

Brief Report**Fractional Exhaled Nitric Oxide in Eosinophilic COPD**

Pablo E. Morejon-Jaramillo¹ Wenli Ni^{1,2} Nicholas Nassikas¹ Andrew Synn¹ Mahmoud Elfeshawy¹ Cailey Denoncourt¹ Sophia Schortmann¹ Brent Coull³ Meghan Rebuli⁴ Wanda Phipatanakul⁵ Mary B. Rice^{1,2}

¹Division of Pulmonary, Critical Care and Sleep Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, United States

²Center for Climate, Health, and the Global Environment, Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States

³Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States

⁴Department of Pediatrics and Curriculum in Toxicology and Environmental Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States

⁵Division of Immunology, Boston Children's Hospital, Boston, Massachusetts, United States

Address correspondence to:

Mary B. Rice
330 Brookline Ave, Dana RW-0659
Boston, MA 02459
Phone: (617) 667-5864
Email: mrice1@bidmc.harvard.edu

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Abstract

Eosinophilic chronic obstructive pulmonary disease (COPD) is a distinct subtype with clinical and biological differences from non-eosinophilic COPD and asthma. Fractional exhaled nitric oxide (FeNO) is an established marker of type 2 airway inflammation in asthma, but its utility in eosinophilic COPD is less well understood. We analyzed baseline data from 176 participants in the Air Purification for Eosinophilic COPD Study (APECS), a randomized controlled trial of former smokers with eosinophilic COPD. At enrollment, FeNO and blood eosinophil counts were measured, and participants reported asthma history and severe COPD exacerbations requiring hospitalization in the prior year. Each 50 cells/ μ L higher eosinophil count was associated with a 3.2% increase in FeNO (95% CI: 0.3 - 6.1%). Asthma history was associated with 29.1% higher FeNO (95% CI: 5.2–58.5%). Elevated FeNO, defined as ≥ 25 or ≥ 50 parts per billion, was linked to greater odds of asthma diagnosis and recent severe exacerbation, although confidence intervals included the null. These findings suggest that FeNO may serve as a practical, noninvasive biomarker of type 2 inflammation in eosinophilic COPD and could help identify patients at higher risk of severe exacerbation.

Introduction

Chronic obstructive pulmonary disease (COPD) remains a leading cause of morbidity and mortality worldwide¹. While treatment has historically emphasized smoking cessation and inhaled therapies, accumulating evidence suggests that the eosinophilic COPD subtype may respond differently to corticosteroids and targeted biologics compared with non-eosinophilic COPD^{2,3}.

Improved characterization of eosinophilic COPD could enhance risk stratification and therapeutic targeting, but practical clinical biomarkers are limited. Blood eosinophils and interleukins are informative but not routinely obtained. Fractional exhaled nitric oxide (FeNO) is a widely available, noninvasive marker of eosinophilic airway inflammation used to monitor asthma; however, whether it is a useful indicator of type 2 inflammation and risk of exacerbation in well-defined eosinophilic COPD that is targeted for biologics, steroids and other therapies, is not well established.

We therefore examined whether FeNO levels are associated with peripheral eosinophil counts, asthma history, and severe exacerbation history among participants in the Air Purification for Eosinophilic COPD Study (APECS). We also evaluated whether clinically defined FeNO thresholds identify subgroups at increased risk of adverse outcomes.

Study Population

We analyzed baseline, pre-randomization data from the Air Purification for Eosinophilic COPD Study (APECS), a randomized controlled trial conducted in the Northeastern United States. Participants were former smokers with spirometry-confirmed COPD (GOLD II–IV), ≥ 10 pack-year smoking history, and an absolute eosinophil count ≥ 150 cells/ μ L within the prior year. The trial protocol has been described previously.

Data Collection

Demographics, medical history, and questionnaire data were obtained at enrollment and entered into REDCap. Participants reported physician-diagnosed asthma and COPD hospitalizations in the past 12 months. Education was categorized as more than some college versus less, and current inhaled corticosteroid use was abstracted from medication records and verified with participants.

FeNO and Eosinophil Measurements

Peripheral blood eosinophils were measured at study entry. FeNO was assessed with the NIOX VERO® analyzer, using standardized ATS/ERS protocols. Two reproducible measurements were averaged.

Statistical Analysis

Linear regression was used to examine associations of FeNO with blood eosinophil count, asthma diagnosis, and COPD hospitalization. Secondary analyses categorized FeNO⁴⁻⁶ as ≥ 25 ppb (mildly elevated) and ≥ 50 ppb (elevated) and assessed associations with asthma and hospitalization using logistic regression. Models adjusted for age, sex, education, BMI, and inhaled corticosteroid use. Eosinophil counts were log-transformed for normality. Sensitivity analyses additionally adjusted for asthma history. Analyses were conducted using R 4.4.2, with $p < 0.05$ considered significant.

Results

A total of 176 participants were included (mean age 71.4 years, 53% female). Nearly half (46%) had severe to very severe COPD. The mean FeNO was 23.2 ppb (SD 20.1); 32% had FeNO ≥ 25 ppb and 8% had FeNO ≥ 50 ppb. The mean eosinophil count was 213 cells/ μ L (SD 178), and 44% reported a history of asthma. In the prior year, 15% had experienced a COPD exacerbation requiring hospitalization (Table 1). Blood eosinophil counts were slightly higher in COPD patients with a previous diagnosis of asthma compared to those without (226 vs. 203 cells/ μ L), but this difference was not statistically significant ($p = 0.41$, Table 2). We also found blood eosinophil counts were slightly higher in COPD patients with a previous diagnosis of asthma compared to those without (238 vs. 196 cells/ μ L), but this difference was not statistically significant ($p = 0.548$).

Higher blood eosinophil count was associated with higher FeNO (Table 3): each 50 cells/ μ L increment corresponded to a 3.2% increase in FeNO (95% CI: 0.3–6.1%). Asthma history was associated with 29.1% higher FeNO (95% CI: 5.2–58.5%). No significant association was observed between recent severe exacerbation and FeNO in continuous analyses.

When FeNO was dichotomized, elevated FeNO (≥ 25 ppb and ≥ 50 ppb) was associated with greater odds of asthma diagnosis and severe exacerbation history, although confidence intervals crossed

the null (Figure 1). Sensitivity analyses adjusting for asthma produced similar results; for example, each 50 cells/ μ L increase in eosinophil count was associated with a 2.9% higher FeNO (95% CI: 0.1-5.8%).

Discussion

In this cohort of older former smokers with eosinophilic COPD, we found that higher FeNO was associated with higher blood eosinophils and a history of asthma. We also observed a pattern of greater odds of severe COPD exacerbation among participants with FeNO above clinical thresholds, although estimates did not reach statistical significance. Very few studies have measured FeNO in eosinophilic COPD. Our findings suggest that FeNO may serve as a practical biomarker of type 2 inflammation in COPD.

Our results align with prior studies showing correlations between FeNO and eosinophil counts in COPD⁷ and extend them by focusing specifically on a well-characterized eosinophilic COPD population. Importantly, associations between FeNO and eosinophils persisted after adjusting for asthma history, supporting an independent role of FeNO in this subtype. FeNO is attractive clinically because it is noninvasive, reproducible, and more widely available than sputum eosinophil or interleukin measurements^{8,9}.

FeNO has also been linked to therapeutic response in COPD⁸, including improved outcomes with inhaled corticosteroids among those with elevated levels. Our findings support the possibility that FeNO could be incorporated into treatment selection⁹ or monitoring strategies in eosinophilic COPD, similar to its established role in asthma.

This study has several limitations. Asthma history was self-reported, which may lead to misclassification. Our cross-sectional design precludes conclusions about causality, and exacerbation history was based on recall. In addition, we lacked direct measurement of airway or pulmonary eosinophils (such as sputum or tissue counts), and instead used blood eosinophil count as a practical proxy for airway type 2 inflammation; however, blood eosinophils only imperfectly correlate with sputum or tissue eosinophilia and can be influenced by concurrent illness or medications, which may affect associations with FeNO. Furthermore, current smokers were excluded from the study. While this exclusion reduces confounding related to active smoking

status, it limits the generalizability of our findings to the broader COPD population, as some current smokers may display elevated FeNO levels. Nonetheless, the standardized measurement protocols, exclusion of active smokers, and detailed phenotyping strengthen the validity of our results.

Conclusion

FeNO was associated with higher blood eosinophil counts and asthma history in patients with eosinophilic COPD and showed a pattern of association with recent severe exacerbation. These findings suggest that FeNO may be a useful, noninvasive marker of type 2 inflammation and risk in this COPD subtype. Prospective studies are needed to determine whether FeNO can guide treatment selection and improve outcomes in eosinophilic COPD.

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Table 1. Baseline characteristics of study participants

	Mean (SD) / N (%)
Age (years)	71.4 (8.5)
Sex (Female)	93 (52.8%)
More than some college education	126 (71.6%)
FEV1 (L)	1.4 (0.5)
FVC (L)	2.6 (0.8)
FEV1/FVC (%)	51.9% (13.7%)
Pack-year	53.7 (54.0)
Use of Inhaled Corticosteroids	137 (77.8%)
COPD Hospitalization in the past year	27 (15.3%)
Absolute Eosinophils (cells/ μ L)	213 (178)
Ever asthma diagnosis	77 (43.8%)
Average FeNO	23.2 (20.1)
FeNO Higher than 25 ppb	56 (31.8%)
FeNO Higher than 50 ppb	14 (8.0%)

Severe to very severe COPD based on FEV1 <50%predicted	81 (46.0%)
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Abbreviations: Parts per billion (ppb), forced expiratory volume in 1 second (FEV1)

Table 2. Characteristics of study participants with and without asthma

	Mean (SD) / N (%)	
	No Asthma	Asthma
Age (years)	72.7 (8.3)	69.8 (8.5)
Sex (Female)	48 (48.5)	45 (58.4)
More than some college education	61 (62.2)	65 (84.4)
FEV1 (L)	1.3 (0.5)	1.5 (0.6)
FVC (L)	2.6 (0.9)	2.8 (0.9)
FEV ₁ /FVC (%)	51.1 (14.2)	52.8 (13.5)
Pack-year	64.95 (67.4)	39.6 (23.4)
Use of Inhaled Corticosteroids	73 (73.7)	64 (83.1)
COPD Hospitalization in the past year	12 (12.1)	15 (19.5)
Absolute Eosinophils (cells/ μ L)	203.5 (117.5)	226.4 (235.4)
Average FeNO	21.2 (21.9)	25.75 (17.2)
FeNO Higher than 25 ppb	25 (25.3)	31 (40.3)
FeNO Higher than 50 ppb	6 (6.1)	8 (10.4)
Severe to very severe COPD based on FEV1 <50%predicted	52 (53.1)	29 (38.2)

Table 3. Associations of asthma history, eosinophil level, and COPD hospitalization with FeNO

	Difference in FeNO (ppb)			
	Multiple regression coefficient ^a	95% CI		p-value
		Low CI	High CI	
Eosinophils (per 50 higher eos/uL)	3.2	0.3	6.1	0.03*
Ever asthma diagnosis	29.1	5.2	58.5	0.02
COPD hospitalization	7.2	-18.5	41.0	0.62

^aModels adjusted for age, sex, use of inhaled corticosteroids, education level and BMI.

Figure 1. Associations of FeNO dichotomized by clinical thresholds with odds of asthma diagnosis and COPD hospitalization history

