CHEST Original Research

COUGH

Exhaled Nitric Oxide Measurement Is Useful for the Exclusion of Nonasthmatic Eosinophilic Bronchitis in Patients With Chronic Cough*

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Background: **Nonasthmatic eosinophilic bronchitis (NAEB) is an important cause of chronic cough, and it can be diagnosed by an induced-sputum (IS) examination. However, an IS examination is a complex and time-consuming procedure, and it has limited clinical application. This study aimed to evaluate the role of exhaled nitric oxide (NO) for the investigation of chronic cough, especially of NAEB.**

Methods: **Two hundred eleven nonsmoking patients with a cough lasting > 3 weeks were enrolled in the study. The patients were examined and investigated with conventional diagnostic tools, including an IS examination. Exhaled NO was measured by a chemoluminescent analyzer.**

Results: **One hundred seventeen patients with adequate IS results were analyzed: asthma, n = 14; NAEB, n = 21; and "others," n = 82. Exhaled NO and IS eosinophils were significantly higher in the asthma group and NAEB group than in the others group. Exhaled NO and IS eosinophils were significantly correlated in the asthma and NAEB groups. In the nonasthmatic group, the sensitivity and specificity of exhaled NO for detecting NAEB, using 31.7 parts per billion as the exhaled NO cutoff point, were 86% and 76%, respectively. Positive and negative predictive values were 47% and 95%, respectively, and positive and negative likelihood ratios were 3.51 and 0.19, respectively.**

Conclusion: **We concluded that exhaled NO measurement may be useful as part of the initial evaluation for chronic cough, especially for the exclusion of NAEB. A low level of exhaled NO suggested little likelihood of NAEB for the nonasthmatic patients with chronic cough.**

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Key words: chronic cough; eosinophil; exhaled nitric oxide; sputum

Abbreviations: IQR = interquartile range; IS = induced sputum; MBPT = methacholine bronchial provocation test; NAEB = nonasthmatic eosinophilic bronchitis; NO = nitric oxide; ppb = parts per billion; ROC = receiver operating characteristic; UACS = upper airway cough syndrome

Upper airway cough syndrome (UACS), previously referred to as *postnasal drip syndrome*, *cough variant asthma*, *gastroesophageal reflux disease*, and *nonasthmatic eosinophilic bronchitis* (NAEB), are the most common causes of chronic cough.[1] In patients with a noninfectious chronic cough who do not smoke and are not receiving an angiotensin-converting enzyme inhibitor, the standard diagnostic approach includes chest radiography, spirometry with a bron-

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chodilator reversibility test, a methacholine bronchial provocation test (MBPT), and an induced-sputum (IS) examination.[2]

IS examination has been used to diagnose cough variant asthma or NAEB because it directly represents airway inflammation.[3–5] However, it is relatively labor intensive and requires laboratory support, and its differential power declines in cases with mild inflammation. Thus, finding an alternative simpler suitable test is essential. In contrast, standardized measurement of exhaled nitric oxide (NO) is a simple, completely noninvasive, reproducible, and useful means of monitoring airway inflammation in patients with asthma.[6,7] In fact, exhaled NO value correlates with airway hyperresponsiveness and sputum eosinophilia.[8,9] The measurement of exhaled NO has been suggested to differentiate asthma in chronic cough patients.[10]

Based on the above information, exhaled NO measurement is also expected to be valuable for diagnosing NAEB. Therefore, we aimed at evaluating the role of exhaled NO for diagnosing NAEB in patients with chronic cough.

Materials and Methods

Subjects

From January 2006 to June 2007, 211 patients with a cough lasting > 3 weeks were enrolled in the study. The following were exclusion criteria: (1) wheezing or crackles on physical examination; (2) current smoker or an ex-smoker who quit within 1 year, (3) decreased lung function (FEV_1 < 80% of the predicted value); (4) abnormal findings on plain chest radiographs; and (5) use of antiasthma medications within the past 2 months. The study was approved by the research ethics committee at Samsung Medical Center, and all subjects gave written informed consent.

Study Design

The enrolled subjects were evaluated prospectively. The subjects filled out a questionnaire on the characteristics of their cough, the aggravating factors, and other combined symptoms such as postnasal drip, nasal itching, sneezing, rhinorrhea, and gastroesophageal reflux-related symptoms. Laboratory tests, plain chest radiographs, paranasal sinus series, pulmonary function studies, allergy skin testing to 55 common allergens, MBPT, IS examination, and exhaled NO assay were also performed for all the enrolled patients. Subjects were considered atopic if they had at least one positive skin-prick response. The patients were classified in three categories (asthmatic, NAEB, and "others") on the basis of MBPT and IS examinations.

Methacholine Responsiveness

The MBPT was performed according to American Thoracic Society guidelines as described previously.[11] The provocative concentration of methacholine causing a 20% fall in FEV_1 was adopted as the marker for bronchial hyperresponsiveness. Bronchial hyperresponsiveness was defined as provocative concentration of methacholine causing a 20% fall in $FEV_1 \leq 8$ mg/mL.

IS Examination

IS examination was performed as described previously.[11] We regarded the prepared sample as being inadequate if squamous cells accounted for > 30% of the cells seen on microcopy. Eosinophilic inflammation was defined as an eosinophil percentage ≥ 3%.

Measurement of Exhaled NO

Exhaled NO was measured using a chemiluminescence analyzer (NOA 280; Sievers Instruments; Boulder, CO). This equipment was sensitive to NO from < 1 parts per billion (ppb) and gave a reproducibility of ± 5%. Exhaled NO values of nonsmoking, nonatopic healthy adults (n = 30; 15 men and 15 women; mean age, 44.1 ± 15.2 years) was 20.5 ± 6.3 ppb in our laboratory. The recommended standard procedures for the measurement of exhaled NO have been announced by the American Thoracic Society and European Respiratory Society.[12] Briefly, the patient inhales NO-free air (containing < 5 ppb) via a mouthpiece to total lung capacity over 2 to 3 s, and then the patient exhales immediately. A nose clip should not be used because this may allow nasal NO to accumulate, and it promotes leakage of NO. However, if subjects cannot avoid nasal inspiration or nasal exhalation, then a nose clip may be used.

Subjects exhale against an expiratory resistance with a positive mouth piece pressure (5 to 20 mm Hg) to close the velopharyngeal aperture during exhalation, which is one way to minimize nasal NO leakage. The expiration flow rate of 0.05 L/s is a reasonable compromise between measurement sensitivity and patient comfort. To achieve a constant expiratory flow, display a target mouthpiece pressure flow to the subject using a computer display while the subject exhales via a fixed expiratory resistance. The constant pressure is achieved by biofeedback of the pressure parameters to the subject, who maintains these parameters within specified limits.

Constant flow exhalations result in a single-breath NO profile that consists of a washout phase followed by an NO plateau. The washout phase is sometimes followed by an early NO peak before the plateau. Early peaks are ignored, and only NO plateaus are interpreted.

Each exhalation should be maintained over 6 s to obtain a plateau in the NO-vs-time profile of at least 3 s. Once a 3-s plateau is achieved, stop the exhalation. Repeated reproducible exhalations should be performed, resulting in three NO plateau values that agree within 10% of the mean value. Exhaled NO is then calculated as the mean of these three values.

Statistical Analysis

Tests for normality (Kolmogorov-Smirnov) were done for the distributions of exhaled NO values and the eosinophil percentage in IS. The Kruskal-Wallis test was applied to compare groups and multiple comparison analysis with least-significant difference using ranks was performed when the Kruskal-Wallis tests were significant. Correlation was determined by using Spearman rank correlation; $p < 0.05$ was considered significant. In the nonasthmatic chronic cough group, the discriminative usefulness of exhaled NO was evaluated by constructing a receiver operating characteristic (ROC) curve where sensitivity vs 1 − specificity was plotted for each possible cutoff point. From the ROC curve, we determined the ideal cutoff point that corresponds to the closest point at the top left-hand corner and that most efficiently discriminates between the absence and presence of disease. A two-by-two table of NO (low/high) vs the NAEB diagnosis (yes/no) was prepared using the ideal cutoff point determined from the ROC curve, and the sensitivity, specificity, the positive