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Using fractional exhaled nitric oxide level to differentiate asthma–COPD overlap syndrome from chronic obstructive pulmonary disease

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Abstract:

INTRODUCTION: Measurement of fractional exhaled nitric oxide (FeNO) is a simple, noninvasive, reproducible, and convenient method for assessing airway inflammation. We here assessed the value of FeNO for distinguishing asthma-COPD overlap syndrome (ACOS) and chronic obstructive pulmonary disease (COPD) in patients hospitalized due to exacerbation of COPD.

METHODS: A total of 100 consecutive patients diagnosed with COPD and hospitalized due to disease exacerbation were included and divided into the COPD-alone group and ACOS group. FeNO was measured at the beginning of hospitalization and at discharge.

RESULTS: There was no correlation between FeNO values measured at the time of hospitalization and hospital duration ($r = -0.10$, $P = 0.334$). However, the mean FeNO value at the beginning of hospitalization was significantly higher in the ACOS group than in the COPD-alone group (25.5 [11–149] vs. 13.0 [5–50]; $P < 0.001$). The initial FeNO value was a good predictor of ACOS, with an optimum value of 18.5 parts per billion (sensitivity, 80%; specificity, 80%; positive and negative predictive values, 63.6% and 90.6%, respectively).

CONCLUSION: The FeNO level can identify ACOS in patients hospitalized for COPD exacerbation, providing a new diagnostic tool for the clinical management of ACOS and COPD.

Keywords:

Asthma-COPD overlap syndrome, chronic obstructive pulmonary disease, fractional exhaled nitric oxide

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Introduction

Measurement of fractional exhaled nitric oxide (FeNO) is a simple, noninvasive, reproducible, and easily administered method for assessing airway inflammation.[1,2] NO is a biomarker in many respiratory diseases, including chronic obstructive pulmonary disease (COPD).[2] However, the significance of FeNO value in COPD remains unclear.

Exacerbation of COPD is associated with increased neutrophilic inflammation, although eosinophilic inflammation is also observed.[3] Response to corticosteroid therapy varies among COPD

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patients.[4,5] Identifying eosinophilic subgroups with high steroid-responses before treatment can help avoid unnecessary steroid administration and the associated side effects.[5]

Sputum eosinophil counts have been shown to be correlated with FeNO levels in patients with severe COPD.[4] An increase in posttreatment forced expiratory volume in 1 s (FEV_1) values were observed in patients with high levels of FeNO, who also had a shorter duration of hospitalization.[4,5]

Patients with asthma-COPD overlap syndrome (ACOS) exhibit characteristics of both asthma and COPD. Diagnosing ACOS is difficult in older patients with a history of allergies and in asthma patients who smoke. A previous study evaluating eosinophilic inflammation found that patients with ACOS had higher FeNO values than those with COPD.[6] However, there have been no studies on the utility of FeNO value for distinguishing between ACOS and COPD exacerbation. This was examined in the present study in patients hospitalized due to exacerbation of COPD.

Methods

Study design

FeNO was measured at the beginning of hospitalization and at the time of discharge for every enrolled patient. The study was approved by the Hospital Ethics Committees (approval number 2014/339). All patients were informed of the objectives of the study and gave their written informed consent before their involvement in the study.

Patients

A consecutive series 100 patients diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria and who were hospitalized due to exacerbation of the disease were enrolled in this study between March 2015 and March 2016. Exclusion criteria were patients receiving systemic treatment with steroids within the month before the study, who had pneumonia, pulmonary embolism, lung cancer, cystic fibrosis, rhinosinusitis, eosinophilic pneumonia, eosinophilic vasculitis, or parasitic disease causing eosinophilia and who refused to submit to FeNO measurement.

Patients were grouped as A, B, C, or D based on the number of exacerbations and hospitalizations and the presence of dyspnea in the combined COPD assessment, which was determined according to the GOLD criteria.[7] Patients with ≥1 exacerbation requiring hospitalization and ≥2 exacerbations not requiring hospitalization were considered as the frequent exacerbation group; the remaining patients were classified as the rare exacerbation group. Dyspnea was scored according to the Modified Medical Research Council (MMRC) dyspnea scale. Patients with an MMRC score ≥2 were considered very symptomatic, and the others were considered less symptomatic.

Patients hospitalized due to COPD exacerbation were monitored according to routine procedures. Patients were administered ipratropium bromide (0.5 mg) and salbutamol (nebul; 2.5 mg) every 6 h, as well as methylprednisolone (40 mg) as a single dose each morning and intravenous theophylline (200 mg) every 12 h. Patients were treated with antibiotics if the amount and purulence of sputum increased. Patients were also administered biphasic positive airway pressure (BPAP) therapy according to the international guidelines.[7]

Fractional exhaled nitric oxide measurement

For every enrolled patient, FeNO was measured at the beginning of hospitalization and at the time of discharge using a chemiluminescence analyzer (NIOX-MINO; Aerocrine AB, Stockholm, Sweden). Patients were required to exhale for 6 s against a pressure of 5 cm H_2O with a flow rate of 50 ml/s, and the concentration of NO in the exhaled breath was measured. Patients were required to avoid smoking or eating for at least 1 h before the measurement.[8]

Evaluation of asthma-COPD overlap syndrome

In patients hospitalized due to COPD exacerbation, the occurrence of ACOS was determined based on radiological images and data from patient records including baseline age, characteristics of respiratory symptoms, family history, and allergies in accordance with the Global Initiative for Asthma guidelines.[9]

Statistical analysis

Data are expressed in a mean ± standard deviation for continuous variables. Categorical variables are summarized as numbers, median, minimum, maximum, and percentages. Conformance of continuous variables to a normal distribution was assessed with the Kolmogorov–Smirnov test. The Student's *t*-test and analysis of variance were used to evaluate normally distributed data, and the Mann–Whitney U and Kruskal–Wallis tests were used for nonnormally distributed data in comparing continuous variables against independent groups. The Tukey and Bonferroni-corrected Mann–Whitney U-tests were used for *post hoc* comparisons. Two dependent groups were compared with the paired sample *t*-test or Wilcoxon signed-rank test. The sensitivity and specificity of FeNO values indicative of ACOS were evaluated by a receiver operating characteristic (ROC) curve analysis. Pearson's correlation was used to assess relationships between

continuous variables. The statistical significance level was determined as $P < 0.05$.

Results

The study included 86 patients after excluding 10 who were unable to complete FeNO measurements and four who developed hospital-acquired pneumonia. Among enrolled patients, 73.3% (n = 63) were male and 26.7% (n = 23) were female. The mean age was 65.12 ± 9.24 years. The proportion of patients who smoked was 19.8% (n = 17), whereas 50% (n = 43) had quit smoking and 30.2% (n = 26) were nonsmokers. Inhaled corticosteroid (ICS) was used by 91.9% of patients (n = 79) during the stable period. Based on clinical presentation, 30.2% of the patient (n = 26) were diagnosed with having ACOS. The mean FEV_1 value was 50.8% ± 16%. According to combined COPD staging, 54.7% of patients (n = 47) were in Group D, 36% (n = 31) in Group C, 1.2% (n = 1) in Group B, and 8.1% (n = 7) in Group A. Evaluation of symptom severity revealed that 59.3% of patients (n = 51) had a MMRC score ≥2; 86% (n = 74) had frequent exacerbations; and 10.5% (n = 9) received BPAP therapy. The demographics and clinical characteristics of patients are shown in Table 1.

Relationship between duration of hospitalization and fractional exhaled nitric oxide

The mean duration of hospitalization was 8 ± 3.2 days. There was no correlation between FeNO values measured at the time of hospitalization and the duration of hospitalization (r = −0.10, P = 0.334). There was no difference in FeNO value measured at the beginning of hospitalization between patients hospitalized for ≤1 week and those hospitalized for >1 week [Table 2].

Relationship between blood eosinophil count and fractional exhaled nitric oxide

There was no correlation between FeNO values and blood eosinophil count measured at the time of hospitalization (r = 0.045, P = 0.68).

Relationship between patient subgroups and fractional exhaled nitric oxide

The median FeNO value at the beginning of hospitalization was 15 parts per billion (ppb), with maximum and minimum values of 149 and 5 ppb, respectively. The median FeNO value of patients with ACOS measured at the beginning of hospitalization was significantly higher (25.5) than that of patients without ACOS (13.0; $P < 0.001$). There was no relationship between patient demographics and clinical characteristics (age, sex, exacerbation of phenotype, smoking, ICS use, symptom score, and need for BPAP) and FeNO values measured during hospitalization [Table 2].

Table 1: Demographics and clinical characteristics of the study population (n=86)

Patient characteristic	Result
Age (mean±SD)	65.12±9.24
Gender, *n* (%)	
Male	63 (73.3)
Female	23 (26.7)
Smoking, *n* (%)	
Smoking	17 (19.8)
Quit smoking	43 (50)
Never smoked	26 (30.2)
Use of inhaled corticosteroid, *n* (%)	
Users	79 (91.9)
Nonusers	7 (8.1)
ACOS, *n* (%)	
No	60 (69.8)
Yes	26 (30.2)
Pulmonary function test (%)	
% FEV_1 (liters)	50.8±16 (1.3±0.5)
% FVC (liters)	72.1±18.3 (2.3±0.8)
FEV_1/FVC	55.6±9.5
GOLD stage, *n* (%)	
A	7 (8.1)
B	1 (1.2)
C	31 (36)
D	47 (54.7)
MMRC score, *n* (%)	
0	12 (14)
1	23 (26.7)
2	6 (7)
3	9 (10.5)
4	36 (41.8)
Exacerbation of phenotype, *n* (%)	
Frequent	74 (86)
Rare	12 (14)
Need for PAP, *n* (%)	
Yes	9 (10.5)
No	77 (89.5)

ACOS: Asthma-COPD overlap syndrome, FEV_1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, GOLD: Global Initiative for Chronic Obstructive Lung Disease, MMRC: Modified Medical Research Council, *n*: Number of patients, PAP: Positive airway pressure, SD: Standard deviation

Distinguishing between asthma-COPD overlap syndrome and chronic obstructive pulmonary disease based on fractional exhaled nitric oxide value

The ROC curve analysis revealed that FeNO value measured at the beginning of hospitalization was a good predictor of ACOS; the optimum FeNO value was 18.5 ppb. The sensitivity, specificity, and positive, and negative predictive values were 80%, 80%, 63.6%, and 90.6%, respectively [Figure 1].

Change in fractional exhaled nitric oxide value from the time of hospitalization to discharge

FeNO values decreased from the time of hospitalization (15 [5–149] ppb) to the time of

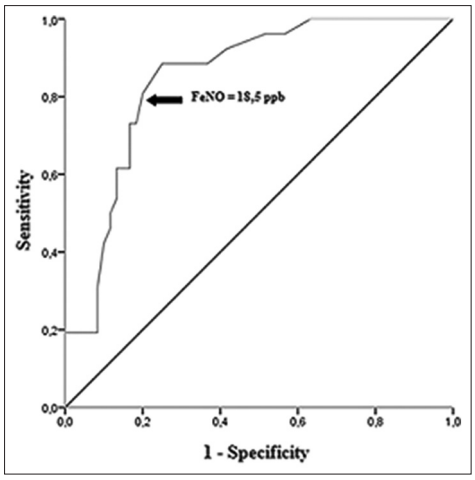

Figure 1: Receiver operating characteristic curve analysis for the relationship between fractional exhaled nitric oxide values measured at the time of hospitalization and presence of asthma-COPD overlap syndrome

discharge (11 [5–49] ppb; $P < 0.001$). The decrease in FeNO was greater in patients with ACOS than in those without ACOS (ΔFeNO = 11 [118-(−21)] vs. 3 [34-(−14)] ppb; $P < 0.001$) [Figure 2].

Discussion

The result of this study shows that FeNO value can distinguish between COPD and ACOS in COPD patients experiencing exacerbation and requiring hospitalization. FeNO values were higher in ACOS patients independent of other variables, and decreased to a greater extent in these patients following treatment.

The fact that reversibility is observed in spirometry tests despite the absence of asthma in COPD patients and that permanent airway obstruction can be detected in patients who smoke in the follow-up to asthma diagnosis makes is challenging to distinguish between these two diseases. The prevalence of ACOS in patient follow-ups to COPD diagnosis has been reported as 15%–55%.[10-12] This large range is likely due to the different diagnostic criteria used by investigators. Therefore, there is a need for objective measurable tests for diagnosing ACOS. FeNO values in patients with ACOS were found to be significantly higher than those of patients with COPD during the stable period.[13] Similarly, in the study of patients with stable ACOS and COPD patients, patients with ACOS have higher FeNO and sputum eosinophils values than in those with COPD, with an optimal FeNO value for differential diagnosis of ACOS and COPD of 25.5 ppb.[14] Another study also reported the prevalence of ACOS in patients with COPD was 30%; when FeNO measurements were compared, the highest values were in patients with asthma. Patients with ACOS have higher FeNO values than in those with COPD, with an optimal FeNO value for differential diagnosis of ACOS

Table 2: Comparison of fractional exhaled nitric oxide values at the beginning of hospitalization in patient groups

Patient characteristic	FeNO hospitalization Median (minimum-maximum)	*P*
ACOS		
Yes	25.5 (11-149)	<0.001
No	13.0 (5-50)	
Age*		
Over the age of 65	23.76±4.16	0.242
<65 years	18.56±1.84	
Sex*		
Male	20.02±2.09	0.449
Female	23.83±6.03	
Smoking		
Smoking	18.0 (5-106)	0.530
Quit	13.0 (5-60)	
Never smoked	17.5 (5-149)	
ICS use		
Yes	15.0 (5-149)	0.867
No	22.0 (-52)	
Symptom score		
Very	17.0 (5-149)	0.515
Less	13.0 (5-106)	
Exacerbation of phenotype		
Frequent	15.0 (5-149)	0.402
Rare	15.5 (5-106)	
Need for PAP		
Yes	11.0 (6-149)	0.115
No	16.0 (5-106)	
Duration of hospitalization (weeks)		
≤1	18.0 (5-52)	0.247
>1	13.5 (5-149)	

*Independent samples test (*t*-test) was used age and sex group (mean±SE). ACOS: Asthma-COPD overlap syndrome, FeNO: Fractional exhaled nitric oxide, ICS: Inhaled corticosteroid, NO: Nitric oxide, PAP: Positive airway pressure, ppb: Parts per billion, SE: Standard error

and COPD of 22.5 ppb.[6] In another study conducted during the exacerbation period with chronic bronchitis, emphysema, and ACOS patients, the FeNO values of patients with ACOS were significantly higher than those of chronic bronchitis and emphysema. Mean FeNO value of patients with ACOS was 73 ppb. There was a positive correlation between blood eosinophil counts and FENO values.[15] In the present study, 30.2% of patients had ACOS, and FeNO levels measured at the beginning of hospitalization were significantly higher in these patients as compared to those with COPD. In addition, the optimal FeNO value for predicting the presence of ACOS was 18.5 ppb, which is similar to the previously reported value. However, there was no correlation between blood eosinophil counts and FeNO values.

Corticosteroids are widely used to treat COPD, although the duration of administration and the necessity for this therapy in all cases of exacerbation are debated.[16-18]

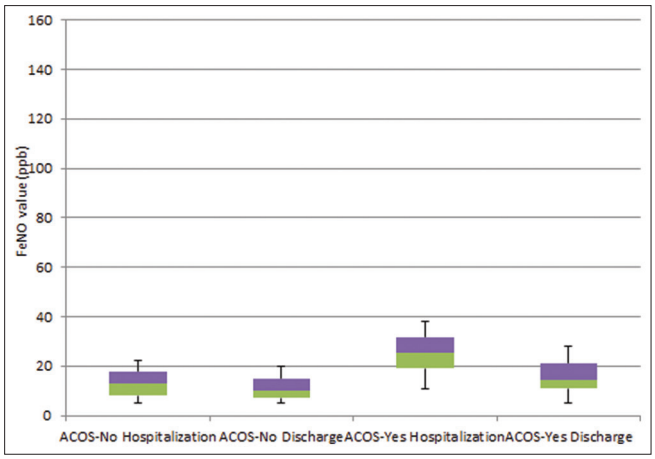

Figure 2: Rate of change of fractional exhaled nitric oxide value in patients with asthma-COPD overlap syndrome

Steroid use has side effects such as hyperglycemia, myopathy, osteoporosis, and gastrointestinal bleeding, and should, therefore, be avoided by COPD patients who have the potential for a steroid response.[4,5,19] In a study of 217 patients admitted to the intensive care unit (ICU) due to COPD exacerbation, there was no difference between those receiving corticosteroid treatment and control patients in terms of mortality and duration of stay in the ICU; although, the incidence of hyperglycemia was significantly higher in the former group.[19] Patients with higher sputum eosinophil counts and FeNO level showed greater improvement in FEV_1 following steroid treatment.[20,21] In patients hospitalized for COPD exacerbation, FeNO value measured during hospitalization was a good predictor of FEV_1 improvement following treatment, with an optimal FeNO value of 26.8 ppb.[5] There was a weakly negative correlation between FeNO value during hospitalization and duration of hospitalization (mean: 10.8 days).[5] In a separate study of patients hospitalized for COPD exacerbation, FeNO value at the beginning of hospitalization was a good predictor of improvement in FEV_1, and FeNO value was positively correlated with sputum eosinophil counts.[4] In contrast, our study found no relationship between FeNO value during hospitalization and duration of hospitalization, which reflects the response to steroid therapy.

There is conflicting evidence regarding the use of consecutive measurements of FeNO level in cases of COPD exacerbation to monitor the level of eosinophilic inflammation. Baseline FeNO level was higher in patients with COPD exacerbation than in healthy controls but decreased on day 4 after hospitalization.[22] In another study, FeNO levels in patients hospitalized due to COPD exacerbation were decreased from the time of hospitalization to the time of discharge.[5] We observed the same trend in our study, with a greater decrease detected in patients with ACOS. However, in another study reporting similar findings, FeNO values did not decrease at discharge but returned to normal during the stable period several months later for reasons that are unclear.[23]

Many factors influence FeNO level, including age, sex, ICS use, smoking, asthma, and disease severity.[24,25] Previous studies have shown that patients with COPD who smoke have lower FeNO levels than those who quit smoking;[26,27] although it was also reported that smoking had no impact on FeNO level in patients who developed COPD exacerbation.[5] The lower FeNO values in patients with COPD was found to be due to the anti-inflammatory effects of ICS.[28,29] FeNO values were found to be unrelated to disease severity ranked according to the GOLD criteria[13] and to disease stage,[6] but was positively correlated with age,[24] although this latter finding was contradicted by another study.[25] We did not observe any relationship between age, sex, smoking, ICS use, disease severity, and FeNO value; the only factor influencing FeNO level at the time of hospitalization was the presence of ACOS. In patients with fixed airway obstruction during the respiratory function test, FeNO value was higher in patients with a history of asthma than in those with a history of COPD.[30] Among patients diagnosed with chronic bronchitis, emphysema, and ACOS, the latter group had the highest FeNO levels.[13] High FeNO levels are presumably associated with ACOS exacerbation since they are observed in patients with ACOS and asthma during the stable period.

The study had some limitations. Although we used the duration of hospitalization as a measure of the response to corticosteroid treatment, some patients experienced delayed discharge due to socioeconomic reasons such as problems with transportation arrangements and inadequate home care conditions. Thus, the response to steroid should be evaluated according to more objective criteria such as improvement in arterial blood gas concentration and FEV_1 value.[4,5] However, our study population consisted of patients with severe COPD, most of whom were unable to comply with the respiratory function test during hospitalization, leaving only the duration of stay as a metric for response to treatment. Establishing an objective definition of ACOS will allow a more accurate assessment of the relationship between FeNO level and ACOS. Finally, the absence of a control group precluded comparisons of FeNO levels in patients with severe COPD to those with stable disease and healthy individuals. We, therefore, used mean values from previous studies in our evaluations.

Conclusion

We found that measurement of FeNO level can be used to identify ACOS in patients hospitalized for COPD exacerbation; although, it cannot be used to predict the response of these patients to therapy. Nonetheless, these findings provide a diagnostic tool that can inform the clinical management of ACOS and COPD.

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Conflicts of interest

There are no conflicts of interest.

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