

Time-dependent effects of inhaled corticosteroids on lung function, bronchial hyperresponsiveness, and airway inflammation in asthma

Vinay Mehta, MD*; Jeffrey R. Stokes, MD†; Abdo Berro, PhD†; Francisco A. Romero, MS†; and Thomas B. Casale, MD†

Background: Exhaled nitric oxide (F_{ENO}) and exhaled breath condensate (EBC) are noninvasive markers that directly measure airway inflammation and may potentially be useful in assessing asthma control and response to therapy.

Objective: To examine the time-dependent effects of inhaled corticosteroids on F_{ENO} and EBC markers concomitantly with lung function and bronchial hyperresponsiveness.

Methods: Eleven steroid-naïve adults with mild-to-moderate persistent asthma were treated with mometasone furoate dry powder inhaler, 400 $\mu\text{g}/\text{d}$, for 8 weeks, followed by a 4-week washout. Forced expiratory volume in 1 second (FEV_1), the concentration of methacholine calculated to cause a 20% decline in FEV_1 (PC_{20}), F_{ENO} , EBC pH, and EBC nitrite measurements before, during, and after treatment were analyzed and compared.

Results: The mean (SEM) FEV_1 increased from 3.01 (0.13) L (82% predicted) to 3.24 (0.18) L (87% predicted) by week 8 ($P < .05$). The PC_{20} level increased from 1.28 (0.31) mg/mL to 2.99 (0.51) mg/mL by treatment week 8 ($P < .05$) and remained relatively stable through washout week 4 ($P < .05$). The F_{ENO} level decreased from 31.1 (4.1) ppb to 20.6 (4.5) ppb by treatment week 1 ($P < .01$), remained low through treatment week 8 ($P < .01$), then trended back to the baseline level by washout week 1 ($P < .01$). The median EBC pH increased from 7.81 (interquartile range, 7.49–8.09) to 8.02 (interquartile range, 7.87–8.12) by treatment week 4, but did not achieve statistical significance. The EBC nitrite level decreased from 17.6 (1.6) μM to 9.3 (0.9) μM by treatment week 8 ($P < .01$), and remained low throughout washout week 4 ($P < .05$). There was a negative correlation between F_{ENO} and PC_{20} (Spearman rank correlation coefficient = -0.50 , $P < .001$).

Conclusion: The F_{ENO} level responded the earliest to treatment and withdrawal of inhaled corticosteroids, whereas changes in EBC markers were delayed but more sustained.

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INTRODUCTION

Asthma ranks among the most common chronic diseases in the United States, with an estimated current prevalence of more than 20 million people.¹ It is characterized by airway inflammation, bronchial hyperresponsiveness (BHR), and variable airflow limitation.² Inhaled corticosteroids (ICSs) constitute the gold standard treatment for persistent asthma and are effective in reducing symptoms, BHR, and airway inflammation.^{2,3} Conventional asthma evaluation and management strategies tend to focus on symptom severity and spirometric lung function parameters.³ However, because asthma is primarily an inflammatory disorder, monitoring airway inflammation is equally important. Exhaled nitric oxide (F_{ENO}) and exhaled breath condensate (EBC) are 2 novel noninvasive methods that can directly measure airway

inflammation and may, therefore, provide a better index of asthma control.^{4,5}

Measurement of F_{ENO} can be readily evaluated by means of a standardized technique⁶ and has been proposed as a marker of asthma severity. Recent data suggest that it may be useful in adjusting ICS therapy because it is decreased by ICSs in a dose-dependent manner.⁷ The EBC reflects the composition of airway lining fluid and is collected by cooling exhaled air. In asthma, the EBC contains high concentrations of nitrogen oxides (nitrites and nitrates)⁸ and has an acidic pH.⁹ The latter appears to be predictive of asthma exacerbations.^{10,11} Although treatment with ICSs has demonstrated improvement in lung function and BHR,¹² its time-dependent effects on these parameters with concomitantly measured markers of airway inflammation have not been extensively studied.

In the present study, we examined the time-dependent effects of ICSs on lung function, BHR, and markers of airway inflammation. Of the current ICS products on the market, we elected to use mometasone furoate dry powder inhaler (DPI) at a medium dose because of its low systemic bioavailability and once-daily dosing.¹³ We performed a comparative analysis on its effects on FEV_1 , the concentration of methacholine calculated to cause a 20% decline in FEV_1 (PC_{20}), F_{ENO} , and

Affiliations: * Allergy, Asthma & Immunology Associates, PC, Lincoln, Nebraska; † Division of Allergy & Immunology, Creighton University Medical Center, Omaha, Nebraska.

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EBC measurements before, during, and up to 4 weeks after an 8-week treatment period in steroid-naïve asthmatic adults.

METHODS

Participants

Twelve steroid-naïve adults aged 20 to 49 years with mild-to-moderate persistent asthma were enrolled; 11 of these individuals completed the study. All participants were ICS naïve and had an FEV₁ of 60% or greater of the predicted value (based on the Hankinson reference equation¹⁴) and a PC₂₀ level of 4 mg/mL or less. Concomitant therapy with leukotriene modifiers and long-acting antihistamines was prohibited and was discontinued 14 and 7 days, respectively, before the screening visit. Postbronchodilator reversibility of airways was demonstrated in some participants but was not a requirement. Active smokers in the preceding 12 months and participants with respiratory tract infections within 2 weeks of screening were excluded.

Study Design

At the screening visit, participants underwent spirometry and a methacholine challenge. Those who satisfied the eligibility requirements proceeded to the F_{ENO} evaluation and EBC collection. Each participant was treated with mometasone furoate DPI, 400 µg/d, dosed in the evening, for 8 weeks, followed by a 4-week washout period. No other asthma medication other than a short-acting β₂-agonist was permitted. Spirometry, F_{ENO} measurement, methacholine challenge, and EBC collection were conducted at each visit during weeks 1, 4, and 8 of drug treatment and during weeks 1 and 4 of drug washout. The FEV₁, PC₂₀, F_{ENO}, and EBC measurements were compared with baseline and end of treatment (week 8) values. Asthma symptoms and other intercurrent events, such as upper or lower respiratory tract infections, were monitored and documented. All participants were asked to document their albuterol use on a daily basis and to keep track of any asthma exacerbations, defined as an increase in shortness of breath, cough, or wheeze. In the event of an upper or lower respiratory tract infection coinciding with a study visit, the assessments were deferred and the participant was asked to return at least 3 days later for reassessment.

All participants provided written informed consent before enrollment. The study was approved by the institutional review board of Creighton University, Omaha, Nebraska.

Spirometry

Spirometry was performed using a KoKo PFT spirometer (nSpire Health, Longmont, Colorado), according to American Thoracic Society guidelines.¹⁵ Each participant executed a standard forced expiratory maneuver from maximal inhalation. A minimum of 3 attempts were evaluated, and the best FEV₁ value was recorded, along with the FEV₁ percentage predicted value based on the Hankinson reference equation.¹⁴

Exhaled Nitric Oxide

Participants were advised to refrain from eating or drinking within 1 hour of the procedure. The F_{ENO} level was measured

by chemiluminescence using an analyzer (model 280i NO Analyzer; Sievers, Boulder, Colorado), which has a sensitivity of less than 1 ppb. The measurements were performed at an expiratory flow rate of 50 mL/s. A minimal exhalation of 6 seconds was required to achieve a stable nitric oxide level. All participants had at least 3 recorded F_{ENO} measurements. Repeated measurements were performed until the values agreed within 10% of the mean. The mean value was recorded as the final F_{ENO} level.

Exhaled Breath Condensate

No food or drink was permitted within 1 hour of the procedure. The EBC sample was collected using a cooling condenser chamber (EcoScreen, Jaeger, Germany). Participants breathed through a mouthpiece and a 2-way nonrebreathing valve, which also served as a saliva trap. They were instructed to breathe at tidal volume with normal frequency for 10 minutes, wearing a nose clip. The sample was collected on ice at –20°C, and aliquots of condensate were transferred to Eppendorf tubes and stored at –70°C.

EBC pH and Nitrite Measurements

The EBC pH was measured by means of a pH meter after argon deaeration for 5 minutes. Nitrite concentrations were determined by chemiluminescence, as previously described.¹⁶ Briefly, nitrite was reduced to nitric oxide with 1% potassium iodide in glacial acetic acid, and the resulting nitric oxide was quantified by a chemiluminescence analyzer after reaction with ozone. Freshly prepared serial dilutions of nitrite solution were used to determine the standard curve. Each sample was evaluated 3 times, and the mean value was recorded as the final nitrite concentration.

Methacholine Challenge

Bronchoprovocation challenge with methacholine (Provocho-line; Roche, Nutley, New Jersey) was conducted according to the manufacturer's recommendations. Isotonic sodium chloride solution, followed by increasing concentrations of methacholine (0.025, 0.25, 2.5, 5, 10, and 25 mg/mL) solutions, was administered using a 5-breath dosimeter¹⁷ (Koko DigiDoser; nSpire Health, Longmont, Colorado). During each inhalation, participants began at functional residual capacity and were instructed to inhale slowly and deeply. The FEV₁ was measured 3 minutes after the fifth inhalation. The procedure was continued until there was a 20% or greater reduction in FEV₁ compared with isotonic sodium chloride solution or until the 25-mg/mL methacholine concentration had been administered. Bronchial responsiveness was reported as PC₂₀.

Statistical Analysis

The participant sample size was determined using a power of 80% for a 2-tailed α=.05. These calculations were based on published studies using similar methods and participants.^{18–20} A mean difference in F_{ENO} of 35% of baseline at 8 weeks using a paired analysis yielded a requirement of 10 participants. A mean difference in methacholine PC₂₀ at 0.5 log

yielded a requirement of 5 participants. A significant difference for EBC nitrate/nitrite at 12 weeks required 11 participants. Thus, taking into consideration the time point references of our study and a dropout allowance of 1 participant, a sample size of 12 participants was chosen.

Data are presented as mean (SEM) when parametrically distributed or as median and interquartile range (IQR) when nonparametrically distributed. The FEV₁ percentage predicted values are based on the Hankinson reference equation.¹⁴ The F_{ENO} and PC₂₀ values were log transformed to normalize their distributions before analysis. An intention-to-treat analysis was conducted on all end points. One participant terminated the study prematurely, and her data were included in the analysis. Differences between visits were analyzed using paired *t* tests or repeated-measures analysis of variance followed by the Tukey-Kramer post hoc test. Spearman or Pearson correlation coefficients were initially used to evaluate relationships among FEV₁, PC₂₀, F_{ENO}, and EBC markers. Potential correlations were subsequently evaluated through rank regression analyses. The analyses were performed across the entire longitudinal data set. A linear mixed-effects model was used to account for intraperson correlation across repeated assessments. All summary statistics and analyses were performed using SAS 9.1 (SAS Institute, Cary, North Carolina) or Prism 5.0 (GraphPad Software, San Diego, California). Statistical significance was set at *P* < .05, 2-tailed.

RESULTS

Participant Disposition and Baseline Characteristics

Of the 18 steroid-naïve asthmatic volunteers screened, 12 qualified (4 men and 8 women) and proceeded to enroll in the study. Participant 11 dropped out after her fourth visit because of relocation to another city (Fig 1). The mean age at enrollment was 31 years. Baseline participant characteristics are summarized in Table 1.

FEV₁, PC₂₀, F_{ENO}, EBC pH, and EBC Nitrite Values

The mean (SEM) FEV₁ at the initial visit was 3.01 (0.13) L (82% predicted) and was increased to 3.24 (0.18) L (87% predicted) by week 8 (*P* < .05) (Fig 2A). The mean (SEM) PC₂₀ increased from 1.28 (0.31) mg/mL at the initial visit to 2.99 (0.51) mg/mL by treatment week 8 (*P* < .05) and remained relatively stable through washout week 4 (*P* < .05) (Fig 2B). The mean (SEM) F_{ENO} decreased from 31.1 (4.1) ppb at the initial visit to 20.6 (4.5) ppb by treatment week 1 (*P* < .01), remained low through treatment week 8 (*P* < .01), then trended back to the baseline level by washout week 1 (Fig 2C).

The median EBC pH increased from 7.81 (IQR, 7.49–8.09) to 8.02 (IQR, 7.87–8.12) by treatment week 4 but did not achieve statistical significance (*P* = .13) (data not shown). The mean (SEM) EBC nitrite level decreased from 17.6 (1.6) μM at the initial visit to 9.3 (0.9) μM by treatment week 8 (*P* < .01) and remained low throughout washout week 4 (*P* < .05) (Fig 2D). The mean FEV₁, PC₂₀, F_{ENO}, and

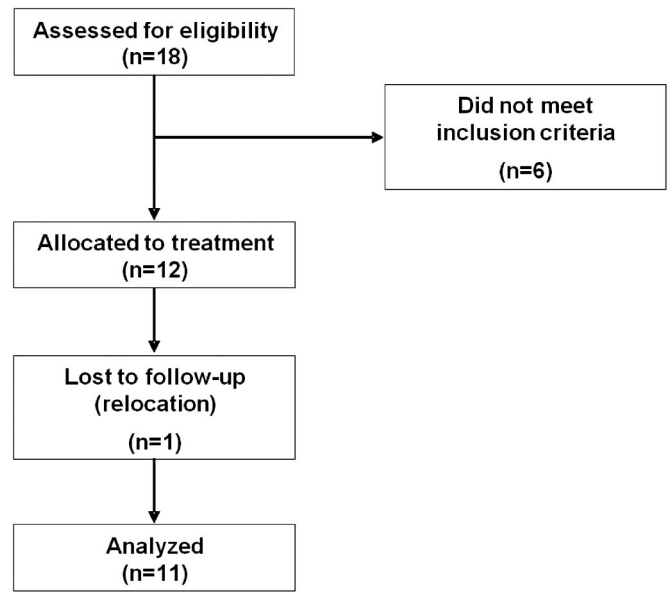


Figure 1. Participant disposition.

EBC nitrite values for each participant across the study are given in Table 2.

Correlations Among FEV₁, F_{ENO}, PC₂₀, EBC pH, and EBC Nitrite

There was a negative correlation between F_{ENO} and PC₂₀ (Spearman rank correlation coefficient = −0.50, *P* < .001) (Fig 3). No other statistically significant correlations were found between any of the other parameters at any given time point.

None of the participants reported any increased asthma symptoms (shortness of breath, cough, or wheeze) or in-

Table 1. Baseline Participant Characteristics

Participant No./sex/age, y	FEV ₁ , % ^a	PC ₂₀ , mg/mL ^a	F _{ENO} , ppb ^a	EBC pH ^b	EBC nitrite, μM ^a
1/M/26	93	3.04	22.1	7.82	12.6
2/F/33	89	0.31	58.2	8.12	28.3
3/M/35	71	1.35	24.9	8.00	27.7
4/F/31	91	1.28	17.8	7.80	13.9
5/M/35	72	0.25	30.4	8.12	19.8
6/F/26	73	0.17	43.3	7.43	19.3
7/F/35	93	0.30	26.4	7.41	14.4
8/M/49	66	0.40	59.0	7.75	16.3
9/F/39	62	3.06	20.4	7.26	11.0
10/F/34	89	1.86	24.5	7.93	19.0
11/F/20	90	0.12	24.6	7.69	16.0
12/F/21	90	2.17	21.9	8.15	13.3

Abbreviations: EBC, exhaled breath condensate; F_{ENO}, exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; PC₂₀, methacholine concentration causing a 20% decrease in FEV₁.

^a Data are presented as mean.

^b Data are presented as median.

creased albuterol use throughout the study. In 2 instances, assessments were deferred for a few days because of upper respiratory tract infections. No other adverse events were reported.

DISCUSSION

To our knowledge, this is the first study to simultaneously compare time-dependent changes in FEV₁, F_{ENO}, PC₂₀, EBC pH, and EBC nitrite in steroid-naïve asthmatic patients before, during, and after ICS treatment.

As demonstrated by this study, spirometric evaluation may not be as sensitive for detecting the short-term effects of ICSs. Indeed, several asthma studies have shown that FEV₁ is slow to change and often lacks discriminating power.¹⁹ In contrast, the F_{ENO} level decreased early with ICS therapy and trended back to pretreatment levels within 1 week of its discontinuation. These findings are consistent with previous observations that have characterized F_{ENO} as a steroid-sensitive “fast responder.”^{20,21} It is continuously produced in the lower airways by nitric oxide synthases, primarily the inducible nitric oxide synthase 2 isoform. The latter is up-regulated in asthma by inflammatory cytokines and suppressed by corticosteroids.^{22,23} The F_{ENO} level has been shown to correlate well with more invasive and costly measures of airway eosinophilia, such as induced sputum,^{24,25} bronchoalveolar lavage,^{26,27} and bronchial biopsy.²⁸ Furthermore, it has been shown that monitoring the F_{ENO} level in patients with asthma

enables anti-inflammatory treatment to be tailored more efficiently, resulting in the reduction of the ICS dose without compromising asthma control.⁷

In our study, the extent and timing of PC₂₀ improvement with ICS treatment paralleled the data from a recent meta-analysis showing a gradual reduction in BHR by 2 to 8 weeks in steroid-naïve asthmatic patients.²⁹ This decline is likely attributable to the suppression of airway inflammatory cells.³⁰ However, several studies have shown a relative dissociation between the decrease in inflammatory cells and BHR.³¹ Furthermore, improvement of BHR can vary significantly among individuals and the factors predictive of improvement remain largely unknown.

Measurement of EBC pH has recently been proposed as a noninvasive tool in the evaluation of asthma. Patients with acute asthma exacerbations can have EBC pH values more than 2 log orders lower than normal, which normalize with ICS therapy.¹⁰ Relationships between EBC pH and asthma severity have also been observed, especially in children.¹¹ Because its measurement is relatively easy to perform, some investigators have postulated that it may be a clinically useful marker for monitoring asthma therapy.^{32,33} However, studies in children and adults with stable asthma have shown little, if any, improvement in EBC pH with ICS treatment.^{34,35} Furthermore, several methodological issues, such as the effect of ambient carbon dioxide, the need for sample deaeration, and the optimal time for measurement, remain to be addressed. In

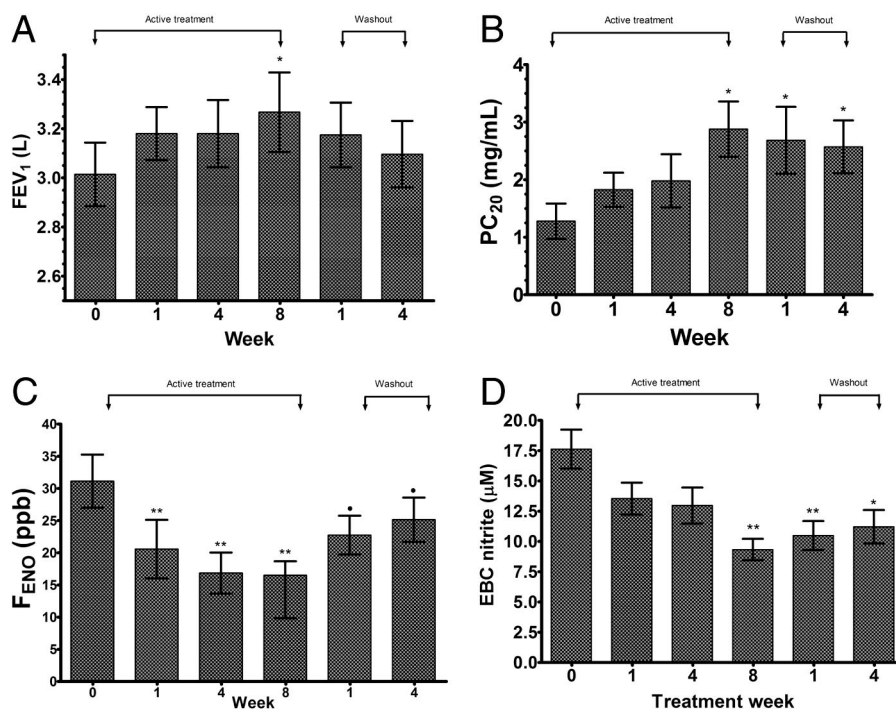


Figure 2. Effects of inhaled corticosteroid therapy on forced expiratory volume in 1 second (FEV₁) (A), the concentration of methacholine calculated to cause a 20% decline in FEV₁ (PC₂₀) (B), exhaled nitric oxide (F_{ENO}) level (C), and exhaled breath condensate (EBC) nitrite level (D). Data are given as mean (SEM). **P* < .05 compared with week 0, ***P* < .01 compared with week 0, and ****P* < .01 compared with week 8.

Table 2. Effects of ICS Therapy on FEV₁, PC₂₀, F_{ENO}, and EBC Nitrite^a

Parameters measured in each participant	Treatment week				Washout week	
	0	1	4	8	1	4
1						
FEV ₁ , %	93	92	95	102	95	98
PC ₂₀ , mg/mL	3.04	2.84	1.38	1.93	2.86	3.24
F _{ENO} , ppb	22.1	15.6	22.7	23.0	32.3	26.5
EBC nitrite, μ M	12.6	16.3	11.4	5.9	7.1	11.0
2						
FEV ₁ , %	89	96	96	97	98	96
PC ₂₀ , mg/mL	0.31	2.65	2.00	5.41	2.76	2.57
F _{ENO} , ppb	58.2	50.9	44.5	28.5	40.9	51.1
EBC nitrite, μ M	28.3	11.4	6.8	11.8	12.9	9.8
3						
FEV ₁ , %	71	78	79	77	72	71
PC ₂₀ , mg/mL	1.35	2.59	0.91	1.94	1.24	1.48
F _{ENO} , ppb	24.9	16.4	18.9	17.7	20.0	25.3
EBC nitrite, μ M	27.7	15.3	10.1	10.9	15.6	6.9
4						
FEV ₁ , %	91	93	94	91	91	94
PC ₂₀ , mg/mL	1.28	3.05	4.47	5.85	5.58	3.52
F _{ENO} , ppb	17.8	7.5	9.5	15.6	24.3	14.2
EBC nitrite, μ M	13.9	12.5	15.8	6.6	10.0	5.1
5						
FEV ₁ , %	72	73	74	79	75	73
PC ₂₀ , mg/mL	0.25	0.94	1.09	3.75	2.78	2.30
F _{ENO} , ppb	30.4	12.4	7.5	8.9	16.2	28.4
EBC nitrite, μ M	19.8	22.6	11.8	8.0	15.8	6.6
6						
FEV ₁ , %	73	80	82	85	89	81
PC ₂₀ , mg/mL	0.17	0.56	0.23	0.80	0.75	0.79
F _{ENO} , ppb	43.3	35.9	28.8	18.9	33.6	38.4
EBC nitrite, μ M	19.3	10.7	23.9	6.1	12.1	20.9
7						
FEV ₁ , %	93	93	94	93	93	95
PC ₂₀ , mg/mL	0.30	0.44	0.42	0.59	0.48	0.46
F _{ENO} , ppb	26.4	14.4	16.4	18.0	15.6	19.1
EBC nitrite, μ M	14.4	14.8	15.0	6.4	4.3	13.8
8						
FEV ₁ , %	66	75	67	84	83	74
PC ₂₀ , mg/mL	0.40	0.57	2.93	4.12	2.06	1.97
F _{ENO} , ppb	59.0	49.3	18.1	17.4	22.0	25.5
EBC nitrite, μ M	16.3	7.6	12.9	13.0	12.9	14.2
9						
FEV ₁ , %	62	69	70	69	66	65
PC ₂₀ , mg/mL	3.06	3.16	5.54	3.08	6.50	5.85
F _{ENO} , ppb	20.4	15.3	9.5	6.5	6.3	11.9
EBC nitrite, μ M	11.0	6.7	19.5	13.8	6.1	7.9
10						
FEV ₁ , %	89	87	84	86	87	86
PC ₂₀ , mg/mL	1.86	2.00	1.38	2.43	1.03	2.21
F _{ENO} , ppb	24.5	14.8	9.3	15.3	25.3	20.5
EBC nitrite, μ M	19.0	10.3	8.8	13.4	6.3	14.1
11						
FEV ₁ , %	90	92	90	90	NA	NA
PC ₂₀ , mg/mL	1.15	1.64	1.45	1.68	NA	NA
F _{ENO} , ppb	24.6	9.5	10.4	12.6	NA	NA
EBC nitrite, μ M	16.0	15.7	13.5	7.4	NA	NA
12						
FEV ₁ , %	90	88	96	90	84	87
PC ₂₀ , mg/mL	2.17	1.45	1.95	2.95	3.47	3.87
F _{ENO} , ppb	21.9	4.9	6.6	8.0	13.7	15.7
EBC nitrite, μ M	13.3	18.5	6.1	8.6	12.4	13.1

Abbreviations: EBC, exhaled breath condensate; F_{ENO}, exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; NA, not applicable (because of subject dropout); PC₂₀, methacholine concentration causing a 20% decrease in FEV₁.

^a Data are presented as mean.

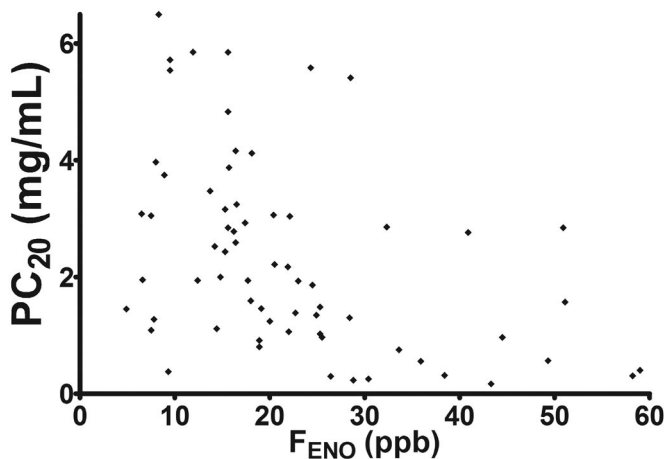


Figure 3. There was a negative correlation between exhaled nitric oxide (F_{ENO}) level and the concentration of methacholine calculated to cause a 20% decline in forced expiratory volume in 1 second (PC_{20}) (Spearman rank correlation coefficient = -0.50 , $P < .001$).

our study, the lack of statistically significant changes in EBC pH is likely explained by the fact that our participants had relatively stable asthma and did not experience any acute asthma exacerbations.

In aqueous solution, nitric oxide reacts with reactive oxygen species to form stable oxides of nitrogen, primarily nitrites and nitrates, which can be measured in EBC. This conversion may be favored by airway acidification. High concentrations of nitrites and nitrates in EBC have been reported in adults and children with asthma.^{36,37} Those treated with ICSs have lower values compared with their steroid-naïve counterparts.³⁷ In our study, EBC nitrite levels declined only after 8 weeks of ICS treatment and remained low throughout washout week 4. This delayed response may be indicative of a lower sensitivity to the effects of ICS therapy and a different kinetic profile compared with F_{ENO} . In addition, it may reflect an element of noneosinophilic inflammation, which tends to respond poorly to ICSs.

Similar to several published studies, we found a significant correlation between F_{ENO} and BHR^{38–40} but no significant correlation among F_{ENO} , FEV_1 , and EBC biomarkers. The absence of such correlations may be attributed to their differences in sensitivity and/or specificity and kinetic profiles in response to ICSs. Furthermore, each parameter may be reflective of a distinct component of the asthma state.

There are several potential shortcomings of our study. First, we recognize the lack of a placebo control arm. This decision was made on ethical grounds after considering the asthma severity of the intended participants and the duration of the study. Second, we did not ascertain the atopic status of the participants. Indeed, atopic asthmatic individuals have been shown to have significantly higher F_{ENO} levels than their nonatopic asthmatic counterparts.⁴¹ Some investigators have even suggested that F_{ENO} may be a marker of atopy rather than asthma per se.⁴² Third, postbronchodilator reversibility

of the airways was not an inclusion criterion for enrollment. This may account for the modest improvement in FEV_1 seen in this study compared with other asthma studies with mometasone furoate DPI.^{43,44} Fourth, although none of the participants reported increased albuterol use or asthma symptoms, symptom control was not formally evaluated. We, therefore, cannot comment on potential correlations between asthma symptom severity and inflammatory and spirometric parameters. However, given the modest changes in FEV_1 during the study, we suspect that there were no significant changes in asthma symptom control. Fifth, with respect to EBC, intraindividual diurnal variability and the lack of standardized collection and analysis procedures render reproducibility and comparison of results with other studies difficult. For example, Leung et al⁴⁵ recently reported a poor agreement in EBC pH between 2 different collection devices. Finally, we acknowledge the fact that one of the participants dropped out of the study prematurely. However, we do not believe that this adversely affected our results because an intention-to-treat analysis was conducted on all end points and our study was sufficiently powered to allow the dropout of 1 participant.

Accurate evaluation of airway inflammation has become an important goal to help achieve good asthma control. Non-invasive markers such as F_{ENO} and EBC, which more directly reflect airway inflammation, may be superior to conventional assessments, such as pulmonary function. On the basis of our data, the F_{ENO} level appears to respond the earliest to treatment and withdrawal of ICSs. On the other hand, changes in EBC markers were delayed but more sustained. However, the current lack of standardized collection and analysis procedures limits its clinical usefulness. In contrast, measurement of F_{ENO} is easy to perform and highly reproducible. Furthermore, the recent introduction of inexpensive handheld devices, such as an airway inflammation monitor (NIOX MINO; Aerocrine, Solna, Sweden), may render it accessible to nonspecialty settings, such as primary care offices and emergency departments. Additional longitudinal studies are necessary, however, before broad conclusions can be reached about its interpretability and usefulness in monitoring asthma control.

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Requests for reprints should be addressed to:
 Vinay Mehta, MD
 600 N Cotner Blvd, Ste 208
 Lincoln, NE 68505
 E-mail: vinay-mehta@hotmail.com