Original Article

Fractional exhaled nitric oxide (FeNO) in chronic obstructive respiratory diseases is associated with the bronchodilator response

Thuy Chau Nguyen[1], Hoa Vi Thi Tran[1], Thanh Hiep Nguyen[1], Mong Hiep Thi Tran[1], Isabelle Godin[2], Olivier Michel[3]^

[1]Department of Family Medicine, Pham Ngoc Thach University of Medicine, Polyclinic of Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Vietnam; [2]School of Public Health, Université Libre de Bruxelles (ULB), Brussels, Belgium; [3]Department of Pneumology, Delta Hospital (CHIREC) and Université Libre de Bruxelles (ULB), Brussels, Belgium

Contributions: (I) Conception and design: TC Nguyen, HVT Tran, I Godin, O Michel; (II) Administrative support: TH Nguyen, MHT Tran, O Michel; (III) Provision of study materials or patients: TC Nguyen, HVT Tran, TH Nguyen, MHT Tran; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: TC Nguyen, HVT Tran, I Godin, O Michel; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Olivier Michel, MD, PhD. Department of Pneumology, Delta Hospital (CHIREC) and Université Libre de Bruxelles (ULB), 211bd du Triomphe, 1050-Brussels, Belgium. Email: olivier.michel@ulb.be.

Background: Among chronic obstructive respiratory diseases (CORDs), the fractional exhaled nitric oxide (FeNO) is a marker of eosinophilic airway inflammation. Few data on FeNO in CORD are available in Vietnam. In this study, we aimed to relate the FeNO with the clinical and functional characteristics of CORD in Vietnam.

Methods: A cross-sectional study was conducted in 235 patients with chronic respiratory symptoms and airways limitation. Clinical evaluation was obtained by questionnaire; pre- and post-bronchodilator (BD) spirometry, eosinophil counts, allergen skin tests and FeNO were measured. Patients were considered as chronic obstructive pulmonary disease (COPD), asthmatics or asthma COPD overlap (ACO) based on GINA/GOLD guidelines. The FeNO levels were related to clinical, spirometric and inflammatory parameters.

Results: They were 93 COPD, 93 ACO and 49 asthmatics. The concentration of FeNO was high (≥25 ppb) in 69.4% asthmatics, 55.9% of ACO and 34.4% COPD. A high FeNO was more frequent among women, younger, asthmatics, former- or non-smokers, low severity (fewer exacerbations and lower airways limitation), BD responsiveness and type 2 (T2) inflammation [history of allergy, elevated blood eosinophils count (BEC), positive skin tests]. A low FeNO was more frequent in patients with X-ray emphysema or history of tuberculosis. The FeNO level correlated positively with the blood eosinophils and the BD responsiveness in non-smokers but negatively with the basal level of airflow limitation.

Conclusions: In Vietnamese non-smokers with chronic obstructive respiratory disease, FeNO is a type 2 biomarker and a significant predictor of BD responsiveness. We hypothesized that this might predict the response to inhaled corticosteroids (ICS).

Keywords: Fractional exhaled nitric oxide (FeNO); asthma; chronic obstructive pulmonary disease (COPD); airways limitation; bronchodilators responsiveness (BD responsiveness)

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^ ORCID: 0000-0002-1528-1277.

Introduction

Chronic obstructive respiratory diseases (CORDs) include asthma and chronic obstructive pulmonary diseases (COPDs). These heterogenous disorders are characterized by different phenotypes related to endotypes defined by the nature of airflow inflammation (AI). In human, AI can be caused by inhaled microbes, tobacco smoke and airborne particles, such as toxins, pollutants, irritants, and allergens (1). The interaction between these environmental exposures and genetic backgrounds can lead to various pattern of AI and consequently, frequent overlap [asthma COPD overlap (ACO)] between asthma and COPD. Therefore, in the current study we evaluated a CORD population as a whole, including asthma, ACO and COPD (2).

The fractional exhaled nitric oxide (FeNO) is a marker of eosinophilic airway inflammation. Airway inflammation can be eosinophilic-related, named type 2 (T2), or non-eosinophilic-related, named non-T2. The measurement of FeNO can contribute to diagnose type 2 asthma and to evaluate its prognosis or to tailor the treatment (3).

FeNO level correlates with airways' eosinophilia in the sputum or in biopsies or bronchoalveolar lavage (4) and with blood eosinophils count (BEC) (5) and immunoglobulin E (IgE) levels (6). There is also concordance between higher FeNO and other T2 markers (7). A high FeNO level is associated with the diagnosis of non-smoker eosinophilic asthma (3,8). While several studies reported an association between high FeNO and the decline in lung function or exacerbations (9,10) among uncontrolled asthmatics, others studies shown no association with asthma severity (11,12) or exacerbations (13). Available data on FeNO in Vietnamese asthmatics are not consistent. The level of FeNO in non-smoker treated asthmatics was negatively related with the airflow limitation (14) while among a similar population, another study reported FeNO as a marker of uncontrolled asthma (15).

In COPD, the interest of FeNO is debated, among others because the smoking habits, disease severity and ICS use, can interfere with the measurements. Actually, FeNO is usually normal in COPD and low in current smokers (8). Few data are available in non-smoker COPD, highly prevalent in Vietnam. Though, an elevated FeNO was associated with an increased risk of exacerbations and type 2 airway inflammation in COPD (16,17). In others studies the decline of the lung function (18,19) or risk of exacerbations (20) seemed unrelated with the FeNO values. Particularly, among type 2 inflammatory COPD, the FeNO was predictive of the response to ICS (21). Smoking is probably the most relevant confounding factor to interpret FeNO among COPD because there is a negative correlation between smoking and the FeNO values (22). To our knowledge, in Vietnam, only one study had measured FeNO among COPD, the last being lower compared to ACO and asthma (23).

Due to the various environmental factors and genetic background in Vietnam, the clinical values of FeNO need to be evaluated in a population of CORD as a whole. Finally, a last interfering factor is the frequent helminthic infection in tropical environments that can interfere with BEC and FeNO (24).

In the present study, we aimed to associate the measurement of FeNO, with their clinical characteristics, lung function parameters and airflow limitation reversibility, in an unselected population of Vietnamese patients with chronic respiratory symptoms and airflow limitation. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1727/rc).

Highlight box

Key findings

- Among Vietnamese patients with chronic obstructive respiratory diseases (CORDs), the fractional exhaled nitric oxide (FeNO) levels correlated positively with the blood eosinophils and the bronchodilator (BD) responsiveness but negatively with the basal airflow limitation.

What is known and what is new?

- In Vietnam, the patients with CORD are frequently treated with oral or inhaled corticosteroids (ICS), leading to a higher risk of infectious, such as tuberculosis. The FeNO is a marker of eosinophilic airway inflammation in CORD that could predict the corticosteroid responsiveness.
- In Vietnam, among non-smokers CORD, the FeNO level was correlated negatively with the basal airflow limitation but positively with the blood eosinophils and the BD responsiveness.

What is the implication, and what should change now?

- Since among non-smokers CORD, FeNO was related with the BD responsiveness, we hypothesized that it could predict the response to ICS. Though, longitudinal studies are needed to confirm the role of FeNO in the treatment strategy of CORD in Vietnam.

Methods

The inclusion criteria were patients older than 18 years with both chronic respiratory symptoms (cough, and/or sputum production, and/or wheezing, and/or dyspnea, and/or chest tightness since >3 months) and basal airflow limitation.

Approximately 3,600 out-patients with respiratory symptoms were seen from November 2020 to May 2021 at the pulmonology unit of Nguyen Tri Phuong Hospital, a general hospital in Ho Chi Minh City. Based on chest X-ray, about 800 patients were excluded due to active tuberculosis, cancer or acute infectious diseases. Lung function tests with bronchodilator (BD) responsiveness test were performed in 2,800 remained patients and only 400 patients presented airflow limitation. We invited these patients to participate to the study and after written informed consent, a total of 235 patients were included to the study.

Demographic characteristics, medical history, smoking habits of studied patients were collected from a survey questionnaire. Then, skin prick tests (SPTs), FeNO and BEC were evaluated. Patients who fully responded to all items in the questionnaire and completed all para-clinical investigations were enrolled to this cross-sectional study.

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of Pham Ngoc Thach University (008/HDDD) and informed consent was taken from all the patients.

Pulmonary function tests

The forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), in L and % of the predicted value (PV) were measured by a trained technician with a spirometer (Medisoft Ltd., Sorinnes, Belgium) after stopping of long-acting BD for >12 hours and/or of short-acting BD for >8 hours, according to the European Respiratory Society (ERS) guidelines (25). For all patients, the BD responsiveness was evaluated 10 minutes after inhalation of 400 mcg salbutamol. Airflow limitation was defined as FEV1/FVC < LLN (lower limit of normality) (26). The reversibility of airflow limitation was defined as (post-BD FEV1 – basal FEV1)/basal FEV1 and expressed in %. Positive BD responsiveness was a post-BD change in FEV1 >12% and >200 mL (27).

An asthmatic patient was defined as a patient with a history of respiratory symptoms that vary in intensity and frequency, such as wheezing, shortness of breath, chest tightness, and cough, often triggered by exercise or emotional stress, with basal airflow limitation normalizing after BD and/or with a positive BD responsiveness (27).

COPD was diagnosed in the presence of persistent respiratory symptoms and post BD persistent airflow limitation (FEV/FVC <0.7) without BD responsiveness, in patient with significant exposure to tobacco smoke or noxious particles or gases (28).

ACO was defined in patients with clinical features consistent with both asthma and COPD, usually with persistent airflow limitation and a positive BD responsiveness (27).

Exacerbation

Exacerbation was defined as any acute worsening in clinical symptoms compared to the baseline, requiring a change in medication treatment, in a patient receiving prophylactic therapy. Severe exacerbation was defined as an acute episode with worsening of baseline symptoms, leading to hospitalization or intensive care unit admission. Patients with recent exacerbation in previous month were excluded from the study (27,28).

FeNO

FeNO assessment was carried out according to the recommendations of the American Thoracic Society and the ERS. FeNO was measured with the Medisoft device (Micro 6000), at the level of 50 mL/second, by technicians trained and certified according to ERS standards. Heavy meals, physical exertion and smoking cigarettes were avoided on the day of the exam. The cut-off 25 and 50 were used for analysis (3).

Other para-clinical investigations such as SPTs, BEC and chest x-ray were evaluated. SPTs were performed with the four most frequent aeroallergens in Vietnamese patients with chronic obstructive respiratory disease [Dermatophagoides farinae (DPF), Dermatophagoides pteronyssinus (DPT), Blomia tropicalis and cockroach] (29).

Statistical analysis

IBM SPSS Statistics version 23.0 (IBM Co., Armonk, NY, USA) was used for data analysis. Quantitative variables were expressed as mean with 95% confidence intervals (CIs). Categorical data were presented as number and percentage.

The differences between categorical variables were tested with χ^2 and Fisher's exact test. The continuous variables without normal distribution were compared using Mann-Whitney *U* test. Spearman's correlation coefficients for continuous variables were determined and logistic

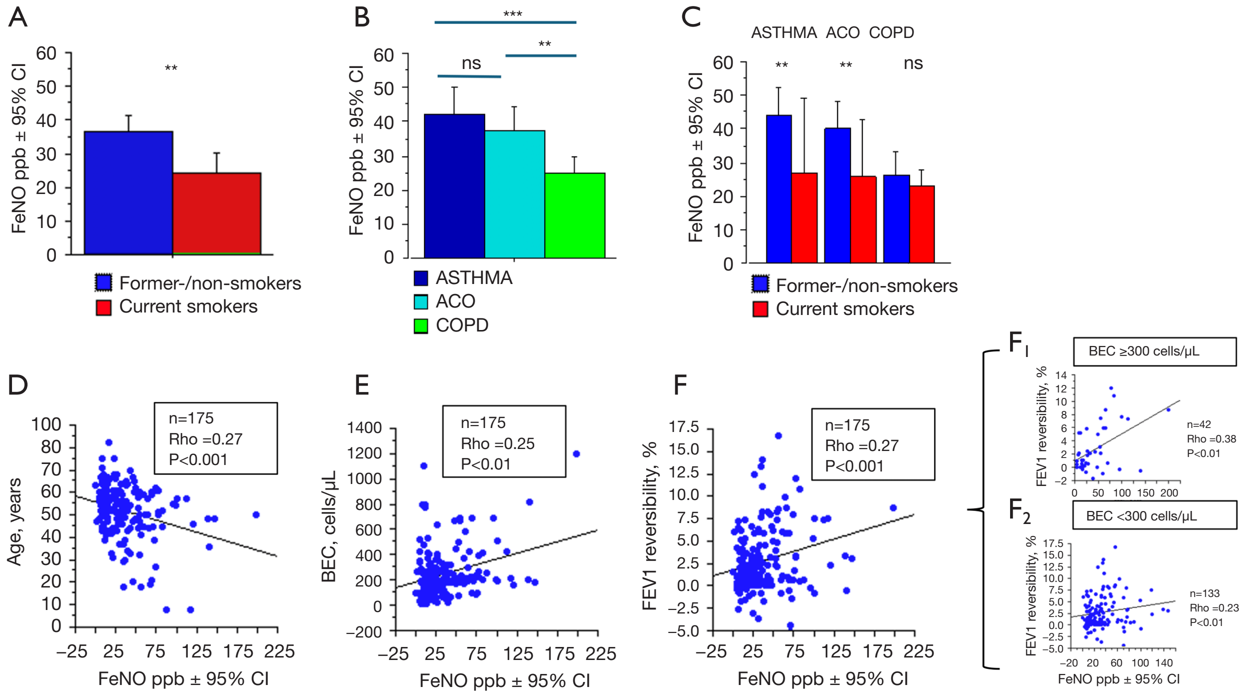

Figure 1 The mean FeNO values and phenotypes (A-C) and its relationship with age (D), BEC (E), FEV1 reversibility (F) when BEC ≥300 cells/μL (F1) or <300 cells/μL (F2) in former or non-smokers. **, P<0.01; ***, P<0.001. ACO, asthma COPD overlap; BEC, blood eosinophils count; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FeNO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume in one second; ns, not significant; ppb, parts per billion.

regression analysis was used to identify factors related with low FeNO. Odds ratios (OR) and 95% CI were calculated and P≤0.05 was defined significant.

Results

Among the 235 CORD patients there were 49 (GINA defined) asthmatics, 93 (GOLD defined) COPD and 93 ACO.

Among the whole population, the mean level of FeNO was 33.4±3.9 ppb. As shown in *Figure 1A*, FeNO was higher among the former- or non-smokers compared to the current-smokers (36.5±4.7 *vs.* 24.3±5.9 ppb; P<0.01). The mean FeNO was significantly lower among COPD (249.0±4.7 ppb) compared to asthmatics (42.3±7.7 ppb) and ACO (37.2±7.3 ppb) (*Figure 1B*).

Patient characteristics in CORD patients (n=235) according to FeNO value (Table 1)

A FeNO value ≥25 ppb was more frequent (P<0.001) in asthmatics (69%) compared to COPD (34%), in ACO (56%) compared to COPD (34%) (P<0.01) but not in ACO (56%) compared to asthmatics (69%).

A low FeNO (i.e., <25 ppb) was associated with male, COPD diagnosis, history of tuberculosis, more frequent (severe or not) exacerbations, heavy smokers, FEV1 <60% PV or with emphysema. Age <60 years was associated with a high FeNO but only among the non-current smokers (P<0.01).

Similar observations were found using the cut-off of 50 ppb FeNO.

Patient characteristics in asthmatics, ACO and COPD according to FeNO values (Table 2)

In *Table 2*, we evaluated FeNO among asthmatics (n=49) compared to ACO (n=93) and COPD patients (n=93). The exacerbations and radiological emphysema were more frequent in patients with <25 ppb FeNO.

Among asthmatics, the T2 inflammation (positive SPTs, BEC ≥150 cells/μL and eosinophils means) was significantly associated with the FeNO ≥25 ppb, while a low FeNO (<25 ppb) was more frequent in patients with exacerbations.

Table 1 The characteristics of CORD patients according to the FeNO level

Parameters	Total (n=235)	FeNO <25 ppb [n=117 (49.8%)]	FeNO ≥25 ppb [n=118 (50.2%)]	P value
Demographic and socio-economic characteristics				
Age (years)	61.5 (60.1–62.9)	63.4 (61.7–65.0)	59.6 (57.3–61.8)	NS*
Age ≥60 years	152 (64.7)	80 (68.4)	72 (61.1)	NS#
Sex				<0.01#
Male	175 (74.5)	96 (82.1)	79 (66.9)	
Female	60 (25.5)	21 (17.9)	39 (33.1)	
Occupation exposure +	154 (65.5)	76 (65.0)	78 (66.1)	NS#
History of tuberculosis +	32 (13.6)	22 (18.8)	8 (6.8)	<0.05†
Diagnosis				<0.001#
Asthma	49 (18.3)	15 (12.8)	34 (28.8)	
ACO	93 (39.6)	41 (35.0)	52 (44.1)	
COPD	93 (39.6)	61 (52.1)	32 (27.2)	
Smoking status				
Never smoker	49 (20.9)	17 (14.5)	32 (27.1)	0.059#
Former-smoker	102 (43.4)	55 (47.0)	47 (39.8)	NS#
Current smoker	84 (35.7)	45 (38.5)	39 (33.1)	NS#
Smoke ≥10 pack-year	150 (63.8)	84 (71.8)	66 (55.9)	<0.02#
Pack-year number	22.6 (19.5–25.6)	28.4 (24.0–32.9)	16.8 (12.7–20.8)	<0.001*
Type 2 inflammation markers				
History of allergy +	95 (40.4)	32 (27.4)	63 (53.4)	<0.001#
Rhinitis +	68 (28.9)	19 (16.2)	49 (41.5)	<0.001#
Eosinophils ≥150 cells/µL	168 (71.5)	75 (64.1)	93 (78.8)	<0.02#
Eosinophils (cells/µL)	255.8 (229.4–282.3)	242.8 (203.5–282.0)	268.8 (232.8–304.7)	0.07*
Skin prick tests +	86 (36.6)	36 (30.8)	50 (42.4)	NS#
Factors of severity				
Pre BD-FEV1 <60% PV	150 (63.8)	85 (72.6)	65 (55.1)	<0.01#
Post BD-FEV1 <60% PV	128 (54.5)	76 (65.0)	52 (44.1)	<0.001#
Post BD-FEV1 (%PV)	57.9 (55.6–60.3)	52.5 (49.2–55.8)	63.4 (60.2–66.5)	<0.001*
BD responsiveness	85 (36.2)	35 (29.9)	50 (42.4)	<0.05#
Exacerbation +	56 (23.8)	38 (32.5)	18 (15.3)	<0.01#
Severe exacerbation +	32 (13.6)	26 (22.2)	6 (5.1)	<0.001#
Rx emphysema +	69 (29.4)	49 (41.9)	20 (16.9)	<0.001#

Data are presented as mean (95% CI) or n (%). *, Mann-Whitney *U* test; #, χ^2 test; †, Fisher exact. +, positive. ACO, asthma COPD overlap; BD, bronchodilator; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CORD, chronic obstructive respiratory disease; FeNO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume in one second; NS, not significant; ppb, parts per billion; PV, predicted value; Rx, chest X-ray.

Table 2 Characteristics of asthma, ACO and COPD patients according to the FeNO

Parameters	Asthmatics (n=49)		ACO (n=93)		COPD (n=93)	
	FeNO <25 ppb (n=15)	FeNO ≥25 ppb (n=34)	FeNO <25 ppb (n=41)	FeNO ≥25 ppb (n=52)	FeNO <25 ppb (n=61)	FeNO ≥25 ppb (n=32)
Age (years)	59.9 (54.6–65.1)	53.1 (48.0–58.3)	64.1 (61.4–66.8)	60.5 (57.5–63.4)	63.8 (61.5–66.1)	64.9 (62.0–67.8)
Male	6 [40]	14 [41]	30 [73]	32 [62]	60 [98]	32 [100]
Current smoker	3 [20]	10 [29]	15 [37]	4 [8]***	22 [36]	14 [44]
Pack-year	3.9 (1.5–6.4)	3.6 (2.0–5.1)	22.3 (13.9–30.7)	15.9 (8.3–23.6)	38.6 (33.5– 43.7)	32.1 (27.5–36.7)
History of allergy	5 [33]	17 [50]	18 [44]	30 [58]	9 [15]	16 [50]***
Past tuberculosis	0	0	9 [22]	9 [17]	13 [21]	1 [3]*
Rhinitis	3 [20]	10 [29]	10 [25]	26 [50]**	6 [10]	13 [41]***
BEC ≥150 cells/µL	11 [73]	33 [97]*	29 [71]	42 [81]	35 [57]	18 [56]
BEC (cells/µL)	191.8 (144.1–239.5)	294.1 (240.3–347.9)#	263.7 (186.1–341.3)	260.4 (205.2–315.6)	241.3 (186.4–296.1)	255.4 (170.2–340.7)
Skin prick tests	3 [20]	23 [68]**	19 [46]	22 [42]	14 [23]	5 [16]
Post BD-FEV1 <60% PV	7 [47]	10 [29]	29 [71]	23 [44]**	40 [66]	19 [59]
Post BD-FEV1 (%)	61.4 (50.8–72.0)	71.1 (64.5–77.6)	50.6 (45.2–56.1)	62.9 (58.7–67.2)###	51.6 (47.0–56.1)	55.9 (50.4–61.4)
Exacerbation	5 [33]	1 [3]**	13 [32]	11 [21]	20 [33]	6 [19]
Severe exacerbation	2 [13]	0	10 [24]	4 [8]*	14 [23]	2 [6]*
Rx emphysema	3 [20]	3 [9]	12 [29]	6 [12]*	34 [56]	11 [35]*

Data are presented as mean (95% CI) or n [%]. Comparisons of FeNO <25 and ≥25 ppb: Mann-Whitney *U* test: #P<0.05, ##P<0.02, ###P<0.01; χ^2 test: *P<0.05; **P<0.02; ***P<0.01. ACO, asthma COPD overlap; BD, bronchodilator; BEC, blood eosinophils count; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FeNO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume in one second; ppb, parts per billion; PV, predicted value; Rx, chest X-ray.

In the COPD group, FeNO ≥25 ppb was associated with rhinitis and history of allergy, but unrelated with T2 AI (i.e., BEC ≥150 cells/µL, eosinophils mean and positive SPTs). A low FeNO was associated with the risk of severe exacerbation and Rx emphysema.

All the 93 COPD patients, defined by post-BD FEV1/FVC <0.7, were ex/current smokers. Only 3 asthmatics were smokers. Conversely, among the ACO, the never smokers and ex/current smokers were 22 (24%) and 71 (76%), respectively. In *Table 3*, we compared the ACO phenotypes in regard with the smoking habits. The non-smoking ACO (exposed to biomass fumes, to environmental pollutants and infectious agents) were more frequently females, with allergies (history and positive SPTs) and had less airflow limitation.

Correlation between FeNO values and characteristics of former-and non-smoker CORD

We showed that current smoking was associated with a lower FeNO (*Figure 1A*), among ACO and asthmatics but not COPD (*Figure 1C*). The FeNO was higher in asthma and ACO compared to COPD but comparable in asthma and ACO (*Figure 1B*). For the following analysis, the current smokers were excluded (*Figure 1D-1F*). By doing so, we shown that the FeNO negatively related with age (*Figure 1D*) while the eosinophilia and the airflow limitation reversibility were related positively with the FeNO (*Figure 1E,1F*). The association between the airflow limitation reversibility and the FeNO was more significant among the patients with BEC ≥300 cells/µL (*Figure 1F$_1$*), compared to BEC <300 cells/µL (*Figure 1F$_2$*).

Table 3 Comparisons between non-smokers and ex/current smokers among the patients with ACO

Parameters	Total (N=93)	ACO		P value
		Never smokers (N=22)	Ex/current smokers (N=71)	
Age (years)	62.1 (60.0–64.1)	61.8 (59.3–64.4)	62.1 (60.2–65.6)	NS†
Male	62 (66.7)	5 (22.7)	57 (80.3)	0.0001‡
History of allergy	48 (51.6)	15(68.2)	33 (46.5)	0.02‡
Rhinitis	36 (38.7)	12 (54.5)	24 (33.8)	NS‡
Past tuberculosis	18 (19.3)	3 (13.6)	15 (21.1)	NS‡
BEC ≥150 cells/µL	71(76.3)	14 (63.6)	57 (80.3)	NS‡
BEC (cells/µL)	261.9 (216.7–307.0)	256.5 (209.1–303.9)	282.8 (150.3–415.3)	NS†
Skin prick tests	41 (44.1)	15 (68.2)	26 (36.6)	0.02‡
FeNO (ppb)	37.2 (29.8–44.5)	35.0 (26.1–43.5)	37.8 (29.1–47.3)	NS†
FeNO ≥25 ppb	52 (55.9)	13 (59.1)	39 (54.9)	NS‡
Pre FEV1/FVC (%)	60.4 (58.8–62.0)	60.4 (58.8–62.0)	60.4 (58.8–62.0)	0.01†
Post FEV1/FVC (%)	61.1 (59.5–62.8)	61.1 (59.5–62.8)	61.1 (59.5–62.8)	NS†
Exacerbation	24 (25.8)	5 (22.7)	19 (26.8)	NS‡
Childhood biomass exposure	81 (87.1)	16 (72.7)	65 (91.6)	NS‡
Rx emphysema	18 (19.4)	3 (13.6)	15 (21.1)	NS‡

Data are presented as mean (95% CI) or n (%). †, Mann-Whitney *U* test; ‡, Fisher's Exact test. ACO, asthma COPD overlap; BEC, blood eosinophils count; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FeNO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; NS, not significant; ppb, parts per billion; Rx, chest X-ray.

The post-BD FEV1 and FEV1/FVC, correlated positively with the FeNO levels (*Figure 2*). This relationship was significant among the former and non- smokers but not among the current smokers (*Figure 2*). The basal FEV1 and FEV1/FVC correlated also positively with the FeNO levels (data not shown).

Factors related to low FeNO on multivariate analysis

We developed a multivariate model adjusted for age, sex and pack-year number which was applied to each parameter with P<0.2 on univariate analysis from *Table 2*. The FeNO <25 ppb remained significantly higher among patients with severe exacerbation and radiological emphysema.

Discussion

This study showed that FeNO was associated with asthma and ACO compared to COPD and was related positively with T2 inflammation, BD responsiveness and negatively with active/cumulative smoking, the risk of exacerbations and, among non-current smokers, the age and the basal airflow limitation.

The concentrations of FeNO were 24.9 ppb among COPD and 42.3 ppb among asthmatics. Consistently in Vietnam, Sy Duong-Quy *et al.* reported a level of 15±8 ppb FeNO in COPD (including 75% current smokers) of, significantly lower compared to 46±28 ppb in asthmatics (23).

FeNO ≥25 ppb was associated with asthma and T2 inflammation markers

The asthmatics were frequently young women with atopic status. A higher FeNO has been reported in allergic status (30), high BEC (7) and asthma (3,8). Consistently, in the present study, the rates of allergic status, BEC ≥150 cells/µL and asthma diagnosis were higher in FeNO ≥25 ppb group, confirming an association between higher FeNO level and allergic asthma.

While a lower prevalence of eosinophilic asthma was observed in the LMICs compared to the HICs (31,32), the asthma eosinophilic AI was frequent (>70%) in the present

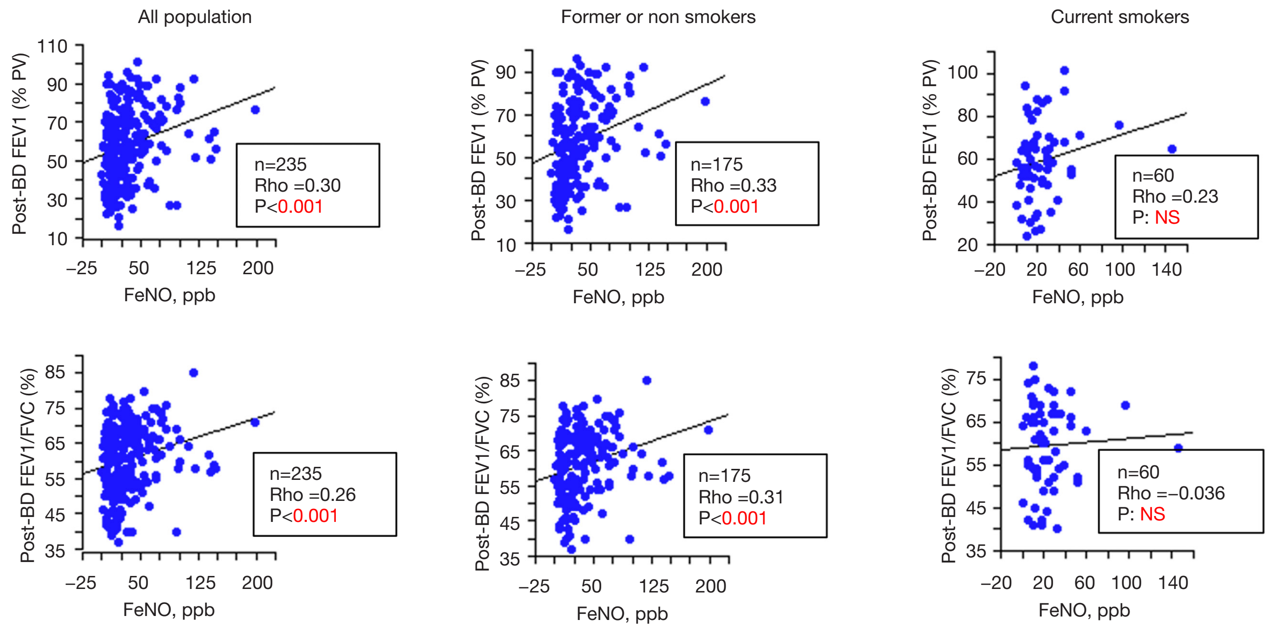

Figure 2 Relationship between FeNO and basal airflow limitation, in former- or non-smokers and current smokers. FeNO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; NS, not significant; Post-BD FEV1, post bronchodilator forced expiratory volume in one second; ppb, parts per billion; PV, predicted value.

study. The asthmatics (but not the ACO or COPD) with FeNO ≥25 ppb were associated with BEC >150 cells/μL and with a higher mean BEC. Moreover, among the CORD patients, not currently smoking, the FeNO concentration was positively related to the BEC.

FeNO <25 ppb was associated with COPD characteristics

The COPD are frequently associated with cigarette smoking, older age and pulmonary emphysema. A history of pulmonary tuberculosis has also been reported as a risk factor for COPD in LMICs (2). In COPD patients, the radiological emphysema, history of tuberculosis and risk of severe exacerbations were associated with FeNO <25 ppb, while type 2 inflammation (rhinitis and history of allergy) was associated with FeNO ≥25 ppb. This suggested a non-type-2 inflammation, among COPD with low FeNO, often characterized by neutrophils (33).

In COPD, the role of FeNO to predict lung function or exacerbation is still debated. Elevated exhaled nitric oxide fraction was associated with increased risk of exacerbation and allergic airflow inflammation in COPD (16,17) whereas decline lung function or risk of exacerbations seemed to have no association with FeNO values (18,19). In Chinese COPD, acute exacerbations in the past year, ICS users, leukocytes and eosinophils counts were associated with high FeNO level (20). Our data were not in line with these observations. However, while the mean concentration of FeNO were comparable between studies, our COPD patients were less frequently current smokers (41%) and less frequently treated with ICS (43%). Since current smoking and ICS interact with blood eosinophils and FeNO, it can explain the discrepancy observations. Among non-current smokers only, we showed a significant relationship between FeNO and blood eosinophilia, as reported among the Chinese COPD.

Since blood eosinophilia is related to FeNO and might be a predictor of the response to inhaled corticosteroids (ICS), the question is to consider FeNO as a predictor on the ICS response among COPD. Though, a systematic review on COPD and ACO, including 38 articles, concluded that there was no cut-off of FeNO to guide ICS therapy in COPD patients (34).

Low level of FeNO was associated with poorer lung function and severe exacerbation in both asthma and COPD patients

In moderate to severe asthma, the FeNO level was associated with the lung function decline and future exacerbations (9,10) and could be a biomarker in tailoring asthma treatment (11). Though in mild asthma, there was no association between the FeNO level and exacerbations (12). In Chinese asthmatics, future exacerbations were associated with poor adherence to the treatment, but not with the FeNO level (13). On the contrary with our data, a weak inverse correlation between FeNO with FEV1 values was reported in non-current smoking Vietnamese asthmatics (14). However, this relation was only present among asthmatics treated with LABA and moreover our patients were more severe (mean FEV1 =64.5% compared to 85.8% PV).

On one side, in severe asthma, BD-responsiveness was associated to a risk of exacerbations (35) and to rapid decline of FEV1. On the other side, the association between elevated FeNO levels and larger BD response was found in non-smoking non-asthmatic and asthmatic subjects in a population of 4,257 participants (36). A relationship between FeNO level and a greater decline in FEV1 over 20 years has also been reported in non-smoking asthmatic subjects. The same authors speculated that achieving control of type-2 inflammation might result in slower lung function decline. Also, in a small population of 29 asthmatics, FeNO may be a predictor of BD-response (37). Consistently, our data showed a significant relationship between FeNO level and the BD-responsiveness, in non-current smokers, whatever the diagnosis of asthma or COPD.

This observation is important because FeNO could be a predictor of ICS response, among the non-smoking CORD and not requiring a specific diagnosis of asthma or COPD. A prospective longitudinal study should be done among COPD and ACO patients (in terms of exacerbations and quality of life) randomized with or without ICS in regard with the FeNO threshold. Sustained this, a Japanese study including a small population of 43 symptomatic COPD, suggested that FeNO predict the response to ICS treatment (21). In adult asthma a systematic review has concluded that FeNO can guide the ICS treatment and reduce the number of exacerbations (38).

If we observed an association between FeNO and BD-responsiveness (and consequently the need for ICS), though the present study shown that the retrospective risk of exacerbations was associated with a low FeNO. One explanation could be that the patients with a low FeNO were more severe, heavy smokers with frequent emphysema and therefore with a higher risk of exacerbations.

Limitations of the study

This cross-sectional design couldn't determine the causality between FeNO level and the prognosis of asthma and COPD such as lung function decline and risk for future exacerbations. FeNO testing is often unavailable in clinical care in Vietnam leading to lack of local literature resources for more comparison. In this study, FeNO values by themselves do not justify a diagnosis or a change in treatment and should be interpreted according to the clinical context and future longitudinal studies. Additionally, we cannot exclude whether lung development disorders such as airway dysanapsis had interfered with the reported data.

Conclusions

In Vietnam, among chronic respiratory obstructive diseases, FeNO is a biomarker of inflammation, clinical severity and airways' reactivity, independently of the specific diagnosis (i.e., asthma or COPD). Being related with the BD responsiveness, it could be a predictor of ICS response, whatever the diagnosis of asthma, ACO or COPD. Future research based on longitudinal studies is needed to evaluate the role of FeNO in treatment strategy of CORD, in Vietnam.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1727/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of Pham Ngoc Thach University (008/HDDD) and informed consent was taken from all the patients.

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