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Original Research Paper

Pulmonary Medicine

ASSESSMENT OF FRACTIONAL EXHALED NITRIC OXIDE CONCENTRATIONS IN PATIENTS OF RHINITIS AND CHRONIC PERSISTENT COUGH IN INDIAN POPULATION - A CROSS SECTIONAL STUDY

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ABSTRACT

Background: Chronic persistent cough and rhinitis frequently coexist and may reflect eosinophilic inflammation involving the upper and lower airways.Fractional exhaled nitric oxide (FeNO) is a simple,non-invasive biomarker of type 2/eosinophilic airway inflammation.This study evaluated the diagnostic significance of FeNO in patients with chronic persistent cough and rhinitis in an Indian population.**Methods:** This cross-sectional observational study was conducted at a tertiary care centre in Mumbai from June 2016 to April 2017. Fifty participants were enrolled: chronic cough (n=20), rhinitis (n=20), and healthy controls (n=10). Participants underwent clinical assessment, complete blood count with absolute eosinophil count (AEC), serum total immunoglobulin E measurement, spirometry with reversibility testing, and FeNO measurement using an online NO VARIO analyser. Intergroup comparisons and correlation analyses were performed, with $p<0.05$ considered statistically significant. **Results:** Mean FeNO levels were significantly higher in chronic cough (43.15±17.2 ppb) and rhinitis (48.6±31.2 ppb) compared with healthy controls (22.8±21.4 ppb; $p<0.05$ for both comparisons). FeNO levels did not differ significantly between chronic cough and rhinitis groups. Using a cut-off value of >25 ppb, elevated FeNO was observed in 16 patients with chronic cough and 16 patients with rhinitis. ROC analysis identified 25 ppb as a potential cut-off for distinguishing chronic cough from healthy controls (AUC 0.74). No significant correlation was observed between FeNO and FEV_1 or AEC. **Conclusion:** FeNO was significantly elevated in patients with chronic persistent cough and rhinitis despite largely preserved spirometry. It may serve as a useful, non-invasive marker of eosinophilic airway inflammation and support clinical evaluation of these patients.

KEYWORDS : Fractional Exhaled Nitric Oxide; Feno; Chronic Cough; Rhinitis; Eosinophilic Airway Inflammation.

INTRODUCTION

Chronic cough is a common respiratory symptom encountered across primary, secondary, and specialist healthcare settings and can have a substantial impact on quality of life. Although often perceived as a trivial complaint, persistent cough may result in considerable physical, psychological, and social morbidity. In a proportion of patients, cough remains unexplained despite systematic evaluation and treatment of recognized causes[1]. An isolated chronic cough may also precede or accompany airway hyperresponsiveness and asthma, highlighting the importance of identifying underlying airway inflammation.

Rhinitis, particularly allergic rhinitis, is another major global health problem affecting individuals across all age groups. It is characterized by IgE-mediated inflammation of the nasal mucosa, with typical symptoms including sneezing, nasal obstruction, and nasal discharge[2,3].

Chronic cough and rhinitis frequently coexist, and increasing evidence supports a common inflammatory pathway involving both the upper and lower airways. The concept of **"one airway, one disease"** recognizes the anatomical and functional continuum between the upper and lower respiratory tract[4]. Consequently, patients presenting with chronic cough and rhinitis may benefit from evaluation for underlying eosinophilic airway inflammation and airway dysfunction.

Fractional exhaled nitric oxide (FeNO) is a simple, non-invasive biomarker of type 2/eosinophilic airway inflammation. Nitric oxide is produced predominantly by the airway epithelium, and inflammatory stimulation results in upregulation of inducible nitric oxide synthase and increased exhaled nitric oxide concentrations[5,6]. FeNO measurement has therefore gained clinical importance in supporting the diagnosis of asthma, identifying eosinophilic airway inflammation, predicting corticosteroid responsiveness, and monitoring airway inflammation. Its relatively simple, standardized, and portable measurement has facilitated its increasing use in clinical practice. Similarly, nitric oxide measurements from the upper airway have been investigated as potential markers of nasal inflammation, particularly in allergic rhinitis[7].

Understanding the association between FeNO and pulmonary function in patients presenting with chronic cough and rhinitis may help identify patients with underlying eosinophilic airway inflammation who could benefit from targeted anti-inflammatory therapy.

AIMS AND OBJECTIVES:

To study the application of fractional exhaled nitric oxide as a diagnostic significance in exhaled air from the upper and lower airways in assessing the eosinophilic mediated inflammation in rhinitis and chronic persistent cough patient.

MATERIALS AND METHODS:

The present study is cross sectional observational study with sample size of 38 (using the formula with confidence interval of 95%, with error margin of 4%) over a period of 10 months from June 2016 to April 2017 in patients visiting OPD in Respiratory Medicine department at Tertiary health Center in Mumbai. Over this 10 months of study, 50 patients were included. The subjects with respiratory and nasal symptoms were divided into individual groups of chronic cough and rhinitis each having 20 patients and the third group comprised of 10 healthy controls. The levels of FeNO was measured, analysed its effects and compared between groups using the independent sample t-test. The univariate analyses of factors

associated with FeNO was done using Pearson correlation. Statistical significance was used at the conventional 5% level ($p<0.05$). **Baseline Assessment:** All the enrolled patients were evaluated for detailed clinical examination with Complete blood counts and Absolute eosinophilic count along with s**pecial investigations like** Spirometry with reversibility, Serum total IgE level, measurement of Exhaled nitric oxide.

1. Spirometry with reversibility by using *JAEGER Master Screen PFT* medical system which recorded their FVC, FEV1, FEV1/FVC ratio and PEF following ERS93 criteria. Patients were subjected to inhalation of 1.25 mg of levosalbutamol after which they were allowed to rest for about 15 minutes and spirometry reprated again after 15 minutes.

2. Serum total IgE by using MINILYSER - TECAN, Austria using Calbiotech kit for the Quantitative determination of Immunoglobulin E (IgE) concentration in Human serum using sandwich enzyme immunoassay technique.

3. Measurement of Exhaled nitric oxide: Inhalation phase: The patient inserts the mouthpiece, inhales for 2 to 3 seconds through mouth to total lung capacity (TLC) and then exhale immediately.

Exhalation phase: The factors which ensure reproducible and standardized measurements are i)Exclusion of nasal NO and ii) Exhalation flow rate standardization.

Plateau Definition: The duration of exhalation must be sufficient (>4 seconds in children<12 years and >6 seconds in children >12 years) and the concentration of NO evaluated over a 3-second window. Repeated, reproducible exhalations will be performed to obtain at least two NO plateau values that agrees with in 10% of each other. In this study, we used measurement by *NO VARIO Analyzer* for measurement of FeNO as an online measurement.

MEASUREMENT METHOD

The ***NO VARIO Analyzer*** performs the ATS / ERS standardized FeNO measurements[5].

The operator gets information about all signals like pressure, flow and NO in a time based display. The animation on the right site of the screen gives the patient opportunity to control his exhalation in the right level of flow and pressure. A flying figure has to be positioned in the middle of the two lines

RESULTS:

The 50 diagnosed patients of chronic cough and rhinitis were enrolled for the study and divided divided in three separate groups. Group A - Chronic cough(20), Group B – Rhinitis(20), Group C – Control (10). The demographic details of the patients in group have been described in table 1

Table: 1 Demographic profile of the study groups

Group	N	Male N (%)	Female N (%)	Age (years) (Mean± SD)	BMI (Kg/m2) (Mean ±SD)	Duration of illness (Months) (Mean ±SD)	Family history of atopy present (%)	Occupation		
								Student N (%)	Housewife N (%)	Office work N (%)
Chronic cough	20	10 (50)	10(50)	35.28±13.6	26.4±4.4	17±5.4	4 (20)	6 (30)	5 (25)	9 (45)
Rhinitis	20	9(45)	11 (55)	31.35±9.4	28.96 ±4.0	7.84±6.6	2 (10)	2 (10)	5 (25)	13 (65)
Control	10	4(40)	6(60)	31.9 ±4.9	25.96 ±5.34	0	0	3 (30)	3 (30)	4 (40)

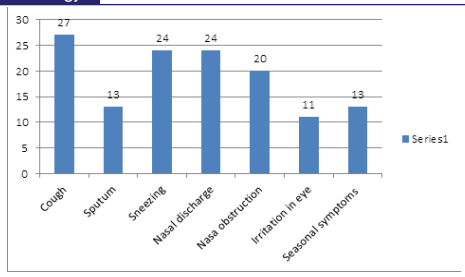


Figure 1.Symptoms distribution

27 (57%) patients had complaint of cough. Other had sneezing and nasal discharge 24 (48%) each. 13(26) patients have compliant of sputum production.

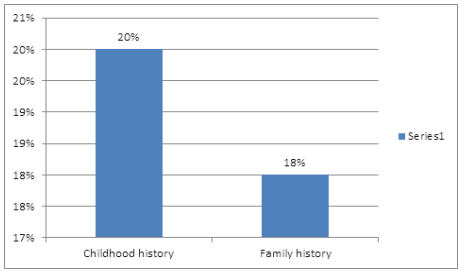


Figure: 2 Family and childhood history

20% of the patient has childhood history of same complaint and 18% gave positive family history for chronic respiratory symptoms.

Table: 2 Investigations of the study groups

Group	AEC (Mean±SD)	% of Eosinophils on DLC (Mean±SD)	S.Total IgE (IU/L) (Mean±SD)
Chronic cough	438.64±227	3.95±2.5	338.4±183.8IU/
Rhinitis	334.05±169.8	4.6 ± 2.46	256.3 ± 195.53
Control	236.6±59.2	1.9 ± 0.8	108.7 ± 98.7

AEC = Absolute eosinophil count, DLC= Differential leukocyte count FENO = Fractional exhaled nitric oxide

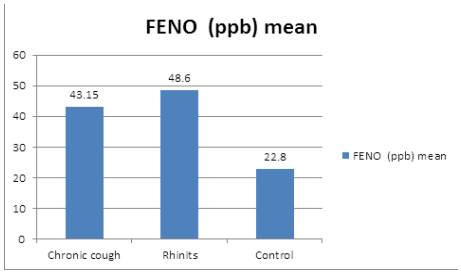


Figure:3 Mean FeNO level in chronic cough and rhinitis

There was no correlation between the AEC and FeNO (r=.313) (p <.231) in chronic cough or rhinitis (r=.31) (p<.0.229).

Table 3: Spirometry of the study groups

Group	FEV1pre-BD(obs) (L) (Mean±SD)	FEV1 (pre-BD%) (L) (Mean±SD)	FVC pre-BD(obs) (L) (Mean±SD)	FVC (pre-BD%) (L) (Mean±SD)	FEV1/ FVC % (Mean±SD)
Chronic cough	2.86±0.9	101.3 ± 19.2	3.5±1.2L	109.1 ± 14.7	77.17±11.2%
Rhinitis	2.99 ± 0.9	108.1 ± 22.1	3.24 ± 1.2	107.54 ± 10.6	76.07±10.2%

Control	2.66 ± 1.32	104.7 ± 10.67	2.74 ± 0.91	102.46 ± 4.6	81.70 ± 7.8%

FEV1 = Forced expiratory volume in 1 second, FVC = Forced vital capacity, pre-BD = pre-bronchodilator

Intergroup comparison - Chronic cough and control group (Group A vs. Group C)

The levels of FENO were higher in chronic cough group and the difference was statistically significant (p<.005). There was no correlation between the AEC and FeNO (r=.313) (p <.231) in chronic cough. There was no correlation between FeNO and FEV1 (r=0.39) (p<.0.41) in either chronic cough or healthy patients

Rhinitis and control group (Group B vs. Group C)

The levels of FENO were higher in allergic rhinitis group as compared to control group, and the difference was statistically significant (p<0.005).There was no correlation between AEC and FeNO (r=.31) (p<.229) in either rhinitis or healthy patient. There was no correlation between FeNO and FEV1 also (r=0.36) (p<.0.32) in this group B and group C.

Chronic cough rhinitis groups (Group A vs. Group B)

The levels of FENO were higher in rhinitis group but the difference was not statistically significant (p<.0254).There is no correlation between AEC and FeNO level in either group also. (r=.18) (p <.268)

Table: 4 Significant FeNO level > 25ppb

Valid No	Mean	Standard Deviation	Median
34	58.00	21.67	59.40
Diagnosis	Valid No	Mean	Standard Deviation
Chronic cough	16	56.74	18.52
Rhinitis	16	59.25	24.99

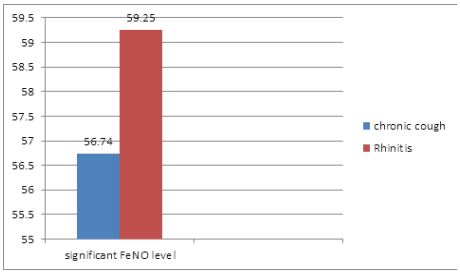


Figure: 4 Significant FeNO level in chronic cough and rhinitis

In our study, we took positive FeNO value was more than 25 ppb as a significant value. We found total 33 out of 50 patients had FeNO value was more than 25 ppb(figure4).

Out of these 32 patients 16 had chronic cough with mean FeNO was *56.74±18.52*ppb, and 16 patients had rhinitis FeNO value was *59.25 ± 24.99*ppb. One healthy patients also had FeNO >25 which was significantly (P<.05) higher in both the condition compare to healthy patients.

Diagnosis of cough variant asthma was made in 16 patients (32%) out of 50 which is statically significant (p< 0.004). Significant difference in FeNO level was found in compare to healthy patients. Similarly significant level of FeNO was found in rhinitis patients (p<0.003).

The overall diagnostic utility of FeNO levels to distinguish chronic cough from healthy was examined by ROC curve analysis, which revealed 25 ppb (AUC 0.74) as the optimal cut-off value. In the univariate analysis, which compared patient characteristics based on this cut-off value (high FeNO levels, >25ppb vs. low FeNO levels, 25 ppb), the factors that were identified to have borderline significant effects on FeNO levels (p < 0.10) were blood eosinophil (/mm3), total serum IgE (IU/ml), and FEV1/FVC. Among them, blood eosinophil (/mm3) and total serum IgE (IU/ml) were excluded from the following multivariate analysis since they were both confounding factors for atopy (%). In the multivariate analysis, atopic status and a diagnosis of chronic cough was identified as independent factors associated with higher FeNO levels.

Table: 5 intergroup comparison of FENO

Group	FENO
Group A vs. Group B	p = 0.607
Group A vs. Group C	p = <0.05
Group B vs. Group C	p = <0.05

p value <0.05 shows significance of difference between two groups

FENO = exhaled nitric oxide

Table: 6 Variables of FeNO according to FEV1 value

	Valid N	Mean	Standard Deviation	
FEV1 Group	<= 70	1	33.20	
	70.1 - 80	0		
	80.1 - 90	5	68.33	6.91
	90.1 - 100	8	49.18	23.79
	100.1 - 110	12	51.06	29.34
	110.1 - 120	21	43.69	26.37
	> 120	3	59.47	38.72

Value of FeNO in different FEV1 level

While compared the FeNO and FEV1, we found that value of FeNO highest for FEV1 between 80.1 to 90 % of normal predictive value although this was not statically significant. (p = 0.87).There is no correlation between FeNO with FEV1 in chronic cough and rhinitis FeNO value was lowest in FEV1 i.e. FEV1 <70% (figure 6). In most of the patients Spirometry is normal but FeNO level remain high which signify that despite of normal Spirometry patients can have eosinophilic airways.

Table: 7 Correlations between different variable

Correlations				
	AEC		S.Total IgE	FeNO value
FEV1(obs) L	Pearson Correlation	-0.053	0.294	0.119
	Sig. (2-tailed)	0.712	0.038	0.410
	N	50	50	50
FEV1(obs)%	Pearson Correlation	0.013	0.735	-0.814
	Sig. (2-tailed)	0.992	0.474	0.395
	N	50	50	50
FVC(obs) L	Pearson Correlation	-0.062	0.353	0.005
	Sig. (2-tailed)	0.669	0.012	0.974
	N	50	50	50
FEV1/FVC(obs)	Pearson Correlation	0.169	-0.140	-0.001
	Sig. (2-tailed)	0.240	0.334	0.993
	N	50	50	50

There was no correlation between FeNO and FEV1 and AEC interchange group A, group B and group C. (Table 7)

DISCUSSION

Eosinophilic airway inflammation leads to increased FeNO release. FeNO measurement is simple non-invasive method and is now used as a clinical biomarker for assessment of airway inflammation and hence it can be used in diagnosis of eosinophilic airway inflammation, to determine steroid responsiveness in cases of airway inflammation. American Thoracic Society clinical guidelines recommend that FENO may be used to support the diagnosis of asthma in situations which require objective evidence.[5]

Asthmatic cough is a major cause of prolonged and chronic cough[8] although the prevalence of chronic cough in Japan is around 78%. In our study (32%) seemed higher than those of the US (15-43%), UK (10-26%).[9]

The exhaled nitric oxide (FENO) levels in the chronic cough group measured between 17 to 84 ppb with mean being 43.15±17.2ppb.The FENO levels in chronic cough subjects were higher as compared to healthy controls (43.15±17.2ppb vs 22.8 ± 21.4) and the difference in FENO levels was statistically significant (p<.005). Takamitsu Asano et al showed that 91% of subjects with intermediate FeNO levels (29.2-58.4 ppb), and all the subjects with high FeNO levels (58.4 ppb) belonged to cough variant asthmatic groups. Therefore, the possibility of asthmatic cough as a cause of chronic cough becomes higher as FeNO levels increase. Previous reports demonstrated that healthy volunteers and non asthmatic cough patients rarely had high FeNO levels (50 ppb).[10]

The exhaled nitric oxide (FENO) levels in the rhinitis group measured between 4.1 to 95 ppb with mean being 48.6 ± 31.2ppb. The FENO levels in rhinitis subjects were higher as compared to healthy controls (48.6 ± 31.2ppb vs. 22.8 ± 21.4), the difference in FENO levels was statistically significant (p<0.005). In a study by Stewart *et al* [9] , the geometric mean (95% confidence interval) of FENO in allergic rhinitis patients was 23.1 (19.0-28.1)ppb and allergic rhinitis patients had statistically significant higher levels (p=.02). Alvarez *et* a1[11] observed the significant correlation of FENO levels in allergic rhinitis patients. He suggested it to be in keeping with previous biopsy findings of eosinophilia throughout the upper and lower airway of these patients, even in absence of bronchial asthma. In a study by Lee *et al*[12], the allergic rhinitis patients without concomitant asthma had higher exhaled nitric oxide levels as compared to healthy subjects.

In our study, the exhaled nitric oxide levels (FeNO) in the control group measured between 5 to 32.5 ppb ppb with mean being 22.8 ± 21.4ppb. In a study by Stewart *et al* [9], in healthy volunteers the FeNO levels ranged from 12.5 – 17.5ppb. In another study by Kharitonov *et al*[13], the exhaled nitric oxide levels in healthy adults group was 16.3±8.4ppb. Olin *et al* [14], in his study of reference values of FENO for adults lifelong never smokers, calculated the upper limits of FeNO ranging from 24.0 to 54.0 ppb, depending on age and height. In an epidemiological study, in healthy Asian children aged 5 to 18 years the Geometric mean FeNO and the upper 95% CI were 13.7 ppb and 49.7 ppb respectively.

Although a useful method for evaluating eosinophilic airway inflammation, sputum induction is complex, time-consuming, and carries the potential to induce bronchoconstriction or pharyngeal discomfort. On the other hand, FeNO measurements seem much more suitable for routine clinical practice because it is less invasive and easier to perform.

Previous reports and our present study of persistent cough patients proposed different FeNO cut-off levels for distinguishing cough variant asthma from non-asthmatic subjects (healthy control or Non asthmatic cough). Because all these studies consistently used the chemiluminescence method for FeNO measurement, the discrepancies of cut-off levels among these studies may be due to different methods of selection of cases (category of asthma) and control group (non-asthma or healthy control) and the varying patients' characteristics. Although all studies were consistent in the observation that FeNO measurement was a useful diagnostic. The studies by Takamitsu Asano[10] designed to determine the optimum cut point to diagnose cough variant asthma using FeNO has usually pointed to a diagnostic cut point from 29.2 ppb. In another study by Stewart *et al* [9], the geometric mean (95% confidence interval) of FeNO in asthma patients was 29.0 (22.5-37.4)ppb with levels being statistically significant higher in comparison to bronchial asthma group (p<.001).Our study found the cut off value for diagnosing cough variant asthma is 25ppb Several factors may affect the validity of FeNO measurements.

In our study, smoking and the effects of medications (inhaled corticosteroids and anti-leukotriene agents and smoking were excluded at study entry. Some reports revealed a correlation between FeNO level and non-specific IgE titer but in our study no correlation was found.

Lung functions tests represent the standard method for assessing asthma such tests do not reflect inflammation or patient self assessment of asthma status. In our study we found that FeNO value were highest in patients whom FEV1 80.1 to 90% of normal predictive value, but this difference was not statistically significant. Accordingly, Sterling and co-workers found no correlation between exhaled NO levels and lung function tests.[11] These findings were also confirmed by Langly et al. who found there was no correlation between exhaled NO and FEV1 in a cross-sectional, hospital-based study of 392 patients with varied asthma severity.[15] SIPPEL et al. found only a weak correlation between FEV1and NO levels.[16] Same fact found in our study there was no correlation between FEV1and NO levels.

Patients in different groups were comparable for baseline parameters (age, sex, height, weight, BMI) as compared to controls. The levels of FENO were significantly higher in chronic cough and rhinitis groups in comparison to healthy subjects. But there was no correlation between FeNO with FEV1 and AEC in either group.

Our study confirmed that measurement of FeNO levels was a relevant diagnostic procedure for prolonged chronic cough.

CONCLUSION

In this study, type of inflammation in patients with chronic persistent cough and rhinitis were evaluated for its correlation with FeNO levels in patients in whom no cause was found on clinical examination and routine lab tests. The study showed significantly higher levels of FeNO in chronic persistent cough and rhinitis groups. It was found that in these patients, FeNO does not correlate with FEV1.

On the basis of this observation it can be conclude that FeNO is a good marker of eosinophilic inflammation in chronic persistent cough and rhinitis patients to support the diagnosis of eosinophilic inflammation and hence FeNO can be used as guide for treating these patients' symptoms.

Limitation of this study:

As this is a preliminary study of evaluation of FeNO was done only on the first visit. In order to evaluate prognostic value of FeNO chronic persistent cough and rhinitis, we feel serial reading will be required.

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