

Original Article

Evaluation of Fractioned Nitric Oxide in Chronic Cough Patients

Y Yildiz, M Igde

Department of Pediatric Allergy and Immunology, Samsun Training and Research Hospital, Samsun, Turkey

ABSTRACT

Introduction: Cough exceeding 3-8 weeks was defined as chronic cough in various guides. Asthma is the most common cause of chronic-specific cough. Causes other than asthma include prolonged bacterial bronchitis and upper airway cough syndrome (UACS). Nitric oxide (NO) causes vascular smooth muscle relaxation, bronchodilation, and oxidant effects via its metabolite, peroxynitrite. An increase in NO results in inflammation, vasodilatation, and bronchial edema. **Materials and Methods:** The study group included 90 patients aged 6-17 years selected from individuals presenting to the Pediatric Immunology and Allergic Diseases Clinic with cough persisting for 4 weeks and 30 other patients representing to the control group. Patients with a history of premature birth and long-term ventilatory support, neuromotor retardation, or chronic lung and heart disease received systemic corticosteroid therapy in the previous 4 weeks, a chest deformity, with any chronic disease or received immunotherapy were excluded from the study. **Results:** The most common diagnosis among the 90 patients in this study was asthma, observed in 27 (30%). Fractional exhaled NO values were highest in the asthma group at 39.5 ± 26.6 parts per billion (ppb) and lowest in the UACS group at 11.6 ± 4.0 ppb. Values in the control group were 17.8 ± 11.1 ppb. The differences between the groups were statistically significant ($P < 0.001$). **Conclusion:** Fractional exhaled NO measurement can be used as a quick and reliable diagnostic method in patients presenting with chronic cough due to its high positive predictive value, its practical nature, the fact that it is a noninvasive method and that it does not require the use of medication.

KEYWORDS: Asthma, chronic cough, fractional exhaled nitric oxide

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INTRODUCTION

Cough "is not a disease, but a vital reflex" and is the most important of the natural defense mechanisms that eliminate particles and secretions from the airways and protect the lower air passages.^[1] It is also an important symptom of respiratory tract conditions and one of the most common causes of hospital admissions among children.^[2,3]

Coughs lasting less than 3 weeks are defined as acute, while those persisting for 3-8 weeks are described as chronic.^[4-6] The majority of patients in studies on the prevalence of chronic cough is younger children (mean age 2-3 years),^[4] and the proportion is higher among preschool children.^[7] Recurrent cough is also more common in males than in females.^[8] A total of 80%

of the patients have been reported to make more than five and 53% to make 10 or more presentations to physicians before presenting to a chest diseases specialist and increasingly more consultations are required for children with chronic cough.^[7,9] Varying results have been obtained in studies investigating the etiology of chronic cough in children. When the underlying conditions are divided into specific and nonspecific causes, the most common conditions seen in the general population are nonspecific causes and particularly prolonged bacterial

Address for correspondence: Dr. Yasin Yildiz, Department of Pediatrics, Samsun Training and Research Hospital, Samsun, Turkey.
E-mail: yasinyildizmd@gmail.com

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bronchitis (PBB), upper airway cough syndrome, and natural healing. Asthma is the most common cause of chronic specific cough.^[10] Specific causes other than asthma include gastroesophageal reflux, infections such as tuberculosis and pertussis, primary ciliary dyskinesia, tracheobronchomalacia, and tracheoesophageal fistula.^[11]

Tests such as posteroanterior lung radiography, the respiratory function test (RFT), the skin prick test, immunoglobulin E (IgE) level measurement, reflux scintigraphy, and 24-h pH monitoring, and so on. are used for the diagnosis of diseases underlying chronic cough.^[11] The fractional exhaled nitric oxide (FeNO) is another test increasingly used in recent times for the diagnosis of asthma, among the most common causes of specific chronic cough.^[16]

Nitric oxide (NO) is synthesized as a result of the oxidation of the amino acid L-arginine with the enzyme nitric oxide synthase in smooth muscle, endothelial cells, and many other mammalian cells. NO performs numerous functions, including blood pressure regulation and reduction of platelet adhesion and aggregation, as well as exhibiting proinflammatory and anti-inflammatory effects.^[8,12] Studies demonstrate that NO plays critical roles in such phenomena as antigen presentation and supply, differentiation of T cell functions in the acquired immune system known as the adaptive immune system and the development of the cell-mediated immune system.^[13-15] The product of the reaction of NO with superoxide, peroxynitrite provides bactericidal and cytotoxic effects against tumor cells. It also increases bronchial blood flow through vasodilation, thereby causing airway edema.^[12]

FeNO refers to NO in exhaled air in parts per billion (ppb), corresponding to nanoliters per liter.^[13] FeNO can be influenced by many factors. FeNO levels in children have been reported to increase with age.^[16,17] Similarly, FeNO levels are higher in men compared with women.^[1] FeNO levels have been reported to decrease in reverse proportion to height.^[19] Greater body mass index (BMI) is associated with higher FeNO levels.^[20] It has also been reported that FeNO levels decrease following exercise,^[1] that smoking reduces FeNO levels by 30%-60%,^[18] and that viral infections of the upper and lower respiratory system increase FeNO levels by 50%-150%.^[18] FeNO levels decline with the use of inhaled and/or oral steroids (fluticasone, methylprednisolone).^[7]

Aim

A total of 44% of patients presenting with chronic cough also exhibit wheezing/hissing in addition to cough,

60% of whom are diagnosed with asthma.^[21] Many international guidelines recommend that FeNO can be used in the diagnosis of asthma.^[4,9,22,25] We, therefore, think that FeNO measurement can represent a useful diagnostic technique at time of diagnosis in 30%-50% of patients with chronic cough. Although numerous studies involving children have investigated the etiology of chronic cough and NO in asthmatic patients, none have investigated FeNO in children with chronic cough. The aim of this study was to investigate FeNO measurement as a practical, fast, and noninvasive technique that can assist the clinician with diagnosis in patients presenting with chronic cough and that can predict the success of treatment.

MATERIALS AND METHODS

Patient selection

Patients aged 6-17 years presenting with cough persisting for more than 4 weeks to the pediatric immunology and allergic diseases polyclinic between November 2013 and October 2014 and 30 other patients representing control subjects were included in the study. Patients who were born prematurely, received long-term ventilation, with neuromotor growth retardation, received systemic corticosteroid therapy within the previous 4 weeks, with chest deformity or any chronic condition (such as asthma, cystic fibrosis, hypertension, autoimmunity, and malignancy), or receiving immunotherapy were excluded.

Diagnosis and treatment

FeNO was measured in all patients and those diagnostic tests (the respiratory function test, the skin prick test, and IgE level measurement etc.) that were indicated were performed. Eosinophil numbers exceeding 4% of the total white cell count was regarded as positive eosinophilia, total IgE > 150 IU/mL as elevated IgE, changes of 12% or more in peak expiratory flow (PEF) measurement following administration of 0.15 mg/kg salbutamol by nebulizer as RFT/reversibility positivity, and erythema in the skin positive control edema (histamine hydrochloride 1 mg/mL) formed by the half urticarial papules or creating larger diameter papules was regarded as positive skin prick test. The tuberculin skin test, mycobacterial culture and acid-resistant bacilli in fasting gastric fluid were performed on patients suspected of tuberculosis.

In line with the modified asthma predictive index, in the presence of one major risk factor (asthma and/or atopic dermatitis in a parent, atopic dermatitis in the patient or sensitivity to aerosols in the patient) or two minor risk factors (food sensitivity, wheezing in the absence of the

common cold, or eosinophil count $\geq 4\%$) in children with recurring wheezing,^[23] the presence of more than two wheezing and/or dyspnea attacks responding to bronchodilator therapy and/or improvement greater than 12% in forced expiratory volume in the first second (FEV1) with spirometry were regarded as asthma.^[24] Clinical findings (history of contact, prolonged fever recalcitrant to nonspecific therapy, and loss of appetite or weight), radiological findings, and tuberculin skin test positivity greater than 15 mm were evaluated as tuberculosis.^[27] Retrosternal burning discomfort, normal posteroanterior lung radiography, absence of daily PEF variation, cough failing to respond to treatment, and response to domperidone and ranitidine therapy within 2 weeks were regarded as gastroesophageal reflux disease.^[2] Upper respiratory tract cough syndrome was diagnosed in the presence of hyperemia in the pharyngeal or nasal mucosa, findings such as postnasal discharge and response to nasal saline solution and oral or nasal decongestant therapy.^[29] PBB was diagnosed in children with isolated cough if this resolved in 2-4 weeks with appropriate antibiotics and in the absence of alternative causes of specific cough.^[18] Resolution of cough without treatment while under observation was defined as natural healing.^[1] Presence of coarse, wheezing daytime cough in which organic causes were excluded, cough ceasing with activity or night-time sleep, and the absence of any underlying diseases in the tests performed were defined as psychogenic cough.^[29]

FeNO MEASUREMENT

For evaluation of FeNO level, American Thoracic Society's the "Interpretation of exhaled nitric oxide levels (FeNO) for clinical applications" is sampled guide.^[4] Factors affecting FeNO levels, such as age, sex, BMI, and exposure to cigarettes were recorded. A NIOX-MINO[®] device produced by Aerocrine AB (Sweden) was used for online FeNO measurement (FeNO were measured directly exhaled breath).

STUDY PROTOCOL

The American College of Chest Physicians 2006 guideline "Introduction to the Diagnosis and Management of Cough" was adopted for chronic cough.^[9] Patients were reassessed at weeks 2 and 4 of treatment. Ethical committee approval from the Educational Planning Commission of the Samsun Training and Research Hospital, Turkey was received on 11/07/2013 (No. 2013/13).

Data were analyzed on IBM SPSS 21.0 software. Significance levels were set at $P < 0.05$.

RESULTS

Females constituted 48.3% ($n = 58$) of the subjects in the study and males 51.7% ($n = 62$). No significant differences were observed between the groups, including the control group ($P = 0.46$). Mean age was 10.8 ± 3.6 (6-17) years, with no significant difference between the control and patient groups ($P = 0.53$). Mean age at onset of cough was 10.5 ± 3.67 (4-17) years, and mean duration of cough was 12.7 ± 30.6 (4-240) weeks. Etiology and epidemiological characteristics of the patients in the study are shown by groups in Table 1. The most frequent cause of chronic cough in the patients in this study was asthma.

Examination of the positivity rates of the diagnostic tests administered to the patients presenting to our clinic with chronic cough revealed significant differences in skin tests and IgE elevations [Table 2].

Girls in the control group had a mean FeNO of 20.6 ± 13.9 (10-50) ppb compared with 15.4 ± 7.6 (9-41) ppb in boys, and no significant difference was observed between the genders ($P = 0.13$). Similarly, no correlation was observed between FeNO and age or BMI in the patients in the control group (P values 0.16 and 0.26, respectively).

Mean FeNO was 21.5 ± 19.3 (5-104) ppb in the total patient group, 21.8 ± 18.5 (6-103) ppb in girls and 21.3 ± 20.3 (5-104) ppb in boys, with no significant differences observed ($P = 0.51$). Similarly, no relationship was observed between FeNO and age or BMI in the patient group (P values 0.24 and 0.9, respectively). The mean FeNO value in the control group was 17.03 ± 11.02 (9-50) ppb compared with 21.52 ± 19.33 (5-104) ppb in the total patient group. The difference was not statistically significant ($P = 0.97$).

Intragroup analysis revealed the highest FeNO value, 39.5 ± 26.6 ppb (6-104), in the asthma group and a statistically significant difference was observed among all the groups ($P < 0.001$). The groups were then compared pair wise, which demonstrated that only the asthma group differed from the other groups (P value 0.007 after correction).

Positivity rates of the diagnostic tests administered in all the diagnosis groups were investigated, and intergroup differences were observed in RFT/reversibility positivity and mean FeNO values [Table 3]. Consistent with the purpose of the study, the reliability of the diagnostic tests in terms of asthma, the most common cause of chronic cough, was evaluated using receiver operating characteristics analysis [Table 4].

Table 1: Diagnoses and epidemiological characteristics

	Number of patients (n)	Mean age (years)	BMI	Gender (M/F)	Cough duration (weeks)
Asthma	27	11.2±3.7	19.5±2.9	11/16	14.3±24.2 (4-120)
UACS	22	9.6±3.8	19.6±4.2	10/12	11.9±24.3 (4-120)
PBB	20	9.7±3.6	19.83±3.3	12/8	18.1±52.3 (4-240)
Natural healing	11	11.5±2.6	20.6±4.1	7/4	5.9±2.7 (4-12)
GERD	6	12.3±4.6	19.0±3.6	5/1	6.5±2.6 (4-11)
Psychogenic	3	12.0±4.0	19.5±2.6	1/2	56.3±0.6 (6-7)
Tuberculosis	1	13	21.3	0/1	12
Control group	30	11±3.4	19.3±4.8	16/14	-
P		0.53	0.78	0.46	0.38

PBB= Prolonged bacterial bronchitis; UACS = Upper airway cough syndrome; GERD = Gastroesophageal reflux disease

Table 2: Positivity rates of diagnostic tests in the study group

Diagnostic test	Patient Group (n=90)		Control Group (n=30)		P
	N	%	n	%	
RFT / reversibility positivity	29	32.2	0	0	*
Skin test positivity	22	24.4	3	10	0.04
IgE elevation	35	38.9	2	6.7	0.01
Eosinophilia at complete blood count	37	41.1	8	26.7	0.19
Purified protein derivative test positivity	1	1.1	0	0	*
Sweat test positivity	0	0	0	0	*

*Comparison could not be performed because the sample number was 0.

Table 3: Comparison of diagnostic tests in patients in all groups

Diagnostic Test	Presence of eosinophilia (%)	Skin test Positivity (%)	RFT/reversibility positivity (%)	IgE elevation (%)	Mean FeNO (ppb)
Asthma	52	30	81	59	39.5±26.6
UACS	59.1	27.3	4.5	50	11.6±4.0
PBB	45	30	20	35	14.6±4.7
Natural healing	0	0	9.1	0	15.1±10.2
GERD	0	33.3	0	0	14.3±6.6
Psychogenic	0	0	0	0	15.7±3.1
Tuberculosis	100	0	100	100	25
Control group	26.7	6.7	3.3	6.7	17.8 ± 11.1
P	0.26	0.95	<0.001*	0.76	<0.001*

PBB = Protracted bacterial bronchitis; UACS= Upper airway cough syndrome; GERD = Gastroesophageal reflux disease

Table 4: Reliability values of diagnostic tests in the etiology of chronic cough

Test	Sensitivity	Specificity	PPV	NPV
FeNO*	0.78	0.92	0.81	0.91
RFT/reversibility	0.81	0.89	0.76	0.92
Ig E elevation	0.60	0.70	0.46	0.80
Skin test positivity	0.30	0.78	0.37	0.72
Presence of eosinophilia	0.52	0.64	0.34	0.75

PPV= Positive predictive value; NPV= Negative predictive value

*FeNO value for positivity was taken as 24 ppb and above

DISCUSSION

Most of the conditions that lead to chronic cough are treatable. Diagnosis of the underlying condition is therefore of critical importance to treatment. Asthma has

been identified as the most common underlying condition in most studies investigating diseases involved in the etiology of chronic cough (3.7%-64.1%).^[26-29] Current guidelines published by the European and American Thoracic Societies emphasize that asthma should be considered the primary cause in differential diagnosis of recurring/chronic cough.^[5,6] In our study, asthma was the most significant cause in 30% of cases.

The depth of laboratory analyses in cases of children with chronic cough depends on findings and suspected etiology. Tests including serum total IgE, peripheral blood eosinophil count, and skin tests can be used to evaluate atopy accompanying chronic cough and in patients in whom atopic asthma is suspected.^[4,9,30] One of

the most important of these tests is RFT/reversibility.^[30] RFT and reversibility tests were performed in all cases and as needed, respectively, for patients who presented with chronic cough in our study.

When used in the diagnosis of patients presenting with chronic cough, the tests listed above are time-consuming (RFT/reversibility), invasive (skin test and blood tests), require bronchoscopy (bronchoalveolar lavage) and involve high costs.^[30] In contrast, measurement of FeNO, a marker of inflammation in airways, is simple, convenient, and noninvasive.^[16] We observed a difference between FeNO levels in the control and patient groups, although this was not statistically significant [Table 3]. When the patient groups were studied individually, mean FeNO values were highest in the asthma group, the difference being statistically significant.

In the diagnosis of asthma, RFT reveals variability as a marker of bronchial narrowing, airway hypersensitivity, and reversibility. It confirms and facilitates the diagnosis of asthma.^[4] Numerous international societies and guidelines also report that FeNO measurement can be used in diagnosing asthma.^[4,17,31] Previous studies have determined a correlation between RFT/reversibility and FeNO or the process of diagnosing asthma and FeNO. One study of asthma patients during acute asthma attack with no clinical signs enrolled as a control group reported FeNO levels of 8.2 ± 0.5 ppb in the control group, 8.8 ± 1.5 ppb in stable asthma patients, and 15.0 ± 1.0 ppb in acute asthma patients, and proposed FeNO as a promising clinical tool in evaluating acute asthma attacks.^[32] RFT and FeNO measurements have been shown to be successful in demonstrating inflammation in the airways. These two parameters have also been shown to be correlated, and asthmatic children can be distinguished from nonasthmatic children using FeNO.^[4,17] Another study investigating the relationship between FeNO levels and bronchial hyperreactivity and pulmonary functions observed a significant negative correlation between FeNO and % FEV₁.^[34]

The statistical significance and power of FeNO measurement in diagnosing asthma as the most common factor in the etiology of chronic cough has also been studied previously. Research has demonstrated that asthmatic cases can be distinguished from nonasthmatic patients using FeNO measurement with 85% sensitivity and 90% specificity.^[33] Another study reported 72.2% sensitivity, 75% specificity, 96.2% positive predictive value (PPV), and 23% negative predictive value (NPV) in determining asthma when a threshold of 25 ppb was adopted for FeNO.^[30] In our study, FeNO measurement exhibited 78% sensitivity, 92% specificity,

82% PPV, and 91% NPV in the diagnosis of asthma. RFT/reversibility tests exhibited 81% sensitivity, 89% specificity, 76% PPV, and 92% NPV. NO measurement in exhaled air and RFT/reversibility tests, regarded as the gold standard, yielded almost identical results in the diagnosis of asthma in patients presenting with chronic cough.

CONCLUSION

A number of different conditions are involved in the etiology of chronic cough. In asthma, the most common of these clinical conditions, FeNO levels increase in contrast to other diseases. FeNO measurement can represent a useful diagnostic tool at time of first presentation in 30%-50% of patients with chronic cough. FeNO measurement can be used as a fast and safe diagnostic method in patients presenting with chronic cough since it is noninvasive, does not require drug administration, and has a high positive predictive power. However, its use in routine practice should also be investigated in terms of cost-effectiveness.

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Conflicts of interest

There are no conflicts of interest.

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