Original Article

Values of fractional exhaled nitric oxide for cough-variant asthma in children with chronic cough

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Background: Chronic cough is a common symptom in children. We wished to explore the value of fractional exhaled nitric oxide (FeNO) for cough-variant asthma (CVA) in children with chronic cough.

Methods: This prospective cohort study was conducted in the Children's Hospital of Soochow University from January 2012 to December 2014. Children aged 6–14 years with a cough of duration >4 weeks were enrolled. They underwent FeNO measurement, sputum cytology and pulmonary function tests.

Results: A total of 115 patients and 25 healthy controls were evaluated. For the diagnosis of CVA, the optimal FeNO cutoff value was 25 ppb with a sensitivity of 84.0%, specificity of 97.1%, positive predictive value of 97.5%, and negative predictive of being 81.4%. The FeNO level had a significant correlation with eosinophil count in sputum (P<0.05). FeNO level in CVA was decreased significantly after treatment (P=0.001).

Conclusions: In children, FeNO measurement might be an excellent method for diagnosing CVA with high sensitivity and specificity.

Keywords: Exhaled nitric oxide; chronic cough; cough-variant asthma (CVA); sputum eosinophils; children

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Introduction

Cough is a common complaint in children, and can develop into chronic cough, mainly including protracted bacterial bronchitis, asthma, upper airway cough syndrome (UACS) (1). Airway inflammation is the basis for most types of chronic cough (2), and inflammatory markers in the airways are very important for the diagnosis of chronic cough. Based on this characteristic, noninvasive therapies, such as fraction of exhaled nitric oxide (FeNO) and sputum testing, have been developed to detect eosinophilic airway inflammation (3,4).

Traditionally, sputum testing has been used to detect airway inflammation, but it is operator-dependent and time-consuming. FeNO has been developed in recent years as a new technology to detect airway inflammation. Clinical evidence suggests that the FeNO level can be used to monitor airway inflammation with high specificity and sensitivity, and reflect the level of inflammatory markers in bronchoalveolar lavage fluid (BALF) (3,5). Moreover, the FeNO level is closely

Table 1 Diagnostic criteria of chronic cough

Causes	Diagnostic criteria
Upper airway cough syndrome	(I) Presence of postnasal discharge, nasal mucosal edema, hyperemia, and faintness
	(II) response to an antihistamine, nasal saline, and/or nasal steroid therapy in 2 to 4 weeks
Cough-variant asthma	(I) An isolated chronic, nonproductive cough lasting for more than 4 weeks
	(II) airflow limitation demonstrated by bronchodilator responsiveness and/or response to inhaled steroid (budesonide, 400 μg/d) within 4 weeks
Postinfectious cough	(I) Lasting more than 4 weeks after the development of acute symptoms of an upper respiratory tract infection
	(II) normal chest radiograph
	(III) normal pulmonary function test results after exclusion of other causes
Gastroesophageal reflux cough	(I) Esophageal pH monitoring showed that the esophageal pH was <4 for more than 5% of the total monitoring time
	(II) response to treatment with a proton pump inhibitor within 2 to 4 weeks
Eosinophilic bronchitis	(I) Normal spirometry with normal airway responsiveness
	(II) eosinophil count >3% in non-squamous cell sputum
	(III) response to glucocorticosteroids
Tic disorders	A neuropsychiatric disorder characterized by a waxing and waning pattern of motor and vocal tics which occur several times a day, nearly every day or intermittently, over the span of more than a year

correlated with the results of bronchial provocation tests in patients with bronchial asthma, as well as in those infected by *Lactobacillus acidophilus*. Several studies have demonstrated an association between an increased FeNO level and the degree of airway inflammation. The FeNO level is increased before asthma and pulmonary dysfunction (6). One study found that the FeNO level decreased after anti-inflammatory therapy using glucocorticoids for 1 week, and is often associated with airway secretions and changes in BALF components (7). The value of using FeNO as a marker of airway inflammation in asthma has been demonstrated (8,9), while its clinical importance in chronic cough has not been well studied.

In China, some studies on application of FeNO measurement in adult patients with chronic cough have been carried out (10-12). We wished to explore the potential value of FeNO measurement to diagnose cough-variant asthma (CVA) in children.

Methods

Study participants and inclusion criteria

The study protocol was approved by the Ethics Committee of Suzhou University (SZU2012-C133; Suzhou, China). Written informed consent was obtained from all parents and children recruited into the study.

This prospective single-center study was conducted at the Children's Hospital of Soochow University (a tertiary hospital that provides services for most children in Suzhou) from January 2012 to December 2014.

Inclusion criteria were: patients aged 6–14 years with cough of duration >4 weeks; cough was the main symptom; lesions were not observed upon chest radiography; use of drugs that could affect the FeNO value had been stopped for >2 weeks.

Exclusion criteria were patients: who were reluctant to undergo FeNO measurement and pulmonary function tests; diagnosed with bronchopulmonary dysplasia, immotile cilia syndrome, tuberculosis, asthma, lung cancer, or other serious systemic diseases.

Healthy schoolchildren with normal indices of lung function and without acute respiratory infection within the previous 4 weeks were enrolled as controls.

Study design

Diagnostic criteria (*Table 1*) were based on clinical guidelines set by the American College of Chest Physicians for

evaluating chronic cough in children (13). A questionnaire on drug treatment was completed. FeNO measurement was done in patients with no lesion shown on chest radiographs. Furthermore, patients underwent spirometry, sputum induction, complete blood count, differential diagnosis of common pathogens for cough. Cough score was recorded by physician. In patients with variable airflow limitation, an increase in FEV_1 of ≥12% predicted after the administration of a bronchodilator (two puffs of albuterol administered via a mask) indicated the presence of reversible air flow limitation.

Cough score

Cough score was defined as a validated verbal category cough scale scoring daytime plus nighttime cough scores (14). This is a validated verbal category score that has been previously used in chronic cough studies in children (14,15). Briefly, daytime scores were as follows: 5 = cannot perform most usual activities due to severe coughing; 4 = frequent coughing which interferes with school or other activities; 3 = frequent coughing but does not interfere with school or other activities; 2 = cough for more than two short periods; 1 = cough for one or two short periods only and 0 = no cough. Nighttime scores were as follows: 5 = distressing cough; 4 = frequent coughs most of the night; 3 = frequent waking due to coughing; 2 = awoken once or awoken early due to coughing; 1 = cough on waking or on going to sleep only and 0 = no cough at night.

FeNO analyses

FeNO was measured following American Thoracic Society/European Respiratory Society guidelines (8) using an exhaled nitric oxide analyzer (NiOx MINO®; Aerocrine, Solna, Sweden). FeNO measurement was done before spirometry and sputum induction.

Spirometry and bronchial provocation tests

Vital capacity was measured using standard instrumentation (MasterScreen; Jaeger, Hoechberg, Germany) in accordance with the standards set by the European Respiratory Society (16). Forced expiratory volume in one second (FEV_1) and the FEV_1: forced vital capacity (FVC) ratio were chosen as indices for analyses. The lung function of participants with FEV_1% predicted >70% was assessed using a personal computer-based spirometer (microQuark; COSMED Rome, Italy) by a quantitative jet-atomization dosing device with histamine phosphate as the excitatory drug. A bronchial provocation test was deemed "positive" if FEV_1 decreased by 20% before the final step. During the test, the amount of histamine phosphate was recorded automatically. The test was defined to be "negative" if FEV_1 decreased by <15% when the maximum amount of histamine phosphate was inhaled.

Sputum cytology

When the baseline FEV_1 after salbutamol inhalation was >70% predicted, a 3% hypertonic saline solution was inhaled *via* an ultrasonic nebulizer for 10 min, as described previously (17). Inhalation was discontinued if sputum was obtained or if the FEV_1 decreased by >20%. Cytospin™ slides were prepared and stained with hematoxylin and eosin, and a differential cell count obtained from 400 non-squamous cells. Only samples with cell viability >70% and squamous-cell contamination <20% were considered (18).

Skin prick test

Thirteen kinds (6 groups) of common aeroallergens was tested, including mites (*Dermatophagoides pteronyssinus*, *D. farinae*, and *Blomia tropicalis*), cockroaches (*Periplaneta americana* and *Blattella germanica*), pollens (*Artemisia vulgaris*, *Ambrosia artemisiifolia*, mixed grasses, and mixed trees), cats (*Felis domesticus*), dogs (*Canis familiaris*), and molds (mold mixes I and IV). Allergens and negative control solutions were supplied by ALK (Hørsholm, Denmark). Atopy was defined as the presence of at least one positive skin reaction to any allergen tested by skin prick test.

Statistical analyses

Statistical analyses were carried out using SPSS v19.0 (IBM, Armonk, NY, USA). Data are expressed as numbers with percentages or as the mean ± SD, as appropriate. The one-sample Kolmogorov-Smirnov test was used to assess the normality of data. Normally distributed continuous variables were compared using the Student's *t*-test. Analysis of variance was done to evaluate differences among groups. Based on the corresponding sensitivity and specificity at a cutoff value of FeNO, a receiver operating curve (ROC) was constructed with 1-specificity as the abscissa and sensitivity as the ordinate. $P<0.05$ was considered significant.

Table 2 Baseline clinical characteristics of enrolled cases

Characteristics	CVA (n=23)	CVA + UACS (n=30)	UACS (n=45)	Other causes (n=17)	Control (n=25)	P value
Age (year)	7±1	7±1	8±1	8±1	8±2	0.56
Gender (M/F)	12/11	14/16	21/24	10/7	14/11	0.87
Height (cm)	132±11	130±10	136±10	134±13	137±12	0.44
Body weight (kg)	30±3	27±3	29±3	31±3	33±3	0.24

CVA, cough variant asthma; UACS, upper airway cough syndrome.

Table 3 Comparison of FeNO, eosinophils, pulmonary function and atopy in different diagnostic category

Parameter	CVA (n=23)	CVA + UACS (n=30)	UACS (n=45)	Other (n=17)	Control (n=25)	P value
FeNO (ppb)[c]	38±14[ab]	37±13[ab]	18±7	19±4	13±5	0.000
FEV_1%[c]	93±14	92±11	99±10	94±10	97±6	0.136
FEV_1/FVC[c]	103±10	104±6	101±19	104±4	94±5	0.908
PD20-FEV_1 (mg)[c]	0.5±0.2[a]	0.6±0.3[a]	1.5±0.7	0.9±0.7	–	0.001
Sputum eosinophils%[c]	10.0±7.1[ab]	14.7±14.5[ab]	1.6±3.3	0.6±0.7	–	0.001
Peripheral blood eosnophils%[c]	4.6±1.8[ab]	4.6±2.6[ab]	2.3±2.0	2.5±1.7	–	0.000
Atopy, n (%)	12 (52.2)	16 (53.3)	19 (42.2)	6 (35.3)	–	0.122

[a], compared with UACS, P<0.05; [b], compared with others, P<0.05; [c], data were expressed as mean ± SD. FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; CVA, cough-variant asthma; UACS, upper airway cough syndrome.

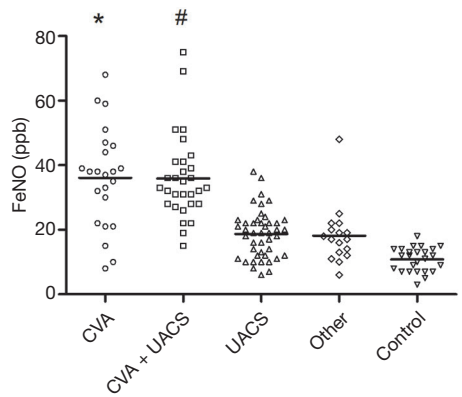

Figure 1 FeNO values by diagnostic category. FeNO values in CVA and CVA + UACS were significantly higher than those in UACS, others and the healthy control (*P<0.01, #P<0.01 respectively). FeNO, fractional exhaled nitric oxide; CVA, cough-variant asthma; UACS, upper airway cough syndrome.

Results

Baseline characteristics

A total of 127 patients met the inclusion criteria, of which 12 declined FeNO measurement. The remaining 115 cases were enrolled in our study. The 12 patients who were excluded did not differ significantly from included patients in terms of mean age at disease onset and sex.

Of these 115 patients, 23 had CVA, 30 had CVA + UACS, 45 had UACS, and 17 had other causes (PIC, GERC, and transient tic disorder). Twenty-five healthy people comprised the control group. Baseline characteristics are shown in *Table 2*. No significant difference between the groups in terms of age, sex, height or weight was recorded.

Comparisons between FeNO levels, eosinophil count, and lung function

FeNO levels in each group are shown in *Table 3* and *Figure 1*. The FeNO level in the CVA group and CVA + UACS group was significantly higher than that in the UACS, other-causes, and control group (P<0.01). The FeNO level in the UACS group was significantly higher than that in the control group (P<0.05). No significant difference in the FeNO value was found between the CVA group and CVA + UACS group (P=0.75).

The eosinophil count in sputum and peripheral blood was similar among groups. The eosinophil count in the CVA group and CVA + UACS group was significantly

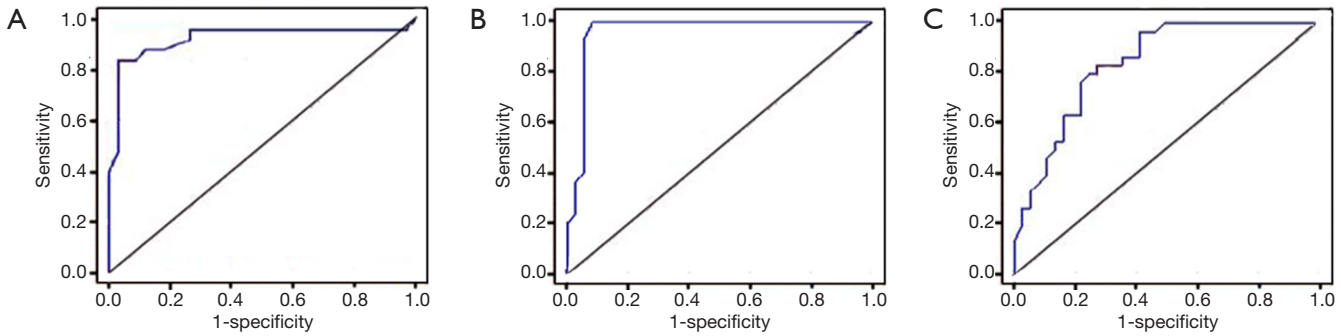

Figure 2 FeNO, sputum eosinophil and PD20 (the provocation dose required to cause a 20% reduction in FEV_1) on CVA. (A) Diagnostic value of FeNO. The area under the ROC curve was 0.93 and the optimal cutoff level of FeNO was 25 ppb, with sensitivity of 84.0% and specificity of 97.1%, for distinguishing CVA from others; (B) diagnostic value of sputum eosinophil. The area under the ROC curve was 0.96 and the optimal cutoff level of sputum eosinophil was 2%, with sensitivity of 99.9% and specificity of 91.7%, for distinguishing CVA from others; (C) diagnostic value of PD20. The area under the ROC curve was 0.84 and the optimal cutoff level of PD20 was 0.76 mg, with sensitivity of 83.3% and specificity of 72.2%, for distinguishing CVA from others. FeNO, fractional exhaled nitric oxide; CVA, cough-variant asthma; ROC, receiver operating curve.

higher than that in the UACS group and other-causes group (P<0.05). No significant difference was found between the UACS group and other-causes group, or between the CVA group and CVA + UACS group, in terms of the eosinophil count (all P>0.05).

The provocation dose required to cause a 20% reduction in FEV_1 (PD20-FEV_1) in the CVA group and CVA + UACS group was significantly lower than that in the UACS group (P<0.05 for both). No significant difference was found between the CVA group and CVA + UACS group (P=0.58). For FEV_1%, FEV1:FVC ratio and cough score, no significant difference was found among groups (all P>0.05).

CVA detection based on FeNO, eosinophil count and PD20

As shown in *Figure 2*, the area under the ROC curve (AUC) was 0.93, and the optimal sensitivity and specificity were at the cutoff value of 25 ppb. When FeNO >25 ppb, CVA detection had a sensitivity of 84.0%, specificity of 97.1%, positive predictive value (PPV) of 97.5%, and negative predictive value (NPV) of 81.4%.

With regard to the eosinophil count in sputum, the AUC was 0.96. An eosinophil count of 2.0% was used as the best value. When the eosinophil count was >2.0%, CVA detection had a sensitivity of 99.9%, specificity of 91.7%, PPV of 92.3%, and NPV of 99.9%.

For PD20, the AUC curve was 0.84. PD20 of 0.76 mg could be used as the best cutoff value. When PD20 <0.76 mg, CVA detection had a sensitivity of 83.3%, specificity of 72.2%, PPV of 75.0%, and NPV of 81.3%.

Correlation between the FeNO level and PD20, eosinophil count in sputum, and lung function

The correlation between the FeNO level and other parameters is shown in *Figure 3*. There was a significant positive correlation between the FeNO level and eosinophil count in sputum (r=0.362, P<0.001), eosinophil count in peripheral blood (r=0.641, P<0.641), but a negative correlation with the airway-reactivity parameter PD20 (r=0.411, P<0.05). In addition, no significant correlation was found between the FeNO level and FEV_1 (r=0.124, P>0.124) or FEV_1:FVC ratio (r=0.027, P>0.05).

Decline of FeNO levels, eosinophils, and cough score after 4-week treatment

FeNO level in CVA (38±14 versus 20±9 ppb), CVA plus UACS (37±13 versus 19±6 ppb) were decreased significantly after treatment (P=0.001), but no significant difference was found in UACS (18±7 versus 17±5 ppb) and other causes group (19±4 versus 16±4 ppb) after the treatment, as shown in *Table 4*.

The ratio of sputum eosinophils in CVA group, and CVA + UACS group reduced significantly after the treatment (P=0.000). For the UACS group, the ratio of sputum eosinophils shows no statistically significant difference before and after the treatment. Cough score, and PD20-FEV_1

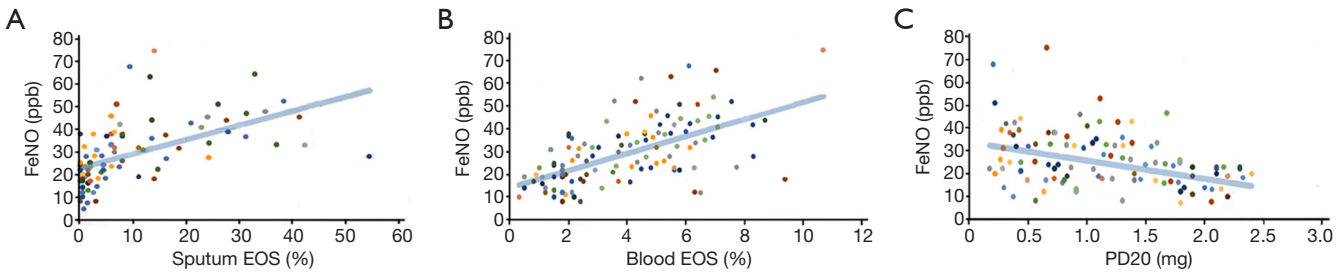

Figure 3 Correlation of FeNO values and other parameters. (A) FeNO was positively correlated with induced sputum eosinophil proportion; (B) FeNO was positively correlated with peripheral blood eosinophil proportion; (C) FeNO was negatively correlated with PD20 (the provocation dose required to cause a 20% reduction in FEV_1). EOS, eosinophil; FeNO, fractional exhaled nitric oxide.

Table 4 FeNO level, sputum EOS% and cough score comparison of before and after the 4-week treatment in children with CVA, CVA + UACS and UACS

Variables	Before treatment			After treatment			P value		
	CVA	CVA + UACS	UACS	CVA	CVA + UACS	UACS	CVA	CVA + UACS	UACS
FeNO	38±14	37±13	18±7	20±9**	19±6**	17±5	0.001	0	0.374
Sputum EOS%	10.0±7.1	14.7±14.5	1.6±3.3	2.9±2.0**	4.3±6.1*	1.2±2.4	0	0.028	0.08
Cough score	3.5±0.7	3.6±0.7	3.2±0.7	1.5±0.8**	1.9±0.9**	1.8±0.8**	0	0	0
PD20-FEV_1 (mg)	0.5±0.2	0.6±0.3	1.5±0.7	0.69±0.4	0.7±0.4	1.5±0.6**	0.093	0.167	0.007

*, P<0.05; **, P<0.01. FeNO, fractional exhaled nitric oxide; CVA, cough-variant asthma; UACS, upper airway cough syndrome; EOS, eosinophil.

level were all significantly decreased in the four groups after the treatment (P<0.01).

Discussion

CVA is relatively common among preschool and school-age children (19,20). Based on data from 115 children with chronic cough and 25 healthy controls, we discovered that the optimal FeNO cutoff value was 25 ppb, with a sensitivity of 84.0%, specificity of 97.1%, PPV of 97.5%, and NPV of 81.4%. Moreover, the FeNO level had a significant correlation with eosinophil count in sputum, cough symptom score, and cough score. The decrease in FeNO level was related significantly to the degree of decrease in the eosinophil count in sputum. Thus, we suggest that FeNO measurement may be useful in CVA diagnosis.

The FeNO level and eosinophil count in sputum have been recognized as important markers of inflammation (21,22). We found that a diagnosis based on the FeNO level can show similar sensitivity to that of sputum testing and bronchial provocation tests. However, with respect to safety and resource consumption, FeNO measurement would be a better choice.

Several demographic and biologic factors can affect the FeNO level: smoking (23), age (24), and immunoglobulin-E level (25). In the present study, the background of enrolled cases (height, age, sex, and body mass index) was adjusted. The FeNO level of children with CVA was significantly higher than that of healthy cases and children with UACS. Similarly, Scollo and colleagues reported that the FeNO level in CVA patients was obviously higher than that of patients with cough due to other causes (26). Also, in children with CVA, the eosinophil count in sputum showed an identical trend with the FeNO level, suggesting the important role of the latter for CVA diagnosis.

Several studies have shown the high specificity and sensitivity of the FeNO level for the diagnosis of asthma. Among school-age children, the sensitivity and specificity can reach 91.4% and 92.0%, respectively (27). Pérez Tarazona and co-workers demonstrated that 19 ppb can be regarded as the threshold FeNO level for the diagnosis of

asthma, with an AUC of 0.93 and sensitivity of 91.4% (28). Yao *et al.* found that 38.8 ppb can be used as the threshold FeNO level for the diagnosis of chronic cough, with an AUC of 0.67 and sensitivity of 64.3% (29). We demonstrated that the optimal FeNO cutoff level for CVA detection can be 25 ppb, with a sensitivity of 84.0% and specificity of 97.1%. These different cutoff levels might have been caused by differences in the demographic and biologic features of patients.

The present study had two main limitations. First, we included only school-age children (6–14 years) in the present study. The relationship between the FeNO level and chronic cough in younger children was not established. Second, data were obtained from a single center. Only multicenter studies can ensure precision, reduce selection bias, and increase the generalizability of the data accrued.

Conclusions

In children, FeNO measurement might be a good method for diagnosing CVA with high sensitivity and specificity.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study protocol was approved by the Ethics Committee of Suzhou University (SZU2012-C133; Suzhou, China). Written informed consent was obtained from all parents and children recruited into the study.

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