Fractional exhaled nitric oxide (FeNo) in different asthma phenotypes

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ABSTRACT

Fractioned exhaled nitric oxide (FeNO) is a noninvasive marker of inflammation in asthmatic patients. FeNO can be used to monitor airway inflammation, but individual responses make tailored interventions based on FeNO difficult. The correlation between the asthma control test (ACT), FEV_1, and FeNO was evaluated in this study to ascertain the correct usage of FeNO with different asthma phenotypes regarding their control, allergy, comorbidity, obesity, age, smoking status, and severity. ACT, pulmonary function, and FeNO in 416 asthmatic patients on combined therapy were retrospective evaluated. Correlations between these parameters and the FeNO levels in different asthma phenotypes were calculated. In the study population, FeNO was 31.8 ± 28.5 parts per billion (ppb), FEV_1 was 83.4 ± 19% and ACT was 19 ± 5.2. ACT scores were negatively correlated with FeNO ($r = -0.31$; $p = 0.002$). FeNO was different in patients with positive and negative skin-prick test ($p < 0.05$), with and without allergic rhinitis ($p < 0.01$), and with and without allergic conjunctivitis ($p < 0.01$). Significantly higher FeNO levels were found with logistic regression analysis only in patients with a history of emergency room visits (ERVs) ($p = 0.024$). The rate of the ERV of the patients with an ACT score more than or equal to 20 and with a FeNO value of more than 35 ppb was 22.9%, but with a FeNO value of less than 35 ppb was 6.5% ($p = 0.004$). Allergy and allergic comorbidities may lead to an increase in FeNO levels. Patients with a history of ERV have markedly higher FeNO levels, although they have an ACT score more than or equal to 20.

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The characteristics of controlled, partly controlled, and uncontrolled asthmatic cases were outlined in the Global Initiative for Asthma (GINA) Guidelines based on symptoms and the results of respiratory function testing.[1] The guidelines also declared that simple questionnaires such as the asthma control test (ACT) were good tools for patient assessment.[2] Accordingly, the Turkish version of ACT was used throughout this study.[3]

To determine the level of airway inflammation, various markers such as bronchial hypersensitivity tests, induced sputum analysis, and fractioned exhaled nitric oxide (FeNO) have been used. Some studies have suggested that monitoring treatment according to these markers will allow for better control to be achieved.[4,5] FeNO measurement stands out as the easiest and most noninvasive alternative among this group of markers. However, one problem related to the use of FeNO for facilitating better control is that conflicting results can be produced and that these alterations of FeNO in different asthma cases are omitted in clinical usage.[5]

ACT, spirometry, and FeNO were measured routinely for assessing asthma control in our patients receiving controller therapy with inhaled steroids and long-acting β-agonists. We experienced some confounding data with FeNO, which we hypothesized may be related to patient phenotype. The aim of this real life study was to investigate retrospectively the correlation of FeNO and ACT measurements with one another and to evaluate FeNO levels in different asthma phenotypes regarding their control, allergy, comorbidity, obesity, age, smoking status, and severity to assess the instability of this measurement, which can be affected by many internal factors.

METHODS

The study was conducted by retrospectively scanning the files of 982 asthma patients who were admitted to our asthma outpatient clinic between January 2008 and December 2013. The study was approved as a retrospective observational study by Cerrahpasa Faculty of Medicine Institutional Review Board (number 604/02-8890). A total of 416 patients who met the study criteria were selected. The last control visit was selected for patients who met the study criteria many times.

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FeNO, ACT, and pulmonary function in 416 asthmatic patients on combined therapy (long-acting β-agonist and inhaled corticosteroids) were retrospectively evaluated. The correlation among these markers and the results of FeNO in different asthma phenotypes were calculated.

Study Population

Study inclusion criteria included the following: 1) patients over 15 years of age who had been on inhaled corticosteroids and long-acting β-agonist for at least three months; 2) patients who had been diagnosed with asthma within the last three months or longer and had previously received treatment for asthma and had an outpatient clinic file at our hospital with all demographic data; and 3) that spirometric examination, ACT, and FeNO measurements were made during the same visit to the outpatient clinic. Asthma severity was classified by the frequency of asthma symptoms, pulmonary function tests, and medication requirements according to the asthma guideline.[1] Other recorded information included the results of skin-prick tests, emergency room visits (ERVs), and hospitalization status in the last year, comorbid conditions, and smoking habits. The data were analyzed in terms of their correlation and interaction with each other.

Study exclusion criteria were 1) cases who were suffering an asthma exacerbation (those who required rescue therapy or were using rapid acting β-agonist more than four times a day for three consecutive days); 2) current use of oral steroids; 3) use of oral steroids within the last three weeks; 4) spirometric examination, ACT, and FeNO measurement not being performed during the same admission to the outpatient clinic, or where tests were deemed invalid as the patient did not take the measures that would affect these tests; 5) cases with a history of infection within the last three weeks; and 6) patients not adhering to prescribed therapies or using incorrect inhaler technique.

Test and Laboratory Parameters

Exhaled nitric oxide measurement. Before spirometry analyses, FeNO parts per billion (ppb) was measured (online) at an exhalation flow rate of 0.05 L/s, during single exhalation, using a portable nitric oxide analyzer device (NIOX MINO Airway Inflammation Monitor; Aerocrine AB, Solna, Sweden). The measurement unit was expressed as ppb. The FeNO measurements were performed according to the American Thoracic Society and European Respiratory Society 2005 guidelines methods.[6] In line with American Thoracic Society and European Respiratory Society guidelines, the normal exhaled NO values during measurements were set as 5–35 ppb for healthy adults and 5–25 ppb for children.[6]

Asthma control test. ACT is a patient-based, five-item questionnaire that can be self-administered by the patient and that is used to identify patients with insufficient asthma control.[2] Patients with ACT scores more than or equal to 20 were considered to be under control (controlled), whereas patients with ACT scores less than or equal to 19 were considered as not being under control (uncontrolled).

Pulmonary function tests. All of the functional measurements were performed according to the methods of the ERS/ATS Task force.[7] The spirometry tests were performed using the ZAN 100 Flow Handy II Germany spirometer device.

Skin test. All patients followed in our asthma outpatient clinic had an epicutaneous prick allergy test (ALK, Albello, Denmark) in the volar surface of the forearm between the wrist and the antecubital fossa, using 11 different allergen extracts.

Body mass index (BMI), which is used as an indicator of relative obesity, was calculated according to the formula BMI = weight (kg)/height^2 (m^2). According to the World Health Organization criteria, those with 40 more than or equal to BMI more than or equal to 30 were considered obese.

Statistical Evaluation

SPSS 15.0 software was used for statistical evaluations. Significance level was set as $p < 0.05$ for all statistical calculations. The Pearson correlation test was used to evaluate the correlation between ACT, FeNO, $\%FEV_1$, asthma duration, and BMI, whereas the Spearman correlation test was applied to evaluate the correlation between ACT, FeNO, and asthma level. The Student's *t*-test was employed in the univariate analysis of ACT and FeNO with gender, hospitalization history, occurrence of ERVs, smoking habits, allergic rhinitis, conjunctivitis, dermatitis, and skin test. Multivariate logistic regression analysis was employed to determine the factors that cause high FeNO in different asthma cases.

RESULTS

A total of 416 patients were included in the study: 122 male (29.3%) and 294 female (70.7%) patients, with a mean age of 41.9 ± 13.9 years. A minority of the patients were currently smoking (8.5%), 16.9% had quit smoking, and 74.6% had never smoked. An ERV within the last year was recorded for 16.8% of the patients, and hospitalization was reported in 5.8% of the total patients.

The percentage of patients with allergic or nonallergic rhinitis was 66.4%, with allergic conjunctivitis was 22.5%, and with atopic dermatitis was 14.4%. Gastro-

esophageal reflux occurred in 26.1%. A positive skin-prick test was recorded in 57.4% of the patients, with 96% having mite sensitivity, 12% having pollen sensitivity, 11% having mold sensitivity, and 3% having cat sensitivity. Obesity according to BMI was recorded in 27.7% of the patients.

In 63% of the cases, an ACT score of 20 or above and an FeNO value less than 35 ppb were recorded. These patients were evaluated to be fully stable or under control. A total of 37% of cases had an ACT score of 20 and above with a FeNO value of over 35 ppb.

The average patient FeNO value was 31.8 ± 28.5 ppb and the average ACT test score of our patients was 19.0 ± 5.2 points. A negative correlation was identified between the ACT score and FeNO ($p < 0.002$, $r = -0.31$). The FEV_1% predictive value of our patients was determined as 83.4 ± 19.3%. FeNO levels were not correlated with FEV_1. A positive correlation was identified between the ACT score and the percentage of predicted FEV_1 ($p < 0.001$, $r = 0.22$). A total of 32% of our patients had ACT more than or equal to 20 and FEV_1 less than 80%; the BMI in these patients was not elevated in comparison with the remaining group ($p > .05$). No correlation was identified between the FeNO level and the severity level of asthma.

The duration of asthma in our patients was 11.5 ± 9.4 years. A negative correlation was identified between FeNO and asthma duration ($p = 0.008$, $r = -0.15$). No correlation was identified between FeNO and BMI. The average age of our patients was 41.8 ± 13.9 years. A negative correlation was identified between patient age and FeNO levels ($p < 0.009$, $r = -0.13$).

The FeNO levels in different groups are shown in Table 1. Upon analyzing FeNO levels with respect to various patient variables, significant differences were identified according to gender ($p < 0.001$), results of skin-prick tests ($p < 0.05$), having undergone an ERV within the last year ($p < 0.01$), allergic rhinitis ($p < 0.01$), and allergic conjunctivitis ($p < 0.01$). No difference was identified in FeNO levels according to smoking status and atopic dermatitis ($p > .05$). Significantly high FeNO levels were found with logistic regression analysis only in patients with a history of ERV ($p = 0.024$). The rate of the ERV of the patients with an ACT score more than or equal to 20 and with a FeNO value of more than 35 ppb was 22.9%, but the rate of the ERV of the patients with an ACT score more than or equal to 20 and with a FeNO value of less than 35 ppb was 6.5% ($p = 0.004$).

Table 1. **FeNO levels in different patient groups**

	Positive or Yes	Negative or No
Female	29.3 ± 25.1	37.9 ± 34.7***
Age ≥ 60	20.4 ± 12.5	33.2 ± 29.5***
BMI ≥ 30	26.7 ± 17.7	31.3 ± 27.6
Smoking history	36.9 ± 42.4	31.9 ± 20.8
Allergic rhinitis	36.0 ± 30.2**	27.9 ± 22.1
Allergic conjunctivitis	43.6 ± 42.8**	30.3 ± 21.7
Atopic dermatitis	34.8 ± 23.2	32.8 ± 29.2
Gastroesophageal reflux	32.0 ± 22.4	33.5 ± 30.3
Last year ERV	41.6 ± 30.7**	31.3 ± 27.4
ACT ≥ 20	27.2 ± 15.2	41.1 ± 37.0***
FEV_1 ≥ 80%	31.8 ± 24.7	33.9 ± 34.5
Skin prick test	39.8 ± 32.9*	29.7 ± 22.4

Data are shown as the mean ± SD.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$ indicate significantly higher FeNO than the other group.*
FeNO = fractioned exhaled nitric oxide; ERV = emergency room visit; BMI = body mass index; ACT = asthma control test.

DISCUSSION

The study has some limitations as a retrospective observational study. Although we had a large number of asthma outpatient cases (n = 982), only 416 met the inclusion criteria. In addition, we could not provide all the parameters of our patients before treatment as our clinic is in a university hospital.

The value of FeNO measurement as an adjunct to clinical assessment of asthma control is still unclear based on a review of studies concerned with this topic.[5,8,9] In this study, a negative correlation was identified when comparing ACT scores with levels of FeNO ($p < 0.002$, $r = -0.31$). The poor correlation result was attributed to multiple patient factors such as different endotypes and phenotypes and different controller therapies with inhaler corticosteroids and LABA. A total of 63% of cases had an ACT score of 20 or above and an FeNO value below 35 and could be evaluated as controlled. In 37% of cases, the ACT score was below 20, despite a low FeNO value. In these cases, when we take into account factors other than inflammation that may decrease ACT, comorbid diseases such as gastroesophageal reflux and psychological disorders may be considered. Cases with an ACT score of 20 and above and an FeNO value of over 35 may be due to inflammation not being reflected in the ACT, such as a positive skin-prick test, having allergic rhinitis, or the possibility of small airway disease in some asthma cases. Studying alveolar NO concentration might be useful in this population.[10–12] Therefore, this situation should be taken into consideration alongside other factors when reviewing asthma treatment.

No correlation was observed between percentage of predicted FEV_1 and FeNO levels. This is because al-

though FeNO reflects actual airway inflammation, FEV_1 measures airway calibre or indirectly indicates airway inflammation. In a study conducted on 450 children of 7–12 years of age, a significant correlation was observed between FeNO and blood eosinophils, especially in those with atopy. In the same study, no correlation was identified between FeNO and spirometry measurements once more.[13] In a study conducted on asthmatic children, Mappa *et al.* found FeNO to be associated with airway hypersensitivity and atopy. However, they also demonstrated that FeNO was not correlated with spirometry measurements.[14]

No correlation was identified with the FeNO level and asthma severity in this study. Farrente *et al.* indicated that the heterogeneity of problematic severe asthma greatly limits the utility of FeNO alone as a biomarker of inflammation.[15] In a similar study, it was reported that FeNO levels correlated with respiratory tract inflammation but did not provide information regarding the nature and severity of asthma.[16]

NO was lower in both healthy smokers and asthmatic smokers. Furthermore, smoking acutely reduces NO levels and increases H_2O_2 levels.[17] In our study, no significant difference in FeNO was found between those who had a history of smoking and those who did not. We hypothesize that smoking asthmatics might have other comorbidities that increase FeNO levels, which could affect our ability to identify a significant difference.

In our study, there was a negative correlation between age and FeNO levels ($p = 0.009$, $r = -0.13$). In terms of gender, there was a significant difference in FeNO levels between men and women ($p < 0.001$). The gender difference in FeNO was not attributed to BMI or spirometry findings, which is consistent with other studies.[18,19] For example, in one study, FeNO was 25% lower in women and 60% higher in those with atopy but was not significantly affected by weight, height, or pulmonary function.[18]

Despite the fact that obesity has been linked to an increase in the prevalence of asthma, a correlation between body fat percentage and FeNO was not identified in studies of men and women.[19] Ciprandi *et al.* found that lung function was significantly impaired in overweight and obese asthmatic patients. However, increased BMI does not affect FeNO values and asthma control level.[20] In our study, no correlation was found between FeNO levels, ACT scores, and BMI. A total of 32% of our patients had ACT more than or equal to 20 and FEV_1 less than 80%; the BMI in these patients was not elevated in comparison with the remaining group ($p > .05$). This finding is not consistent with the results of Ciprandi *et al.*, who concluded that "BMI assessment should be routinely considered in asthmatic patients to reveal bronchial obstruction, also, in controlled asthma."[20]

Increased FeNO has been shown in patients with bronchiectasis, allergic rhinitis, and asthma. During inflammation, inducible nitric oxide synthase expression increases in response to specific and nonspecific stimuli.[21] In our study, FeNO was significantly increased in asthma patients with allergic rhinitis ($p < 0.01$) or allergic conjunctivitis. It should be taken into consideration that these allergic comorbidities may lead to an increase in FeNO levels.

A significant difference was found in FeNO according to skin-prick test positivity ($p < 0.05$). This is consistent with another study that found a significant correlation between skin-prick test positivity and FeNO in asthma patients who were not using steroids.[22] Grzelewski *et al.* found that asthmatic patients allergic to cat dander had elevated FeNO.[23] We found a low level of cat allergy in our study group. Yilmaz *et al.* also found very low levels of cat and dog allergy in pet shop workers in Turkey.[24] Sahiner *et al.* found a low level of aeroallergen sensitization in children with asthma during the first 2 years of life in Turkey.[25] We consider that an allergic phenotype on its own might be sufficient to elevate FeNO levels.

The correlation between FeNO and atopy and various parameters was lost after multivariate logistic regressions; significantly increased FeNO levels were found upon logistic regression analysis only in patients with a history of ERVs. Many phenotypes have a variety of factors that can increase or decrease FeNO, such as allergy (can increase FeNO), female gender (decreased FeNO), ACT below 20 (high FeNO), and elderly (low FeNO). However, exacerbations reflect inflammation, and they may continue after many months. Because FeNO increases in response to inflammation, exacerbations within the previous year that led to an ERV were the only significant factor left after multivariate regression analysis. This finding is consistent with a recent review on FeNO, in which Ricciardolo indicated that FeNO provides additional information in distinguishing different asthma phenotypes but also pointed out difficult/severe asthma cases for this purpose.[26] In their prospective study, Gelb *et al.* found that 85% of the patients with FeNO more than 28 ppb and FEV_1 less than 76% had at least one exacerbation during an 18-month period.[27] Zeiger *et al.* highlighted the independent relationship between FeNO levels more than 300% of predicted with increased future one-year asthma impairment and risk in asthmatic patients using inhaled corticosteroids.[28] We also found that the rate of the ERV of the patients with an ACT score more than or equal to 20 and with a FeNO value of more than 35 ppb was significantly higher than the rate of the ERV of the patients with an ACT score more than or equal to 20 and with a FeNO value of less than 35 ppb ($p = 0.004$). We speculate that asthmatics with elevated FeNO should be treated more

aggressively with antiinflammatory therapy and followed more closely, including follow-up FeNO levels to make sure that airway inflammation is suppressed. Prospective studies need to be performed to determine whether strategies to decrease FeNO can prevent subsequent exacerbations.

CONCLUSIONS

Various parameters are used in the clinical assessment and monitoring of asthma control. In our study, an increase in FeNO was associated with a decrease in the ACT score. FeNO was above 35 ppb in 37% of the cases even when ACT was more than 20, and it will be valuable in terms of treatment management to examine FeNO in cases that are assumed to be under control based on ACT.

By univariate analysis, FeNO levels increased in the presence of allergic rhinitis, allergic conjunctivitis, and a positive skin test. In accordance with the current literature, FeNO levels were higher in males. In both our study and in others, FeNO was shown to interact with other parameters such as age, gender, ERV, and the presence of atopy. Therefore, along with clinical and functional data, each individual should be assessed according to his/her own predicted optimum FeNO value. However, because significantly higher FeNO levels were found with multivariate logistic regression analysis only in patients with a history of ERV, these patients could be examined and treated using a different phenotyping approach.

REFERENCES

1. Global Strategy for asthma management and prevention. Available from http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf [last accessed April 6, 2014].
2. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol 113:59–65, 2004.
3. Uysal MA, Mungan D, Yorgancioglu A, et al. The validation of the Turkish version of Asthma Control Test. Qual Life Res 22:1773–1779, 2013.
4. Jatakanon A, Lim S, Kharitonov SA, et al. Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma. Thorax 53:91–95, 1998.
5. Szefler SJ, Mitchell H, Sorkness CA, et al. Management of asthma based on exhaled nitric oxide in addition of guideline based treatment for inner city adolescents and young adults: a randomised controlled trial. Lancet 372:1065–1072, 2008.
6. 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;171:912–930.
7. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 26:319–338, 2005.
8. Shaw DE, Berry MA, Thomas M, et al. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. Am J Respir Crit Care Med 176:231–237, 2007.
9. Smith AD, Cowan JO, Brassett KP, et al. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med 352:2163–2173, 2005.
10. Lehtimäki L, Kankaanranta H, Saarelainen S, et al. Peripheral inflammation in patients with asthmatic symptoms but normal lung function. J Asthma 42:605–609, 2005.
11. Fujisawa T, Yasui H, Akamatsu T, et al. Alveolar nitric oxide concentration reflects peripheral airway obstruction in stable asthma. Respirology 18:522–527, 2013.
12. Mahut B, Trinquart L, Le Bourgeois M, et al. Multicentre trial evaluating alveolar NO fraction as a marker of asthma control and severity. Allergy 65:281–292, 2010.
13. Steerenberg PA, Janssen NA, de Meer G, et al. Relationship between exhaled NO, respiratory symptoms, lung function, bronchial hyperresponsiveness, and blood eosinophilia in school children. Thorax 58:242–245, 2003.
14. Mappa L, Cardinale F, Camodeca R, et al. Exhaled nitric oxide and air trapping correlation in asthmatic children. Allergy 60: 1436–1439, 2005.
15. Farrente G, Malizia V, Antona R, et al. The value of FeNO measurement in childhood asthma: uncertainties and perspectives. Multidiscip Respir Med 8:50, 2013.
16. Sippel JM, Holden WE, Tilles SA, et al. Exhaled nitric oxide levels correlate with measures of disease control in asthma. J Allergy Clin Immunol 106:645–650, 2000.
17. Horváth I, Donnelly LE, Kiss A, et al. Exhaled nitric oxide and hydrogen peroxide concentrations in asthmatic smokers. Respiration 7:463–468, 2004.
18. Taylor DR, Mandhane P, Greene JM, et al. Factors affecting exhaled nitric oxide measurements: the effect of sex. Respir Res 15:8–82, 2007.
19. De Winter-de Groot KM, Van der Ent CK, Prins I, et al. Exhaled nitric oxide: the missing link between asthma and obesity? J Allergy Clin Immunol 115:419–420, 2005.
20. Ciprandi G, Schiavetti I, Bellezza Fontana R, et al. Overweight and obesity as risk factors for impaired lung function in patients with asthma: a real-life experience. Allergy Asthma Proc 35:62–71, 2014.
21. Steerenberg PA, and van Amsterdam JG. Measurement of exhaled nitric oxide. Methods Mol Biol 279:45–68, 2004.
22. Kharitonov SA, and Barnes PJ. Clinical aspects of exhaled nitric oxide. Eur Respir J 16:781–792, 2000.
23. Grzelewski T, Majak P, Jerzyńska J, et al. The association between fractional exhaled nitric oxide (FeNO) and cat dander in asthmatic children. Nitric Oxide 25:288–293, 2011.
24. Yilmaz I, Oner Erkekol F, Secil D, et al. Cat and dog sensitization in pet shop workers. Occup Med (Lond) 63:563–567, 2013.
25. Sahiner UM, Buyuktiryaki AB, Yavuz ST, et al. The spectrum of aeroallergen sensitization in children diagnosed with asthma during first 2 years of life. Allergy Asthma Proc 34:356–361, 2013.
26. Ricciardolo FL. Revisiting the role of exhaled nitric oxide in asthma. Curr Opin Pulm Med 20:53–59, 2014.
27. Gelb AF, Flynn Taylor C, Shinar CM, et al. Role of spirometry and exhaled nitric oxide to predict exacerbations in treated asthmatics. Chest 129:1492–1499, 2006.
28. Zeiger RS, Schatz M, Zhang F, et al. Elevated exhaled nitric oxide is a clinical indicator of future uncontrolled asthma in asthmatic patients on inhaled corticosteroids. J Allergy Clin Immunol 128:412–414, 2011. □