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 (FeNO) has been recommended for observational studies and clinical trials of asthma, FeNO has not been examined in studies of childhood asthma in Latin America. Objective. To examine the relationship between FeNO 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. FeNO < 20 parts per billion (ppb) and ≥20 ppb. Adequate FeNO measurements were obtained in 134 (83.2%) of 161 eligible children. Results. Children with FeNO < 20 ppb had significantly higher scores on the ACT/C-ACT than those with FeNO ≥ 20 ppb (median [interquartile range]: 23 [20.8–25] vs. 21 [18–24], p = .002, respectively). Compared to children with FeNO ≥ 20 ppb, those with FeNO < 20 ppb had a higher baseline predicted forced expiratory volume (FEV1) [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, FeNO was significantly inversely correlated with the participants’ ACT/C-ACT score and predicted FEV1, and directly correlated with positive ECT. Conclusion. Among Mexican children with persistent asthma, low levels of FeNO (<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 monitor 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 (FeNO) as a surrogate marker of eosinophilic inflammation of the airways. FeNO values have been found to be higher in allergic asthmatic schoolchildren (8–10) and preschoolers (11–13) than in controls. FeNO 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 spum (16), and FeNO (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 FeNO 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
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 ≥20 or C-ACT ≥20 was considered indicative of adequate asthma control (4, 5). \( \text{FE}_{\text{NO}} \) determinations were performed according to the international guidelines (18, 19). Children were advised not to use salbutamol or long-acting \( \beta_2 \)-agonists (LABA) (6 or 12 hrs, respectively), not to eat lettuce or Chinese food, or drink carbonated beverages within 12 hours prior to the \( \text{FE}_{\text{NO}} \) 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 \( \text{FE}_{\text{NO}} \) 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 \( \text{FEV}_1 \) 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 valved 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 \( \text{FE}_{\text{NO}} \) values in the two categories: <20 ppb or ≥ 20 ppb, in accordance with recent international guidelines (22). Univariate analysis was performed between groups using the chi-squared test for categorical variables and \( r \)-Student or Mann–Whitney U-tests for continuous variables (with normal or non-normal distribution, respectively). Multivariable analysis was performed with \( \text{FE}_{\text{NO}} \) 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, \( \text{ACT}/\text{C-ACT} \) score, and baseline predicted \( \text{FEV}_1 \); and in the second model, in order to avoid co-linearity, baseline predicted \( \text{FEV}_1 \) was replaced by positive ECT. Finally, when appropriate, a Pearson’s or Spearman’s coefficient correlation between \( \text{FE}_{\text{NO}} \) and \( \text{ACT}/\text{C-ACT} \) and lung function was calculated. Two-tailed \( p \)-values of ≤0.05 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 \( \text{FE}_{\text{NO}} \) determinations and were suitable for data analysis. Twenty-seven children were excluded (inadequately performed basal spirometry or \( \text{FE}_{\text{NO}} \)). Among the 134 children, the mean age was 10.26 ± 2.7 years and 52.2% were males. Eighty-two (61.2%) patients had a \( \text{FE}_{\text{NO}} < 20 \) 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 \( \text{FE}_{\text{NO}} < 20 \) ppb vs. \( \text{FE}_{\text{NO}} ≥ 20 \) ppb (Table 1). However, children with \( \text{FE}_{\text{NO}} < 20 \) ppb were younger than those with \( \text{FE}_{\text{NO}} ≥ 20 \) ppb (\( p = .051 \)). Rhinitis and parental asthma were significantly more prevalent in children with \( \text{FE}_{\text{NO}} < 20 \) ppb. Children with \( \text{FE}_{\text{NO}} < 20 \) ppb had significantly higher scores of \( \text{ACT}/\text{C-ACT} \) than those with \( \text{FE}_{\text{NO}} ≥ 20 \) ppb (\( p = .02 \)). A significantly larger amount of patients with adequate asthma control (ACT or C-ACT>20) belonged to \( \text{FE}_{\text{NO}} < 20 \) than to \( \text{FE}_{\text{NO}} ≥ 20 \) group (80.5% vs. 61.5%, respectively, \( p = .027 \)) (Table 1 and Figure 1). Moreover, children with \( \text{FE}_{\text{NO}} < 20 \) ppb had significantly higher baseline predicted \( \text{FEV}_1 \) than those with \( \text{FE}_{\text{NO}} ≥ 20 \) ppb (\( p = .001 \)). And the prevalence of patients with a positive ECT was higher among those with \( \text{FE}_{\text{NO}} ≥ 20 \) ppb than \( \text{FE}_{\text{NO}} < 20 \) group (\( p = .001 \)) (Table 1). Among those children without asthma medication (\( n = 84 \)), 66% had \( \text{ACT}/\text{C-ACT} < 20 \) and 59% had \( \text{FE}_{\text{NO}} ≥ 20 \) ppb, indicating that their asthma was not controlled; and the average of their baseline predicted \( \text{FEV}_1 \) was 90.69 ± 13.5. There were no differences in \( \text{ACT}/\text{C-ACT} \) scores and \( \text{FE}_{\text{NO}} \) groups between those children with and without ECT (data not shown).

In the first logistic regression model, baseline predicted \( \text{FEV}_1 \) remained significantly related to \( \text{FE}_{\text{NO}} \). In the second model, \( \text{ACT}/\text{C-ACT} \) score and positive ECT remained significantly correlated with \( \text{FE}_{\text{NO}} \) (Table 2). Finally, \( \text{FE}_{\text{NO}} \) was significantly inversely correlated with \( \text{ACT}/\text{C-ACT} \) score and baseline predicted \( \text{FEV}_1 \), and directly correlated to positive ECT (Table 3).

**Discussion**

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

Recently, from prospective clinical trials and observational studies, \( \text{FE}_{\text{NO}} \) has been recommended as a supplemental outcome for the characterization of asthma patients (23). In this observational study, \( \text{FE}_{\text{NO}} \) values had a significant inverse correlation with \( \text{ACT}/\text{C-ACT} \) and with baseline predicted \( \text{FEV}_1 \), and direct correlation with positive ECT. Some studies in adults showed significant correlation between \( \text{FE}_{\text{NO}} \) and ACT scores and lung function, whereas others did not (24–26). In 100 American
EXHALED NITRIC OXIDE IN ASTHMATIC LATINO CHILDREN

TABLE 1.—Demographic characteristics between FE\textsubscript{NO} groups.\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>FE\textsubscript{NO} &lt; 20 n = 82</th>
<th>FE\textsubscript{NO} ≥ 20 n = 52</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>53.7</td>
<td>50</td>
<td>.73</td>
</tr>
<tr>
<td>Age (year)</td>
<td>9.9 ± 2.7</td>
<td>10.83 ± 2.5</td>
<td>.051</td>
</tr>
<tr>
<td>Wheezing in first 3 years (%)</td>
<td>60</td>
<td>50</td>
<td>.334</td>
</tr>
<tr>
<td>Parental asthma (%)</td>
<td>0</td>
<td>11.9</td>
<td>.003</td>
</tr>
<tr>
<td>Dermatitis (%)</td>
<td>22.7</td>
<td>26.2</td>
<td>.66</td>
</tr>
<tr>
<td>Rhinitis (%)</td>
<td>78</td>
<td>94.2</td>
<td>.014</td>
</tr>
<tr>
<td>Wheezing without colds (%)</td>
<td>96</td>
<td>97.62</td>
<td>1.00</td>
</tr>
<tr>
<td>ACT or C-ACT score</td>
<td>23 (20.8–25)</td>
<td>21 (18–24)</td>
<td>.002</td>
</tr>
<tr>
<td>% of controlled asthma (by ACT or C-ACT)</td>
<td>80.5</td>
<td>61.5</td>
<td>.027</td>
</tr>
</tbody>
</table>

Treatment (%):
- None
- ICS or montelukast
- ICS + LABA

% predictive FE\textsubscript{V} \textsubscript{1} baseline
- FE\textsubscript{NO} < 20 ppb: 94 (92.5–99.4)
- FE\textsubscript{NO} ≥ 20 ppb: 83 (81–89.9)

Positive exercise challenge test (%)
- FE\textsubscript{NO} < 20 ppb: 42.7
- FE\textsubscript{NO} ≥ 20 ppb: 71.2

\textsuperscript{a}Numbers are expressed as: %, mean ± SD, or median (interquartile range: 25–75) when corresponded. \textsuperscript{b}by Freeman–Halton test.

Notes: ACT—asthma control test; C-ACT—child asthma control test; FEV\textsubscript{1}—flow expiratory volume during first second; ICS—inhaled corticosteroid; LABA—long-acting beta agonists.

ACT/C-ACT score (median, 25–75 percentile) between FE\textsubscript{NO} groups.

![ACT/C-ACT score](image)

TABLE 2.—Multivariate analysis for factors related to FE\textsubscript{NO} < 20 or FE\textsubscript{NO} ≥ 20 groups.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.11 (–0.1 to 0.3)</td>
<td>.34</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>–0.68 (–2.7 to 1.4)</td>
<td>.52</td>
</tr>
<tr>
<td>ACT/C-ACT score</td>
<td>–0.07 (–0.2 to 0.7)</td>
<td>.31</td>
</tr>
<tr>
<td>Baseline predicted FE\textsubscript{V} \textsubscript{1}</td>
<td>–0.07 (–0.1 to –0.03)</td>
<td>.002*</td>
</tr>
<tr>
<td>Model 2:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.11 (–0.1 to 2.9)</td>
<td>.21</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>–1.34 (–3.4 to 0.8)</td>
<td>.21</td>
</tr>
<tr>
<td>ACT/C-ACT score</td>
<td>–0.14 (–0.2 to –0.02)</td>
<td>.019*</td>
</tr>
<tr>
<td>Positive ECT</td>
<td>1.50 (0.5 to 2.5)</td>
<td>.002*</td>
</tr>
</tbody>
</table>

\textsuperscript{*}significant p-value

Notes: ACT—asthma control test; C-ACT—child asthma control test; FEV\textsubscript{1}—flow expiratory volume during first second.

asthmatics patients, ages 6–86 years, Khalili et al. (26) found no association between FE\textsubscript{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\textsubscript{NO} and C-ACT. Piacentini et al. (27) conducted a study in 200 Italian asthmatics and found that FE\textsubscript{NO} had a significant correlation with C-ACT and lung function (FEV\textsubscript{1} and FEV\textsubscript{2}/FVC) only among those with “newly diagnosed” asthma but not in the “follow-up” group. Piacentini et al. concluded that FE\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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), $\text{FE}_{\text{NO}}$ 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.

$\text{FE}_{\text{NO}}$ is a surrogate marker of eosinophilic inflammation, and a relationship between $\text{FE}_{\text{NO}}$ and eosinophilic airway inflammation [eosinophils measured in sputum, bronchoalveolar lavage (BAL) and biopsies] has been reported (24). In addition, allergic rhinitis can directly influence $\text{FE}_{\text{NO}}$ levels (31). We found an association between rhinitis and $\text{FE}_{\text{NO}}$ 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 $\text{FE}_{\text{NO}}$ for clinical applications suggest using cut points rather than reference values when interpreting $\text{FE}_{\text{NO}}$ 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 ≥20) had $\text{FE}_{\text{NO}}$ levels > 20 ppb. Potential explanations could be a subgroup of children with poor asthma symptom perceptions in whom objective measures like $\text{FE}_{\text{NO}}$ 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 $\text{FE}_{\text{NO}} < 20$ 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 reflux), 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 $\text{FE}_{\text{NO}}$.

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 $\text{FENO}$ 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 $\text{FE}_{\text{NO}}$ 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 $\text{FE}_{\text{NO}}$ values for monitoring and assessing treatment requirement. Changes in $\text{FE}_{\text{NO}}$ in relation to a baseline would be more helpful as $\text{FE}_{\text{NO}}$ 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 $\text{FE}_{\text{NO}}$ for asthma monitoring.

In conclusion, we found in a sample of Latin American asthmatic schoolchildren, that those with low levels of $\text{FE}_{\text{NO}}$ (<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 $\text{FE}_{\text{NO}} ≥ 20$ ppb.

**CONFLICT OF INTEREST**

The authors have no conflict of interest to declare.

**REFERENCES**


