beta 2 agonist;
SPT	skin prick test.

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