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Fractional Exhaled Nitric Oxide Has a Good Correlation with Asthma Control and Lung Function in Latino Children with Asthma

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Background. Although the measurement of fractional exhaled nitric oxide (FE_{NO}) has been recommended for observational studies and clinical trials of asthma, FE_{NO} has not been examined in studies of childhood asthma in Latin America, *Objective*. To examine the relationship between FE_{NO} and indicators of disease control or severity [asthma control test/childhood asthma control test (ACT/C-ACT), lung function, and exercise challenge test (ECT)] in Mexican children with persistent asthma, *Methods*. Children (6–18 years of age) with persistent asthma were consecutively recruited in a tertiary asthma clinic and divided into two groups, e.g. FE_{NO} < 20 parts per billion (ppb) and ≥20 ppb.Adequate FE_{NO} measurements were obtained in 134 (83.2%) of 161 eligible children, *Results*. Children with FE_{NO}<20 ppb had significantly higher scores on the ACT/C-ACT than those with FE_{NO} ≥ 20 ppb (median [interquartile range] :23 [20.8–25] vs. 21 [18–24], $p = .002$, respectively). Compared to children with FE_{NO} ≥20 ppb, those with FE_{NO} <20 ppb had a higher baseline predicted forced expiratory volume ($FEV_{1)}$ [94% (92.5%–99.4%) vs. 83% (81%–89.9%), $p = .001$] and a lower probability of having a positive ECT (42.7% vs. 71.2%, $p = .001$). In addition, FE_{NO} was significantly inversely correlated with the participants' ACT/C-ACT score and predicted FEV_1, and directly correlated with positive ECT, *Conclusion*. Among Mexican children with persistent asthma, low levels of FE_{NO} (<20 ppb) are associated with better asthma control, and higher lung function.

Keywords adolescents, asthma, asthma control test, correlation, fraction of exhaled nitric oxide, Latin America, school children

INTRODUCTION

Adequate control of childhood asthma should aim to prevent or minimize the diurnal and nocturnal symptoms, disease exacerbations, and use of rescue medication, as well as improve lung function and overall quality of life without adverse medication effects (e.g. alterations in growth and development) (1–3). Monitoring asthma control should involve not only the following of symptoms and lung function, but also minimally invasive inflammatory markers (1).

The Spanish versions of the Asthma Control Test (ACT) (4) for adolescents and adults and the child-ACT (C-ACT) (5) for children age 6 to 11 years are commonly used to monitoring asthma control, and the ACT is validated in Spanish (6). A good correlation between C-ACT and spirometry in Japanese asthmatic children has been demonstrated (7). Also, one of the most common non-invasive tools for evaluating inflammation in asthmatic children is the fractional exhaled nitric oxide (FE_{NO}) as a surrogate marker of eosinophilic inflammation of the airways. FE_{NO} values have been found to be higher in allergic asthmatic schoolers (8–10) and preschoolers (11–13) than in controls. FE_{NO} has a good correlation with other eosinophilic inflammation tests and with the level of asthma control, especially in those asthmatics without inhaled corticosteroids (ICS) use. Therefore, its value could be more important at the beginning of the treatment, adding a new dimension to the traditional clinical tools and lung function (14).

Biomarkers and physiologic parameters (e.g. bronchial hyperreactivity to methacholine (15), eosinophils in sputum (16), and FE_{NO} (17)) could lead to better asthma control in children, but there have been no published studies of "multi-dimensional" asthma control in children with asthma in Latin America.

The objective of this study was to explore the correlation between ACT, spirometry, exercise challenge test (ECT), and FE_{NO} in a sample of Mexican children with persistent asthma.Our hypothesis is that these parameters have a good correlation with each other. We know from other studies that these parameters do tend to correlate, but there are no studies documenting this in Latino American asthmatic children.

MATERIAL AND METHODS

We evaluated 161 consecutive children with persistent asthma (6–18 years of age) who were referred by their pediatricians to our asthma clinic, a tertiary center at Children´s Hospital, and CIMA Hospital in Chihuahua, Mexico. All the children were born in Mexico and had at least three generations of Mexican ancestry. During the

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first visit, a standardized questionnaire about asthma morbidity (onset, number of exacerbations/year, hospitalizations), anti-asthmatic therapy, allergic diseases (dermatitis and rhinitis), and parental asthma was completed. In addition, the ACT (for children 12–19 years of age) and C-ACT (for children 6–11 years of age) questionnaires were administered; an ACT score $\geq$20 or C-ACT $\geq$20 was considered indicative of adequate asthma control (4, 5).FE_{NO} determinations were performed according to the international guidelines (18, 19). Children were advised not to use salbutamol or long-acting *B*2-agonists (LABA) (6 or 12 hrs, respectively), not to eat lettuce or Chinese food, or drink carbonated beverages within 12 hours prior to the FE_{NO} determinations, and they were not to have had respiratory infections in the preceding three weeks. In addition, they were not to ingest any food or liquids two hours before the determinations. A FE_{NO} was performed with on-line NIOX-MINO® (Stockholm, Sweden) using one inspiration/expiration technique (18).

The next day, an exercise challenge test (ECT) and spirometry were performed in a subset of 92 children, according to the American Thoracic Society (ATS) guidelines (20). A positive ECT was defined as a 10% fall in FEV_1 from baseline. We used predicted values from a classic study by Knudson et al. (21). After the end of the ECT, every child received 200 mcg of salbutamol by a metered dose inhaler (MDI) with valvulated mask (Volumatic®), and spirometry was performed again to ensure return to baseline values.

This study was approved by the hospital's Ethics and Research Committee and written informed consent and permission of both parents and/or guardians were obtained at the beginning of the study.

Data Analysis

For this analysis, the population was divided into two groups according to the FE_{NO} values in the two categories: <20 ppb or $\geq$ 20 ppb, in accordance with recent international guidelines (22). Univariate analysis was performed between groups using the chi-squared test for categorical variables and *t*-Student or Mann–Whitney U-tests for continuous variables (with normal or non-normal distribution, respectively). Multivariable analysis was performed with FE_{NO} categories as the dependent variable, and those variables significantly associated in the univariable analysis as independent variables. Two models were performed: the first included age, rhinitis, parental asthma, ACT/C-ACT score, and baseline predicted FEV_1; and in the second model, in order to avoid co-linearity, baseline predicted FEV_1 was replaced by positive ECT. Finally, when appropriate, a Pearson's or Spearman's coefficient correlation between FE_{NO} and ACT/C-ACT and lung function was calculated. Two-tailed *p*-values of $\leq$.05 were considered significant. SPSS v 15.0 statistical software package (IBM, Armonk, New York) was used for the analysis.

RESULTS

One hundred and thirty-four out of one hundred and sixty-one (83.2%) asthmatics recruited who met the inclusion criteria for the study could successfully perform FE_{NO} determinations and were suitable for data analysis. Twenty-seven children were excluded (inadequately performed basal spirometry or FE_{NO}). Among the 134 children, the mean age was 10.26 $\pm$ 2.7 years and 52.2% were males. Eighty-two (61.2%) patients had a FE_{NO} < 20 ppb.

There were no differences in terms of gender, onset of asthma during the first 3 years of life, dermatitis, wheezing without colds, or treatment among children with FE_{NO}<20 ppb vs. FE_{NO} $\geq$20 ppb (Table 1). However, children with FE_{NO} < 20 ppb were younger than those with $FE_{NO}$$\geq$20 ppb ($p = .051$). Rhinitis and parental asthma were significantly more prevalent in children with FE_{NO} < 20 ppb. Children with FE_{NO} < 20 ppb had significantly higher scores of ACT/C-ACT than those with FE_{NO} $\geq$ 20 ppb ($p = .02$). A significantly larger amount of patients with adequate asthma control (ACT or C-ACT>20) belonged to FE_{NO} < 20 than to FE_{NO} $\geq$ 20 ppb group (80.5% vs. 61.5%, respectively, $p = .027$) (Table 1 and Figure 1). Moreover, children with FE_{NO} < 20 ppb had significantly higher baseline predicted FEV_1 than those with FE_{NO} $\geq$ 20 ppb ($p = .001$). And the prevalence of patients with a positive ECT was higher among those with FE_{NO} $\geq$ 20 ppb than FE_{NO} < 20 group ($p = .001$) (Table 1). Among those children without asthma medication ($n = 84$), 66% had ACT/C-ACT < 20 and 59% had FE_{NO} $\geq$ 20 ppb, indicating that their asthma was not controlled; and the average of their baseline predicted FEV_1 was 90.69 $\pm$ 13.5.There were no differences in ACT/C-ACT scores and FE_{NO} groups between those children with and without ECT (data not shown).

In the first logistic regression model, baseline predicted FEV_1 remained significantly related to FE_{NO}. In the second model, ACT/C-ACT score and positive ECT remained significantly correlated with FE_{NO} (Table 2). Finally, FE_{NO} was significantly inversely correlated with ACT/C-ACT score and baseline predicted FEV_1, and directly correlated to positive ECT (Table 3).

DISCUSSION

This study showed for the first time in Latin American asthmatic children that those with FE_{NO} < 20 ppb had significantly better asthma control (ACT or C-ACT>20), better lung function, and less positive ECT than those with higher FE_{NO} levels.

Recently, from prospective clinical trials and observational studies, FE_{NO} has been recommended as a supplemental outcome for the characterization of asthma patients (23). In this observational study, FE_{NO} values had a significant inverse correlation with ACT/ C-ACT and with baseline predicted FEV_1, and direct correlation with positive ECT. Some studies in adults showed significant correlation between FE_{NO} and ACT scores and lung function, whereas others did not (24–26). In 100 American

TABLE 1.—Demographic characteristics between FE_{NO} groups.[a]

	$FE_{NO} < 20$ $n = 82$	$FE_{NO} \geq 20$ $n = 52$	*p*-value
Males (%)	53.7	50	.73
Age (year)	9.9 ± 2.7	10.83 ± 2.5	.051
Wheezing in first 3 years (%)	60	50	.334
Parental asthma (%)	0	11.9	.003
Dermatitis (%)	22.7	26.2	.66
Rhinitis (%)	78	94.2	.014
Wheezing without colds (%)	96	97.62	1.00
ACT or C-ACT score	23 (20.8–25)	21 (18–24)	.002
% of controlled asthma (by ACT or C-ACT)	80.5	61.5	.027
Treatment (%):			
None	59.8	67.3	
ICS or/and montelukast	6.1	7.7	
ICS + LABA	34.1	25.0	.529[b]
% predictive FEV_1 baseline	94 (92.5–99.4)	83 (81–89.9)	.001
Positive exercise challenge test (%)	42.7	71.2	.001

[a]Numbers are expressed as: %, mean ± SD, or median (interquartile range: 25–75) when corresponded; [b]by Freeman–Halton test.
Notes: ACT—asthma control test; C-ACT—child asthma control test; FEV1—flow expiratory volume during first second; ICS—inhaled corticosteroid; LABA—long-acting beta agonists.

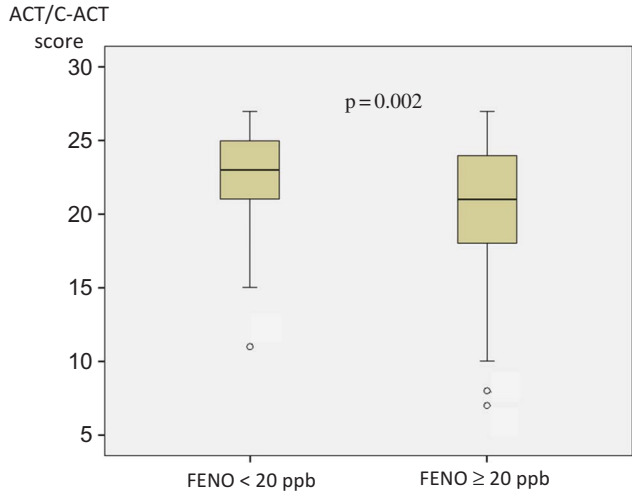

FIGURE 1. ACT/C-ACT score (median, 25–75 percentile) between FE_{NO} groups.

TABLE 2.—Multivariate analysis for factors related to $FE_{NO} < 20$ or $FE_{NO} \geq 20$ groups.

Factors	Adjusted OR (95% CI)	*p*-value
Model 1:		
Age	0.11 (−0.1 to 0.3)	.34
Rhinitis	−0.68 (−2.7 to 1.4)	.52
ACT/C-ACT score	−0.07 (−0.2 to 0.7)	.31
Baseline predicted FEV_1	−0.07 (−0.1 to −0.03)	.002*
Model 2:		
Age	0.11 (−0.1 to 2.9)	.21
Rhinitis	−1.34 (−3.4 to 0.8)	.21
ACT/C-ACT score	−0.14 (−0.2 to −0.02)	.019*
Positive ECT	1.50 (0.5 to 2.5)	.002*

*significant *p*-value
Notes: ACT—asthma control test; C-ACT—child asthma control test; FEV1—flow expiratory volume during first second.
Only factors that were significant in the univariate analysis were included (parental asthma drop due to few observations). $FE_{NO} \geq 20$ was considered as a reference group.

TABLE 3.—Correlations between FE_{NO} and ACT/C-ACT and lung function.

	Rho	*p*-value
ACT/ C-ACT score	−0.24	.005
FEV_1 basal	−0.36	.0005
Positive ECT	0.28	.0011

Notes: ACT—asthma control test; C-ACT—child asthma control test; ECT—exercise challenge test; FEV_1—flow expiratory volume during first second.

asthmatics patients, ages 6–86 years, Khalili et al. (26) found no association between FE_{NO} levels and asthma control when using five different evaluation tools, including ACT.

Only a few studies done exclusively in children have evaluated the correlation between FE_{NO} and C-ACT. Piacentini et al. (27) conducted a study in 200 Italian asthmatic children and found that FE_{NO} had a significant correlation with C-ACT and lung function (FEV_1 and FEV_1/FVC) only among those with "newly diagnosed" asthma but not in the "follow-up" group. Piacentini et al. concluded that FE_{NO} is not a substitute for other markers of disease control, in particular in children receiving regular controller medication. Another recent study (28) conducted in 107 asthmatic children (mean age = 12 ± 2.9 year) showed no correlation between FE_{NO} and a German modification of C-ACT, but the majority of children were on regular asthma controller medication. In contrast, a recent study done in American school-age asthmatics reported that higher FE_{NO} levels were associated with increased use of beta-2 agonists and predicted their use at three months' follow-up, but only among children who are not on ICS (29). We also found a good correlation between ACT or C-ACT and FE_{NO}, but most of our patients (62.7%) were not under controller therapy. In the biomarker section of a 2012 report entitled *Standardizing Asthma Outcomes in Clinical Research: Report of the Asthma*

Outcomes Workshop (23, 30), FE_{NO} is recommended as a supplemental outcome in clinical trials that seek to evaluate the effects of interventions on airway disease and/or characterize corticoid-response phenotypes of asthma.

FE_{NO} is a surrogate marker of eosinophilic inflammation, and a relationship between FE_{NO} and eosinophilic airway inflammation [eosinophils measured in sputum, bronchoalveolar lavage (BAL) and biopsies] has been reported (24). In addition, allergic rhinitis can directly influence FE_{NO} levels (31). We found an association between rhinitis and FE_{NO} only in the univariate analysis. Unfortunately, we did not measure the biological marker of eosinophilic inflammation in our patients.

A mixed population-based study in Southern California ($n = 2568$ children, aged 7–10) showed that Asian-Americans and Hispanics had a significant increase (higher among Asian) of FeNO values compared to non-Hispanic white children (32). The last ATS guidelines on interpretation of FE_{NO} for clinical applications suggest using cut points rather than reference values when interpreting FE_{NO} levels (22). In the present study, we chose 20 ppb as a cutoff as was described previously (22, 24, 27). Approximately 32.7% of our patients who had their asthma controlled (ACT or C-ACT $\geq$20) had FE_{NO} levels > 20 ppb. Potential explanations could be a subgroup of children with poor asthma symptom perceptions in whom objective measures like FE_{NO} may be essential for accurate evaluation, or perhaps different parameters could be measured. In contrast, 44% who had non-controlled asthma (by ACT or C-ACT) had FE_{NO} < 20 ppb, and in this case, they may have adequately addressed the atopic inflammation in their airways but continue to have symptom persistence for other reasons, including comorbidities (e.g. sinusitis, gastroesophageal reflex), non-eosinophilic asthma, or pseudo-asthma. The value of ACT was complementary to, but not a surrogate for, other objective measurements of airway disease, e.g. spirometry, challenge provocation tests, sputum eosinophils, and FE_{NO}.

Monitoring multiple parameters over time and characterizing their fluctuations might provide new tools to characterize the dynamic and complex nature of asthma better than individual mean values; and in this way, identify subjects at risk of exacerbations (33, 34). Recently, a meta-analysis (35) showed that adding FENO does not improve asthma control in comparison with symptoms with or without spirometry/peak flow in children and adults. Therefore, a combination of more than one clinical and laboratory parameters might be a better option for asthma monitoring.

There are some limitations in this study. First, a selection bias is always possible when convenient samples are studied. Second, objective markers of eosinophilic airway inflammation (e.g. bronchoalveolar lavage or induced sputum) were not evaluated. Third, other factors that influence FE_{NO} levels, such as residential traffic-related pollution exposures (36), and second-hand tobacco were not evaluated (22). Fourth, as a cross-sectional study, it is impossible to use these individual FE_{NO} values for monitoring and assessing treatment requirement. Changes in FE_{NO} in relation to a baseline would be more helpful as FE_{NO} values themselves do not justify a diagnosis or change in treatment, rather it should be interpreted in relation to the clinical context (22). Therefore, large prospective studies to clarify these issues among Latino asthmatic children need to be performed with cost-effective analysis before the massive implementation of FE_{NO} for asthma monitoring.

In conclusion, we found in a sample of Latin American asthmatic schoolchildren, that those with low levels of FE_{NO} (<20 ppb) had significantly better asthma control (higher levels of ACT/C-ACT); higher lung function (baseline predicted FEV_1), and less positive exercise challenge test than those with $FE_{NO} \geq 20$ ppb.

Conflict of interest

The authors have no conflict of interest to declare.

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