

Study of Fractional Exhaled Nitric Oxide among Chronic Obstructive Pulmonary Disease Patients in Acute Exacerbation

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Abstract: *Context and Background:* FeNO helps in detection and monitoring of eosinophilic airway inflammation, determining the likelihood of corticosteroid responsiveness and the potential need for the same in treatment. The role in asthma, where increased FeNO reflects eosinophilic mediated inflammatory pathways in central and/or peripheral airway sites and implies increased inhaled and systemic corticosteroid responsiveness has been extensively studied. COPD being a non-eosinophilic inflammatory condition, steroids are considered to have minimal role in the management of stable disease. The aim of this study is to determine whether FeNO rises in an acute exacerbation of COPD and the demographic characteristics related to the same. *Methods:* A total of 100 COPD patients in exacerbation who were able to perform FeNO were evaluated with detailed history and physical examination, complete and differential blood count and spirometry. Patients' FeNO was measured after admission using a portable hand-held machine called NO-BREATH in the sitting position. Those patients with active tuberculosis or other significant comorbidities and unable to perform FeNO were excluded along with those on immunosuppressants. *Results:* With mean age of 58.5 years, 68% patients of the study population had insignificant FENO levels (less than 25 ppb), 31% between 25-50ppb (indeterminate levels) and only 1 patient above 50 ppb. 92% patients had normal blood eosinophils and 73% had raised blood neutrophils. Smoking was the most common risk factor (97%) with a mean smoking index -436.4. *Conclusion:* Most patients of COPD exacerbation in this study had insignificant FENO levels. Smoking in males and exposure to noxious stimulants in females was the commonest risk factor for COPD

Keywords: FeNO, Chronic Obstructive Pulmonary disease, Eosinophils, ACOS

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) has become a serious cause of mortality and morbidity worldwide. It has become the third largest cause of mortality worldwide.¹ 90 % of these deaths occur in low- and middle-income countries. More than 3 million people died of COPD in 2012, accounting for 6% of all deaths globally.² COPD represents an important public health challenge that can be treated and prevented. The COPD burden is projected to increase globally in the coming years because of continuing exposure to the COPD risk factors and the aging of the population.

Cigarette smoking is the most commonly encountered risk factor for COPD. Cigarette smokers have higher prevalence of respiratory symptoms and lung function abnormalities and a greater annual decline in rate of decline in FEV1 than non-smokers.³ Passive exposure to cigarette smoke, also known as Environmental Tobacco Smoke (ETS) have also found to contribute to respiratory symptoms and COPD.⁴ According to Rotterdam Study, the overall incidence of COPD was approximately 9/1000 PY (person years) with a higher

incidence in males and in smokers. The study also found that proportion of never smokers among COPD cases is substantial and higher in females than in males.⁵ Along with the well - recognized risk of occupations involving exposure to organic and inorganic dusts, less obviously "risky" occupations, such as construction, plastics manufacturing, pesticide use and utility work may carry an increased risk of COPD. The risk of adverse occupational exposure is particularly important in workers who smoke or have other factors that raise their risk for COPD, such as Alpha-1-Antitrypsin deficiency.⁶

Exhaled nitric oxide (FeNO) is a non-invasive easily measurable biomarker that is proving to be an excellent surrogate for eosinophilic inflammation in the lungs of patients who have Bronchial Asthma. Preliminary studies have shown FeNO to be helpful in diagnosing and assessing severity and control for Bronchial Asthma. The level of FeNO reflects the degree of eosinophilic inflammation in the airways.⁷

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Levels below 25 ppb are considered low, between 25-50 are considered indeterminate and greater than 50 is considered as high as per ATS guidelines.⁸

Some studies have shown the correlation between elevated FeNO in COPD with increased spirometric response to ICS. FeNO was also found to be increased in patients with COPD exacerbations, compared to the levels observed in patients with stable COPD.⁹

Bronchial Asthma can coexist with Chronic Obstructive Pulmonary Disease (COPD), particularly in older adults, a condition labelled the Asthma COPD Overlap Syndrome (ACOS).¹⁰ ACOS shares clinical and spirometric features of Bronchial Asthma and COPD. Additionally, while airway inflammation in COPD is generally neutrophilic, COPD patients may have features of Bronchial Asthma and thus a component of allergic airway inflammation. This allergic airway inflammation in patients with COPD can be found out using fractional exhaled nitric oxide (FeNO). Since FeNO is useful for identifying patients with allergic airway inflammation who will have a beneficial response to treatment with an inhalational corticosteroid, these data may have important implications for the management of COPD patients. This study was conducted to study the FeNO levels in COPD patients with acute exacerbation, clinical features and demographic patterns of these patients.

Context and Background

FeNO helps in detection and monitoring of eosinophilic airway inflammation, determining the likelihood of corticosteroid responsiveness and the potential need for the same in treatment. The role in asthma, where increased FeNO reflects eosinophilic mediated inflammatory pathways in central and/or peripheral airway sites and implies increased inhaled and systemic corticosteroid responsiveness has been extensively studied. COPD being a non-eosinophilic inflammatory condition, steroids are considered to have minimal role in the management of stable disease. The aim of this study is to determine whether FeNO rises in an acute exacerbation of COPD and the demographic characteristics related to the same.

2. Materials and Methods

This was a prospective cross-sectional study conducted in the Department of Pulmonary Medicine at a tertiary care hospital. Ethics approval was obtained from the institute's ethics committee.

COPD patients in acute exacerbation who were able to do a FeNO test, aged 18 years and above of either gender presenting to the Department of Pulmonary Medicine, were included in the study, after taking written informed consent. Those with active tuberculosis, significant comorbidities, poor general condition and on immunosuppressants were excluded from the study.

Detailed clinical, personal and exposure history was documented with special attention to tobacco smoking and noxious stimuli exposure. Complete and differential Blood counts were done by the investigators. Previous Spirometry (as per ATS guidelines) values of the patients were noted.

All subjects were managed with standard treatment as per latest guidelines and recommendations (Global Initiative for Chronic Obstructive Lung Disease 2023) for treatment of acute exacerbation of COPD.¹⁰

Patients' FeNO was measured after admission using a portable hand-held machine called NO-BREATH in the sitting position in following steps:

- 1) Initialization: patient exhales out to room air
- 2) Inspiration: maximal inspiration through ambient NO-free filter that guarantees repeatable conditions
- 3) Expiration: controlled expiration at chosen flow rate
- 4) Sample collection and gas analysis with display of results

Test was conducted 3 times using a hand-held NO-BREATH device to measure FENO. FENO value above 50 ppb was considered positive as per the NO-BREATH FENO software that was used to measure the FENO and FENO value below 25 ppb was considered insignificant. The maximum value obtained among the 3 readings was considered for analysis.⁸ The data collected were tabulated and analysed to attain the study objectives.

3. Results

In the study entitled "Study of Fractional Exhaled Nitric Oxide among Chronic Obstructive Patients in acute exacerbation" conducted in the Department of Pulmonary Medicine over a period of 2 years, data from 100 patients of COPD in exacerbation were analysed. Out of 100 patients in this study, 85 were males and 15 were females. The mean FeNO value was found to be 20.14ppb. (SD: 12.5; median: 23 ppb [IQR 15–33]; range: 4–54 ppb) 68% had FeNO value less than 25 ppb, 31% had FeNO value between 25-50 ppb and only 1% had FeNO value more than 50 ppb. In this case, 25 ppb for FeNO was used as the cut-off for further analysis.

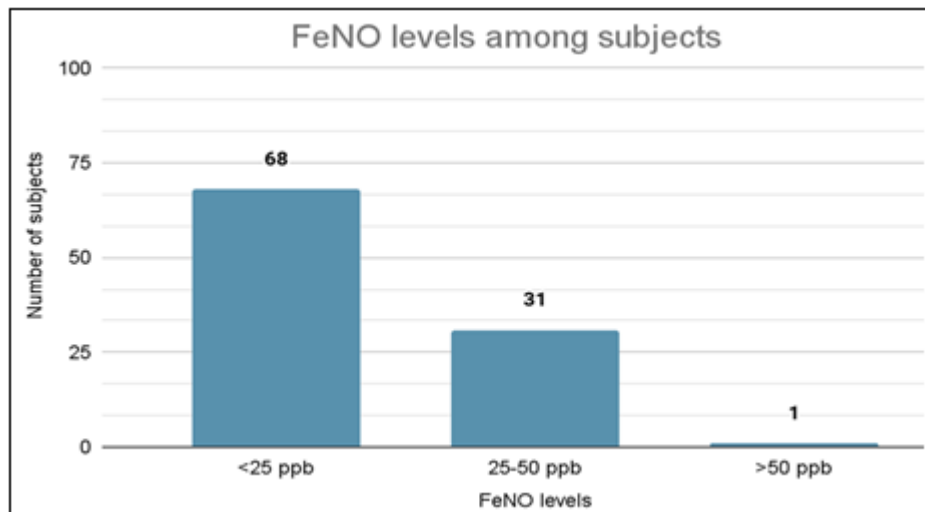


Figure 1: Distribution of FeNO levels among subjects

The study showed that most (94%) of the patients were between 40 and 80 years of age and had only 6 patients less than 40 years of age with the mean age found to be 58.55 years. The mean age among the FeNO<25 ppb was found to be 58.57 years and 58.68 years among the FeNO between 25-50 ppb group. The lone patient who had FeNO more than 50 ppb was aged 53 years.

84% of patients gave a history of smoking in this study. Among females, one out of 15 (6.7%) gave a history of smoking whereas 83 out of 85 (97.6%) male subjects were smokers. Test of significance between smoking and gender was done using the chi-square test. P-value for the chi-square test was less than that of 0.05 which indicated that there was a positive association between smoking and male gender.

Out of the 68 patients with FeNO< 25 ppb, 57 had a history of smoking (83.8%). 26 patients (83.9%) were smokers among the 31 patients with FeNO between 25-50 ppb and the one patient with FeNO >50ppb was also a smoker.

Smoking Indices of the patients were analysed and it was observed that patients with high FeNO had relatively low Smoking Index.

44 COPD patients including all the female subjects in the study gave a history of exposure to some noxious stimulants. Tests of significance between exposure history and gender using the chi-square test indicated that there was positive association between exposure history and Female gender. The duration of COPD among the patients who presented in exacerbation was analysed with their FeNO values and it was found that patients with FeNO <25 ppb had a mean duration of

COPD of 7.13 years. Patients with FeNO between 25 and 50 ppb and >50 ppb had mean duration of COPD as 5.48 years and 2.0 years respectively, thereby indicating that lower values of FeNO were associated with longer duration of COPD. The Blood Eosinophils % of the COPD patients who presented in exacerbation was studied and it was noted that 92% of the patients had normal eosinophils% (6% and less) whereas 8% of patient had their blood eosinophils% raised (more than 6%).

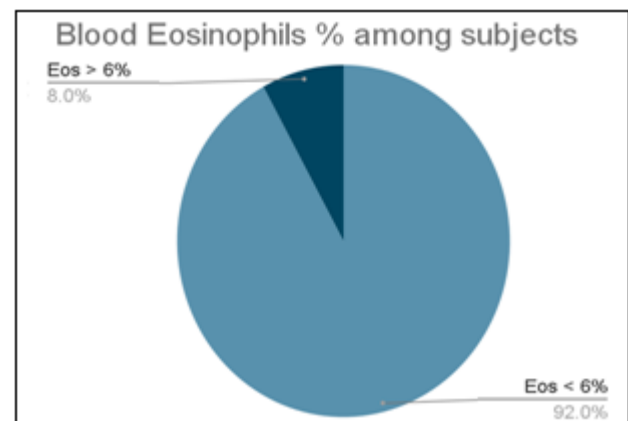


Figure 2: Distribution of Blood Eosinophils % among subjects

The relationship between Blood Eosinophils % and FeNO showed that patients with FeNO <25 ppb had mean eosinophils% of 2.49%, patients with FeNO between 25-50 ppb had mean eosinophils % of 5.19% and patients with FeNO > 50 ppb had mean eosinophils% was 10%.

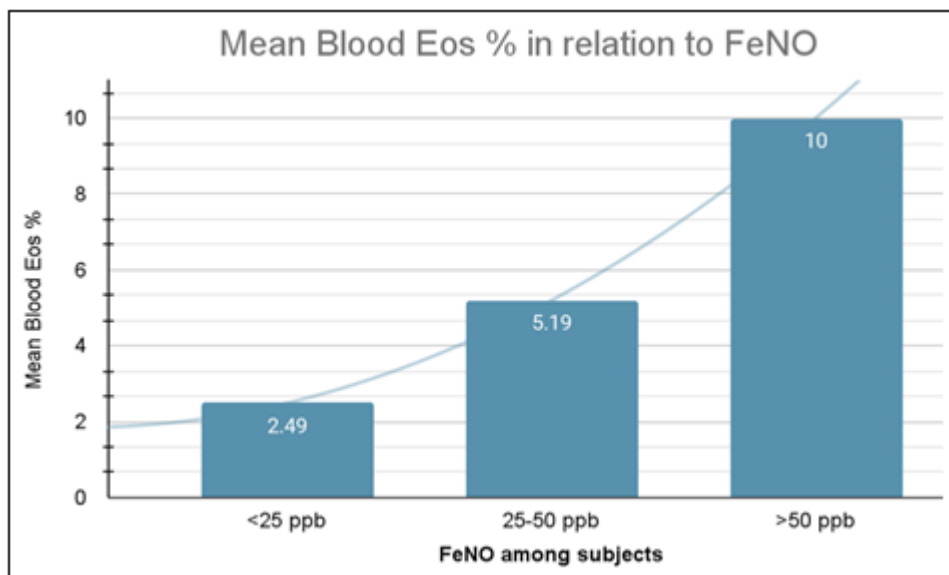


Figure 3: Relation between mean blood Eosinophil% with FeNO among subjects

Pearson correlation analysis was done between FeNO values and the blood eosinophils %. The large positive correlation value for FeNO and eosinophils% (0.841) with p – value less than that of 0.05 indicates strong significant positive correlation between FeNO and blood eosinophils%, indicating that as blood eosinophils% increased, FeNO values increased.

In this study, 63% of patients had their blood neutrophils% more than 70% and the rest 37 % had normal blood neutrophils % (less than and equal to 70%) but showed almost no correlation between FeNO and blood neutrophils %.

In this study, 35 patients who presented in exacerbation belonged to GOLD GRADE II severity of airflow obstruction based on post bronchodilator FEV1, 54 patients belonged to GOLD GRADE III and eleven patients belonged to GOLD GRADE IV.

The mean FEV1 among the 100 patients was found to be 45.49% predicted.

The degree of obstruction among the patients was analysed with respect to FeNO values. The mean value of FEV1% predicted among patients with FeNO<25 ppb was 45.19 of percentage predicted, 45.06 % predicted among the patients with FeNO between 25-50 ppb and 59 % predicted among the patients with FeNO>50 ppb.

4. Discussion

In this study, data from 100 COPD patients who presented in acute exacerbation were analysed.

Out of 100 patients in our study, 15 were females and 85 were males. Most of the COPD patients (44%) belonged to the age group of 60 to 80 years followed by 36 % patients belonging to 40-60 years age group. 52% had BMI in the normal range (18.5-24.9).

Most of the COPD patients who presented in exacerbation had low or insignificant FeNO values (68%). Only 1% of the patients had a significant FeNO value (>50ppb) with the highest value obtained being 54 ppb. The rest 31% of patients had FeNO between 25 and 50ppb. The mean FeNO of the study population was found to be 20.14ppb. This was contradictory to the study conducted by Zhiyu Lu et al wherein raised FENO was Observed in patients with COPD exacerbation.⁹ In the study conducted by Ambrosino et al, none of the patients of COPD had FeNO > 25 ppb.¹¹ Only 2 comparative studies could be found on literature search.

Smoking was found to be the most common risk factor for developing COPD in the males, as 97.6% of males had history of smoking. There was only 1 female smoker. Significant association was found between smoking and male gender. Smoking was found to be the most common risk factor among males. The mean smoking index was found to be 434.64. There was no association found between smoking and FeNO in this study. Similar finding was noted in study conducted by Herath et al among Sri Lankan males wherein insignificant FENO levels were seen among smokers.¹²

The next most common risk factor was exposure to noxious stimulants. All 15 females gave a positive exposure history and 29 males had history of exposure to noxious stimulants. Significant association was found between exposure history and female gender. Thus, exposure to noxious stimulants was observed to be the most common risk factor among females. The study showed no association between exposure history and FeNO. Similar finding was noted in study conducted by Benka Coker ML et al among Honduran women where in there was no significant association noted between indoor pollution and FeNO.¹³

Most of the patients (97%) had presented with complaints of breathlessness, followed by cough and fever. The mean

duration of COPD among the study subjects was found to be 6.49 years.

Most of the patients (92%) had normal blood eosinophils%, whereas only 8% of patients had raised blood eosinophils%. There was significant positive correlation between FeNO and blood eosinophils% and the FeNO value was observed to increase with increase in blood eosinophils%. Most of the patients (73%) in the study had raised blood neutrophils% and the rest 37 % had normal blood neutrophils%. No correlation was found between FeNO and blood neutrophils%. Similar finding was noted in study by Tseliou E et al among refractory asthma patients wherein a low FENO < 20 ppb was associated with neutrophilia.¹⁴

5. Conclusion

There was no significant association between FeNO levels and COPD exacerbation in our study. Smoking was the most common risk factor, particularly among males followed by exposure to noxious stimulants; which was more common among females. Both smoking and exposure to noxious stimulants had no co-relation with FeNO levels in this study. Most of the patients had raised neutrophils and normal levels of eosinophils. Increase in Eosinophil levels was associated with rise in FeNO levels. There was significant association of neutrophilia with COPD exacerbations in this study.

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