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An Elevated Bronchodilator Response Predicts Large Airway Inflammation in Mild Asthma

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Summary. Exhaled nitric oxide (eNO) is elevated in asthmatics and is a purported marker of airway inflammation. The bronchodilator response (BDR) has also been shown to correlate with markers of airway inflammation, including eNO at 50 ml/sec ($FE_{NO,50}$) which is comprised of NO from both the proximal and distal airways. Using eNO at multiple flows and a two-compartment model of NO exchange, the eNO signal can be partitioned into its proximal [$J'aw_{NO}$ (nl/sec)] and distal contributions [CA_{NO} (ppb)]. We hypothesized that the BDR reflects the inflammatory status of the larger airways with smooth muscle, and thus would correlate with $J'aw_{NO}$. In 179 predominantly (95%) Hispanic children with mild asthma (69 steroid naïve), and 21 non-asthmatic non-atopic controls, spirometry and eNO at multiple flows were measured prior and 10 min following inhalation of albuterol. A trumpet-shaped axial diffusion model of NO exchange was used to characterize $J'aw_{NO}$ and CA_{NO}. The BDR correlated moderately ($r = 0.44$) with proximal airway NO ($J'aw_{NO}$), but weakly ($r = 0.26$) with distal airway/alveolar NO (CA_{NO}), and only in inhaled corticosteroid naïve asthmatics. A BDR cut point as low as $\geq$8% had a positive predictive value of 83% for predicting an elevated $J'aw_{NO}$ or $FE_{NO,50}$. We conclude that the BDR reflects inflammation in the large airways, and may be an effective clinical tool to predict elevated large airway inflammation. **Pediatr Pulmonol. 2010; 45:174–181.** © 2010 Wiley-Liss, Inc.

Key words: nitric oxide; inflammation; NO; pulmonary function.

INTRODUCTION

Asthma is a chronic inflammatory disease which can involve all parts of the respiratory tract[1–3] and airway inflammation may still be present in even seemingly well-controlled asthmatics.[4] Research in adults with asthma has demonstrated that improved control can be achieved through the use of surrogate markers of airway inflammation to modulate asthma treatment rather than waiting for symptoms to recrudesce or lung function to decline.[5,6] Thus, there is a need for a simple, non-invasive index of airway inflammation in children, ideally customized to manage the inflammation and prevent disease sequelae.

Exhaled nitric oxide (eNO) at a flow of 50 ml/sec ($FE_{NO,50}$) is significantly elevated in the majority of steroid naïve asthmatics,[7] reduced upon administration of oral and inhaled corticosteroids (ICS)[8,9] and is thus generally accepted to be a non-invasive biological marker of airway inflammation.[10] Longitudinal studies have investigated the use of $FE_{NO,50}$ as an index of asthma control.[4,11–13] The results of these studies have been mixed, as two studies demonstrated that $FE_{NO,50}$ was not predictive in reducing the dose of corticosteroid or predicting exacerbation.[11,13] Furthermore, $FE_{NO,50}$ is inherently non-specific regarding the origin of NO in the lungs[14] and the recommended exhalation flow of

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50 ml/sec[15] is low enough to cause the concentration to be predominately of proximal airway origin;[16] hence, the distal contributions are effectively ignored. However, by applying simple mathematical models of pulmonary NO dynamics, the eNO signal can be partitioned into proximal airway [$J'aw_{NO}$, (nl/sec), maximum airway flux, generations 1–16] and distal airway/alveolar contributions [CA_{NO}, (ppb), alveolar NO concentration, generations 17–23]. Increased $J'aw_{NO}$ with normal CA_{NO} has been reported in adults[17] and children[18] with mild asthma, whereas CA_{NO} is increased in asthmatics with enhanced symptoms and more severe disease.[16,18,19] Furthermore, $J'aw_{NO}$ and CA_{NO} have been shown to correlate with markers of airway inflammation and airway dysfunction.[20] These findings indicate distinct patterns of airway inflammation in asthma, and suggest that the region-specific eNO parameters (i.e., $J'aw_{NO}$ and CA_{NO}) provide information of possible clinical utility.

The bronchodilator response (BDR), currently recommended for the diagnosis of asthma,[1] is an easily administered test that is widely available to clinicians. It has more recently been thought to reflect bronchial lability[21] and could represent a surrogate marker of airway inflammation,[22–24] airway remodeling,[25] and responsiveness to ICS.[26,27] A key finding relating BDR to airway inflammation in children has been its relationship to $FE_{NO,50}$.[22,24,28] However, the relationship between BDR and both $J'aw_{NO}$ and CA_{NO} in asthma has not been reported, but could potentially enhance the clinical interpretation of the BDR.

The purpose of this study was to evaluate the relationship of the BDR to $FE_{NO,50}$, $J'aw_{NO}$, and CA_{NO} in children with mild asthma. We hypothesized that the BDR, as a marker of bronchial lability, reflects the inflammatory status of the larger smooth muscle containing airways. Thus, the BDR would correlate with $J'aw_{NO}$ and may be a simple yet useful test to assess large airway inflammation in children with mild asthma.

METHODS

Study Subjects

Two hundred consecutive patients with asthma who presented to the Children's Hospital of Orange County (CHOC) Breathmobile® for an asthma evaluation participated in the study. Criteria for the diagnosis of asthma included a previous history of recurrent coughing, wheezing, shortness of breath (at rest or following exercise), and symptomatic improvement following short acting bronchodilator.[1] Patients were excluded from the study if they had any other heart or lung disease, any smoking within the past 5 years, or they were treated with ICS for <8 weeks. Short and long acting β_2 agonists were withheld for 12 hr prior to the study. Additionally, 21 children without asthma were enrolled in the study to serve as non-asthmatic controls. The inclusion criteria for the non-asthmatics included no history or clinical evidence of acute or chronic respiratory disease, non-atopic, and normal spirometry. Each subject and their guardian began their visit by reading and completing the requirements stated in the informed consent documents; the consent form had been approved by the University of California, Irvine and CHOC Institutional Review Boards.

Study Design and Methods

Skin prick tests were performed by the nurse and assessed by the physician. The skin prick test revealed atopy to common aeroallergens (cat, dog, feathers, cockroach, dust mites, mold, weeds, trees, and grasses), and the patient was considered atopic if positive to at least one antigen. Asthma symptoms were quantified using the validated asthma control test (ACT) for children (age 6–11 years)[29] and adults (age 12–17 years).[30]

The eNO measurements at multiple flows (50, 100, and 200 ml/sec; NIOX Flex, Aerocrine Ltd, Stockholm, Sweden) were performed prior to the pre-bronchodilator spirometric maneuver. The order of the exhalation flows were randomized and eNO measurements were performed in triplicate at each flow, in accordance with ATS/ERS guidelines.[15]

Standard spirometry was performed (WinDx Spirometer, Creative Biomedics International, San Clemente, CA) in accordance with ATS criteria.[31] To determine the BDR, albuterol (180 mcg; 2 puff with spacer) was appropriately administered. The subjects were asked to wait 10 min for the medication to take effect, before repeating the eNO measurements and spirometry. The BDR was calculated as the percent change in FEV_1 following administration of albuterol.

Analysis

The average eNO concentration at each flow was calculated following current ATS/ERS guidelines.[15] During an eNO maneuver, a steady state mean alveolar or distal airway/alveolar concentration (CA_{NO}, ppb) enters the conducting airway compartment (net transfer is convection minus diffusion) where upon additional NO is transferred from the airway walls ($J'aw_{NO}$, nl/sec). Based on the structure of the validated trumpet-shaped two-compartment model with axial diffusion,[32] the proximal airway NO flux or $J'aw_{NO}$ represents the signal from the conducting region of the lungs (Weibel generations 1–16), and the distal airway/alveolar concentration or CA_{NO} represents the signal from the respiratory region of the lungs (Weibel generations 17–23). We then applied a linear least squares analysis to a plot of the average NO elimination rate (product of average eNO and average flow) versus the average exhalation flow to estimate $J'aw_{NO}$ (nl/sec, maximum

airway flux) and CA_{NO} (ppb, alveolar NO concentration).[33]

Data are reported using median and range (minimum–maximum), or number of subjects and proportion. Clinical characteristics were compared among the asthmatics and non-asthmatic controls using the Kruskal–Wallis and the chi-square test. For variables with significant differences among the groups, paired comparisons were applied with Bonferroni's multiple comparison adjustment. Spearman rank-order correlation and Spearman partial rank-order correlation were calculated to examine the strength of associations amongst age, the BDR, other spirometric measurements, and eNO measurements within ICS naïve and ICS-treated groups. Thus, the correlation was considered, regardless of *P*-value, strong if the absolute value was >0.7, moderate if it ranged between 0.3 and 0.7, weak if it ranged between 0.1 and 0.3, and no correlation if <0.1. We further applied different cut points of BDR to calculate sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV). Significance level was set at 0.05 and analysis was performed using SAS 9 (Cary, NC).

RESULTS

Baseline Patient Characteristics

Two hundred children with asthma, and 21 non-asthmatic non-atopic children between the ages of 6 and 17 years were enrolled into the study. In both study populations 95% of the participants reported an ethnicity of Hispanic. All of the enrolled subjects were able to perform the eNO, and baseline spirometric maneuvers. However, among the asthmatic subjects, 1 subject was excluded due to missing spirometric data, and 20 were excluded from the analysis since their eNO did not fit the linear model of NO exchange; this was due to a negative estimated CA_{NO} (i.e., non-physiologic interpretation). Data on the BDR was collected in 167 of the remaining 179 children with asthma and in 13 of the non-asthmatic non-atopic children.

The non-asthmatic control and asthmatic pre-bronchodilator characteristics are shown in Table 1. In this table the asthmatics were stratified on the basis of ICS use. ICS naïve was defined as no oral or ICS within the last 8 weeks and ICS treated was defined as prescribed ICS treatment for at least 8 weeks. The study groups were similar in age, gender, and ethnicity. With regards to atopic status, ~80% of the asthmatics tested positive to one or more of the common aeroallergens. A significant group difference was found in FEV1/FVC ($P = 0.03$), where the ICS-treated group was significantly lower than non-asthmatic non-atopic group, as well as the ACT score ($P = 0.007$) in which the ICS-treated group had a higher score than ICS naïve. No other significant differences in pre-bronchodilator spirometry were observed between the non-asthmatic controls and asthmatics, independent of ICS use.

The BDR and pre-bronchodilator eNO parameters are presented in Table 2. No difference was found in BDR, but a significant group difference was found in all three nitric oxide measurements, where $FE_{N0,50}$, $J'aw_{NO}$, and CA_{NO} were significantly higher in the ICS naive group compared to ICS-treated group, and $FE_{N0,50}$ and $J'aw_{NO}$ were also significantly higher in both the ICS naïve group and ICS-treated group compared to non-asthmatic controls.

Non-Asthmatic Values for $J'aw_{NO}$ and CA_{NO}

By measuring eNO at multiple flows in 21 non-asthmatic non-atopic children we were able to estimate the upper limits of normal for $FE_{N0,50}$, $J'aw_{NO}$, and CA_{NO}. In the non-asthmatic children, the median and range of $FE_{NO,50}$, $J'aw_{NO}$, and CA_{NO} were found to be 8.5 (2.2–15.3) ppb, 0.7 (0.1–1.4) nl/sec, and 1.5 (0.1–2.2) ppb, respectively. Analysis of this distribution and rounding up

TABLE 1— Demographics of Subjects and Baseline Spirometry

	Non-asthmatic non-atopic control (n = 21)	ICS-treated asthma (n = 110)	ICS naïve asthma (n = 69)	Overall test *P*-value[1]	Paired comparison result[2]
Age (years)	10 (6–17)	11 (6–17)	10 (6–17)	0.57	—
Gender: male	12 (57%)	45 (65%)	72 (65%)	0.57	—
Atopic	—	82 (75%)	59 (86%)	0.1	—
ACT	—	22 (11–27)	20 (10–27)	0.007	ICS treated > ICS naïve
FEV_1 (%)	106 (93–118)	105 (75–149)	108 (67–149)	0.63	—
FVC (%)	104 (89–124)	106 (73–147)	106 (71–145)	0.82	—
FEV_1/FVC (%)	90 (84–102)	87 (70–100)	88 (72–101)	0.032	Control > ICS treated
FEF_{25-75} (%)	103 (90–176)	100 (45–185)	107 (48–178)	0.24	—

ICS, inhaled corticosteroid; ACT score (≤19 indicative of poor asthma control, scale 0–30).
Data are presented as median (range).
[1]Chi-square test for gender and atopic and Kruskal–Wallis test for all other variables.
[2]Bonferroni's multiple comparison adjustment was applied for paired comparison.

TABLE 2— BDR and Baseline Exhaled Nitric Oxide Parameters

	Non-asthmatic non-atopic control (n = 21)	ICS-treated asthma (n = 110)	ICS Naïve asthma (n = 69)	Overall test *P*-value[1]	Paired comparison result[2]
BDR (%)	5.3 (0.6–6.6) [n = 13]	6 (0–22.5) [n = 102]	6.8 (0.7–35.5) [n = 69]	0.041	None
$FE_{NO,50}$ (ppb)	8.5 (2.2–15.3)	13.8 (3.7–158.4)	36.1 (5.1–186.2)	<0.0001	Control < ICS treated < ICS naive
$J'aw_{NO}$ (nl/sec)	0.7 (0.1–1.4)	1.1 (0.1–14)	2.8 (0.2–17)	<0.0001	Control < ICS treated < ICS naive
CA_{NO} (ppb)	1.5 (0.1–2.2)	1 (0.006–5.1)	1.5 (0.02–13.4)	0.032	ICS treated < ICS naive

ICS, inhaled corticosteroids.
Data are presented as median (range).
[1]Kruskal–Wallis test for all other variables.
[2]Bonferroni's multiple comparison adjustment was applied for paired comparison.

the maximum value to two significant digits provides a conservative estimate of a threshold for elevated exhaled NO, proximal airway NO and distal airway/alveolar NO in our subject populations: $FE_{NO,50} \geq 16$ ppb, $J'aw_{NO} \geq 1.5$ nl/sec, and $CA_{NO} \geq 2.3$ ppb. These results are similar to the findings of other reports using the two-compartment model[14] to partition eNO in non-asthmatic children[16,34] when adjusting for the effect of axial diffusion of NO.

Correlations With Pulmonary Function Tests and eNO

In our data, age was either only weakly correlated or not correlated with pulmonary function or eNO (ranged between −0.28 and 0.30). In the ICS naïve group, the BDR had a moderately positive correlation with $FE_{NO,50}$ (r = 0.46) and $J'aw_{NO}$ (r = 0.44), a weak correlation with CA_{NO} (r = 0.26) (Fig. 1), and a moderately negative correlation with FEV_1/FVC (r = −0.51) and percent predicted FEF_{25-75} (r = −0.48). Also, FEV_1/FVC was found to have a moderately negative correlation with $FE_{NO,50}$ (r = −0.39) and $J'aw_{NO}$ (r = −0.38), and a weak correlation with CA_{NO} (r = −0.21). The partial correlation between BDR and $FE_{NO,50}$ (or $J'aw_{NO}$) was further calculated to remove possible influence of FEV_1/FVC, and the correlation reduced to 0.31 for $FE_{NO,50}$ and 0.29 for $J'aw_{NO}$. In the ICS-treated group, the BDR only weakly correlated with $FE_{NO,50}$ (r = 0.18) and $J'aw_{NO}$ (r = 0.19), and did not correlate with CA_{NO} (r = 0.005) (Fig. 1). Gender did not impact the pattern of correlations. Furthermore, only 37 children (10 ICS naïve and 27 ICS treated) non-atopic asthmatic children completed the BDR measurement, and thus atopic and non-atopic were not evaluated separately.

Sensitivity and Specificity of eNO With Various BDR Threshold

Since BDR had the highest correlations with $FE_{NO,50}$ and $J'aw_{NO}$ in the ICS naïve subjects, we evaluated various cut points of BDR to find a potential optimal threshold to predict an elevated $FE_{NO,50}$ (≥16 ppb) and elevated $J'aw_{NO}$ (≥1.5 nl/sec). At a BDR of 12%, the sensitivity, specificity, PPV, and NPV for $J'aw_{NO}$ was 0.31, 1.00, 1.00, and 0.34, respectively. The corresponding values for $FE_{NO,50}$ were nearly identical; the only

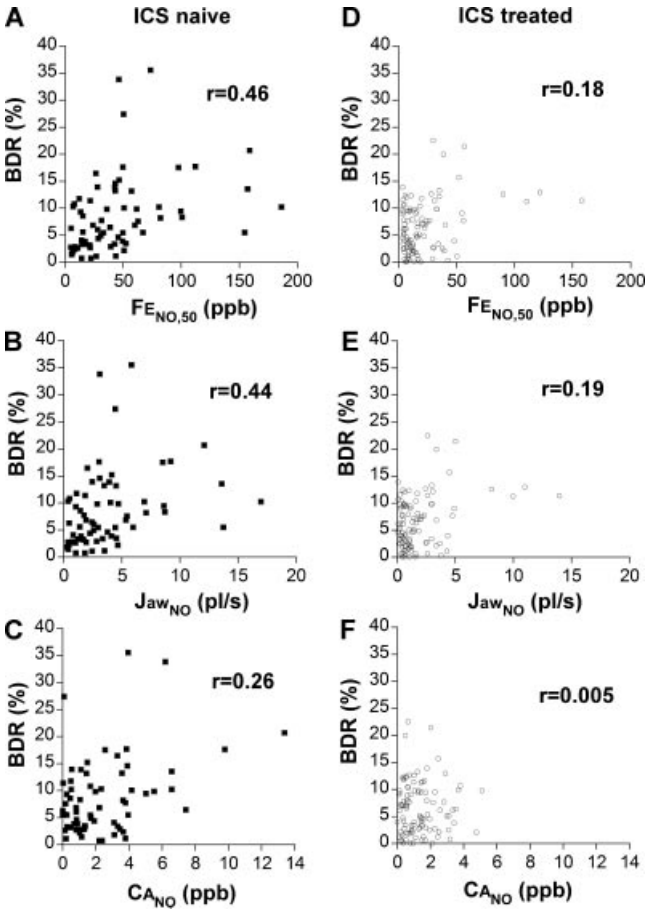

Fig. 1. Relationship between bronchodilator response and exhaled nitric oxide parameters. The exhaled nitric oxide at 50 ml/sec ($FE_{NO,50}$) and proximal airway NO flux ($J'aw_{NO}$) correlate with the bronchodilator response (BDR) only in the inhaled corticosteroid (ICS) naïve population. Distal airway/alveolar concentration (CANO) does not correlate with either steroid treated or steroid naïve subjects. Solid squares represent the ICS naïve patients and the circles represent the ICS-treated patients.

TABLE 3— Effect of Varying the BDR Cut Point on Sensitivities, Specificities, Positive Predictor Values, and Negative Predictive Values

	BDR ≥8%	BDR ≥9%	BDR ≥10%	BDR ≥11%	BDR ≥12%
$FE_{NO,50}$					
Sensitivity (%)	49	45	39	33	31
Specificity (%)	69	75	81	94	100
PPV (%)	83	85	86	94	100
NPV (%)	31	31	30	31	32
$J'aw_{NO}$					
Sensitivity (%)	50	46	40	33	31
Specificity (%)	71	76	82	94	100
PPV (%)	83	85	86	94	100
NPV (%)	33	33	33	33	34

BDR, bronchodilator response; $FE_{NO,50}$, exhaled nitric oxide at a flow of 50 ml/sec; $J'aw_{NO}$, maximum airway nitric oxide flux; PPV, positive predictor value; NPV, negative predictor value.

difference being a NPV of 0.32. Lowering the BDR cutoff step wise in 1% intervals to 8% resulted in increased sensitivity, decreased specificity, decreased PPV, and decreased NPV (Table 3). Of interest was a PPV of 0.83 for a BDR cut point of 8% for both elevated $FE_{NO,50}$ and elevated $J'aw_{NO}$.

DISCUSSION

Our study has investigated the relationship between the BDR, proximal airway ($FE_{NO,50}$ and $J'aw_{NO}$) and distal airway/alveolar (CA_{NO}) NO in both ICS naïve and ICS-treated mild pediatric asthma populations. Our main finding is the positive correlation between the BDR and non-invasive markers of inflammation in the proximal airways in ICS naïve asthmatic children only (Fig. 1), and a PPV of 83% for a BDR as low at 8% for predicting (or ruling in) elevated large airway nitric oxide. This result improves our understanding of the BDR and suggests that bronchodilator-induced changes in FEV_1 reflect, in part, large airway inflammation.

Most physicians have access only to spirometry as an objective measure to assess asthma disease activity. However, several studies have found inconsistent or poor relationships between lung function and asthma symptoms or severity in children, because many asthmatic children have near normal spirometric values even when they demonstrate symptoms of persistent asthma.[35] In our study, we found no difference in baseline spirometry between ICS naïve and ICS-treated asthmatics, and only a small difference between FEV1/FVC in our control group and the ICS-treated group (Table 1). These results suggest that in children with mild asthma, ICS use may not be related to baseline spirometry.

In contrast to baseline spirometry, the BDR is a dynamic measure of bronchodilation from baseline. Previous research has demonstrated a weak yet significantly relevant, positive relationship between the BDR and $FE_{NO,50}$, in either mixed (ICS treated and ICS naïve).[22,28] or ICS naïve[24] pediatric asthma populations, which is consistent with our results (Fig. 1). However, we have shed insight into the relationship between the BDR and region-specific eNO, that is, Jaw_{NO} and CA_{NO}, in separate ICS treated and ICS naïve populations. Our observation that ICS treatment, which primarily targets the proximal airways, is associated with a lower $FE_{NO,50}$, and $J'aw_{NO}$ (Table 2), and abolishes the positive relationship (Fig. 1) strongly suggests that the BDR is closely linked to proximal airway inflammation. These results are consistent with the findings that ICS-induced reduction of peripheral airway eosinophils (assessed using bronchial biopsy) is associated with an attenuation of bronchodilator responsiveness.[23] Furthermore, inflammation in the distal airways/alveoli is only weakly associated with the BDR (Fig. 1). This finding is consistent with the scant smooth muscle from the terminal bronchioles (approximately generation >14) and beyond and the two-compartment model partitioning of the airways in the proximal airway compartment (generations 0–16) and the distal airways/alveoli (generations 17–23).

The current definition of a positive BDR, ≥12% reversibility and ≥200 ml increase in initial FEV_1, has been established primarily in adults.[1] However, there is no clear consensus about what constitutes a positive BDR in children with asthma. Studies have suggested that BDR ≥9% distinguishes children with asthma from children without asthma.[36,37] It has also been reported that patients with at least a 12% BDR had significantly higher $FE_{NO,50}$.[22] A recent study by Sharma et al.[38] suggested that consistent BDR ≥12% was associated with poor long-term control and increased morbidity. However, subjects who had a BDR of ≥10% had clinical outcomes similar to those with a BDR of ≥12%, suggesting that a lower BDR threshold may be appropriate in children with asthma.[38] Our results indicate that if the BDR is ≥8%, there is a very high probability (>83%, PPV) that $FE_{NO,50}$ and $J'aw_{NO}$ will also be elevated. In other words, the BDR may be a good tool to predict (or rule in), but a poor tool to rule out,

elevated proximal airway NO. In concurrence with previous reports,[38] our findings suggest that the guideline criteria defining a ''positive'' BDR as $\geq$12% may be too high in children with asthma.

The clinical usefulness of ruling-in large airway nitric oxide using the BDR is not known. The evidence of using $FE_{NO,50}$, which is closely correlated with $J'aw_{NO}$, to predict steroid-responsiveness,[39] diagnose asthma,[40] or checking compliance with ICS[41] suggest a clinical utility. Unfortunately, several recent longitudinal studies have examined the potential of using $FE_{NO,50}$ to monitor and treat asthma,[12,13,42–44] and have not been able to determine a specific clinical benefit, such as reducing exacerbations, when compared to traditional guidelines (e.g., symptoms, spirometry). However, asthma randomized treatment algorithm (ASTRAL) studies require very specific design criteria, and these early studies examining $FE_{NO,50}$ as a basis for managing asthma have serious design issues as recently reviewed.[45] Hence, the potential role of $FE_{NO,50}$ (or large airway NO and potentially BDR) on asthma management has not been firmly established.

Our pediatric population was predominately Hispanic. Ethnicity may impact response to inhaled bronchodilators due to genetic differences in β_2 receptors.[46] However, our results are consistent with previous studies with respect to the significant positive relationship (albeit weak) between $FE_{NO,50}$ and the BDR. The upper limit for $FE_{NO,50}$ ($\geq$16 ppb) is lower than that reported in a recent multicenter trial in which the upper limit of normal in children 4–17 years was 25 ppb.[47] This may be due to the relatively small number of control subjects in our study, the predominantly Hispanic population, or, more likely, the absence of atopic children. Only 0.8% of the children in the multicenter trial reported an ethnicity of Hispanic, while 14% were atopic. The presence of atopy increases $FE_{NO,50}$.[48,49] The results for the range and upper limit of $J'aw_{NO}$ and CA_{NO} are similar to the findings of other reports using the two-compartment model[14] to partition eNO in non-asthmatic children[16,34] when adjusting for the effect of axial diffusion of NO. However, a large database of proximal and distal NO values has yet to be reported, and values in our patient population may be lower than other ethnic groups based on $FE_{NO,50}$.

An additional feature of the study is that 10% of the patients did not fit the two-compartment model of NO exchange in the lungs. However, the model was successfully applied in all of the non-asthmatic non-atopic children. These results are similar to the findings of Paraskakis et al.[16] and may be related to heterogeneous ventilation and inflammation patterns in some asthmatic subjects[50] which is not captured by the single path two-compartment model. It may be appropriate to apply a multicompartment model of NO exchange dynamics to these children to characterize proximal and distal nitric oxide.[51] Finally, our population can be characterized clinically and by spirometry as mild asthmatics; hence, one might predict a small response to a bronchodilator (e.g., baseline FEV_1 near the ''ceiling''). However, BDR peaks in children 8–9 years of age[52] which may contribute to our observation of a significant BDR and a moderate relationship between large airway NO and BDR. In addition, a stronger correlation may be present in a more severe population of children that has a lower baseline FEV_1 and more inflammation.

In summary, the BDR shows moderate correlation with proximal or large airway ($FE_{NO,50}$, $J'aw_{NO}$) nitric oxide only in ICS naïve children with mild asthma, and thus suggests that the BDR reflects, in part, inflammation in the large airways. Although the traditional positive BDR cut point has been $\geq$12%, a value as low as $\geq$8% may have utility in the context of pediatric asthma as a simple technique to predict large airway inflammation and thus potential responsiveness to ICS.

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