ORIGINAL ARTICLE

Use of Exhaled Nitric Oxide in Predicting Response to Inhaled Corticosteroids for Chronic Cough

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OBJECTIVE: **To evaluate our experience with patients who presented with chronic cough and how exhaled nitric oxide predicted response to inhaled corticosteroid (ICS) therapy.**

PATIENTS AND METHODS: **This retrospective observational study of 114 patients evaluated for chronic cough with measured exhaled nitric oxide and methacholine challenge testing was conducted from December 1, 2004, through November 30, 2005. Clinical records were extracted. Patients with no documented follow-up were contacted by telephone and administered a questionnaire.**

RESULTS: **In 64 patients, ICS therapy was started or the current ICS dose increased. Forty-one patients had elevated exhaled nitric oxide levels (defined as ≥35 ppb), 36 (88%) of whom had significant improvement in their chronic cough (likelihood ratio of a positive response, 4.9; 95% confidence interval, 2.2-10.9). Twenty-three patients with exhaled nitric oxide levels in the reference range were also prescribed ICS, and only 2 had cough improvement (likelihood ratio of a negative response, 0.07; 95% confidence interval, 0.02-0.25). Patients had documented follow-up that ranged from 4 weeks to 16 months. A cutoff of 38 ppb was found to best differentiate ICS responders and nonresponders.**

CONCLUSION: **Measurement of exhaled nitric oxide accurately predicted response to ICS therapy for chronic cough. Patients with a positive exhaled nitric oxide test result had a strong likelihood of response to ICS, whereas a negative exhaled nitric oxide test result indicated an unlikely response to ICS. This finding may potentially have an impact on how patients with chronic cough are evaluated and treated.**

***Mayo Clin Proc.* 2007;82(11):1350-1355**

ATS = American Thoracic Society; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; MCT = methacholine challenge testing; NPV = negative predictive value; PPV = positive predictive value

Chronic cough (lasting >8 weeks) is one of the most common reasons that adult patients present for evaluation to a primary care physician. Studies confirm that asthma, gastroesophageal reflux disease, and upper airway cough syndrome (formerly known as postnasal drip syndrome) alone or in combination are responsible for 92% to 100% of cases of chronic cough.[1,2] Asthma or cough variant asthma has been reported in 24% to 29% of patients with chronic cough.[3,4] Nonasthmatic eosinophilic bronchitis, characterized by eosinophilic airway inflammation in the absence of bronchial hyperreactivity, is also an increasingly recognized cause.[5] Both cough due to asthma and eosinophilic bronchitis are readily responsive to treatment with inhaled corticosteroids (ICS).

Diagnostic evaluation of chronic cough may entail multiple tests to rule out the most common causes of cough. Recently published guidelines recommend an empiric integrative diagnostic approach to the diagnosis of chronic cough.[6,7] When asthma is suspected, spirometry with bronchodilator is often used to look for evidence of variable airway obstruction. If the results of spirometry are inconclusive and clinical suspicion remains, methacholine challenge testing (MCT) is frequently used to diagnose or exclude asthma as a cause of cough. Although a negative MCT result virtually excludes asthma, a positive test result is nonspecific and can be due to a variety of causes, including postnasal drip and gastroesophageal reflux disease.[8] Furthermore, a negative MCT result does not preclude a response to ICSs as a treatment for cough (eg, eosinophilic bronchitis).[9]

Measurement of exhaled nitric oxide has been shown to provide an accurate assessment of lower airway eosinophilic inflammation and to correspond to sputum eosinophilia and airway hyperresponsiveness.[10,11] It is increasingly being used in the diagnosis of asthma and in monitoring response to treatment.[12,13] Exhaled nitric oxide levels have been shown to be high in patients with chronic cough due to asthma.[14] A recent study also demonstrated the accuracy of exhaled nitric oxide in predicting response to corticosteroids in patients with nonspecific respiratory symptoms.[15]

The aim of this study was to assess the utility of using exhaled nitric oxide in the evaluation and treatment of chronic cough. Specifically, we attempted to assess the usefulness of exhaled nitric oxide in predicting response to ICS for the treatment of chronic cough.

PATIENTS AND METHODS

After approval from the Mayo Clinic Institutional Review Board, a retrospective observational study was performed using a clinical database of 114 patients referred to our pulmonary medicine division for evaluation of chronic cough from December 1, 2004, through November 30,

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2005. Inclusion criteria included age older than 18 years, uncontrolled chronic cough (defined as lasting >8 weeks), normal or nonlocalizing chest radiograph findings, documented MCT results, and measurement of exhaled nitric oxide levels within 1 day of each other. Only patients who had started ICS therapy or who had their current ICS doses altered were included in the study. Patients taking angiotensin-converting enzyme inhibitors and current smokers were excluded.

For patients who met inclusion criteria, clinical records were reviewed, and clinical data were abstracted with particular attention to patient demographics, spirometry results, MCT results, exhaled nitric oxide levels, current and previous corticosteroid dosages, treatment plans, final diagnoses, and follow-up data. At follow-up, patients were considered to have had a response to ICS therapy if they met all the following criteria: (1) physician-documented significant improvement in cough, (2) no further diagnostic studies ordered for assessment of cough, and (3) no alteration in ICS dose. Patients without documented follow-up were contacted by telephone and administered an institutional review board–approved telephone questionnaire to assess subjective response in cough to ICS.

Exhaled Nitric Oxide Measurement

Exhaled nitric oxide measurements were performed using a rapid-response chemiluminescent nitric oxide analyzer integrated with a data acquisition computer (Sievers 280i; Sievers, Boulder, CO) with daily 2-point calibration. The test was conducted according to the American Thoracic Society (ATS) guidelines.[16] The seated patient inhaled to total lung capacity through a charcoal filter to remove ambient nitric oxide, then exhaled against resistance to maintain a target exhalation pressure of 16 cm H_2O, which was displayed on the computer. The resultant expiratory flow was 0.05 L/s. The patient continued to exhale until the nitric oxide signal was stable for 3 seconds. The steady-state nitric oxide plateau was taken as the exhaled nitric oxide value. Repeated exhalations were performed to achieve 3 exhaled nitric oxide values that agreed within 10%. At this flow rate, an exhaled nitric oxide level of 35 ppb was considered the upper limit of normal.[17]

Methacholine Challenge Testing

We performed MCT according to our standard laboratory protocol. A single breath inhalation of either 5 or 25 mg/mL of methacholine was administered via a Hudson Micro Mist 1880 nebulizer (Hudson RCI, Durham, NC) and KoKo Dosimeter (Ferraris Respiratory, Louisville, CO). To achieve the ATS-recommended dose per actuation, the dosimeter was set to 0.8 second. The resulting dose delivered was 9 μL (0.009 g). All actuations were reproducible within 10%.

Three minutes later a forced vital capacity maneuver was performed. If the forced expiratory volume in 1 second (FEV_1) did not decline by 20% or more, 4 additional breaths of 25 mg/mL of methacholine were administered. Three minutes later forced vital capacity maneuvers were repeated. A positive MCT result was defined as a 20% decrease in FEV_1 induced by methacholine.

Statistical Analyses

JMP version 6.0.0 was used for statistical analyses (SAS Institute Inc, Cary, NC). Comparisons between the ICS-responsive and -unresponsive groups were made with the *t* test for normally distributed data and the Wilcoxon rank sum test for nonparametric data, with $P<.05$ considered statistically significant. Two-by-two tables of exhaled nitric oxide (low/high) vs ICS responsiveness (yes/no) were prepared using 35 ppb of exhaled nitric oxide as the cut point. Two-by-two tables of MCT (positive/negative) vs ICS responsiveness (yes/no) were also prepared. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios were calculated for each table. A receiver operating characteristic curve was plotted to determine the optimal exhaled nitric oxide level that differentiated ICS responsiveness. Results are expressed as mean ± SD unless otherwise noted.

RESULTS

Of the 114 patients who underwent MCT and measurement of exhaled nitric oxide as part of a chronic cough evaluation, 64 met entry criteria in that either they were prescribed ICS or their current ICS dosage was altered for treatment of chronic cough. Patients in the ICS-responsive and -unresponsive groups did not differ in age, sex, body mass index, cough duration, FEV_1, or follow-up duration (Table 1). No differences were found in final ICS dose or use of bronchodilators between the ICS-responsive and -unresponsive groups. Three patients in the ICS-unresponsive group and 6 patients in the ICS-responsive group were already taking ICS for treatment of cough before evaluation and had their ICS dose increased after MCT and exhaled nitric oxide measurement. Final diagnoses are listed in Table 1. Asthma, diagnosed on the basis of symptoms and positive MCT results, appeared to be more prevalent in the ICS-responsive group. Gastroesophageal reflux disease, postnasal drip syndrome, and multiple final diagnoses were more common in the ICS-unresponsive group. Forty-two of the 64 patients had documented follow-up that ranged from 4 weeks to 16 months. Twenty-two patients were contacted by telephone with an institutional review board–approved telephone script.

TABLE 1. **Demographic and Clinical Data of the Study Patients***

Variable	ICS Unresponsive (n=26)	ICS Responsive (n=38)	*P* value
Age, y	48±17	46±13	.43
Female, No. (%)	15 (58)	23 (61)	.82
BMI	28.7±6.7	29.1±10.1	.42
Smoking history, No. (%)	4 (15)	6 (16)	.96
Cough duration, mo	43 (22-63)	40 (18-58)	.36
FEV_1, % predicted	98±10	94±8	.43
Current ICS use, No. (%)	3 (12)	6 (16)	.63
Final ICS dose, μg/d†	419±120	445±85	.495
Albuterol or LABA, No. (%)	12 (46)	21 (55)	.32
Follow-up, mo	6 (1-10)	5 (1-9)	.32
Final diagnoses, No. (%)			
Asthma	5 (19)	26 (68)	<.001
GERD	12 (46)	3 (8)	<.001
PNDS	15 (58)	2 (5)	<.001
EB	0 (0)	8 (21)	.01
Other	5 (18)	3 (5)	.18
>1 Diagnosis	10 (36)	4 (11)	.008

*Values are presented as mean ± SD or median (interquartile range) unless indicated otherwise. BMI = body mass index; EB = eosinophilic bronchitis; FEV_1 = forced expiratory volume in 1 second; GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroids; LABA = long-acting β-agonist; PNDS = postnasal drip syndrome.
†Fluticasone equivalent units.

Exhaled Nitric Oxide and ICS Response

The mean exhaled nitric oxide level of responders to ICS was 51.25±20.1 ppb (Figure 1). The mean exhaled nitric oxide level of nonresponders to ICS was 26.0±16.5 ppb. Nine patients were currently taking ICS and had their ICS dose increased for treatment of cough. In this subset of patients, the mean exhaled nitric oxide level of responders to ICS was 44.8±3.1 ppb vs 35±4.3 ppb for nonresponders (Figure 2).

Of the 64 patients who were prescribed ICS or had their ICS dose increased for chronic cough, 41 were found to have elevated exhaled nitric oxide levels (>35 ppb). On follow-up, 36 (88%) of the 41 in the group with high exhaled nitric oxide levels had documented significant improvement in their chronic cough, whereas 5 (12%) were nonresponders. Twenty-three patients with exhaled nitric oxide levels in the normal range (<35 ppb) were prescribed ICS, 2 (9%) of whom had documented significant improvement in chronic cough. The remaining 21 patients (91%) in the group with exhaled nitric oxide levels in the normal range reported no improvement in cough.

Of the 64 patients who started ICS therapy or had their ICS dose increased, 39 had a positive MCT result. Among these, 25 (64%) responded to ICS, whereas 14 (36%) did not. Twenty-five patients with a negative MCT result were prescribed ICS; 13 (52%) responded to ICS, but 12 (48%) had no response.

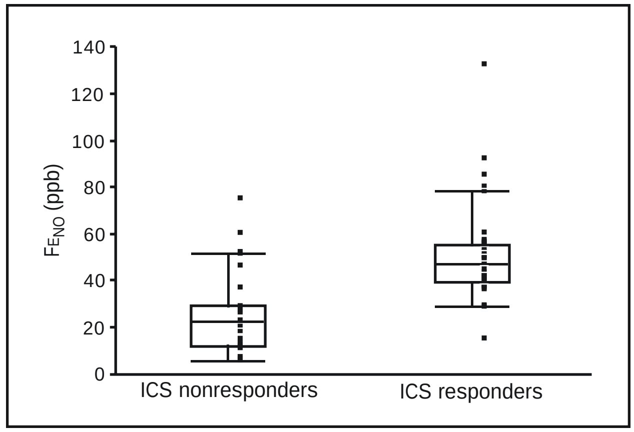

FIGURE 1. Mean fractional expired nitric oxide (FE_{NO}) levels in inhaled corticosteroid (ICS) responders and nonresponders (51.25±20.1 ppb vs 26.0±16.5 ppb; *P*<.001). Error bars indicate SD.

The PPV of response to ICS in patients with elevated exhaled nitric oxide levels was 0.88 (95% confidence interval [CI], 0.75-0.95), yielding a likelihood ratio of a positive response of 4.9 (95% CI, 2.2-10.9) (Table 2). An exhaled nitric oxide level in the normal range was associated with an NPV of 0.91 (95% CI, 0.75-0.98), yielding a likelihood ratio of a negative response of 0.07 (95% CI, 0.02-0.25). In contrast, MCT had a PPV of 0.64 (95% CI, 0.48-0.77) and an NPV of 0.48 (95% CI, 0.3-0.67) for response to ICS. A receiver operating characteristic curve was plotted and demonstrated that an exhaled nitric oxide level of 38 ppb resulted in the best combination of sensitivity and specificity in differentiating response and nonresponse to ICS (Figure 3). The area under the receiver operating characteristic

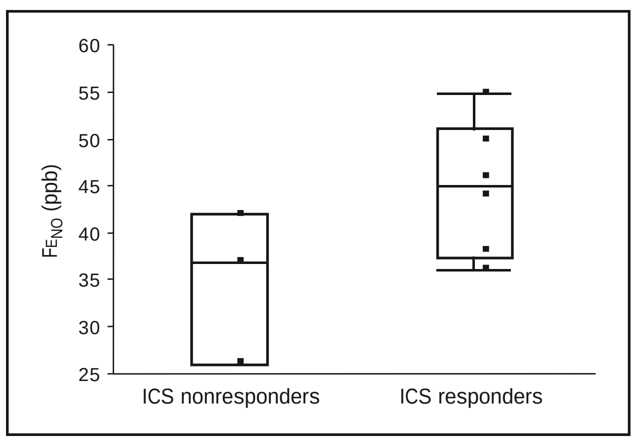

FIGURE 2. Mean fractional expired nitric oxide (FE_{NO}) levels in inhaled corticosteroid (ICS) responders and nonresponders who had their current ICS dose increased for the treatment of chronic cough (44.8±3.1 ppb vs 35±4.3 ppb). Error bars indicate SD.

TABLE 2. **Sensitivity, Specificity, PPV, NPV, and LRs***

Variable	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR Positive	LR Negative
Fe_{NO} >35 ppb	95 (83-99)	80 (62-92)	88	91	4.9 (2.2-10.9)	0.07 (0.02-0.25)
Fe_{NO} >38 ppb	90 (76-96)	85 (76-96)	90	85	5.8 (2.3-14.4)	0.12 (0.05-0.25)
MCT	66 (50-79)	46 (29-65)	64	48	1.2 (0.8-1.9)	0.74 (0.4-1.4)

*Numbers in parentheses are 95% confidence intervals. Fe_{NO} = fractional expired nitric oxide; LR = likelihood ratio; MCT = methacholine challenge test; NPV = negative predictive value; PPV = positive predictive value.

curve was 0.87. Using a cutoff of 35 instead of 38 yielded a PPV of 90% and an NPV of 85%.

DISCUSSION

We have demonstrated that exhaled nitric oxide levels correlate with ICS response and appear to accurately predict response to ICS in patients with chronic cough. Patients with an elevated exhaled nitric oxide level had a moderately high likelihood of response to ICS, whereas an exhaled nitric oxide level in the normal range made response to ICS unlikely. The accuracy of exhaled nitric oxide measurement in predicting response to ICS for chronic cough appears to be better than that of MCT.

Chronic cough is one of the most common presenting symptoms reported to both primary care physicians and respiratory care specialists. Diagnostic evaluation often involves multiple tests to diagnose or rule out the most common causes of chronic cough. Asthma and nonasthmatic eosinophilic bronchitis are 2 common etiologies of chronic cough, and both are readily responsive to ICS.[9,18]

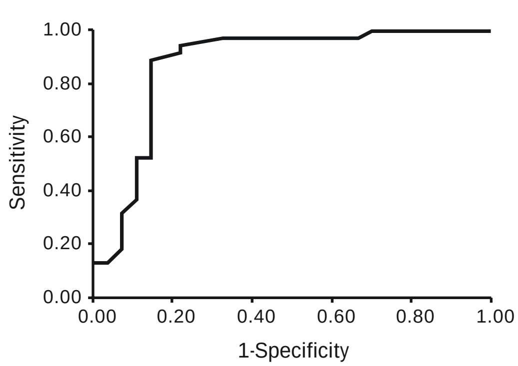

FIGURE 3. Receiver operating characteristic curve of fractional expired nitric oxide and inhaled corticosteroid response (area under the receiver operating characteristic curve = 0.87).

However, diagnosis is often difficult and may require specialized testing, such as MCT for asthma or examination of induced sputum for eosinophilic bronchitis. Even when diagnostic testing is available, results are often inconclusive, and empiric treatment has an important role in cough evaluation and treatment guidelines.[6,7,19] However, empiric treatment can be costly and have adverse effects in the absence of clinical improvement. Our study results suggest that exhaled nitric oxide may have a role in the evaluation of chronic cough.

Measurement of exhaled nitric oxide is a comparatively simple, noninvasive test that has been shown to be useful in the diagnosis of asthma and in monitoring asthma control.[12,20] Measurement of exhaled nitric oxide indirectly measures the degree of lower airway eosinophilic inflammation, which is present in asthma and eosinophilic bronchitis.[21,22] The magnitude of the exhaled nitric oxide level has been shown to correlate with sputum eosinophilia and airway hyperresponsiveness. Levels of exhaled nitric oxide are decreased in smokers and by treatment with ICS.[23-25] Exhaled nitric oxide levels have been shown to differentiate patients with asthma from those without asthma. Elevated exhaled nitric oxide levels have also been found in patients with eosinophilic bronchitis; however, use of exhaled nitric oxide measurement in the diagnosis of eosinophilic bronchitis remains controversial.

Chatkin et al[14] recently demonstrated a role for exhaled nitric oxide measurement in the evaluation of chronic cough. They showed that exhaled nitric oxide measurement has a high specificity and high NPV for excluding asthma as a cause of chronic cough. They further postulated that the use of exhaled nitric oxide measurement might avoid the need for more invasive testing, such as bronchial provocation testing with methacholine. The increasing availability and decreasing cost of exhaled nitric oxide testing make this a convenient point-of-service test as part of the office visit.

Compared with MCT or induced sputum, measurement of exhaled nitric oxide involves considerably less time and cost. For example, at our institution, MCT can take from 45 minutes to 2 hours in patients with a positive test result who may require several doses of albuterol metered-dose inhalers or nebulization to reverse bronchoconstriction. In contrast, measurement of exhaled nitric oxide can take as little as 5 to 20 minutes. In addition, although MCT can be associated with potential adverse effects, such as wheezing, dyspnea, and chest pain, exhaled nitric oxide measurement is a noninvasive test with little if any documented adverse effects.[26] Our study demonstrates the clinical usefulness of exhaled nitric oxide measurement in predicting corticosteroid responsiveness in patients with chronic cough. Use of exhaled nitric oxide measurement may streamline how patients with chronic cough are evaluated and treated.

Inhaled corticosteroids are an important treatment modality for patients with chronic cough. Chronic cough due to asthma or eosinophilic bronchitis is readily responsive to ICS, and responsiveness to ICS is considered the criterion standard for diagnosing asthma as the cause of cough.[27] Recently, Smith et al[15] showed that exhaled nitric oxide measurement accurately predicted corticosteroid response in 52 patients who presented with undiagnosed nonspecific respiratory symptoms. Corticosteroid response in that study was defined on the basis of improvements in FEV_1, morning peak flow, provocative concentration of adenosine monophosphate, and reductions in composite symptom score. They determined that a cutoff of 47 ppb optimally predicted improvements in these indices with ICS. In the current study, we showed that exhaled nitric oxide measurement may have a role in chronic cough evaluation because of its usefulness in differentiating patients with ICS-responsive and -unresponsive cough. However, exhaled nitric oxide levels can be elevated in patients with chronic cough of several potential origins (ie, asthma, eosinophilic bronchitis, bronchiectasis), and the use of exhaled nitric oxide measurement alone is unlikely to provide a conclusive diagnosis. Our results suggest that exhaled nitric oxide measurement can identify patients with an ICS-responsive chronic cough and may serve to avoid inappropriate and potentially harmful therapy with ICS in nonresponders.

At the ATS recommended flow rate of 0.05 L/s, 35 ppb is considered the upper limit of normal, and values greater than this are interpreted as being high.[26] In the current study, an exhaled nitric oxide level of 38 ppb appeared to best differentiate ICS-responsive patients from -unresponsive patients. However, the use of 35 ppb as a cutoff still resulted in high PPVs and NPVs for determining ICS responsiveness. Our findings suggest that exhaled nitric oxide measurement may be most useful in ruling out corticosteroid-responsive patients with chronic cough, thereby reducing cost and potential adverse effects with ineffective therapy. Because many patients who present to a specialist may have already been prescribed an ICS, measurement of exhaled nitric oxide may be valuable to assess the degree of control of airway inflammation. This information is not available with MCT. However, we found no significant difference in exhaled nitric oxide levels between ICS responders and nonresponders in patients already taking ICS for the treatment of cough. Our numbers, however, were small, and further studies are needed to determine whether a role exists for exhaled nitric oxide measurement in monitoring ICS treatment of chronic cough.

Several limitations are inherent to a retrospective study. Response to ICS was determined with clinical documentation that reflected patients' and physicians' subjective measurements regarding the improvement or lack of improvement in cough. A specific cough quality-of-life measurement instrument was not used; two-thirds of patients had documented follow-up data based on clinical notes, and the remainder of follow-up data was based on a telephone call questionnaire. Despite these limitations, a patient's subjective improvement in cough is potentially the most clinically meaningful index by which responsiveness to ICS may be measured. Furthermore, we used stringent criteria to define ICS responsiveness, requiring documentation that no further evaluation or treatment was considered for cough. A prospective study using a validated questionnaire is ongoing. Finally, we examined a select group of patients: those for whom the clinician elected to institute ICS therapy. Prospective testing in less select groups of patients with chronic cough is needed to identify the value of exhaled nitric oxide measurement in a broader population. For the present, the test seems most applicable to patients with chronic cough in whom the physician is considering use of ICS, rather than to patients in whom non–corticosteroid-responsive etiologies are considered more likely.

CONCLUSION

We found that exhaled nitric oxide accurately predicts response to ICS in patients with chronic cough. Patients with elevated exhaled nitric oxide had a high likelihood of response to ICS, whereas an exhaled nitric oxide level in the normal range made response to ICS unlikely. The results of our study suggest that exhaled nitric oxide may have a role in the evaluation and treatment of patients with chronic cough and may preclude the need for more invasive testing.

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