Original Article

Correlation of exhaled nitric oxide, nasal nitric oxide and atopic status: A cross-sectional study in bronchial asthma and allergic rhinitis

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ABSTRACT

Objective: Exhaled nitric oxide (FE_{NO}) and nasal nitric oxide (n NO) measurement is an area of ongoing research in the study of airway inflammation. The atopic status is known to influence the levels of FE_{NO} and n NO. This study was undertaken to study the relationship between nitric oxide measurements in bronchial asthma and allergic rhinitis along with their correlation with atopic profile of Indian population. **Materials and Methods:** Ninety subjects were recruited for the study comprising of 25 each of bronchial asthma (BA), allergic rhinitis (AR), bronchial asthma with allergic rhinitis (BA-AR) and 15 healthy controls. These were assessed for atopy and exhaled breath analysis of nitric oxide. The measurements of FE_{NO} and n NO levels were done using NIOX chemiluminescence analyzer. Atopy was assessed by skin prick testing (SPT) against 58 common aero-allergens and subjects with ≥1 positive SPT were labeled as atopic. **Results:** The BA-AR and BA groups had higher FE_{NO} levels in comparison to the control ($P < 0.05$) and AR group ($P < 0.05$). The AR and BA-AR groups had higher n NO levels compared to the control group ($P < 0.05$) and BA group ($P < 0.05$). The increasing FE_{NO} levels significantly correlated with the increase in the number of allergen sensitization in patients suffering from BA-AR ($P < 0.05$). However, the BA group showed a weaker positive correlation ($P = 0.07$). **Conclusion:** FE_{NO} is a non-invasive marker of airway inflammation. Also, FE_{NO} levels correlate with presence and degree of atopy in BA and AR. Simultaneously, n NO could be a surrogate marker of rhinitis.

KEY WORDS: Asthma, atopy, nitric oxide, rhinitis, skin prick testing

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INTRODUCTION

The nitric oxide (NO) in the lung/airways has a key role as a vasodilator, bronchodilator, neurotransmitter and inflammatory mediator.[1-4] Exhaled nitric oxide (FE_{NO}) and nasal nitric oxide (n NO) measurement is an area of ongoing research in the study of airway inflammation.

The FE_{NO} level measurement has been validated and standardized for supporting the diagnosis in cases of eosinophilic inflammation of airways, bronchial hyperreactivity and asthma.[5]

FE_{NO} levels have been higher in atopic than non-atopic bronchial asthma patients and some studies also reported that healthy atopic subjects without symptoms or signs of airway disorders have higher FE_{NO} levels than non-atopic subjects.[6,7] Similarly the effect of clinical atopy, with atopic cases having higher levels as compared to non-atopic cases.[4]

To the best of our knowledge, the literature on exhaled breath and nasal nitric oxide from India is lacking. Hence, this study was undertaken to answer the question about the relationship between the noninvasive methods of nitric oxide measurements in bronchial asthma and allergic rhinitis and their correlation with atopic profile of Indian population.

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MATERIALS AND METHODS

Study design and demographics

The diagnosed patients of bronchial asthma (BA), allergic rhinitis (AR) and bronchial asthma with allergic rhinitis (BA-AR) were enrolled for the study from the outpatient clinics. A total of 90 subjects (36 females and 54 males) aged between 6-38 years were evaluated and they were divided into 4 groups: Group A - 25 Bronchial asthma (without allergic rhinitis); Group B - 25 Allergic rhinitis (without bronchial asthma); Group C - 25 Bronchial asthma with allergic rhinitis and Group D - 15 controls. Patients from all the 4 groups were further subdivided into atopic and non-atopic subgroups based on the skin prick test results for the purpose of analysis. The diagnosis of asthma and allergic rhinitis were based on Global Initiative for Asthma (GINA)[8] and Allergic Rhinitis and its Impact on Asthma (ARIA) [2008][9] respectively. The subjects with inability to satisfactorily perform the nitric oxide maneuver were excluded. Other exclusion criterion were 1) Smoker (Former and current smokers) 2) Inhaled/nasal/oral steroid intake in preceding one month 3) Episode of upper or lower respiratory tract infection in the preceding one month and 4) History of urticaria/eczema. All the 90 subjects underwent a battery of investigations including baseline spirometry, FE_{NO} and n NO measurements, skin prick tests and blood sampling, absolute eosinophil counts and serum total IgE levels.

Written informed consent was obtained from all subjects/parents (in case of subject's age <18 years) to participate in the study. The study protocol was approved by institutional ethical committee.

Measurement of FE_{NO} and n NO

The measurements of exhaled nitric oxide and nasal nitric oxide was performed using NIOX chemiluminescence analyzer (Aerocrine AB, Solna, Sweden) in accordance with the 2005 ATS/ERS recommendations.[10]

The patient was inserted the mouthpiece, inhaled through mouth to total lung capacity (TLC) and then immediately exhaled at a constant flow rate (50 mL/s) to residual volume without breath-holding. The duration of exhalation had to be sufficient (>4 seconds in subjects <12 years and >6 seconds in subjects >12 years). Repeated, reproducible exhalations were performed to obtain at least two NO plateau values that agreed with in 10% of each other. The mean level of two reproducible recordings was used as the result value. The n NO measurement was done using the same analyzer by the nasal aspiration method. The measurements were always performed at the same place and the sampling timing was between 10-11 am.

Skin prick testing

Skin prick testing (SPT) to 58 common aeroallergens was performed in all the patients as per standard guidelines.[11] These are the commonest aeroallergens in clinical practice of allergy in India as per the study by Singh *et al*.[12] Atopy was defined as a positive skin prick test (wheal diameter of >3 mm as compared to buffer saline as control) for at least ≥1 aeroallergen.[11]

Measurement of serum total IgE and absolute eosinophil counts

Serum Total IgE was estimated by ELISA method using MINILYSER - TECAN, Austria, Calbiotech kit as per manufacturer's instructions. The number of peripheral blood eosinophils was counted in EDTA containing blood samples using an automated analyzer.

Spirometry with reversibility

Spirometry was performed on a dry, rolling-seal spirometer of the Benchmark model lung function machine (P.K. Morgan, Kent, UK). Maximal expiratory flow volume curves were obtained as per the ATS recommendations.[13]

Statistical analysis

All data analysis was performed using SPSS statistical package version 16.0 for windows (SPSS, Chicago, IL, USA). The data was examined for distribution and homogeneity of variances was checked before applying parametric tests. The data on FE_{NO} and n NO were expressed as mean ± SD. The variables were compared between the four groups using one-way analysis of variance (ANOVA) and the *post hoc* Bonferroni alpha significant difference test for multiple comparisons. The univariate analyses of factors associated with FE_{NO} was done using Pearson correlation. The conventional 5% level ($P < 0.05$) was considered to be statistically significant.

RESULTS

The demographic characteristics of all the four groups are shown in Table 1. Of the total 90 subjects, 54 were males and rests of 36 subjects were females. Overall there were 54 atopic and 36 non-atopic patients in the study. The mean ages, age distribution, anthropometric variables (height, weight, BMI) were normally distributed amongst all the groups.

Table 1: Patient demographics and laboratory investigations

Group	*N*	M/F	Age (years) (mean±SD)	Height (cms) (mean±SD)	Weight (kgs) (mean±SD)	BMI (Kg/m^2) (mean±SD)	Serum total IgE (IU/L) (mean±SD)	AEC (cells/μL) (mean±SD)
A	25	16/9	23.28±9.4	155.52±18.4	58.88±18.5	23.53±4.4	658.56±483.8	364.64±227.3
B	25	14/11	24.72±9.4	158.40±14.8	58.08±16.3	22.64±4.0	538.24±505.4	366.08±263.6
C	25	14/11	23.84±7.4	159.92±9.4	57.80±13.9	22.34±3.7	707.32±387.4	495.80±270.4
D	15	10/5	25.47±4.9	163.00±8.2	61.07±1.36	22.7±3.4	73.93±52.6	156.60±59.2

AEC: Absolute eosinophil count, SPT: Skin prick test, FE_{NO}: Exhaled nitric oxide, n NO: Nasal nitric oxide, Group A: Bronchial asthma, Group B: Allergic rhinitis, Group C: Bronchial asthma with allergic rhinitis, Group D: Controls, M/F: Male/Female

Exhaled nitric oxide (FE_{NO})

The mean levels of FE_{NO} in all the four groups are depicted in Table 1. All the three groups had higher FE_{NO} levels compared to the control group [Table 1]. The BA and BA-AR groups had significantly higher levels than the AR group [Figure 1a]. Also, the BA-AR group had higher FE_{NO} levels when compared to the BA group although the comparison failed to reach statistical significance.

Nasal nitric oxide (n NO)

The mean levels of n NO in all the four groups are shown in Table 1. The AR group and BA-AR group had significantly higher n NO levels as compared to the control and BA groups [Figure 1b]. However, the BA group had n NO levels lower than the control group.

Atopic profile and nitric oxide levels

The control group had 8 atopic subjects and 7 non-atopic subjects. The FE_{NO} levels between the atopic and non-atopic control subjects did not differ significantly ($P = 0.771$). The atopic patients suffering from BA, AR and BA-AR had statistically significant higher levels of FE_{NO} in comparison to non-atopic patients of same group [Figure 2]. However, in comparison the mean n NO levels did not differ significantly; between the atopic and non-atopic patients in all the four groups.

Number of positive responses on skin prick test and nitric oxide levels

The patients in all the four groups were further subdivided into 3 sub-groups on the basis of number of positive responses on SPT; 0, 1-3 and >3. The FE_{NO} and n NO levels were analyzed in these subgroups [Table 2]. The FE_{NO} levels positively and significantly correlated with the number of positive responses on SPT in patients suffering from BA-AR ($P < 0.05$). The BA group and AR group also showed a positive correlation albeit a weaker one ($P = 0.07$). However, no significant correlation of n NO levels and number of positive response on SPT were found in any of the four groups.

Serum total IgE, AEC, spirometry and nitric oxide levels

The serum total IgE and AEC levels were significantly higher in BA, AR and BA-AR groups when compared to the control group. However, no significant difference was found

Table 2: Correlation of FE_{NO} and n NO with SPT positivity of number of allergens

Groups	Number of allergens positive on SPT			*P* value
	0	1-3	>3	
FE_{NO} (ppb)				
A	25.37±15.3 (*n*=8)	36.22±14.4 (*n*=9)	43.12±18.8 (*n*=8)	0.079
B	11.73±5.7 (*n*=12)	21.00±14.9 (*n*=6)	19.14±8.3 (*n*=7)	0.077
C	26.11±10.3 (*n*=9)	46.82±21.0 (*n*=11)	57.20±86.0 (*n*=5)	<0.05
D	11.14±3.5 (*n*=7)	9.20±2.7 (*n*=5)	22.33±13.6 (*n*=3)	0.326
n NO (ppb)				
A	72.25±57.2 (*n*=8)	136.94±171.04 (*n*=9)	88.00±53.8 (*n*=8)	0.469
B	245.50±102.6 (*n*=12)	312.92±153.26 (*n*=6)	270.71±116.7 (*n*=7)	0.792
C	312.94±118.9 (*n*=9)	371.04±150.0 (*n*=11)	302.50±51.2 (*n*=5)	0.448
D	96.50±65.28 (*n*=7)	98.90±39.5 (*n*=5)	182.50±126.0 (*n*=3)	0.427

FE_{NO}: Exhaled nitric oxide, n NO: Nasal nitric oxide, Group A: Bronchial asthma, Group B: Allergic rhinitis, Group C: Bronchial asthma with allergic rhinitis, Group D: Controls, *n*: No. of patients in the study group

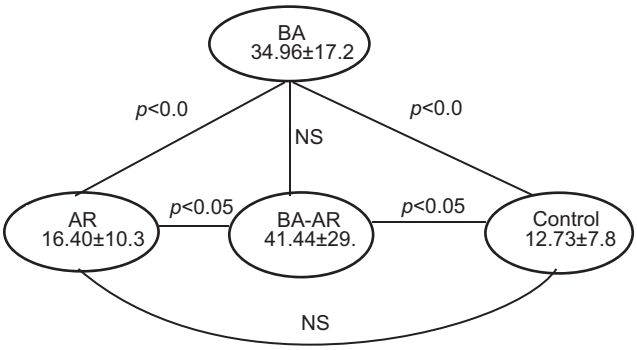

Figure 1a: Intergroup comparison of FENO levels ppb (mean ± SD); *P* < 0.05 – statistically significant; NS- Not significant; BA- Bronchial asthma; AR- Allergic rhinitis: BA-AR- Bronchial asthma with allergic rhinitis

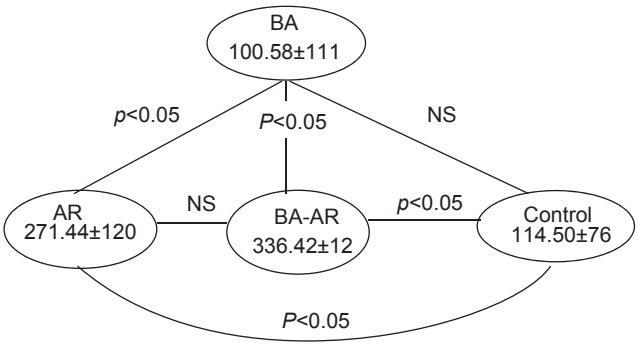

Figure 1b: Intergroup comparison of n NO levels ppb (mean ± SD); *P* < 0.05 – statistically significant; NS- Not significant; BA- Bronchial asthma; AR- Allergic rhinitis: BA-AR- Bronchial asthma with allergic rhinitis

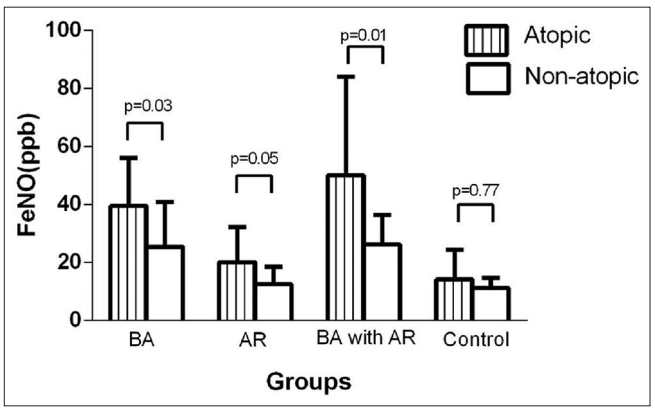

Figure 2: Intragroup comparison of FENO levels between atopic and non-atopic patients; P < 0.05 - statistically significant BA- Bronchial asthma; AR- Allergic rhinitis: BA-AR- Bronchial asthma with allergic rhinitis

in their levels in atopic and non-atopic patients in each of the four groups. In the study, overall FE_{NO} levels correlated significantly with serum total IgE levels ($P = 0.002$), however n NO levels were not significantly correlated with serum total IgE levels ($P = 0.254$). The AEC levels also correlated positively and significantly with FE_{NO} levels ($P = 0.004$) and n NO levels ($P = 0.01$). The PFT parameters FEV_1, FVC and FEV_1/FVC did not show a significant correlation with either FE_{NO} or n NO levels.

DISCUSSION

Exhaled nitric oxide (FE_{NO}) measurement is non-invasive, simple and well tolerated method and is now used as a clinical biomarker for assessment of airway inflammation.[5] Similarly, nasal nitric oxide (n NO) measurement is useful in the diagnosis, treatment and follow-up of patients with nasal pathology, especially because as it is noninvasive.[14]

In the present study we have demonstrated that healthy individuals had mean FE_{NO} levels of 12.73 ± 7.8 ppb whereas other studies on Chinese, African population and data from asthma and allergy research group had mean FE_{NO} levels ranging from 20-39ppb.[15-18] In a study by Ciprandi *et al.*,[19] the children suffering from asthma and rhinitis had mean FE_{NO} levels of 41 ppb, with asthma had 37 ppb and those with rhinitis had 31 ppb ($P < 0.001$). We also found that FE_{NO} levels were highest in BA-AR group (41.44 ± 29.9 ppb) followed by BA group (34.96 ± 17.2 ppb) and AR group (16.40 ± 10.3 ppb). In agreement with the literature, we observed higher FE_{NO} levels in BA and BA-AR groups in comparison to the control group ($P < 0.05$) and AR group ($P < 0.05$). No statistical difference was found among any other groups for FE_{NO} levels. The findings are consistent with previous studies.[19,20]

The measurement of nasal inflammation in AR would rely on detecting increased levels of nasal NO resulting from increased expression of iNOS (inducible nitric oxide synthase), akin to the increase of exhaled nitric oxide levels in bronchial asthma.[21] In a study by Stewart *et al.*,[17] the mean n NO levels of 853.3 ppb in AR and 763.4 ppb in BA-AR groups were higher in comparison to 674.1 ppb levels in BA group. In our study also the n NO levels in AR (271.44 ± 120.3 ppb) and BA-AR groups (336.42 ± 124.6 ppb) were significantly higher in comparison to BA group (100.58 ± 111.2 ppb) and control group (114.50 ± 76.0 ppb). The above findings are attributed to increase in local production of nitric oxide in nasal epithelium in patients suffering from allergic rhinitis.[17,21] We did not find any statistical difference among any other groups for n NO levels. These results were in agreement with the previous studies by Kharitonov *et al.*,[22] and Lee *et al.*[23]

The effect of presence and degree of clinical atopic conditions on FE_{NO} levels has been addressed in the literature. The higher FE_{NO} levels in atopic asthmatics has been documented, however the effect of atopy on FE_{NO} levels of healthy subjects requires further validation.[6,24] Rouhos *et al.*,[25] in his study showed atopic constitution, defined as positive skin prick test results,which does not increase FE_{NO} levels in healthy nonsmoking adults with no signs or symptoms of airway disorders. Similar to this study, we also found no significant difference in FE_{NO} levels with respect to atopic status in the control group.

In the present study the atopic BA, AR and BA-AR subjects had significantly higher FE_{NO} levels in comparison to non-atopic subjects of the same group. Previous studies by Jouvaville *et al.*[18] and Gratziou *et al.*[26] have also found the similar result. In a study by Kumar *et al.*[27] the atopic allergic rhinitis subjects had statistically significant higher FE_{NO} levels when compared to non-atopic subjects. Similar result was observed in the present study and this supports the hypothesis of a presence of subclinical inflammation of lower airways, and may predict development of asthma in future.

We found higher levels of nNO in atopic subjects of BA, AR and BA-AR in comparison to non-atopic subjects; though the relationship was statistically not significant. Olin *et al.*[6] and Kharitonov *et al.*[4] in their studies observed similar results.

The association between the degree of atopy and FE_{NO} levels has been studied by Ho *et al.*[28]and Strunk *et al.*,[29] and they concluded that as number of positive responses on skin prick test increases, the FE_{NO} levels also increases. We also found the similar positive correlation between FE_{NO} levels and number of positive responses on SPT in BA-AR group ($P < 0.05$). Similarly, atopic BA subjects also showed a positive correlation albeit a weaker one ($P = 0.07$). The plausible explanation for this finding has been attributed to difference of inflammatory cells recruitment in atopics (eosinophilic) and non-atopic asthmatics (neutrophilic) as well as to cell activity of NO producing cells.[18] However, in a study by Moore *et al.*,[30] in asthmatics FE_{NO} was not always associated with the number of positive skin prick test response. Thus, there exists a complex relationship between atopic profile and FE_{NO} levels which requires further evaluation. Also, we found no significant association between n NO levels and the number of allergens positive on SPT in any of the groups of our study.

The higher FE_{NO} and n NO levels in atopic subjects could be attributed to induction of iNOS enzyme. iNOS is the characteristic enzyme found in association with mucosal mast cells, eosinophils, and T-lymphocyte activation as described in cases of allergic rhinitis and bronchial asthma.[31,32] In bronchial biopsies of asthmatics an up regulation of expression of iNOS has been observed and immuno-cytochemical studies have also demonstrated expression of NOSs in human nasal mucosa.[33-35]

The FE_{NO} and n NO levels are known to be influenced by age, sex, height, smoking and atopy status of the individual.[5] In current study, all the groups (AR, BA, BA with AR and Controls) were comparable with respect to all these factors except the atopic status. Hence, we could evaluate correlation of atopic status with FE_{NO} and n NO levels. This was the strength of our study.

The work is limited by the small number of subjects enrolled. Hence, a further large-scale population based study is required for assessing applicability of FE_{NO} and n NO levels in evaluation of BA and/or AR patients.

FeNO and nNo may serve as non-invasive marker of airway inflammation and atopy. Hence, they can be used for early recognition of airway inflammation and also as a guide for follow-up and management of BA and AR. This requires further large scale studies to validate the levels of FE_{NO} and n NO and simultaneously confirm the correlation with atopic status.

CONCLUSIONS

In conclusion, the FE_{NO} levels reflect the inflammatory activity of the airway epithelium and is associated with presence as well as degree of atopy in a sensitized patient, determined by positive skin prick test results to common aeroallergens. The study also highlights the need for evaluation of patient for the existence of allergic rhinitis or bronchial asthma in cases with higher FE_{NO} levels. The n NO levels can be used as an inflammatory marker for supporting the diagnosis of coexisting allergic rhinitis in bronchial asthma patients. Further, large scale studies are required to develop reference equations and cutoff values for FE_{NO} and n NO levels to aid in diagnosis and follow-up in Indian population.

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