



Letter

Fractional exhaled nitric oxide change in pediatric patients after emergency department care of asthma exacerbations

Fractional exhaled nitric oxide (FeNO) is a marker of eosinophilic airway inflammation. We previously reported that FeNO levels were associated with acute asthma exacerbation severity measured by the percentage of predicted forced expiratory volume in 1 second.¹ In addition, FeNO was higher in African-American participants in this population compared with white participants.

For asthma control monitoring, the American Thoracic Society defines an FeNO change of 20% as clinically significant.² However, studies examining the change of FeNO after acute asthma exacerbations have been limited by small samples and few participants with FeNO levels above 30 parts per billion (ppb).^{3,4} The objective in the present study was to examine the change of FeNO in pediatric patients after acute exacerbations and at a time of improved asthma control, which was defined as no current respiratory symptoms and no need for systemic corticosteroids during the preceding 4 weeks. We hypothesized that pediatric patients with asthma who had clinically meaningful elevations of FeNO during acute exacerbations would have lower FeNO at the time of improved asthma control. We also hypothesized that African-American participants would have higher FeNO levels than white participants at the time of improved asthma control.

We recruited 40 African-American and 40 white participants from our previous study of 436 participants 5 to 17 years old who presented to our tertiary urban children's hospital emergency department (ED) with acute asthma exacerbations and who had FeNO values above the median at the time of the acute exacerbation.^{1,5} We excluded participants who received systemic corticosteroids within the preceding 4 weeks or who had signs or symptoms of a viral respiratory infection because these events could significantly decrease or increase FeNO.⁶ Recruitment of the cohort of 80 participants required using the entire pool of eligible parent-study participants. At the time of acute exacerbations, these participants ($N = 436$) had a median FeNO level of 39 ppb (interquartile range [IQR] 21–64) and higher levels were observed in African-American participants ($n = 244$, median 45 ppb, IQR 26–75) compared with white participants ($n = 191$, median 32 ppb, IQR 16–54, $P = .001$ for difference). Variables obtained at each visit included baseline demographics, FeNO measurement, secondhand smoke exposure, current asthma medications, asthma severity, and the Global Initiative for Asthma (GINA) 4-part asthma symptom control instrument.⁷ FeNO was measured using a Niox MINO

analyzer (Aerocrine, Solna, Sweden). Our institutional review board reviewed and approved the study protocol.

Univariate differences in FeNO values between the acute exacerbation and the time of improved control were assessed using a paired t test, and differences between African-American and white participants were assessed using an independent t test. For FeNO response values, multiple linear regression analysis was used to adjust for age and sex and analysis of covariance was used to adjust for FeNO at the time of exacerbation, age, and sex. Logarithmic transformation of FeNO values was used to meet the assumption of normality. The bootstrap method was used to correct for intra-subject correlation among repeated measures of FeNO. Parental consent and participant assent were obtained for each participant.

During the enrollment period from April 2013 to February 2014, 80 participants were examined (median age 13 years, IQR 11–16; 40 African-American participants [50%]; 49 boys [61%]; 25 with secondhand smoke exposure [31%]; 67 who used albuterol [4%]; 36 who used inhaled corticosteroid [45%]). Although all participants had improved control since the preceding acute exacerbation, only 40 (50%) had controlled asthma measured using the GINA instrument.⁷ Median FeNO value at the time of improved asthma control was 53 ppb (IQR 30–81) in all participants compared with 60 ppb (IQR 49–76) at the time of the preceding acute exacerbation (Table 1). For all participants there was a 23.8% (95% confidence interval 10.7–34.5, $P < .001$) FeNO decrease from the time of exacerbation to the time of improved control after adjustment for age, sex, and race. In African-American participants, there was a 25.8% (95% confidence interval 7.04–40.9) FeNO decrease between these time points after adjustment for age and sex. The FeNO change in white participants also was significant (FeNO decrease of 21.8%, 95% confidence interval 5.5–37.5) after adjustment for age and sex. At the time of improved asthma control, FeNO levels in African-American participants (60 ppb, IQR 30–73) were not significantly higher than levels in white participants (40 ppb, IQR 28–84, $P = .38$) in univariate or multivariable analysis that adjusted for the FeNO value at the time of acute exacerbation, age, and sex.

In the present study of participants who had elevated FeNO levels during acute asthma exacerbations, FeNO was shown to decrease by more than 20% at a time of improved asthma control, although only 50% of participants had controlled asthma measured using the GINA instrument. Because viral respiratory infection was an exclusion criterion, participants likely had allergy- or irritant-induced elevations of FeNO. African-American participants had more frequent decreases in FeNO greater than 20% (eTable 1). Although the difference of median FeNO between African-American (60, IQR 30–73) and white (40, IQR 28–84) participants might appear clinically meaningful, it was not statistically significant. This could be a result of insufficient power given the

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Table 1
Associations of FeNO with demographic and asthma characteristics

	FeNO level (ppb) at ED visit		FeNO level (ppb) at follow-up visit			
	Median (IQR)	Geometric mean (95% CI)	Median (IQR)	P value ^a	Geometric mean (95% CI)	P value ^b
All participants	60 (49–76)	62.7 (57.6–68.2)	53 (30–81)	.001	47.8 (40.8–56.0)	<.001
African-American	62 (55–88)	70.1 (63.2–77.8)	60 (30–73)	.011	52.0 (42.7–63.4)	.012
White	52 (42–72)	56.1 (49.6–63.4)	40 (28–84)	.036	43.9 (34.2–56.2)	.026

Abbreviations: CI, confidence interval; ED, emergency department; FeNO, fractional excretion of nitric oxide; IQR, interquartile range.

^aPaired *t* test; FeNO values were natural logarithmically transformed.^bMultiple linear regression with bootstrap method to correct variances for intrasubject correlation; FeNO values were logarithmically transformed.

sample size. However, this finding also suggests that baseline eosinophilic airway inflammation might be similar during periods of improved control but higher in African-American children during acute exacerbations.

Limitations of this study include that we did not assess for atopy, which is associated with elevated FeNO.² In addition, participants with low FeNO during acute asthma exacerbations were not enrolled, and there could be recruitment bias because the present study required participant effort to return to the clinic. The study of a larger cohort with minimal loss to follow-up could increase the understanding of FeNO at a time of improved asthma control in this population. Moreover, the difference in analyzer output between measurements could account for the observed change in FeNO. However, the within-device analytic precision of the MINO device is less than 3% of measured NO concentration for values lower than 75 ppb.⁸

In conclusion, our results suggest that in white and African-American children with elevated FeNO levels during acute asthma exacerbations, FeNO levels decrease significantly at a time of improved asthma control. However, at the time of improved asthma control, differences of FeNO between African-American and white children might not persist.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2014.11.002>.

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eTable 1

Characteristics of 80 participants evaluated for FeNO after pediatric ED visit for acute asthma exacerbation

Characteristic	African-American (n = 40)	White (n = 40)
Age (y), median (IQR)	13.0 (11.0–16.0)	13.0 (11.0–16.2)
Boys, n (%)	26 (65)	23 (57)
BMI (kg/m ²), median (IQR)	18.0 (16.2–20.3)	16.7 (15.4–20.2)
GINA chronic asthma control, n (%)	16 (40)	24 (60)
Interval between ED and improved control evaluations, median (IQR)	4.0 (3.2–4.8)	4.0 (3.4–4.7)
Medications in use at time of ED visit, n (%)		
Albuterol (inhaled)	35 (88)	32 (80)
Inhaled corticosteroid	20 (50)	16 (40)
Leukotriene receptor antagonist	17 (42)	11 (28)
Systemic CCS at or immediately before ED arrival, n (%)	37 (92)	34 (85)
Medication in use at time of follow-up visit, n (%)		
Albuterol (inhaled)	37 (92)	38 (95)
Inhaled corticosteroid	17 (42)	17 (42)
Leukotriene receptor antagonist	12 (30)	14 (35)
Participants with >20% decrease of FeNO, n (%)	21 (53)	16 (40)

Abbreviations: BMI, body mass index; CCS, corticosteroid; ED, emergency department; FeNO, fractional excretion of nitric oxide; GINA, Global Initiative for Asthma criteria for well-controlled vs uncontrolled asthma; IQR, interquartile range.