INTRODUCTION

Cough is one of the most common symptoms for which patients seek medical attention (1), however proper diagnosis of its etiology is often difficult (2). Morice et al. report that the most common diagnoses in patients with chronic cough are cough variant asthma (CVA), sinobronchial syndrome (SBS), and gastroesophageal reflux disease (GERD), followed by eosinophilic bronchitis (EB) and post-infectious cough (PIC), and angiotensin-converting enzyme inhibitor-induced cough (3). In Japan, the prevalence of GERD, the most common diagnoses in patients with chronic cough are cough variant asthma (CVA), sinobronchial syndrome (SBS), and gastroesophageal reflux disease (GERD), followed by eosinophilic bronchitis (EB) and post-infectious cough (PIC), and angiotensin-converting enzyme inhibitor-induced cough (3). In Japan, the prevalence of GERD, the most common diagnoses in patients with chronic cough is 10 (4.1%), and Others in 35 (14.4%). FeNO values were significantly higher in CVA and BA as compared to PIC, AC, GERD, and Others. In the multivariate analysis, the only FeNO value was identified as independent factors to discriminate CVA and non-CVA cough. These findings indicated that FeNO measured by using NOV could be used as a diagnostic marker of intractable cough, especially for the differential diagnosis of CVA from non-CVA cough. J. Med. Invest. 67: 265-270, August, 2020

Keywords: fractional exhaled nitric oxide, NIOX VERO®, etiology of cough, cough variant asthma

MATERIALS AND METHODS

Patients

We retrospectively analyzed 243 consecutive patients who...

Abbreviations

CVA, cough variant asthma ; SBS, sinobronchial syndrome ; GERD, gastroesophageal reflux disease ; EB, eosinophilic bronchitis ; BA, bronchial asthma ; PIC, post-infectious cough ; AC, atopic cough ; FeNO, fractional exhaled nitric oxide ; NOV, NIOX VERO® ; ppb, parts per billion ; IgE, immunoglobulin E ; SD, standard deviation ; BMI, body mass index ; ROC, receiver operating characteristic ; CI, confidence interval

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visited the Department of Respiratory Medicine, Shikoku Central Hospital of the Mutual aid Association of Public School teachers from April 2018 through June 2019, with a chief complaint of cough. Inclusion criteria were as follows: 1) age ≥ 15 years, 2) being able to undergo FeNO measurement, and 3) providing informed consent to participate in the study. Patients were excluded if they: 1) were in lactation and breastfeeding, 2) were in a pregnancy, 3) had significant psychological problems, 4) had abnormal chest radiograph findings that may explain the cough, or 5) had taken systemic corticosteroids, antihistamines, anti-leukotriene agents, medications for cough within the previous two weeks. Patients with respiratory symptoms other than cough, such as fever, sputum, shortness of breath, wheezes and stridor, were included. For the comparison of FeNO values, age-matched 30 healthy volunteers were also included.

The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the Institutional Review Board of our institution (approval number: 2019-1-1, approval date: 2019/5/16). The statement on consent to participate in this study was obtained from patients by the disclosure of information for participation.

**Study Design**

Questionnaires concerning past and/or present illness, occupation, cough duration, other respiratory symptoms and current smoking status including the number of cigarettes smoked per day and smoking duration were assessed. The smoking index was defined as multiplying the numbers of cigarette pack smoked per day by smoking years (pack-years), to estimate how much the patient was exposed to smoking.

All patients underwent FeNO measurement. FeNO values were measured by NOV electrochemical analyzer (Aerocrine AB, Solna, Sweden) at a flow rate of 50 mL/second, according to the American Thoracic Society/European Respiratory Society recommendations (12) and were expressed as parts per billion (ppb). The patients were asked to empty their lungs and then inhale deeply through the filter to total lung capacity. Next, they exhaled slowly through the filter and regulated their exhaled flow rate through assistance by an animation display. The exhalation time was adjusted to 10 seconds for all patients. Measurements were repeated until one acceptable value was obtained, as judged by the machine. Blood tests included peripheral blood white blood cell count, peripheral blood eosinophil count, serum non-specific immunoglobulin E (IgE), and serum antigen-specific IgE as appropriate. A chest radiograph was also evaluated in order to exclude other undiagnosed diseases.

The diagnoses of the etiology of cough were made as follows. BA was diagnosed when patients had cough as the predominant symptom while together with wheezes and/or dyspnea, and either positive airway reversibility or reversible airflow obstruction (13). A diagnosis of CVA was based on the sole complaint of cough, not accompanied by wheezes or dyspnea, which was relieved by β2-agonists, and positive airway reversibility or reversible airflow obstruction (4). AC was diagnosed based on the presence of atopic status and response of coughing to histamine H1 receptor antagonist, but not to inhaled β2-agonist (4, 14). PIC was diagnosed when cough was preceded by an acute respiratory tract infection that was not complicated by pneumonia and eventually resolved spontaneously (4). SBS was diagnosed based on findings of chronic sinusitis on sinus imaging and improvement of cough and symptoms related to chronic sinusitis with macrolide antibiotics (4, 15). GERD-related cough was suspected by the presence of 1) classic reflux symptoms of heartburn, indigestion, chest discomfort, throat clearing, dysphonia, dysphagia, and belching and/or 2) typical characteristics of cough that is triggered by phonation, rising, lying, eating, and intake of certain food. A diagnosis was confirmed when cough was relieved by proton pump inhibitors with or without gastrointestinal prokinetic agents (16).

**Statistical analysis**

The significant differences between populations were evaluated with Fisher’s exact test in categorized variables and Student’s t-test in continuous variables. Data are described as the means ± standard deviations (SDs), unless otherwise stated. Correlations between FeNO values and blood eosinophil counts and total serum IgE titers were analyzed by Spearman’s rank correlation test. Intended for 195 patients whose final diagnoses were other than BA, the univariate analysis was done to evaluate the patient characteristics that were significantly associated with the diagnosis of CVA; specifically, these factors were age, gender, body mass index (BMI), smoking status, smoking index, cough duration, past and/or present illness, blood eosinophil count, total serum IgE titer, and FeNO value. Variables that had a P-value of < 0.05 in the univariate analysis were included in the multivariate logistic regression analysis to evaluate which one predict the diagnosis of CVA. The cut-off value for distinguishing CVA from non-CVA except for BA was determined by receiver operating characteristic (ROC) curve analysis. Two-tailed P-values of < 0.05 were considered significant. All analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (17).

**RESULTS**

From April 2018 through June 2019, 243 consecutive patients with a chief complaint of cough were enrolled in this study. Their clinical characteristics are listed in Table 1. The mean age was 52.6 years, with a range of 16-89. Eighty-seven patients (35.8%) were male, and 156 (64.2%) were female. The mean cough duration was 8.1 weeks (range: 0.14-104 weeks), and the mean BMI was 23.2 ± 3.9 kg/m² (range: 14.8-37.1 kg/m²). Seventy-eight patients (32.1%) had smoking experience (current or former), and the mean smoking index was 8.0 ± 16.9 pack-year (range: 0.0-87.5 pack-year). Seventy-five patients (30.0%) had the past history of BA. The past and/or present illness of allergic diseases except for BA, SBS and GERD were observed in 112 (46.1%), 51 (21.0%), and 45 (18.5%) patients, respectively.

Among 243 patients, final diagnosis of the etiology of cough was CVA in 74 (30.5%), BA in 48 (19.8%), PIC in 52 (21.4%), AC in 24 (9.9%), GERD-related cough in 10 (4.1%), and Others in 35 (14.4%) (Table 2). BA and CVA constituted more than a half (50.2%) of the whole population. Comparison of patients with cough according to etiology is shown in Table 3. Compared with CVA group, BA group had significantly lower BMI and higher smoking experience, PIC group had significantly lower blood eosinophil count, and AC group were significantly younger. The cough duration in PIC group was significantly shorter than other etiologies. The earlier admission in this group seemed to be mainly attributed to their more serious symptoms such as fever, sore throat, chilliness, other than cough.

FeNO values were significantly higher in patients with CVA (40.1 ± 26.0 ppb) and in those with BA (40.4 ± 33.3 ppb) than in PIC (15.6 ± 7.7 ppb), AC (17.9 ± 9.9 ppb), GERD (14.9 ± 4.7 ppb), and Others (17.1 ± 9.4 ppb; P < 0.05 each). There was no significant difference of FeNO values in patients with CVA and BA (Figure 1). FeNO values in 30 healthy volunteers (16.6 ± 6.5 ppb) were also significantly lower compared with CVA and BA, while no difference was observed from those in PIC, AC, GERD, and
Others (data not shown). FeNO values significantly correlated with blood eosinophil counts (r = 0.35, P < 0.01), and total serum IgE titers (r = 0.17, P = 0.03) (data not shown).

The proper diagnosis of the etiology of cough is often troublesome (2). The diagnosis of BA is considered to be made easier than other etiologies of cough due to the existence of wheezes in chest auscultation, but the differential diagnosis of CVA from non-CVA other than BA is extremely difficult due to few positive findings in physical examination. To facilitate the differential diagnosis of the etiology of cough and to identify the factors which predict the diagnosis of CVA, we next focused on 195 patients whose final diagnoses were other than BA. In the univariate analysis, which compared the patient characteristics that were significantly associated with the diagnosis of CVA, the factors that were identified to have significant effects (P < 0.05) were smoking status, past history of BA, blood eosinophil count, total serum IgE titer, and FeNO value (Table 4). These five variables were included in the following multivariate logistic regression analysis to evaluate which one predict the diagnosis of CVA. In the multivariate analysis, only FeNO value was identified as independent factors associated with the diagnosis of CVA (Table 5).

Finally, we exploratory sought to determine the best cut-off point of FeNO to discriminate CVA and non-CVA other than BA. The overall diagnostic utility of FeNO value to distinguish these two groups was examined by ROC curve analysis, which revealed 23 ppb, with an area under the ROC curve of 0.87 (95% confidence interval (CI); 0.82-0.93), as the optimal cut-off value (Figure 2). This resulted in a sensitivity and specificity of 85.1% and 81.1%, respectively.

### Table 1. Patient characteristics.

| Variables                  | Number | Age, years | Gender, N (%) | BMI, kg / m² | Smoking status, N (%) | Smoking index, pack-year | Cough duration, weeks | Past and / or present illness, N (%) |
|---------------------------|--------|------------|---------------|--------------|-----------------------|------------------------|----------------------|-------------------------------------|
|                           | 243    | 52.6 ± 19.1 (16-89)* | Male 87 (35.8%) | 23.2 ± 3.9 (14.8-37.1)* | Current 24 (9.9%) | 8.0 ± 16.9 (0.0-87.5)* | 8.1 ± 14.8 (0.14-104)* | BA 74 (30.0%) AD 112 (46.1%) SBS 51 (21.0%) |

Data are described as the means ± SDs. *Numbers in parentheses indicated ranges of each variable. BMI, body mass index; BA, bronchial asthma; AD, allergic diseases; SBS, sinobronchial syndrome; GERD, gastroesophageal reflux disease.

### Table 2. Etiology of cough in our study population.

| Diagnosis                  | Number (%) |
|----------------------------|------------|
| Cough variant asthma       | 74 (30.5)  |
| Bronchial asthma           | 48 (19.8)  |
| Post-infectious cough      | 52 (21.4)  |
| Atopic cough               | 24 (9.9)   |
| Gastroesophageal reflux disease | 10 (4.1)  |
| Sinobronchial syndrome     | 9 (3.7)    |
| Chronic obstructive pulmonary disease | 8 (3.3) |
| Interstitial lung diseases | 5 (2.1)    |
| Chronic aspiration         | 4 (1.6)    |
| Drug-induced cough         | 2 (0.8)    |
| Chronic heart failure      | 2 (0.8)    |
| Not otherwise specified    | 5 (2.1)    |

### Table 3. Comparison of patients with cough according to etiology.

| Variables                  | CVA | BA | PIC | AC | GERD | Others |
|----------------------------|-----|----|-----|----|------|--------|
| Number                     | 74  | 48 | 52  | 24 | 10   | 35     |
| Age (years)                | 51.8 ± 17.2 | 53.3 ± 19.7 | 47.4 ± 18.6 | 40.0 ± 16.6* | 49.1 ± 17.1 | 71.0 ± 11.6* |
| Gender (male / female)     | 28 / 46 | 20 / 28 | 13 / 30 | 6 / 18 | 5 / 5 | 15 / 20 |
| BMI (kg / m²)              | 23.8 ± 3.9 | 21.6 ± 3.5* | 23.9 ± 3.5 | 22.8 ± 4.8 | 22.7 ± 2.4 | 23.8 ± 3.9 |
| Smoking status (current / former / never) | 11 / 12 / 51 | 8 / 18 / 22* | 1 / 8 / 43 | 0 / 4 / 20 | 0 / 2 / 8 | 4 / 10 / 21 |
| Smoking index (pack-year)  | 5.8 ± 12.6 | 11.1 ± 17.3 | 3.2 ± 9.0 | 2.3 ± 6.8 | 8.2 ± 17.6 | 19.4 ± 28.9* |
| Cough duration (weeks)     | 8.0 ± 15.9 | 10.7 ± 20.7 | 2.6 ± 2.0* | 6.7 ± 10.7 | 8.5 ± 7.9 | 14.4 ± 15.5 |
| Blood eosinophil (μL)      | 305 ± 231 | 467 ± 670 | 187 ± 175* | 234 ± 201 | 190 ± 103 | 195 ± 177* |
| Total serum IgE (IU / mL)  | 502 ± 1227 | 942 ± 2288 | 202 ± 505 | 254 ± 322 | 99 ± 127 | 216 ± 475 |

Data are described as the means ± SDs. *P < 0.05 compared with CVA. CVA, cough variant asthma; BA, bronchial asthma; PIC, post-infectious cough; AC, atopic cough; GERD, gastroesophageal reflux disease; BMI, body mass index; IgE, immunoglobulin E; IU, international unit; SD, standard deviation.
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Figure 1. Comparison of FeNO values in each group of patients with a chief complaint of cough. FeNO values were significantly higher in patients with CVA and BA than in those with PIC, AC, GERD, and Others ($p < 0.05$ each, by Student’s t-test). There was no significant difference of FeNO values in patients with CVA and BA. Data are shown as the means ± standard errors. *$p < 0.05$ compared with the patients with CVA and BA.

Table 4. Univariate analysis of factors affecting the diagnosis of CVA and non-CVA in patients with cough.

| Variables             | CVA   | non-CVA | P-value |
|-----------------------|-------|---------|---------|
| Number                | 74    | 121     | 0.733   |
| Age (year)            | 54.0 ± 18.6 | 53.0 ± 18.8 | 0.441   |
| Gender (male / female)| 28 / 46 | 39 / 82 | 0.437   |
| BMI (kg / m$^2$)      | 24.0 ± 4.0 | 23.5 ± 3.8 | 0.355   |
| Smoking status (current / former / never) | 11 / 12 / 51 | 5 / 21 / 92 | 0.040   |
| Smoking index (pack-year) | 5.8 ± 12.6 | 8.1 ± 18.9 | 0.666   |
| Cough duration (weeks) | 8.0 ± 15.9 | 7.2 ± 10.9 | 0.001   |
| History of BA (N [%]) | 22 [29.7] | 12 [9.9] | 0.001   |
| History of AD (N [%]) | 33 [45.0] | 54 [44.6] | 1.000   |
| History of SBS (N [%]) | 16 [21.6] | 22 [18.2] | 0.580   |
| History of GERD (N [%]) | 17 [23.0] | 21 [17.4] | 0.356   |
| Blood eosinophil (/μL) | 305 ± 231 | 199 ± 176 | < 0.001 |
| Total serum IgE (IU / mL) | 502 ± 1227 | 213 ± 451 | 0.048   |
| FeNO (ppb)            | 40.1 ± 26.0 | 16.1 ± 7.8 | < 0.001 |

Data are described as the means ± SDs.

CVA, cough variant asthma; BMI, body mass index; BA, bronchial asthma; AD, allergic diseases; SBS, sinobronchial syndrome; GERD, gastroesophageal reflux disease; IgE, immunoglobulin E; IU, international unit; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; SD, standard deviation.

Table 5. Multivariate logistic regression analysis for prediction of CVA diagnosis in patients with cough.

| Parameter             | Odds ratio (95% CI) | P-value |
|-----------------------|---------------------|---------|
| FeNO (ppb)            | 0.868 (0.824-0.914) | < 0.001 |
| History of BA         | 0.318 (0.086-1.170) | 0.085   |
| Smoking status        | 2.600 (0.747-9.050) | 0.133   |
| Blood eosinophil (/μL)| 0.999 (0.997-1.000) | 0.576   |
| Total serum IgE (IU / mL) | 1.000 (0.999-1.000) | 0.966   |

CVA, cough variant asthma; CI, confidence interval; FeNO, fractional exhaled nitric oxide; BA, bronchial asthma; IgE, immunoglobulin E.

Figure 2. The ROC curve analysis for distinguishing CVA from non-CVA other than BA as the etiology of cough. The overall optimal cut-off value was 23 ppb, with an area under the ROC curve of 0.87 (95% CI: 0.82-0.93). This resulted in a sensitivity and specificity of 85.1% and 81.1%, respectively.
DISCUSSION

Since a new hand-held device for FeNO measurement, NOV, has not been used for many years in clinical practice, and few studies have been performed to measure FeNO values obtained using NOV, its diagnostic utility has not been fully elucidated. In this study, we sought to investigate the performance of NOV for the evaluation and differential diagnosis of the etiology of cough. FeNO values were significantly higher in patients with CVA and BA as compared to those with PIC, AC, GERD, and Others, and significantly correlated with blood eosinophil counts and total serum IgE titers. Moreover, only FeNO value was identified as independent factors to discriminate CVA and non-CVA in the multivariate analysis. These findings indicated that FeNO values measured by using NOV was a relevant diagnostic tool for the patients suffering from intractable cough.

It is well established that FeNO values are higher in patients with CVA and BA than in healthy controls (18). Kowal et al. reported the cut-off value to differentiate a chronic cough with and without BA was 40 ppb (sensitivity, 0.88; specificity, 0.83) (19). Matsunaga et al. demonstrated that the cut-off value of FeNO 22 ppb measured by using NIOX MINO® was associated with the highest combination of sensitivity (90.8%) and specificity (83.9%) to discriminate asthmatic patients and control subjects (20), which was comparable with our results obtained by using NOV. The present study indicated a cut-off value of 23 ppb (sensitivity, 0.85; specificity, 0.81) for differentiation between CVA and non-CVA other than BA. The discrepancies of cut-off levels among these studies may be attributed to different methods of selection of cases (category of BA and CVA) and control group (CVA, non-CVA or healthy control) and the varying patients’ characteristics. Lúdvíksdóttir et al. reported that atopic patients with BA had a significantly higher mean exhaled NO than non-atopic subjects with BA (21). In this study, FeNO values had a significantly positive correlation with blood eosinophil counts and total serum IgE titers. These data support that FeNO is a useful marker to monitor the eosinophil inflammation in patients with CVA and BA patients.

The difference in FeNO values between BA and CVA seems controversial. Although our study demonstrated these significant differences, other reports reported otherwise (22). Since a degree of mucosal and broncholarveolar eosinophilia between BA and CVA are similar (23), there is a possibility that varying influences of confounding factors, such as atopic status (24), and disease severity may have affected the results. Several factors may affect the validity of FeNO measurements. In patients with BA, Matsunaga et al. proposed that FeNO values should be evaluated while considering the influence of allergic rhinitis and smoking (20). Previous studies also revealed that atopic status and diagnosis were independent determinants of FeNO values in patients with prolonged and chronic cough and that atopy itself was responsible for elevated FeNO values even among subjects without BA or lower airway symptoms (25), which may lead to misdiagnosis of asthma. Therefore, taking these factors into account seemed to be inevitable when evaluating FeNO values in prolonged and chronic cough.

There are now several manufacturers of FeNO analyzers. Consequently, reports of FeNO measurement have often used different equipment (26). Therefore, FeNO values were reported to be significantly different among the equipment used, while the procedure of FeNO measurement has been standardized. Inoue et al. demonstrated that NIOX devices (e.g., NIOX®, NIOX MINO® and NOV) showed higher FeNO values in the low-FeNO population, whereas NObreath® showed higher values in the high-FeNO population (27), indicating the effectiveness of the device appeared to be controlled by the FeNO value in the target population. On the contrary, FeNO values measured by different devices were shown to have good correlation and clinically acceptable agreement between NIOX® and NIOX MINO® (28), NIOX MINO® and NOV (29), NObreath® and NOV (27), respectively. These findings indicated that each device was able to give clinical guidance with similar accuracy.

Several major limitations need to be considered in interpreting our findings. First, this is a retrospective study with somewhat small number of patients. Thus, it is difficult to draw definite conclusions about the utility of FeNO measurement obtained using NOV for diagnosing the etiology of cough in daily practice. Second, as this study was performed in only one institution, the results should not be universalized to the general population. Third, we did now specify cough duration in eligibility criteria. Thus, not only patients with prolonged and chronic cough but those with acute phase of cough were also included in this study. Forth, current diagnostic criteria for CVA might not be precise because 1) they are often based on positive airway reversibility and might not preclude post-viral cough and 2) are premised on good clinical response to asthma therapy and might not encompass refractory asthma. The present findings on CVA need to be interpreted cautiously. Further large-scale studies would be required to show the more clinically significant data in the future.

In conclusion, we investigated the clinical utility of FeNO measurement obtained using NOV for diagnosing the etiology of cough in this study. FeNO values were significantly higher in patients with CVA and BA as compared to those with PIC, AC, GERD, and Others, and significantly correlated with blood eosinophil counts and total serum IgE titers. Moreover, only FeNO value was identified as independent factors to discriminate CVA and non-CVA in the multivariate analysis. These findings indicated that FeNO values measured by using NOV could be used as a diagnostic marker of cough, especially for the differential diagnosis of CVA from non-CVA.

CONFLICT OF INTEREST DISCLOSURE

All authors state that they do not have any financial or other relationships for the present study that might lead to a conflict of interest.

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