Original Article

Fractional exhaled nitric oxide is a useful adjunctive modality for monitoring bronchial asthma

Venkatnarayan Kavitha, Anant Mohan, Karan Madan, Vijay Hadda, GC Khilnani, Randeep Guleria

Department of Pulmonary Medicine and Sleep Disorders, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Background and Objective: To evaluate the utility of fractional exhaled nitric oxide (FeNO) in monitoring asthma control. **Materials and Methods:** Steroid naïve nonsmoking asthmatics were recruited and followed for 6–8 weeks on standard treatment. Serial measurements of FeNO, peak expiratory flow rate (PEFR) variability, forced expiratory volume in 1 s (FEV1), bronchodilator reversibility (BDR), and asthma control test (ACT) score were measured at baseline and after 6–8 weeks of treatment. **Results:** One hundred and fifty-one patients were recruited over an 18-month period. These comprised 79 males (52.3%) with mean (standard deviation) age of 34.2 (11.6). Mean (SD) FeNO levels at baseline and after therapy were 45.4 (35.9) and 38.4 (23.7) ppb, respectively ($P = 0.01$). Baseline FeNO correlated strongly with FEV1 ($r = -0.78$, $P < 0.001$), ACT score ($r = -0.76$, $P < 0.001$), PEFR variability ($r = -0.74$, $P < 0.001$), and moderately with BDR ($r = 0.50$, $P < 0.001$). After treatment with inhaled steroids, the correlation remained strong with ACT score ($r = -0.68$, $P < 0.001$) but weakened with PEFR variability ($r = -0.34$, $P = 0.01$) and FEV1 ($r = -0.36$, $P = 0.01$). **Conclusions:** FeNO may be useful as an adjunctive noninvasive modality to assess asthma control in both steroid naïve asthmatics and asthmatics on treatment. However, the suboptimal sensitivity and specificity may limit its utility as a point-of-care single monitoring tool.

KEY WORDS: Asthma, asthma control test, nitric oxide, peak expiratory flow rate

Address for correspondence: Dr. Anant Mohan, Room No 3098, 3rd Floor, Teaching Block, All India Institute of Medical Sciences, New Delhi - 110 029, India.
E-mail: anantmohan@yahoo.com

INTRODUCTION

Asthma is a heterogeneous disease characterized by chronic airway inflammation and defined by variable expiratory airflow limitation.[1,2] Over the last decade, several scientific advances have improved our understanding of asthma pathophysiology, notable among which being the development of biomarkers measurable in the exhaled breath. In this context, fractional exhaled nitric oxide (FeNO) is proposed as a simple and reliable tool for accurate monitoring of patients with asthma. The utility of estimating FeNO in asthmatics has been demonstrated for diagnosis, to identify likely steroid responders and as a guide to titrate the dose of steroids.[3,4] However, it is still uncertain whether FeNO can serve as an equally reliable monitoring tool for asthma as other commonly used parameters such as symptoms, forced expiratory volume in 1 s (FEV1), peak flow variability, and quality of life measures. Adequately powered studies, especially from the Indian subcontinent are lacking. This study was thus conceived to evaluate the utility of FeNO as a monitoring tool for asthma control and its agreement with various other conventional monitoring parameters.

MATERIALS AND METHODS

Patients with newly diagnosed asthma were prospectively recruited from the pulmonary medicine outpatient of a

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/0970-2113.201322

How to cite this article: Kavitha V, Mohan A, Madan K, Hadda V, Khilnani GC, Guleria R. Fractional exhaled nitric oxide is a useful adjunctive modality for monitoring bronchial asthma. Lung India 2017;34:132-7.

large, tertiary care referral center in Northern India over an 18-month period. Written informed consent was obtained from all the patients or legally authorized representatives and prior approval was obtained from the Institute Ethics Committee.

Bronchial asthma was defined as the presence of at least two of the following criteria: history of recurrent or episodic attacks of chest tightness, breathlessness and cough, presence of wheeze on auscultation, and evidence of obstructive defect on spirometry with significant bronchodilator reversibility (BDR).[2]

Patients using oral or inhaled steroids, leukotriene antagonists, or antihistamine drugs in the previous 6 weeks were excluded from the study. Smokers were excluded to avoid the confounding effect of smoking on FeNO and also to avoid inclusion of other obstructive airway diseases and have a more homogeneous population of asthmatics. Patients with acute respiratory tract infection in the past 4 weeks, and those patients who were unable to or unwilling to perform the tests required in the study were also excluded from the study.

Following a detailed clinical examination, the assessment of asthma control was made according to the Global Initiative for Asthma (GINA) guidelines[1,2] and the asthma control test (ACT) questionnaire.[5] Spirometry was performed in all patients and FEV1/forced vital capacity and postbronchodilator responses were noted. Serum total IgE was analyzed by enzyme immunoassay using Phadia 100 ImmunoCap Allergy and Immune Testing equipment. FeNO was measured before any other respiratory tests using a handheld Niox Mino – point-of-care device.[6] This is an electrochemical sensor-based gas analyzer with integrated software to accurately measure nitric oxide molecules at very low concentrations. Patients were advised not to eat or drink or do strenuous exercise for an hour before the test and avoid short-acting inhaled bronchodilators for at least 6 h before testing. All patients were asked to follow the medical advice of their treating physician, and no changes in medications were made by the study team. Patients were also asked to maintain a diary for peak expiratory flow rate (PEFR) monitoring for 1 week after inclusion. PEFR was measured daily early in the morning before bronchodilator therapy using portable peak flow meters, and PEFR variability was calculated as minimum morning prebronchodilator PEFR over 1 week expressed as percentage of the recent best (Min%Max).

After 4–8 weeks, all patients were reviewed for response evaluation, and clinical evaluation, pulmonary function test, FeNO, ACT, and PEFR variability were repeated. Symptom diaries were also reviewed and patients were classified as controlled, partly controlled, and uncontrolled according to GINA guidelines.[2] The details of the medications used during this period were also noted.

Statistical analysis

Data were recorded on a predesigned proforma and managed on Excel spreadsheet. Categorical variables were summarized by frequency (%), and Chi-square test was used to compare them. Quantitative variables were assessed for approximate normality. Variables following approximately normal distribution were summarized by mean ± standard deviation (SD).

Paired *t*-test or Wilcoxon signed-rank test were used for the difference in mean values at baseline and after treatment based on the normality of data. The relationship between FeNO and other parameters was computed by Spearman's rank correlation both at baseline and at follow-up. Analysis of variance was used to compare the FeNO values at baseline and after treatment according to the level of asthma control, and *post hoc* comparison was done using Bonferroni test. Receiver operating characteristic curve was plotted to assess the performance of FeNO in discriminating patients with controlled and uncontrolled asthma. Sensitivity, specificity, positive predictive value and negative predictive value, and likelihood ratios were calculated for FeNO in differentiating patients with controlled and uncontrolled asthma. STATA version 11.0 (StataCorp, Texas) was used for analysis. In this study, all statistical tests were two-tailed, and $P \leq 0.05$ was considered statistically significant.

RESULTS

A total of 151 patients were screened, and 100 of these completed the follow-up assessment. However, PEFR monitoring was available for 49 (49%) patients only [Figure 1]. The study group included 79 men (52.3%) and 72 women (47.6%) with mean (± SD) age of 34.2 ± 11.6 years (range, 14–60 years). The median (interquartile range) duration of illness was 6 years (3–12 years). Among all patients, 62 (41%) had a family history of asthmatic illness and 52 (34.4%) had a history of allergic rhinitis.

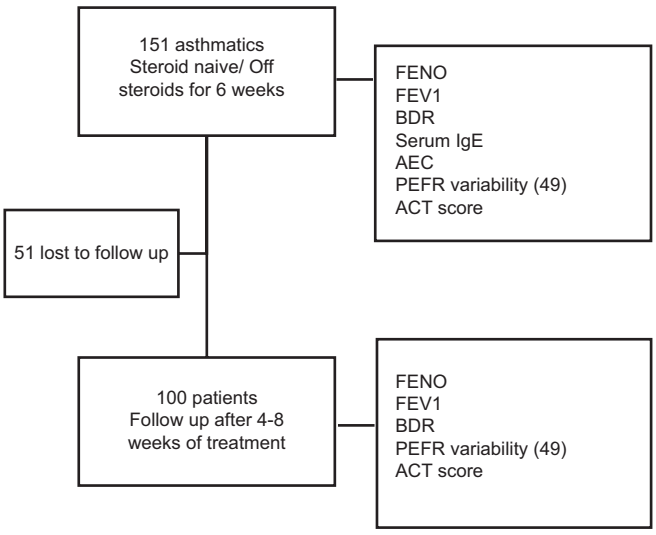

Figure 1: Procedure of patient recruitment and reassessment

After inclusion, patients received treatment based on the discretion of the treating physician. Inhaled corticosteroids (ICS) with long-acting beta-agonists were the most commonly used medications ($n = 92$). Leukotriene antagonists were prescribed to 82% and 6% received systemic steroids. Eight patients were on rescue inhaled short-acting beta-agonists only. All patients received education for inhaler use and need for compliance during assessment. The results of various clinical, physiological, and laboratory parameters at inclusion and follow-up were as summarized in Table 1.

The severity of obstruction was stratified according to the American Thoracic Society guidelines on interpretation of pulmonary function tests[7], and FeNO values were stratified accordingly. Significant increase in FeNO was observed between patients stratified according to severity [Table 2].

The level of control of asthma was also assessed according to GINA guidelines as controlled, partly controlled, and uncontrolled. FeNO values according to asthma control are summarized in Table 3 and were significantly different between groups ($P < 0.001$).

The correlation between various parameters and FeNO values were performed at baseline and at follow-up. A significant correlation was found between FeNO levels and FEV1, BDR, ACT score, PEFR variability, absolute eosinophil count, and IgE levels ($P < 0.001$). The correlation coefficients for each of the variables at baseline and at follow-up were as shown in Table 4. At follow-up, a significant correlation was observed between FeNO values and FEV1, PEFR variability, and ACT score ($P < 0.05$). Of these parameters, however, the strength of correlation was weak with all except ACT score ($r = -0.68$). Similarly, a significant correlation was found between change in FeNO with the change in FEV1, BDR, ACT score, and PEFR variability, with the strength of association strongest with change in PEFR variability, followed by ACT score, and FEV1.

To evaluate the discriminative value of FeNO in differentiating patients with controlled and uncontrolled symptoms, a receiver operating curve was plotted. Using a cutoff value of FeNO ≥48 ppb at baseline and FeNO ≥36 ppb at reassessment, a sensitivity and specificity of 66.6% and 65.5%, respectively, was achieved [Table 5 and Figure 2].

DISCUSSION

The lack of a gold standard monitoring tool for asthma control leads to a marked degree of heterogeneity in methods of assessment. Consequently, validation of a reliable and noninvasive marker for the above purpose is required. In spite of the fact that asthma is an inflammatory airway disorder, till date no inflammatory marker has been included in the monitoring algorithm of asthma. In our attempt to evaluate FeNo as a feasible monitoring tool, we included nonsmokers with newly diagnosed asthmatics who were either treatment naïve or who were off steroid therapy (inhaled and systemic)

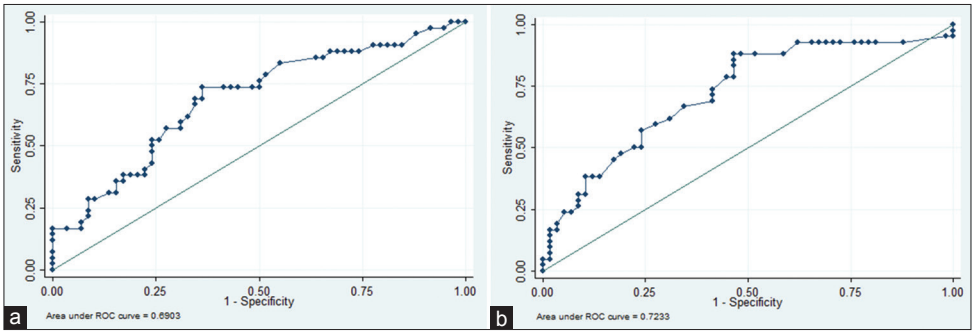

Figure 2: Receiver operating characteristic curve for fractional exhaled nitric oxide at baseline (a) and follow up (b) to discriminate patients with well controlled and uncontrolled symptoms

Table 1: Clinical, physiological, and laboratory parameters at inclusion (*n*=100)

Parameters*	Baseline values	Follow-up values	Mean (range) difference	*P*
FeNO levels (ppb)	45.4±35.9	38.4±23.7	16.2±41.2 (−86-212)	<0.001
FEV1 (% predicted)	66.3±17.0 (28-103)	69.7±11.2	−6.9±14.5 (−59-34.8)	<0.001
FEV1/FVC ratio	70.6±11.8 (34-96.8)	74.8±13.2 (34-114)		
BDR (%)	15 (12-22)	12 (2-32)	6.9±9.9 (−10-30)	<0.001
PEFR variability (Min%Max)	78.8±10.8 (52.9-98.6)	84.6±7.5	−5.7±12.0 (−41.3-22.2)	0.001
ACT score	20.9±2.8 (11-25)	21.4±2.0	−1.1±2.7 (−13-5)	<0.001
Absolute eosinophil count (/μL)	450 (250-770)	NA		
Serum IgE levels (IU/ml)	543 (324-868)	NA		

*All values expressed as mean±SD (range) or median (IQR). NA: Not available, SD: Standard deviation, ACT: Asthma control test, FeNO: Fractional exhaled nitric oxide, IQR: Interquartile range, PEFR: Peak expiratory flow rate, FEV1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, BDR: Bronchodilator reversibility

for the last 6 weeks. Our study group comprised an almost equal proportion of mild and moderately severe asthmatics in contrast to most previous reports that included predominantly milder disease.[8,9] This could probably be attributed to the recruitment of patients from outpatient visits where patients with mild symptoms are likely to present.

Table 2: Fractional exhaled nitric oxide values according to severity of airflow obstruction

Severity of obstruction	FEV1 (% predicted)	*n* (%)	Median (IQR) FeNO (ppb)	*P*
Mild	>70	65 (43)	21 (13-34)	<0.001
Moderate	60-69	32 (21.1)	39 (30-48)	
Moderately-severe	50-59	28 (18.5)	48 (35-64)	
Severe	35-49	19 (12.5)	82 (66-101)	
Very severe	>35	7 (4.6)	132 (98-162)	

All values expressed as frequency (%) or median (IQR). IQR: Interquartile range, FEV1: Forced expiratory volume in 1 s, FeNO: Fractional exhaled nitric oxide

Table 3: Fractional exhaled nitric oxide values according to asthma control

Level of control	Posttreatment values (*n*=100)		*P*
	n (%)	Median FeNO values (ppb)	
Controlled	40 (40)	25.5 (8-131)	<0.001
Partly controlled	41 (41)	35 (6-120)	
Uncontrolled	19 (19)	40 (25-101)	

All values expressed as frequency (%) or median (IQR). IQR: Interquartile range, FeNO: Fractional exhaled nitric oxide

Table 4: Summary of correlations between fractional exhaled nitric oxide and other parameters

Parameter	Correlation coefficient baseline (*n*=151)	Correlation coefficient follow up (*n*=100)	Correlation coefficient for mean difference (*n*=100)
FEV1			
r	−0.78	−0.36	−0.72
P	<0.001	0.01	<0.001
BDR			
r	0.50	0.26	0.46
P	<0.001	0.06	<0.001
ACT score			
r	−0.76	−0.68	−0.73
P	<0.001	<0.001	<0.001
PEFR variability			
r	−0.74	−0.34	−0.85
P	<0.001	0.01	<0.001
AEC			
r	0.30	NA	NA
P	<0.001		
IgE			
r	0.18	NA	NA
P	0.02		

NA: Values not available at follow-up. ACT: Asthma control test, PEFR: Peak expiratory flow rate, FEV1: Forced expiratory volume in 1 s, AEC: Absolute eosinophil count, BDR: Bronchodilator reversibility

We observed that the FeNO values steadily increased as the severity of airflow obstruction worsened among our patients. Our study was not adequately powered to develop the upper cutoff values of FeNO for asthma severity stratification, which might have further established the value of measuring FeNO as a surrogate, or at least a complementary modality for assessing disease severity. The association of FeNO with asthma severity has been demonstrated previously in thirty adolescents, but similar data in adults are sparse.

After 4–6 weeks of treatment that comprised predominantly of ICS, nearly 40% of the patients had achieved symptomatic control. This is comparable to the control achieved in two recent studies, wherein adequate control was achieved in 23.1% and 34.2% patients using the ACT score and GINA guidelines, respectively.[8,9] Overall, compared to baseline, values being higher in uncontrolled asthma compared to patients with well-controlled symptoms. The reduction in FeNO among our patients was less compared to some previous reports, which reported FeNO reduction of >40% in 59 smoking asthmatics (18.1 ppb versus 33.7 ppb).[10] This again may partly be explained by the relatively higher proportion of severe patients in our group, leading to an apparent lower fall in FeNO.

The reliability of FeNO as a marker of asthma control is yet unclear. Our study has shown some degree of correlation between baseline FeNo and other asthma monitoring parameters. The utility of FeNo in discriminating poorly controlled asthma from well-controlled subjects was reported in 274 patients by Kostikas *et al*.[11] They observed that FeNo was higher in poorly controlled subjects but proved inferior to ACT scoring, implying thereby that although FeNo may identify poor asthma control, it cannot replace clinical judgement and may perhaps be useful in a select group of asthmatics only.

A strong correlation was observed among our patients between FeNO and FEV1, PEFR variability, and ACT score at baseline. However, following treatment, the strength of this correlation was maintained with ACT score alone. Our results are comparable to the previous reports by Papakosta *et al*.,[8] who found significant correlations between FeNO and ACT score ($r = -0.211$, $P = 0.007$) at baseline but not after treatment with steroids, and with Senna *et al*.,[12] who found an excellent correlation between exhaled nitric oxide and ACT in 27 newly diagnosed asthmatics ($r = 0.7$, $P = 0.001$). Conversely, Bernstein

Table 5: Sensitivity and specificity of fractional exhaled nitric oxide in discriminating patients with controlled and uncontrolled asthma

Parameter	Cutoff value (ppb)	Sensitivity (%)	Specificity (%)	Correctly classified	Positive LR	Negative LR	AUC
FeNO baseline	≥48	66.6	65.5	66.0	1.9	0.5	0.69
FeNO follow-up	≥36	66.6	65.5	66.0	1.9	0.5	0.72

LR: Likelihood ratio, AUC: Area under the curve, FeNO: Fractional exhaled nitric oxide

et al.[13] evaluated FeNo into two different ethnic groups and found lack of correlation between ACT and FeNo across populations. Thus, it may be inferred by the above results that in steroid naïve asthmatics, FeNO reflects severity of symptoms, airflow obstruction, PEFR variability, and airway hyperresponsiveness.

We also observed a significant correlation between FeNO and FEV1, BDR, PEFR variability, and ACT score after treatment. Although the association of posttreatment FeNO with markers of pulmonary functions, such as FEV1 and PEFR have not been well studied, a weak correlation between ACT score and FeNO in patients already on anti-asthma treatment has been demonstrated previously.[14] The strength of association was stronger in steroid naïve patients than those on steroid therapy. This is compatible with the findings of the most previous studies which showed a weaker correlation of FeNO with pulmonary functions in patients on ICS than those off ICS.[8] The precise reason for this observation is unclear but is probably related to the local anti-inflammatory effect of ICS on airways manifesting as a decline in FeNO.

We found a significant correlation between baseline FeNO and serum IgE and absolute eosinophil count. It has previously been seen that FeNO values are higher in the eosinophilic phenotype of asthma and our results corroborate the hypothesis that FeNO may also contribute to or reflect the degree of airway hyperresponsiveness.[15,16] However, whether this association is maintained after ICS treatment could not be assessed since follow-up IgE, and AEC values were not available.

We also tried to determine a FeNO value which could reliably differentiate well controlled from poorly controlled asthma. However, as evident from Figure 2, we found that FeNO has poor discriminative value for predicting asthma control when used as a single test both at baseline or following treatment. Previous investigators have made similar attempts with variable results. In an analysis of 274 patients with asthma, the presence of FeNO >30 ppb indicated poor control in 88.3% of the patients and provided an area under curve of 0.790 for identifying poorly controlled asthma, performing better in nonsmokers.[11] Ozier *et al*.[17] demonstrated that a FeNO cutoff value of 31 ppb was able to predict the loss of control in 60% of previously controlled asthmatics, with a negative predictive value of 97%. Michils *et al*.[18] also showed that a decrease >40% in FeNo indicates adequate asthma control with a positive predictive value of 83%. Using receiver operating characteristics curve analyses, they proposed a higher cutoff value of 45 ppb to exclude well-controlled asthma with a predictive value of 88%. It has also been suggested that the clinical value of measuring FeNO is seen in active smoking asthmatics as well.[10] On the other hand, Jones *et al*.[19] reported a poor sensitivity and negative predictive value using FeNO measurement (25% for both) for predicting a loss of control after steroid withdrawal. Similarly, no difference in FeNO was observed among asthma patients with maintained control or loss of control following reduction of ICS dose over a 3 months period.[4] It was thus inferred that either FeNO does not correlate well enough with airway inflammation in mild-to-moderate asthma or the episodes of loss of control were due to reasons other than increased airway inflammation. However, it must be noted that most of these studies were different from ours in that they included a higher proportion of persistent and atopic asthma[18] or a much milder asthma group.[17]

Our study had a few limitations. The study population was heterogeneous in the sense that it included patients across the spectrum of asthma severity. Approximately, half of the patients had relatively mild symptoms. Although this was done to simulate a real-life scenario, disease severity would have affected the choice of treatment. Second, treatment was physician dependent and not standardized for all patients. We did not assess the atopic status of the patients which may have a bearing on the results. Compliance to the treatment prescribed was not ascertained, and this might have affected the level of asthma control. It may be argued that FeNO may be influenced by several patient-related modifiable and nonmodifiable factors such as age, sex, height, atopy, and smoking status, although this was not found to be the case in a recent analysis of absolute versus % predicted FeNO levels in 52 asthma patients.[20] In spite of these shortcomings, we feel that the results add substantially to the existing knowledge regarding the clinical relevance of FeNO in asthma monitoring. Further studies using a protocolized management strategy and homogenous patient population based on disease severity and a longer follow-up could provide further clarity on the practical use of FeNO.

CONCLUSION

We conclude that FeNO correlates well with traditionally used markers of asthma control and may be a useful adjunctive tool for monitoring asthma. However, it lacks sufficient sensitivity and specificity to function as a single parameter for asthma control in treatment naïve as well as in patients on ICS treatment. In settings, where self-monitoring with PEFR is unreliable or difficult, FeNO may prove useful as a simple noninvasive measure of asthma control. It has the advantage of ease of performance even in patients with severe airflow obstruction. At the same time, it must also be emphasized that serial measurements seem to be more informative in a given patient than single time values. Further studies are required to assess the role of FeNO in assessing response to therapy, titrating ICS therapy based on FeNO, and evaluating the discriminative value of FeNO between asthma and related conditions such as allergic bronchopulmonary aspergillosis.

Thus, we conclude that FeNO may be used as an adjunctive noninvasive modality to assess asthma

control in both steroid naïve asthmatics and asthmatics on treatment. However, the suboptimal sensitivity and specificity may limit its use as a point-of-care single monitoring tool.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM, *et al*. A summary of the new GINA strategy: A roadmap to asthma control. Eur Respir J 2015;46:622-39.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2015. Available from: www.ginasthma.org. [Last accesssed on 2016 Jan 01].
3. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, *et al*. An official ATS clinical practice guideline: Interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011;184:602-15.
4. Wilson E, McKeever T, Hargadon B, Hearson G, Anderson J, Hodgson D, *et al*. Exhaled nitric oxide and inhaled corticosteroid dose reduction in asthma: A cohort study. Eur Respir J 2014;44:1705-7.
5. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, *et al*. Development of the asthma control test: A survey for assessing asthma control. J Allergy Clin Immunol 2004;113:59-65.
6. Alving K, Janson C, Nordvall L. Performance of a new hand-held device for exhaled nitric oxide measurement in adults and children. Respir Res 2006;7:67.
7. Gardner RM, Hankinson JL. Standardization of spirometry-1987 ATS update (American Thoracic Society). J Occup Med 1988;30:272-3.
8. Papakosta D, Latsios D, Manika K, Porpodis K, Kontakioti E, Gioulekas D. Asthma control test is correlated to FEV1 and nitric oxide in Greek asthmatic patients: Influence of treatment. J Asthma 2011;48:901-6.
9. Visitsunthorn N, Prottasan P, Jirapongsananuruk O, Maneechotesuwan K. Is fractional exhaled nitric oxide (FeNO) associated with asthma control in children? Asian Pac J Allergy Immunol 2014;32:218-25.
10. Michils A, Louis R, Peché R, Baldassarre S, Van Muylem A. Exhaled nitric oxide as a marker of asthma control in smoking patients. Eur Respir J 2009;33:1295-301.
11. Kostikas K, Papaioannou AI, Tanou K, Giouleka P, Koutsokera A, Minas M, *et al*. Exhaled NO and exhaled breath condensate pH in the evaluation of asthma control. Respir Med 2011;105:526-32.
12. Senna G, Passalacqua G, Schiappoli M, Lombardi C, Wilcock L. Correlation among FEV, nitric oxide and asthma control test in newly diagnosed asthma. Allergy 2007;62:207-8.
13. Bernstein JA, Davis B, Alvarez-Puebla MJ, Nguyen D, Levin L, Olaguibel JM. Is exhaled nitric oxide a useful adjunctive test for assessing asthma? J Asthma 2009;46:955-60.
14. Shirai T, Furuhashi K, Suda T, Chida K. Relationship of the asthma control test with pulmonary function and exhaled nitric oxide. Ann Allergy Asthma Immunol 2008;101:608-13.
15. Jatakanon A, Lim S, Kharitonov SA, Chung KF, Barnes PJ. Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma. Thorax 1998;53:91-5.
16. Syk J, Undén AL, Alving K. Relationship between exhaled nitric oxide and IgE sensitisation in patients with asthma: Influence of steroid treatment. Clin Respir J 2009;3:143-51.
17. Ozier A, Girodet PO, Bara I, Tunon de Lara JM, Marthan R, Berger P. Control maintenance can be predicted by exhaled NO monitoring in asthmatic patients. Respir Med 2011;105:989-96.
18. 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.
19. Jones SL, Kittelson J, Cowan JO, Flannery EM, Hancox RJ, McLachlan CR, *et al*. The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. Am J Respir Crit Care Med 2001;164:738-43.
20. Leon de la Barra S, Smith AD, Cowan JO, Peter Herbison G, Robin Taylor D. Predicted versus absolute values in the application of exhaled nitric oxide measurements. Respir Med 2011;105:1629-34.