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Evaluation of fractional exhaled nitric oxide in patients with chronic cough based on causes

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Abstract

Introduction: Cough is a common complaint in clinics, and diagnosing sub-acute or chronic cough is very important.
Objectives: This study aimed to evaluate the association between fractional exhaled nitric oxide (FeNO) and causes of chronic cough and also, answer to this question that can we use FeNo for the diagnosis of the causes of chronic cough
Patients and Methods: In this descriptive-analytical cross-sectional study, 90 patients with a complaint of cough lasting more than three weeks were assessed. Spirometry and a methacholine stimulation test, complete blood count (CBC) serum IgE-diff, and FeNO were performed for all patients.
Results: The mean age of the patients was 48.5±11.41 years, and 56.7% were male. Regarding medical history, 22.4% had asthma, 6.7% had chronic obstructive pulmonary disease (COPD), and 68.9% had no history of respiratory disease. Gastric reflux was detected in 42.2%. The mean duration of the onset of cough in the studied patients was 25.6±38.6 months. There was a significant correlation between the FeNO and IgE levels (P=0.048). The mean level of FeNO was 25±6.7 in patients with asthma, 57.3 ±18.7 in patients with COPD, and 22.8±1.6 in patients without a history of respiratory disease (P=0.002).
Conclusion: This study's findings showed a positive and significant correlation between FeNO and IgE. In addition, the FeNO level was significantly different based on the spirometry findings and respiratory diseases of asthma and COPD.

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Introduction

Cough is one of the most common complaints in medicine, and it is classified into three groups based on the duration of the cough, including coughs less than three weeks or acute, between 3 to 8 weeks or subacute, and more than eight weeks or chronic cough (1,2).

Cough after an acute viral infection of the respiratory tract is the most common cause of acute cough (3). *Chronic cough* is usually defined as a cough lasting more than eight weeks and is one of the challenging symptoms seen in daily visits. Chronic cough is one of the critical symptoms of important chronic respiratory diseases such as asthma (cough variant asthma) and non-asthmatic eosinophilic bronchitis. It can also be one of the characteristics of extrapulmonary manifestations such as gastroesophageal reflux disease (GERD) and upper airway cough syndrome (UACS) (3-5).

Key point

Fractional exhaled nitric oxide measurement can provide a simple non-invasive diagnostic tool to support treatment decisions for patients with a history of cough.

There is still a diagnostic challenge in managing and controlling chronic cough, which is related to the complexity of its underlying causes, such as UACS, GERD, eosinophilic inflammation of the airways, and other cases (4).

The fractional exhaled nitric oxide (FeNO) ratio has been introduced as a non-invasive method in diagnosing various respiratory inflammatory disorders (6). The measurement of FeNO is a method that has been suggested to examine patients with chronic cough

associated with eosinophilic airway diseases (7,8).

This method provides information about airway disorders, including asthma, allergic alveolitis, cystic fibrosis, scleroderma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), and Sjogren's syndrome (9). Unlike other non-invasive airway tests, FeNO is reproducible, easy to perform, and acceptable to patients (10). We therefore conducted a study to evaluate FeNO results in patients with chronic cough based on causes.

Objectives

This study aimed to evaluate the association between FeNO and causes of chronic cough and ability of FeNO to diagnose causes of chronic coughs.

Patients and Methods

Study design

This descriptive-analytical cross-sectional study was performed on 90 patients with a cough complaint referred to Masih Daneshvari and Labbafinezhad hospitals in Tehran. Inclusion criteria were having a complaint of chronic cough, being older than 18 years, and having no history of lung cancer. Exclusion criteria were smoking, using systemic corticosteroids, using inhalant corticosteroid during 72 hours before tests, using tea or coffee from the morning of the day of tests, having coryza manifestations during three weeks before tests, and those unable or unwilling to provide written consent for participation in the study.

Our study contained 207 patients with a history of chronic cough that persisted for over three weeks, who referred to Masih Daneshvari and Labafinejad hospitals. After carefully evaluation about the inclusion and exclusion criteria, 90 patients were assessed. This study was conducted from the start of January 2019 to the end of December 2019.

Lung computed tomography (CT) scan, sinus CT scan, spirometry, and methacholine stimulation test were done. Blood laboratory test (including complete blood count (CBC) and serum immunoglobulin E (IgE) (less than 100 u/mL was expected)) was obtained. A GERD questionnaire was fulfilled for patients to evaluate the GERD-related cough (11). Then, the FeNO test was performed for all patients. An electrochemical FeNO measurement system was conducted to determine FeNO concentrations (Niox Mino FeNO analyzer, Aerocrine, Solna, Sweden). The material specification and operation standard of American Thoracic Society/European Respiratory Society (ATS/ERS) were followed when performing the FeNO detection procedure (12). Here, FeNO served as the primary detection indicator, and its formula is 1 part per billion (ppb) = 1109 mol/L. The method involved asking the patients to exhale as much as possible, having them breathe in deeply and out evenly while maintaining a steady airflow, and holding the detector filter firmly in their mouths. The expiratory velocity and duration were chosen at 50 milliseconds and 10 seconds, respectively.

Demographic data, underlying disease, drug history, duration and type of cough, and the results of tests were recorded in a researcher-made checklist.

Statistical analysis

The data were analyzed through SPSS version 20. Quantitative variables were expressed as mean and standard deviation. Independent T-test, Kruskal Wallis test, one-way ANOVA, and Pearson's correlation with a significance level of less than 0.05 were performed.

Results

At the start of the study, 207 participants were evaluated. Then, 110 were excluded Finally, 90 participants were evaluated. Finally, 90 participants were evaluated. The mean age of the patients was 48.5±11.41 years;56.7% (n = 51) were male, and 43.3% (n = 39) were female. Regarding medical history, 22.4% (n = 22) had asthma, 6.7% (n = 6) had COPD, and 68.9% (n = 62) had no history of respiratory disease. The use of inhaled corticosteroids was mentioned in 30% (n = 27). The mean duration of the onset of cough in the studied patients was 25.6 ± 38.6 months (2 to 120 months).

According to Table 1, in patients with COPD, the duration of cough was 94 ± 41.8 months; in patients with asthma, it was 46.22 ± 36.8 months; and in patients with no history of respiratory diseases, it was 11.7 ± 27.4 months ($P < 0.001$). The type of cough was dry in 88.9% (n = 80) and wet in 11.1% (n = 10).

According to Table 2, the mean serum eosinophil in patients with asthma was 5.8 ± 3.7 cells/μL; in patients with COPD, it was 2 ± 0.8 cells/μL, and in patients without a history of respiratory disease, it was 3.1±2 cells/μL. There was a significant difference in serum eosinophil across groups ($P < 0.001$).

Table 3 shows that the mean serum IgE in patients with asthma was 146.7 ± 79.9 UI/mL; in patients with COPD, it was 46.3 ± 23 UI/mL, and in patients without a history of respiratory disease, it was 96.5 ± 80.2 UI/mL, the data indicates a notable disparity between IgE levels and respiratory conditions ($P = 0.007$). The highest level of IgE is found in patients with asthma.

Spirometry results

Spirometry results were normal in 60% (54 patients) of

Table 1. Comparison of onset cough duration across groups (COPD, asthma, and without respiratory disease)

Duration of cough	N	Mean	SD	*P* value*
COPD	6	94	41.8	
Asthma	22	46.22	36.8	<0.001
Without respiratory disease	62	11.74	27.4	

COPD, Chronic obstructive pulmonary disease.
*P value based on Kruskal Wallis test.

Table 2. Comparison of serum eosinophil across groups (COPD, asthma, and without respiratory disease)

Duration of cough	N	Mean	SD	*P* value*
COPD	6	2	0.8	<0.001
Asthma	22	5.8	3.7	
Without respiratory disease	62	3.1	2	

COPD, Chronic obstructive pulmonary disease.
**P* value based on one-way ANOVA test.

Table 3. Comparison of serum IgE across groups (COPD, asthma, and without respiratory disease)

Duration of cough	N	Mean	SD	*P* value*
COPD	6	46.3	23	0.007
Asthma	22	146.6	79.9	
Without respiratory disease	62	96.5	80.2	

COPD, Chronic obstructive pulmonary disease.
**P* value based on one-way ANOVA test.

chronic cough patients and obstructive in 40% (36 cases).

FeNO based on the history of respiratory diseases

Table 4 presents the mean FeNO levels: 27.3 ± 6.7 ppb in patients with asthma, 57.3 ± 45.8 ppb in patients with COPD, and 23.2 ± 13.2 ppb in individuals without a history of respiratory disease. There was a significant difference between FeNO and respiratory diseases ($P = 0.002$).

As shown in Table 5, a noteworthy finding in the study was the presence of a positive significant correlation observed between the elevation of FeNo and the escalation of IgE level ($P = 0.048$ and $r = 0.21$). Conversely, no significant correlation was identified between the levels of serum eosinophil and FeNo ($P = 0.85$, $r = -0.02$).

As indicated in Table 6, the mean FeNO level in patients with normal spirometry was 24.6 ± 1.9 ppb, and in patients with obstructive respiratory pattern according to spirometry, the mean FeNO was 29.4 ± 5.5 ppb, which shows a significant difference between FeNO and Spirometry findings ($P = 0.033$). The mean FeNO level in patients with gastrointestinal reflux was 22.8 ± 3.9 ppb. In patients without gastrointestinal reflux, the mean FeNO was 29.2 ± 3.2 ppb, which shows no significant difference between FeNO and gastric reflux ($P = 0.21$).

Discussion

In this descriptive-analytical investigation, a total of 90 individuals presented symptoms of cough enduring more than 3 weeks. As per the outcomes of the research, the mean age of the participants was 48.5±11.41 years and 56.7% were male. A percentage of 22.4 had a medical record of asthma, 6.7% had a medical history of COPD, and 68.9% did not report any prior respiratory conditions. According to the GERD questionnaire, gastric reflux was detected in 42.2% of cases. 31.6% of patients with asthma and 5.3% of patients with COPD had gastric reflux, but no

Table 4. Comparison of FeNO level across groups (COPD, asthma, and without respiratory disease)

Duration of cough	N	Mean	SD	*P* value*
COPD	6	57.3	45.8	0.002
Asthma	22	27.3	6.7	
Without respiratory disease	62	23.2	13.2	

COPD, Chronic obstructive pulmonary disease.
**P* value based on one-way ANOVA test.

Table 5. Assessment of the correlation between FeNO, serum IgE, and eosinophil

Pearson's correlation	IgE	Serum eosinophil
FeNO	0.209*	-0.020
P value	0.048	0.853
N	90	90

IgE, Immunoglobulin E.
*Based on Pearson's correlation.

Table 6. Comparison of FeNO level by spirometry and gastrointestinal reflux

Variable		FeNO level		*P* value*
		Mean	SD	
Spirometry	Normal	24.6	1.9	0.033
	Obstructive respiratory pattern	29.4	5.5	
Gastrointestinal reflux	Yes	22.8	3.9	0.210
	No	29.2	3.2	

**P* value based on one-way ANOVA test.

significant relationship between respiratory diseases and gastric reflux was observed ($P = 0.4$).

The mean duration of the onset of cough in the studied patients was 25.6 ± 38.6 months. In patients with COPD, the duration of cough was 94 ± 41.8 months compared to patients with asthma, 46.2 ± 36.8 months, and in patients with no history of respiratory diseases, it was 11.7 ± 27.4 months. There was a significant difference in the duration of cough in the patients ($P = 0.0001$). In the spirometry, the results were expected in 60% of patients with chronic cough, and an obstructive pattern was seen in 40% of patients. A significant relationship was found between the mean eosinophil and IgE levels in relation to respiratory diseases ($P < 0.005$) and between the mean FeNO and respiratory diseases observed ($P = 0.002$). Notably, the highest FeNO levels were observed in patients with COPD.

In a previous study, it was mentioned that chronic cough is more prevalent in women than men. The evidence from cough clinics worldwide reveals a 2-to-1 prevalence of female patients, presumably suggesting a more considerable cough reflex sensitivity, although there is a potential association between genders. An identical female gender imbalance of 1.39 in pauci-eosinophilic asthma was found in a recent extensive database analysis by Price and colleagues (13-15). In the current study, it was observed that there was a similar proportion of gender in patients

who were referred to our clinic. The difference between our findings and previous findings about the effect of gender on cough involvement should be investigated in further studies.

In the study by Qian et al, in 107 patients with acute, subacute, and chronic cough, there were correlations between FeNO and serum IgE levels. The cutoff of 25 for FeNO was sensitive to diagnosing the cause of chronic cough (16). In the current study, we observed a significant positive correlation between IgE levels and FeNO, consistent with the findings of Qian et al. In the current study, the cutoff for FeNO was not assessed to diagnose chronic cough but we found that FeNO is a suitable method for diagnosing sub-acute and chronic cough.

In the study by Sato et al, which was conducted on the clinical value of the FeNO test for the diagnosis of prolonged cough in 71 patients, based on the findings of this study, FeNO had a significant relationship with non-specific and specific IgE, BHR, FEV/FVC and eosinophil (17). The present study showed a significant correlation between the increase of IgE and the spirometry findings with the increase of FeNO. The findings of these two studies were similar. It can be said that the FeNO test is a valuable test for the diagnosis of non-acute cough.

According to the study by Nakajima et al, FeNO values in people with asthmatic cough (24.7 ± 30.4 ppb) and asthmatic-infectious cough (17.4 ± 33.2 ppb) were significantly higher than those with cough was only infectious (13.7 ± 2.3 ppb) ($P = 0.008$ and $P < 0.0001$, respectively) (18). In our study, the mean FeNo in patients with asthma was 27.3 ± 6.9; in patients with COPD, it was 57.3 ± 45.8; and in patients without respiratory disease, it was 23.2 ± 13.2, which is in agreement with the findings of the above study.

Conclusion

This study's findings showed a positive and significant correlation between FeNO and IgE. In addition, the FeNO level was significantly different based on the spirometry findings and respiratory diseases of asthma and COPD.

Limitations of the study

One of our limitations was the small sample size of study participants. It is recommended that future studies include a larger number of individuals for investigation.

Authors' contribution

Conceptualization: Shima Abbasi, Alireza Kashefizadeh, Atefeh Abedini, Amir Behnam Kharazmi, Sara Rashki Ghalenoo.
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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Ethical code # IR.SBMU.MSP.REC.1400.400). Prior to any intervention, all participants provided written informed consent. The study was extracted from Shima Abbasi's thesis in the Department of Internal Medicine at this university (Thesis #210818). The authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

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