Measurement of Nasal Nitric Oxide Is Useful for the Diagnosis of Sinusitis-Induced Prolonged Cough

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Upper airway cough syndrome (UACS), the most common cause of prolonged cough, is diagnosed based on clinical findings without specific diagnostic test. The concentration of nitric oxide in nasal cavity air (nNO) is influenced by allergic rhinitis and/or sinusitis, both of which are common causes of UACS. We measured nNO levels in patients with UACS and those with other causes. We also examined the usefulness of measuring nNO for differentiating patients with sinusitis from those without sinusitis. The study included 93 adult patients with prolonged cough lasting more than three weeks. Etiologies of cough were identified and nNO was measured at the initial investigation. UACS was diagnosed in 58 patients (62.4%), and sinusitis was identified in 11 (19.0%) of the 58 patients with UACS. Levels of nNO in UACS did not differ from non-UACS etiologies (316.2 ± 129.2 vs. 334.9 ± 88.2 ppb; p = 0.452), suggesting that the measurement of nNO could not discriminate UACS from other etiologies of prolonged cough. However, patients with sinusitis showed significantly decreased nNO levels (190.1 ± 114.8 ppb) compared with patients with UACS without sinusitis (345.7 ± 114.6 ppb; p < 0.001) and non-UACS patients (334.9 ± 88.2 ppb; p < 0.001). In a receiver operating characteristic curve analysis for the diagnosis of sinusitis in prolonged cough, the best sensitivity (73.2%) and specificity (81.8%) were obtained with a nNO cutoff value of 279.0 ppb. These findings imply that the measurement of nNO could be useful for diagnosis of prolonged cough associated with sinusitis.

Keywords: prolonged cough; nasal nitric oxide; upper airway cough syndrome; sinusitis


Cough is one of the most common and troublesome respiratory symptoms presenting to general physicians and respirology and allergy specialists (Irwin and Madison 2000). Prolonged cough, lasting more than three weeks, should be evaluated for its cause and should be treated based on etiology (Irwin et al. 2006). Current guidelines on prolonged cough recommend that an evaluation be conducted for the most common causes in sequence using available diagnostic tests (Morice et al. 2006; Pratter et al. 2006c; Morice et al. 2007). Studies on the causes of chronic cough, which last more than 8 weeks, have found that upper airway cough syndrome (UACS), previously referred to as postnasal drip syndrome, is most common, followed by cough-variant asthma (CVA) and gastroesophageal reflux disease (GERD), although frequencies of diseases can vary depending on study populations and diagnostic criteria (Pratter 2006b; Chung and Pavord 2008). In addition, UACS was the second leading cause of subacute cough, lasting from 3 to 8 weeks (Kwon et al. 2006). However, there are neither pathognomonic findings nor specific diagnostic tests for UACS, and the diagnosis of UACS is usually made based on symptoms, physical examination, radiographic findings, and response to the specific treatment of UACS (Pratter 2006a). If there was a specific test for UACS, similar to the methacholine bronchial provocation test (MBPT) for CVA (Irwin et al. 1997), we would enhance the ability to correctly diagnose UACS and reduce unnecessary diagnostic tests and medications.

Fractional exhaled nitric oxide (FeNO) reflects eosinophilic airway inflammation. The measurement of FeNO has been reported to be useful in the management of asthma (Taylor et al. 2006). Patients with asthma have shown higher levels of FeNO (Alving et al. 1993) and can be diagnosed more readily and accurately with FeNO measure-
ments (Smith et al. 2004). In the diagnosis of prolonged cough, FeNO has been shown to be useful in the diagnosis of CVA (Chatkin et al. 1999; Fujimura et al. 2008; Sato et al. 2008) and non-asthmatic eosinophilic bronchitis (Oh et al. 2008), as well as in the prediction of responses to inhaled corticosteroids (Hahn et al. 2007). While measurement of nitric oxide (NO) has been attempted in the evaluation of lower airway causes of prolonged cough, it has not been assessed for its usefulness in the diagnosis of UACS. NO is also synthesized in the upper airway and is present in the upper airway in higher concentrations than in the lower respiratory tract (Silkoff et al. 2000). The concentration of NO in nasal cavity air (nNO) has been reported to be increased in patients with allergic rhinitis (Arnal et al. 1997; Kharitonov et al. 1997), a common cause of UACS, although there is conflicting data (Palm et al. 2003). Additionally, nNO can be affected by other upper airway diseases, such as sinusitis (Degano et al. 2005), primary ciliary dyskinesia (Wodehouse et al. 2003), and cystic fibrosis (Balfour-Lynn et al. 1996). These findings suggest that measurement of nNO, in addition to FeNO, may be useful in the evaluation of prolonged cough.

In this study, we examined the clinical usefulness of nNO measurement in the diagnosis of prolonged cough. We aimed to evaluate whether levels of nasal nitric oxide (nNO) are elevated in patients with UACS, compared with other causes of prolonged cough. Additionally, because sinusitis is a major cause of UACS and significantly affects nNO levels, we examined whether nNO could differentiate the patients with sinusitis and without sinusitis in patients with prolonged cough.

**Methods**

**Design and subjects**

We consecutively enrolled adult patients with prolonged cough, lasting more than three weeks, who visited or were referred to our allergy specialist clinic at a university hospital between January 2008 and December 2009. Exclusion criteria were (1) current medication for prolonged cough, (2) current smoker, (3) wheezing in history or on chest examination, (4) abnormal findings on chest radiographs, and (5) previous history of nasal or sinus surgery. After obtaining informed consent, patients were evaluated for causes of prolonged cough and submitted for measurement of nNO and FeNO at the first visit. This study was approved by the institutional review board.

**Determination of causes of prolonged cough**

To determine the causes of prolonged cough, patients were asked about their upper and lower respiratory symptoms and gastroesophageal symptoms, any medication for combined diseases, any recent respiratory infection, and smoking status using a questionnaire. After history taking and physical examination, they underwent the following sequence of tests: chest radiographs, paranasal sinus (PNS) series radiographs, spirometry, and MBPT.

In principle, if a specific etiology was suspected based on clinical findings and diagnostic tests, a specific medication was administered. Only when there was significant response to the treatment, did we regard the specific etiology to be confirmed. If there were neither related symptoms nor a positive diagnostic test, the following etiologies were considered, in sequence, based on their previously reported prevalence in prolonged cough: UACS, CVA, and GERD (Pratter et al. 2006c). First, UACS was suspected as an etiology if patients had any upper airway symptoms, such as rhinorrhea, sneezing, nasal itching, nasal stuffiness, or postnasal drip, or if patients experienced drainage in the posterior pharynx and/or a cobblestone appearance of the pharyngeal mucosa. Diagnosis of UACS was made, if patients suspected of having UACS responded to empirical treatment with oral first-generation H1 antihistamines and decongestants for 2 weeks (Pratter 2006a). Additionally, if patients did not have any specific symptoms except cough or any specific physical or diagnostic test findings, silent UACS was considered (Pratter et al. 2006c). Among patients with UACS, sinusitis was evaluated using PNS radiographs. Sinusitis was diagnosed if there was an air-fluid level or opacification in the sinuses (Pratter et al. 1999). For those who showed positive MBPT, CVA was considered and managed with inhaled corticosteroids and long-acting β2-agonists for 2 weeks. CVA was confirmed as the cause of prolonged cough if patients responded to this treatment (Dicpinigaitis 2006). When patients showed gastroesophageal symptoms or cough refractory to empirical treatment for UACS and CVA, we offered empirical treatment for GERD with a proton pump inhibitor and diagnosed GERD in cases of significant response. Next, if cough developed with symptoms of the common cold and persisted for 3-8 weeks, and there was no evidence of other etiologies, a diagnosis of postinfectious cough was considered. If they showed resolution of cough with or without prescribed symptomatic treatment, postinfectious cough was diagnosed.

**Measurement of nNO and FeNO**

Levels of nNO and FeNO were measured prior to spirometry using a Sievers NOA280i NO analyzer (GE Analytical Instruments, Boulder, CO, USA) according to ATS/ERS recommendations (American Thoracic Society 2005). For the measurement of nNO, the subjects were requested to exhale against respiratory resistance for 10 s to close the velopharyngeal aperture and minimize the leakage of nasal NO. An olive was placed in one nostril and connected to a vacuum pump. Air in the nasal cavity was aspirated via the olive at a flow rate of 700 mL/min (Struben et al. 2006b). A sampling tube connected to a side hole delivered aspirated air to a NO analyzer. The mean concentration of nNO was obtained at the plateau. Measurement of nNO was repeated up to six times to obtain three acceptable nNO values that were within 10% of each other. The mean of the three acceptable values was determined to be the level of nNO.

FeNO was measured as described previously (Kim et al. 2010). Briefly, FeNO levels were assessed online during a single slow breath of at least 10 cmH₂O against resistance to a closed velum. The expiratory flow rate was set at 50 mL/s. The measurement of FeNO was repeated up to eight times until three acceptable FeNO values within 10% of each other were obtained. The mean values of FeNO were then recorded.

**Statistical analyses**

Comparisons of nNO levels between cough etiology groups were made using the Kruskal-Wallis test. If the Kruskal-Wallis test was significant, post hoc multiple comparison test were performed. Additionally, the effects of cough etiologies on nNO levels were examined using multivariate linear regression analysis (forward stepwise), adjusting for age, gender, height, weight, FeNO, and ambient
NO concentration. These variables were selected a priori, because these factors have been suggested to affect nNO levels. A receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of nNO in discriminating sinusitis-induced cough from other causes of prolonged cough. From the ROC curve, the ROC area under the curve and the optimal cutoff value with the highest sensitivity and specificity were determined. Statistical analyses were performed using SPSS (ver. 17.0; SPSS, Chicago, IL, USA), and p values < 0.05 were deemed to indicate statistical significance.

Results

Etiologies of prolonged cough

Of 119 subjects who visited our clinic for prolonged cough during the study period, 93 (aged 18-71 years) were eligible for the study and were evaluated for the etiology of their prolonged cough. The most common cause of prolonged cough was UACS, which was diagnosed in 58 patients (62.4%), followed by CVA (19.4%, n = 18), postinfectious cough (16.1%, n = 15), and GERD (7.5%, n = 7). Other causes (7.5%, n = 7) included angiotensin-converting enzyme inhibitor-induced cough (n = 3), chronic bronchitis (n = 2), and unexplained (n = 2). In 93 enrolled subjects, a single etiology for prolonged cough was found in 81 (87.1%), while the other 12 patients (12.9%) had two etiologies: 9 patients with both UACS (2 sinusitis, 7 non-sinusitis) and CVA and 3 patients with both UACS (1 sinusitis, 2 non-sinusitis) and GERD (n = 3). The characteristics of the cough etiology groups are shown in Table 1.

nNO in cough etiology groups

Levels of nNO for the whole group were normally distributed, from 71 to 651 ppb, with a mean value of 323.3 ± 115.3 ppb. The mean values ± s.d. of nNO and FeNO in the etiology groups are presented in Table 2. FeNO levels in patients with CVA were significantly higher than those with other etiologies (60.6 ± 66.8 vs. 28.2 ± 20.1 ppb; p = 0.013). FeNO levels did not correlate with nNO levels.

Levels of nNO in patients with UACS did not differ from those with non-UACS (316.2 ± 129.2 vs. 334.9 ± 88.2 ppb; p = 0.452). Sinusitis was identified in 11 (19.0%) of 58 patients with UACS and showed significantly lower levels of nNO (190.1 ± 114.8 ppb) than those in patient with UACS without sinusitis (345.7 ± 114.6 ppb; p < 0.001) and non-UACS patients (334.9 ± 88.2 ppb; p < 0.001; Fig. 1). Thus, nNO in patients with sinusitis was significantly lower than in patients with non-sinusitis causes (190.1 ± 114.8 vs. 341.1 ± 97.4 ppb; p < 0.001). This effect of UACS on nNO persisted after adjustment for age, gender, height, weight, FeNO, and ambient NO concentration. Next, we examined whether nNO could discriminate sinusitis from non-sinusitis causes of prolonged cough using an ROC curve analysis. Fig. 2 shows the ROC curve for nNO levels, and the area under the curve was 0.855. The best sensitivity

<table>
<thead>
<tr>
<th>Variables</th>
<th>UACS (n = 58)</th>
<th>CVA (n = 18)</th>
<th>Postinfectious (n = 15)</th>
<th>GERD (n = 7)</th>
<th>Others (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43.1 ± 13.5</td>
<td>46.5 ± 16.8</td>
<td>42.1 ± 10.1</td>
<td>52.6 ± 10.7</td>
<td>45.1 ± 10.3</td>
</tr>
<tr>
<td>Female gender, % (n)</td>
<td>72.4 (42)</td>
<td>72.2 (13)</td>
<td>53.3 (8)</td>
<td>71.4 (5)</td>
<td>28.6 (2)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>161.6 ± 8.0</td>
<td>158.2 ± 9.1</td>
<td>161.9 ± 7.0</td>
<td>159.7 ± 8.0</td>
<td>163.7 ± 6.8</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60.6 ± 9.5</td>
<td>58.1 ± 8.4</td>
<td>60.9 ± 7.6</td>
<td>62.1 ± 8.4</td>
<td>65.0 ± 12.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.2 ± 3.5</td>
<td>23.2 ± 2.5</td>
<td>23.2 ± 2.3</td>
<td>24.5 ± 4.3</td>
<td>24.1 ± 3.2</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>99.3 ± 14.7</td>
<td>98.4 ± 18.5</td>
<td>98.0 ± 14.8</td>
<td>102.7 ± 13.2</td>
<td>107.3 ± 11.1</td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
<td>103.6 ± 13.9</td>
<td>97.0 ± 20.1</td>
<td>102.2 ± 18.2</td>
<td>111.4 ± 12.6</td>
<td>111.7 ± 11.9</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>80.3 ± 9.1</td>
<td>75.1 ± 9.4</td>
<td>80.7 ± 9.0</td>
<td>82.8 ± 4.4</td>
<td>79.4 ± 6.1</td>
</tr>
<tr>
<td>Cough duration, weeks</td>
<td>25.8 ± 75.6</td>
<td>30.3 ± 62.4</td>
<td>4.8 ± 1.6</td>
<td>17.6 ± 13.3</td>
<td>16.1 ± 15.6</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± s.d., except for gender.
UACS, upper airway cough syndrome; CVA, cough variant asthma; GERD, gastroesophageal reflux disease; BMI, body mass index; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s.

“Others” includes angiotensin-converting enzyme inhibitor-induced cough (n = 3), chronic bronchitis (n = 2), and unexplained (n = 2).

Twelve patients had two cough etiologies: UACS + CVA (n = 9) and UACS + GERD (n = 3).

<table>
<thead>
<tr>
<th>Variables</th>
<th>UACS (n = 58)</th>
<th>CVA (n = 18)</th>
<th>Postinfectious (n = 15)</th>
<th>GERD (n = 7)</th>
<th>Others (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nNO, ppb</td>
<td>316.2 ± 129.2</td>
<td>293.4 ± 109.8</td>
<td>319.5 ± 90.2</td>
<td>361.6 ± 106.3</td>
<td>334.0 ± 100.2</td>
</tr>
<tr>
<td>FeNO, ppb</td>
<td>31.0 ± 31.6</td>
<td>60.6 ± 66.8</td>
<td>24.4 ± 13.0</td>
<td>32.9 ± 14.7</td>
<td>34.2 ± 22.7</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± s.d.
UACS, upper airway cough syndrome; CVA, cough variant asthma; GERD, gastroesophageal reflux disease.
and specificity (81.8%) was obtained with a cutoff value of 279.0 ppb.

**Discussion**

Current guidelines on cough recommend that the etiologies of prolonged cough should be identified using diagnostic tests and empirical treatment. However, there are few tests available with high diagnostic values, especially for the diagnosis of UACS, the most common cause of prolonged cough (Pratter 2006a). In this study, we evaluated, for the first time, the role of nNO measurement in the assessment of prolonged cough etiologies. Levels of nNO were not elevated in patients with UACS compared with other causes. However, sinusitis, among various diseases in UACS, showed significantly lower levels of nNO compared with non-sinusitis UACS and non-UACS. These findings suggest that measurement of nNO may be useful in the diagnosis of sinusitis-induced prolonged cough.

The major finding of this study is that there was no significant difference in nNO levels between prolonged cough with and without UACS. These findings may be explained by the heterogeneity of UACS. Basically, UACS is not a single disease entity, but rather refers to a combination of various upper airway diseases causing cough (Pratter 2006a). Thus, it consists of a variety of diseases involving the nasal cavities and PNS, such as allergic rhinitis, nonallergic rhinitis, nonallergic rhinitis with eosinophilia, and bacterial sinusitis. The utility of nNO in the diagnosis and management of allergic rhinitis has been extensively studied (Struben et al. 2006a). Concentrations of nNO seem to be elevated in allergic rhinitis, compared with controls, by way of increased expression of inducible NO synthase (Arnal et al. 1997; Kharitonov et al. 1997; Yuksel et al. 2008), although some studies have not found a significant difference (Henriksen et al. 1999; Maniscalco et al. 2001). Levels of nNO have been correlated with IL-5 values and the duration of the disease in patients with allergic rhinitis (Profita et al. 2006). Additionally, nNO was increased during the pollen season and after allergen challenge and decreased after treatment with intranasal corticosteroids (Kharitonov et al. 1997). However, other studies reported no significant increase in nNO in patients with allergic rhinitis (Henriksen et al. 1999), even after allergen challenge (Maniscalco et al. 2001). These seemingly conflicting data on nNO levels in allergic rhinitis may be due to difference in the subjects studied and definitions of cases. A great portion of nNO originates from PNS (Lundberg and Weitzberg 1999), and the presence of sinusitis could affect the concentrations of nNO (Maniscalco et al. 2007). However, most studies on nNO in allergic rhinitis have not reported the presence of sinusitis in allergic rhinitis subjects.

We found that, among UACS patients, concentrations of nNO in patients with sinusitis were significantly lower than in those without sinusitis. Furthermore, levels of nNO in sinusitis were much lower than those in non-UACS; thus, measurement of nNO discriminated sinusitis from non-sinusitis causes in patients with prolonged cough. These findings are consistent with previous reports on nNO levels in sinusitis. In acute or chronic sinusitis, levels of nNO have been reported to be reduced, compared with healthy controls (Baraldi et al. 1997; Lindberg et al. 1997; Deja et al. 2003); however, other studies have not confirmed this (Arnal et al. 1999; Lundberg et al. 2003; Wodehouse et al. 2003). Treatment of sinusitis with antibiotics restored...
decreased nNO levels in children (Baraldi et al. 1997) and adults (Degano et al. 2005). The mechanisms for reduced nNO in sinusitis are not yet understood. A possible explanation is impaired passage of sinus NO into the nasal cavity via narrowed sinus ostia, induced by mucosal congestion and increased mucus secretion. An important role of ostial patency in nNO concentration was suggested in a study by Bommarito et al. (2008), who reported that levels of nNO in chronic rhinosinusitis with polyps were significantly lower than those in chronic rhinosinusitis without polyps.

In nasal polyposis, the nNO concentration was inversely correlated with the number of occluded sinuses (Arnal et al. 1999). Thus, measurement of nNO may be useful in the investigation of prolonged cough etiologies and could be a useful method for identifying sinusitis-induced cough. Based on these findings, we could expect that low nNO levels could predict response to antibiotics in patients with prolonged cough, as we can predict inhaled corticosteroids response in chronic cough patients with high FeNO (Hahn et al. 2007). Further prospective studies are needed to test this hypothesis.

In our study, we found significantly higher levels of FeNO in CVA compared with those in other etiologies. Our findings confirm the previous observation that FeNO could be used in the diagnosis of CVA (Chatkin et al. 1999; Fujimura et al. 2008; Sato et al. 2008). However, there was no relationship between FeNO and nNO levels; also, FeNO levels in UACS, regardless of the presence of sinusitis, did not differ from those in the other etiologies. These findings indicate that measurement of nNO and FeNO in prolonged cough should be used in the diagnosis of sinusitis and CVA, respectively. Because both nNO and FeNO can be measured with the same NO analyzer, sequentially in a short period of time, we believe that both parameters could be used as helpful biomarkers in the assessment of prolonged cough etiologies in clinical practice.

There are some limitations of this study. First, the small size of the study population may have made it impossible to detect significant differences. Because we tried to preliminarily evaluate the diagnostic role of nNO in the evaluation of prolonged cough, thus the study was performed in a single center and the number of enrolled subjects was relatively small. Although a multicenter study could enroll more patients than this study in a short period of time, heterogeneity in diagnosing cough etiologies may develop between centers. Second, the selected cutoff value of nNO in our study might not be applicable to other populations. Unlike FeNO, the reference values of nNO have not been well-established because they can vary depending on the measurement protocols, including transnasal flow (Silkoff et al. 1999), nasal air sampling methods, and breath hold methods. Surprisingly, even standard transnasal flow has not been recommended (American Thoracic Society 2005). In addition to the measurement factors, demographic and physiologic factors of the subjects and ambient air could possibly affect nNO levels. While the reference values of FeNO were suggested based on the physiologic or pathologic condition of the subjects, such as age, height, and atopy (Olin et al. 2007), the reference equations for nNO in healthy subjects have not been developed yet. Thus, it is suggested that reference values and the nNO cutoff value should be determined for each measurement protocol. For the wider application of nNO in clinical practice, these limitations for nNO measurement will need to be overcome, including standardization of measurements and the establishment of reference values and factors affecting nNO (Scadding and Scadding 2009). Third, we defined the sinusitis case based on the plain radiographs of PNS without use of CT scan. There are no universally accepted diagnostic criteria of sinusitis and the diagnosis of sinusitis can vary depending on the applied methods. Usually, sinusitis is diagnosed clinically and radiologically with use of PNS radiography or osteomeatal unit (OMU) CT. In terms of radiologic diagnosis of sinusitis, the sensitivity of OMU CT is superior to simple PNS radiographs. However, due to limited clinical availability in the management of chronic cough, the use of OMU CT is frequently inapplicable. Furthermore, the usefulness of simple PNS radiographs in the evaluation of chronic cough was well appreciated in the previous study by Pratter et al. (1999). Lastly, because we did not perform induced sputum analysis in the investigation of cough etiologies, nonasthmatic eosinophilic bronchitis (NAEB) could not be identified. Thus, nNO levels in NAEB were not determined in this study. Because we compared nNO levels between UACS with and without sinusitis and the other cough etiologies, non-recognition of NAEB did not seem to affect our results.

In summary, we have tested if measurement of nNO is useful in the evaluation of prolonged cough for the first time. While nNO levels in UACS in general did not differ from the other causes of prolonged cough, concentrations of nNO were reduced in patients with sinusitis. Measurement of nNO was useful in discriminating sinusitis-induced prolonged cough from non-sinusitis causes. A large prospective study is necessary to validate the role of nNO measurements in the investigation of prolonged cough etiologies.

Conflicts of Interest

The authors report no conflicts of interest.

Acknowledgments

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