RESEARCH PAPER

Fractional Exhaled Nitric Oxide for Identification of Uncontrolled Asthma in Children

RAJ KUMAR MEENA, DINESH RAJ, RAKESH LODHA AND S K KABRA

From Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi , India.
Correspondence to: Professor SK Kabra, Division of Pulmonology, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110 029, India. skkabra@hotmail.com
Received: June 22, 2015; Initial review: August 20, 2015; Accepted: January 14, 2016

Objectives: To determine the utility of Fractional Exhaled Nitric Oxide (FENO) in the identification of uncontrolled asthma in children on therapy, and to identify its cut-off value for determining asthma control.

Methods: 207 children (age 5-15 y) with physician-diagnosed asthma on therapy with at least 12 months follow up were enrolled. Spirometry and FENO measurements were performed. Asthma control was assessed as per GINA guidelines. Sensitivity and specificity of various cut-off values of FENO (15 ppb, 20 ppb, 25 ppb, 30 ppb) for identification of status of control of asthma were calculated.

Results: 156 (75%) children had uncontrolled or partly controlled asthma and 51 children were assessed to have controlled asthma. Median (IQR) FENO in children with controlled and uncontrolled asthma was 16 (11-23) ppb and 13 (11-25) ppb, respectively (P=0.26). No FENO cut-off had a reasonable combination of sensitivity and specificity to discriminate between controlled and uncontrolled asthma.

Conclusion: FENO, in itself, does not have good discriminatory value in assessment of controlled and uncontrolled asthma in children on asthma therapy.

Keywords: *Airway inflammation, Asthma control, Diagnosis, Spirometry*

Asthma is the commonest chronic respiratory disorder encountered in clinical practice in children. Standard guidelines are available which help in monitoring of asthma based on clinical assessment and spirometry [1]. Clinical assessment may have problems of under- or over-reporting, and presence of a normal spirometry does not necessarily establish asthma control. Fractional exhaled nitric oxide (FENO), which is an indirect evidence of airway inflammation, has recently been suggested to help in guiding routine management of asthma [2]. As the target of asthma management is control of airway inflammation and FENO is a surrogate of airway inflammation, it is imperative to relate FENO to asthma control.

FENO is a simple non-invasive test and can be easily measured in pediatric office practice. FENO measurements decrease in a dose dependent fashion in response to treatment with inhaled corticosteroids (ICS) [3,4]. FENO has been shown to correlate with the degree of airway hyper-responsiveness, and the numbers of eosinophils in induced sputum [5]. Few studies have evaluated the relationship between asthma control as per Global Initiative for Asthama (GINA) guidelines and FENO measurements [6-8]. Data are limited from India on the utility of FENO in management of childhood asthma [9]. We prospectively evaluated the utility of FENO in identification of uncontrolled asthma in selected Indian children with asthma. The secondary objective was to identify cut-off value of FENO for determining asthma control.

METHODS

This cross-sectional study was carried out in the Pediatric Chest Clinic of a tertiary-care hospital in Northern India over 19 months. Children aged between 5-15 years with physician-diagnosed asthma, on treatment with a regular follow up of at least 12 months, were enrolled in the study after obtaining informed consent from parents. Children not able to perform spirometry and those with acute exacerbation of asthma (any severity) were excluded from the study.

Details of history and physical examination were recorded in a structured form. FENO was measured by using NIOX Mino (Aerocrine AB, Solna, Sweden) portable machine using standard guidelines [2]. Spirometry was performed using portable spirometer (Superspiro MK2 Micro Medical Ltd, UK) as per American Thoracic Society (ATS) guidelines [10]. Asthma control was assessed as per GINA guidelines [1]. The study was approved by the Institutional ethics committee of our institute.

From the existing information, it was expected that 90% of the partly controlled/uncontrolled asthma would have FENO of ≥20 ppb. Required sample size for estimating this sensitivity with a precision of 7.5% and confidence level of 95% was 63. From the data of our Pediatric Chest Clinic (unpublished), we expected 30% of asthmatics might be partly controlled/uncontrolled. Therefore, we needed to screen 210 children with asthma to identify 63 children with partly controlled/ uncontrolled asthma.

Statistical analysis: Statistical analysis was performed using Stata 9.0 statistical software. Number of children with uncontrolled or partly controlled asthma with exhaled NO ≥20 ppb were calculated to determine the sensitivity. For the purpose of analysis, uncontrolled asthma included both partly controlled and uncontrolled children as per GINA guidelines. Receiver operating characteristics (ROC) curves were constructed using various cut-off values of FENO and optimal cut off value was calculated. A *P* value of less than 0.05 was considered significant.

RESULTS

A total of 207 children with asthma were enrolled in the study. Median (IQR) FENO was 14 (10, 23) ppb. Minimum FENO was 5 ppb (<5 value was considered equal to 5 ppb) and maximum FENO value was 110 ppb. Seventy-one (34.3%) children had an FENO value of 20 ppb or above. Based on the GINA guidelines, out of 207 study participants, 156 (75%) had uncontrolled or partly controlled asthma. Fifty-one (25%) participants were assessed to have controlled asthma. Median (IQR) FENO in children with controlled asthma was 16 (11, 23) ppb as compared to 13 (11, 25) ppb for uncontrolled asthma (*P*=0.26) (***Fig* 1**). The area under the curve was 0.448, suggesting poor discriminatory value of FENO for control of asthma (***Fig.* 2**). ***Table* I** shows sensitivity and specificity of various cut-off values of FENO (15 ppb, 20 ppb, 25 ppb, 30 ppb) for identification of uncontrolled asthma. None of the cut-off values had a good discriminatory value to identify asthma control. We compared the characteristics of children with controlled and uncontrolled asthma (***Table* II**). The groups did not differ in terms of baseline variables (age, sex, family history of asthma or allergy). Uncontrolled children had poorer lung function and were more likely to be using higher doses of inhaled corticosteroids (***Table* II**).

DISCUSSION

In this cross-sectional study on 207 children, we observed that FENO has a poor discriminatory power to differentiate between controlled and uncontrolled/partly controlled asthma as assessed by GINA guidelines. Earlier studies have evaluated the utility of FENO measurements in assessing asthma control, and there is evidence in support [11-15] as well as against [16-19] agreement of FENO with different measures of asthma control.

GINA guidelines assess control over the preceding four weeks. On the other hand, FENO measurement is a

TABLE I DIFFERENT CUT-OFFS OF FENO FOR ASSESSMENT OF UNCONTROLLED ASTHMA

FENO cut-off value	*Sensitivity (%)*	*Specificity (%)*
≥15 ppb	46.2	41.9
≥20 ppb	33.3	62.7
≥25 ppb	25.6	80.4
≥30 ppb	21.2	84.3

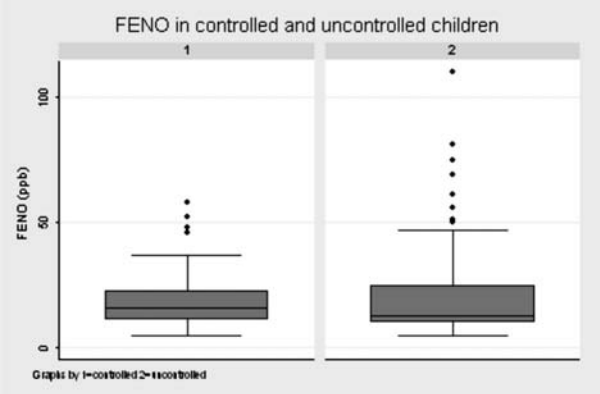

FIG. 1 *Box-plot graph showing the distribution of FENO values in children with controlled and uncontrolled asthma.*

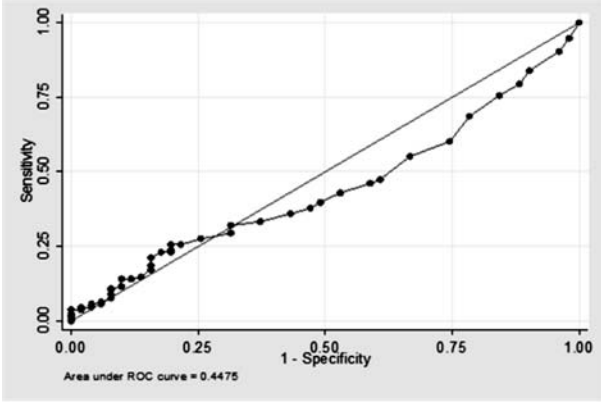

FIG. 2 *ROC curve at different cut off values of FENO.*

TABLE II COMPARISON OF CHARACTERISTICS OF CHILDREN WITH CONTROLLED AND UNCONTROLLED ASTHMA

	Controlled, n=51	*Uncontrolled, n=156*	*P value*
Age, mean (SD)	120.5 (34.4)	123.0 (37.0)	0.67
Males, *n* (%)	35 (68.6)	119 (76.3)	0.27
Family history of asthma or allergy, *n* (%)	34 (66.7)	94 (60.3)	0.66
ICS doses			
Low, *n* (%)	40 (78.4)	95 (60.9)	0.02
High, *n* (%)	11 (21.6)	61 (39.1)	
FENO, median (IQR)	16 (11-23)	13 (11-25)	0.26
FENO < 20 ppb, *n* (%)	32 (63)	104 (67)	0.609
FENO ≥20 ppb, *n* (%)	19 (37)	52 (33)	
FEV_1 % predicted, mean (SD)	97.8 (13.0)	87.3 (18.2)	0.0002
PEFR % predicted, mean (SD)	91.2 (17.1)	75.5 (19.8)	<0.0001
FEV_1/FVC ratio % predicted, mean (SD)	101.1 (10.9)	97.9 (11.0)	0.0681
Family history of asthma or allergy, *n* (%)	34 (66.7)	94 (60.3)	0.6692

reflection of inflammation on the day of assessment. There is a possibility that a measure of control which takes into account the previous four weeks, and FENO measurement which assesses inflammation on the day of assessment, may not show good agreement, as shown by our study.

Corticosteroids (either inhaled or systemic) are known to bring down FENO levels. A recent study of two distinct populations (United States and Spain) showed that the correlation between asthma control (as defined by Asthma Control Test [ACT]) and FENO was only observed for the Spain site in ICS-naive patients [16]. They concluded that lack of correlation of ACT with FENO probably reflects the heterogeneity of asthma patients who have varied asthma severity and treatment regimens. A longitudinal study in unselected asthmatic patients by Michils, *et al*. [20] showed that FENO was a useful marker of asthma control for those patients treated with low doses of ICS but not for patients on high-to-medium ICS. They suggested that changes in FENO values, rather than absolute cut-off points (i.e. personalized FENO profiles), may be more useful. This suggests that ICS doses might have to be taken into account when using FENO to assess asthma control.

Khalili, *et al*. [7] assessed the correlation between FENO and asthma control (using 5 different asthma control evaluation tools) in 100 asthmatics (children and adult). No significant association was found between FENO level and asthma control based on Asthma Control Questionnaire (ACQ) (P=0.99), ACT (P=0.53), National Asthma Education and Prevention Program (NAEPP) (P=0.53), Joint Task Force Practice parameter (JTFPP) (P=0.30), or GINA (P=0.86) criteria. However, they concluded that commonly used asthma control evaluation tools do not accurately reflect the status of airway inflammation as reflected by FENO, and use of such tools may lead to inappropriate clinical decision making and result in suboptimal short-term and long-term care. In our study, FENO had a poor sensitivity and specificity in predicting asthma control. An earlier study noted a weak but positive correlation between FENO and not well-controlled asthma [19]. Yavuz, *et al*. [21] evaluated the role of the C-ACT and FENO in identifying children with not well-controlled asthma. C-ACT score of ≤22 had 69% sensitivity and 77% specificity in identifying not well-controlled asthma, whereas an FENO value of ≥19 ppb had 61% sensitivity and 59% specificity in patients with at least 3 visits.

The present study has certain limitations. Various factors/comorbidities affecting FENO measurements including atopy, allergic rhinitis, eczema, sleep-disordered breathing, and allergen exposure were not measured and adjusted for in the analysis. The shorter exhalation used for FENO measurements of younger children (5-8 years) may also have caused bias.

To summarize, FENO measurement does not seem to have good discriminatory value in assessment of controlled and uncontrolled asthma in children between 5-15 years of age on treatment for asthma. Monitoring of children with asthma should routinely include standard asthma control tools and spirometry. Measurement of FENO may give useful information regarding airway inflammation but cannot be used as a surrogate for asthma control.

WHAT IS ALREADY KNOWN?

- Asthma control can be objectively documented with Fractional exhaled nitric oxide (FENO) values

WHAT THIS STUDY ADDS?

- FENO values do not have discriminatory value for identification of asthma control using GINA guidelines for assessment of asthma.

Contributors: RKM: study design, data collection, analysis and manuscript writing, DR: data analysis and manuscript writing, RL: study design, analysis and manuscript writing; SKK: study design, data analysis, and manuscript writing. He will act as guarantor for the study.
Funding: M/s Aerocrine provided material for carrying out this research. M/s Aerocrine did not have any role in study design, data collection, data analysis or manuscript writing; *Competing interests:* None stated.

REFERENCES

1. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2015. Available from: *http://www.ginasthma.org/.* Accessed 13.10.2015
2. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, *et al*., on behalf of ATS Committee on Interpretation of Exhaled Nitric Oxide (FENO) for Clinical Application. 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.
3. Kharitonov SA, Donnelly LE, Montuschi P, Corradi M, Collins JV, Barnes PJ. Dose-dependent onset and cessation of action of inhaled budesonide on exhaled nitric oxide and symptoms in mild asthma. Thorax. 2002;57:889-96.
4. Jones SL, Herbison P, Cowan JO, Flannery EM, Hancox RJ, McLachlan CR, et al. Exhaled NO and assessment of anti-inflammatory effects of inhaled steroid: dose-response relationship. Eur Respir J. 2002;20:601-8.
5. 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.
6. 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.
7. 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.
8. Waibel V, Ulmer H, Horak E. Assessing asthma control: symptom scores, GINA levels of asthma control, lung function, and exhaled nitric oxide. Pediatr Pulmonol. 2012;47:113-8.
9. Raj D, Lodha R, Mukherjee A, Sethi T, Agrawal A, Kabra SK. Fractional exhaled nitric oxide in children with acute exacerbation of asthma. Indian Pediatr. 2014;51:105-11.
10. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, *et al*. Standardisation of spirometry. Eur Respir J. 2005;26:319-38.
11. Volbeda F, Broekema M, Lodewijk ME, Hylkema MN, Reddel HK, Timens W, *et al*. Clinical control of asthma associates with measures of airway inflammation. Thorax. 2013;68:19-24.
12. 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.
13. Delgado-Corcoran C, Kissoon N, Murphy SP, Duckworth LJ. Exhaled nitric oxide reflects asthma severity and asthma control. Pediatr Crit Care Med. 2004;5:48-52.
14. Meyts I, Proesmans M, De Boeck K. Exhaled nitric oxide corresponds with office evaluation of asthma control. Pediatr Pulmonol. 2003;36:283-9.
15. Sippel JM, Holden WE, Tilles SA, O'Hollaren M, Cook J, Thukkani N, *et al*. Exhaled nitric oxide levels correlate with measures of disease control in asthma. J Allergy Clin Immunol. 2000;106:645-50.
16. 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.
17. Green RJ, Klein M, Becker P, Halkas A, Lewis H, Kitchin O, *et al*. Disagreement between common measures of asthma control in children. Chest. 2013; 143:117-22.
18. Ito Y, Adachi Y, Itazawa T, Okabe Y, Adachi YS, Higuchi O, *et al*. Association between the results of the childhood asthma control test and objective parameters in asthmatic children. J Asthma. 2011;48:1076-80.
19. Vijverberg SJ, Koster ES, Koenderman L, Arets HG, van der Ent CK, Postma DS, *et al*. Exhaled NO is a poor marker of asthma control in children with a reported use of asthma medication: a pharmacy-based study. Pediatr Allergy Immunol. 2012;23:529-36.
20. Michils A, Baldassarre S, Van Mvylam A. Exhaled nitric oxide and asthma control: A longitudinal study in unselected patients. Eur Respir J. 2008;31:539-46.
21. Yavuz ST, Civelek E, Sahiner UM, Buyuktiryaki AB, Tuncer A, Karabulut E, *et al*. Identifying uncontrolled asthma in children with the childhood asthma control test or exhaled nitric oxide measurement. Ann Allergy Asthma Immunol. 2012;109:36-40.