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Validity of Fractional Exhaled Nitric Oxide and Small Airway Function Indices in
Diagnosis of Cough Variant Asthma

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Abstract

Background: Fractional exhaled nitric oxide (FeNO) is a non-invasive method used to reveal the eosinophilic inflammation of airway and to diagnose and manage asthma. The diagnostic value of FeNO in patients with cough variant asthma (CVA) is poorly understood. Small airways remain an important aspect of CVA. The use of FeNO measurement or its combination with the small airway function in differentiating CVA patients from chronic cough patients is unexplored.

Methods: From December 2012 to June 2016, patients with chronic nonproductive cough for more than 8 weeks without any wheezing or dyspnea, fever or blood-stained sputum, and abnormalities on X-ray or larger airways function based on physician's opinion were subjected to FeNO, pulmonary function, and bronchial hyperresponsiveness (BHR) tests. Patients who obtained positive BHR were diagnosed with CVA. Receiver operating characteristic (ROC) curves were obtained to evaluate the clinical value of FeNO and small airways indices in CVA diagnosis. The optimal cutoff point for the level of FeNO was also determined.

Results: A total of 450 patients were enrolled, among which 150 patients had CVA. The FeNO value in CVA was significantly higher than that in NCVA group [42(41) parts per billion (ppb) vs. (16(11) ppb), $P < 0.05$]. The area under the ROC curve was estimated as 0.874 for FeNO. An optimal cutoff point of 25 ppb had respective sensitivity and specificity values of 81.3% and 84.0% in differentiating CVA patients from NCVA patients. The CVA group showed small airway dysfunction, and the small airway resistance was significantly higher than in the NCVA group. The area under the ROC curve of FeNO combined with MEF (% predicted) was 0.883, and that combined with MEF50 (% predicted) was 0.886.

Conclusions: The measurement of FeNO is a noninvasive, reproducible, and sensitive method of differentiating CVA patients from NCVA patients. A combination of the level of FeNO (≥ 25 ppb) and the abnormal small airway function suggested higher CVA possibility, thereby resulting in a

rapid diagnosis. Unnecessary treatments are avoided. This finding provides a new perspective for the management of patients with CVA

Key words

Fractional exhaled nitric oxide; cough variant asthma; chronic cough; small airways

Chronic cough is a common medical problem among patients who visit local hospitals in China, and cough variant asthma (CVA) is one of its major causes (1, 2). However, CVA diagnosis remains difficult because chronic nonproductive cough has a wide range of etiologies. Etiologies for chronic nonproductive cough include CVA, atopic cough, eosinophilic bronchitis, gastroesophageal reflux-related cough, and upper airway cough syndrome. Chronic cough is defined by the Chinese Thoracic Society as a sole or predominant symptom that persists for 8 weeks, and is not accompanied by abnormal shadows appearing on chest X-ray. According to different studies in China, CVA accounts for 14% to 51% of chronic cough (1, 3–6).

CVA is a specific form of asthma that solely presents with coughing (7). According to the guidelines, the diagnosis of CVA should be based on laboratory evidence of bronchial hyperresponsiveness and/or therapeutic efficacy (8). Bronchial hyperresponsiveness test (BHR) is time-consuming and has a high risk of inducing severe bronchospasm (9). In addition, this variant of asthma presents a diagnostic problem based on therapeutic efficacy; some problems include difficult treatment, placebo effect, and natural improvements (10).

Fractional exhaled nitric oxide (FeNO) is a non-invasive method for reflecting eosinophilic inflammation of the airway (11). As a new biomarker, FeNO is widely used to directly detect eosinophilic airway inflammation and to guide asthma diagnosis (12, 13). The diagnostic value of FeNO in patients with CVA is only evaluated in few studies with a small sample size, and the optional cut-off level of FeNO in CVA remains unknown (14–16). Asthma is a heterogeneous

disease that affects both small and large airways. Most studies focused on larger airways. Small airways remain an important aspect of CVA, although they are frequently ignored. Therefore, this study aims to explore the function of FeNO measurement with small airways indices in the diagnosis of CVA. To our knowledge, this study is the first to report the role of FeNO and its combination to small airways in CVA.

Materials and methods

Subjects

We collected information from patients with chronic coughs who accepted BHR and FeNO tests at the First Affiliated Hospital of Sun Yet-Sen University from December 2012 to June 2016. This study retrospective enrolled these chronic cough patients according to the following criteria: (1) age 18–75 years old; (2) experienced chronic nonproductive cough that has lasted for more than 8 weeks, without fever or blood-stained sputum; and without wheezing or shortness of breath; (3) without abnormalities on X-ray or larger airway function; (4) without treatment of any oral corticosteroid in the last 4 weeks, and without respiratory tract infection within 8 weeks; (5) non-smokers or ex-smokers with cessation of smoking for at least 6 months prior to the study; and (6) no history of asthma or other lung diseases, including but not limited to obliterative bronchiolitis, bronchiectasis, and cystic fibrosis.

The study was approved by the Ethical Committee of the First Affiliated Hospital of Sun Yet-Sen University. The requirement for approval and the signed informed consent form were waived by the institutional review board because the study has no intervening trials and has a retrospective nature.

Methods

CVA diagnosis is according to the recommendations of the Chinese National Guidelines on the diagnosis and management of cough (17). Patients with a positive BHR without any asthmatic symptoms, such as wheezing or dyspnea, were diagnosed with CVA. Medical information and patient characteristics were obtained from the medical charts of the patients.

Measurements

Pulmonary Function Test

PFT and BHR were performed using a pneumotachograph-based system according to the European Respiratory Society (ERS) recommendation (18). The percentage predicted values (% predicted) were calculated from the published normative data of healthy Chinese adults. The maximal expiratory flow rates at 75% (MEF75), at 50% (MEF50), and at 25% (MEF25) were obtained from the forced flow-volume curves. The maximal mid-expiratory flow is the average of expiratory flows at 25%–75% of the forced vital capacity. All subjects were asked to repeat the procedure at least thrice at each testing session, and the best values were noted.

Measurement of BHR to histamine

PFT values were performed in each subject prior to the measurement of BHR. Patients who received PC20 (the provocative concentration of histamine required to induce a 20% fall in FEV₁) of 8 mg/ml or less were defined as hyperresponsive.

Exhaled Nitric Oxide Measurements

FeNO level was evaluated according to the ATS/ERS recommendations using NIOX MINO analyzer (Aerocrine, Solna, Sweden) (19). Subjects were informed to deeply inhale NO-free air and immediately exhale in full via a mouthpiece at a constant flow rate (50 ml/s) for 10 s.

Statistical analysis

All continuous variables were checked for normal distribution by the Kolmogorov–Smirnov normality test. Normally distributed variables are expressed as mean $\pm$ standard deviation, whereas skewed variables are expressed as the median (interquartile range, IQR). The unpaired two-tailed Student's t-tests and Mann-Whitney U-tests were applied to examine difference between the two groups for normally and non-normally distributed parameters, respectively. The chi-square test was used to compare categorical variables between two groups. Receiver operating characteristic (ROC) curve analysis was performed to determine the ability of FeNO, and indices were combined to discriminate CVA and Non-CVA chronic cough. All tests were two-sided, and the level of significance was set at a $p < 0.05$. The analyses were conducted using

Statistical Package for the Social Sciences (SPSS 19.0 Chicago, IL, USA). Receiver-Operating Characteristic (ROC) curves were performed with Medcalc (MedCalc Software 15.2, Mar-iakerke, Belgium).

Results

1. Demographics of study subjects

According to the inclusion criterion, a total of 450 patients were enrolled in this study and 150 (33.33%) patients were diagnosed with CVA. Patients with CVA showed higher FeNO levels than the NCVA group ($P < 0.05$). The function of small airways (MEF, MEF25, MEF50, and MEF75) was significantly lower in the CVA group compared with the non-CVA group ($P < 0.05$). The clinical characteristics of the patients, including PFT values and FENO levels, are presented in Table 1.

2. Comparison of FeNO level between the CVA group and NCVA group

A significant difference in FeNO value was observed between the two groups ($P < 0.05$). The level of FeNO in patients with CVA was 42 (41) parts per billion (ppb; median [interquartile range]), which is significantly higher compared with the NCVA group (16[11] ppb; ($P < 0.05$)) (Figure 1).

3. Comparison of small airway resistance among the groups

Figure 2 shows the small airway resistance indices of the two groups. Differences were observed across the groups. Both groups have normal large airway function and have no difference in FEV1 (% predicted) (Figure 2a). The CVA group has small airway dysfunction, and its small airway resistance was significantly higher than that of the NCVA group (Figures 2b, c, d, and e)

4. Optimal FeNO level to define CVA

To distinguish CVA from chronic nonproductive cough, the constructed ROC curve (Figure 3) defines the optimal cutoff value for the level of FeNO. The area under the ROC curve was 0.874. The sensitivity and specificity of FeNO in detecting CVA from non-CVA were 81.33% and 84.00% at a cutoff point of 25 ppb, respectively. When using 30 ppb as the cutoff point, the specificity is 90.33%. Table 2 lists the sensitivity and specificity values for the tested different criteria.

5. Diagnostic value of small airway resistance and predictive value for CVA by combining FeNO and small airway resistance (Figures 4, 5).

Figure 4 shows that the area under the ROC curve of FeNO was 0.874, whereas that of MEF, MEF25, MEF50, MEF75, and MVV (% predicted) was 0.666, 0.650, 0.671, 0.567, and 0.589, respectively. The area under the ROC curve of FeNO combined with MEF (% predicted) was 0.883, and that combined with MEF50 (% predicted) was 0.886 (Figure5).

Discussion

The diagnosis of CVA based on therapeutic efficacy leads to drug abuse and difficult diagnosis (20, 21). In the Chinese National Guidelines on Diagnosis and Management of Cough, detection using PFT and BHR is recommended as the first line test for the diagnosis of CVA (17). PFT is applied to almost the entire tertiary hospitals in China. However, BHR is used only in 65.1% of these hospitals and is mostly distributed in the grade-A tertiary hospitals (22). Although these tests are valuable, BHR is time-consuming and labor dependent. This study used a large sample of patients with chronic cough. We are the first to evaluate the value of FeNO combined with small airways in CVA prediction.

In this study, FeNO measurement can be used as a diagnostic tool for distinguishing CVA from chronic cough. In our study, the area under the ROC curve was estimated to be 0.874 for FeNO, and the optimal diagnostic cutoff point was 25 ppb (with 81.3% sensitivity and 84.0% specificity). When using 30 ppb as the cutoff point, the specificity was 90.3%. This finding suggested that the FeNO measurement is useful in CVA diagnosis from chronic cough or in the exclusion of CVA. However, Fang Yi et al. (23) reported that in distinguishing CVA from chronic cough, the optimal cutoff point for FeNO is 33.5 ppb (with 69.6% sensitivity and 85.1% specificity). Their study obtained higher optimal cutoff point and lower sensitivity than those in our study. According to Maniscalco (24), the optimal cutoff point that distinguishes CVA from chronic cough is 33.0 ppb (with 92% sensitivity and 88% specificity). Higher optimal cutoff point

and sensitivity were observed compared with our study. The inclusion criteria of patients and the sample sizes explain the differences found in our study.

The pathophysiological features of CVA are similar to those of typical asthma. The small airways account for a large part of the total surface of the airway, and play an important role in the pathophysiology of asthma (25, 26). The PFT values for small airway function (MEF, MEF25, MEF50, and MEF75) with CVA group were lower than with NCVA group. The PFT values of large airways (FVC and FEV1) were not significantly different between the CVA and NCVA groups ($P>0.05$). The forced expiratory volume in one second (FEV1) is often used to monitor asthma control and large airway function that usually occurs in CVA patients (27, 28). In our study, small airway dysfunction was present in a large proportion of CVA patients at baseline; these patients have normal large airway function. Therefore, the measurement of small airway function contributes to the diagnosis of CVA.

Increased FeNO concentration at enrollment was correlated with a decline in small airway function in CVA group. ROC analysis results showed the level of FeNO ≥ 25 ppb and abnormal MEF(% predicted) and MEF50(% predicted) in CVA group with an area under the curve (AUC) of 0.883 (95% CI: 0.85, 0.91) and 0.886 (95% CI: 0.85, 0.92). This study is the first to report the use of FeNO combined with small airway resistance in diagnosis of patients with CVA.

Several limitations are observed in this retrospective study. First, we use the BHR to determine hyper-responsiveness and to confirm the subjects of CVA, thereby leading to false positive and negative results. Second, as a biomarker, the FeNO values can be influenced by some factors. We excluded current smokers and tried our best to exclude cases with concomitant disease that may affect the outcome. However, we did not exclude ex-smokers because Wagener et al. (29) reported that the smoking history does not affect FeNO. Hence, the conclusion will not be biased by this situation. Third, although we included the subjects with cough that persisted for 8 weeks, very few post-infection subjects were included in our sample. The cutoff value and the sensitivity and specificity of FeNO may differ with the situation.

In conclusion, more than half of CVA subjects showed evidence of small airway dysfunction. FeNO levels are higher in patients with CVA compared with other causes of chronic cough and are correlated with small airway disease. FeNO measurement is a diagnostic tool that can be used as an alternative to BHR tests for differentiating CVA from chronic cough. A combination of the level of FeNO (≥ 25 ppb) and abnormal small airway function suggest the probability of CVA. The measurements of FeNO and small airway resistance are simple, reproducible and noninvasive. Diagnosis based on the pathophysiological condition of the patient rather than on the therapeutic response of the patients resulted in rapid diagnosis and avoided unnecessary treatments.

The Declaration of Interest

The authors have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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Table 1 Baseline characteristics of 150 patients with CVA and 300 patients with NCVA

Parameter	CVA (N = 150)	NCVA (N = 300)	p
Mean age, years	39.82±12.90	41.22±13.11	0.285
Sex (M:F), n	45:105	106:194	0.29
Height (cm)	161.92±7.65	162.93±7.58	0.183
Weight (kg)	59.91±10.19	60.36±11.49	0.687
Body surface area (m ²)	1.63±0.15	1.64±0.17	0.543
FeNO (ppb), median (interquartile range)	42 (41)	16 (11)	0.000
VC (%predicted)	97.22±11.09	95.12±11.40	0.063
MVV (% predicted)	95.64±15.59	99.86±14.82	0.005
FVC (% predicted)	104.04±12.06	101.96±11.95	0.083
FEV1 (% predicted)	98.83±12.41	100.97±10.94	0.074
FEV1/FVC	81.09±6.50	84.15±5.72	0.000
PEF (% predicted)	85.86±17.82	84.15±18.53	0.186
MEF (% predicted)	88.56±24.24	100.45±19.56	0.000
MEF25 (% predicted)	84.98±30.90	100.24±30.75	0.000
MEF50 (%predicted)	82.63±22.87	95.21±21.81	0.000
MEF75 (% predicted)	84.83±18.85	90.32±22.69	0.007

Notes: The pulmonary function values are presented as percentage predicted values (% predicted). Data are expressed as mean ± SD unless otherwise indicated.

Abbreviations: CVA, Cough variant asthma; M, male; F, female; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; VC, vital capacity; MVV, maximum voluntary ventilation; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; PEF, peak expiratory flow; MEF, maximal midexpiratory flow; MEF25, forced expiratory flow at 25% of the FVC; MEF50, forced expiratory flow at 50% of the FVC; MEF75, forced expiratory flow at 75% of the FVC.

Table 2 Diagnostic value of FeNO on different cutoff points.

	Threshold	Sensitivity	Specificity
FeNO value	>18 ppb	89.33	60.67
FeNO value	>19 ppb	88.67	64.67
FeNO value	>20 ppb	86.00	68.67
FeNO value	>21 ppb	84.00	71.33
FeNO value	>22 ppb	82.67	73.33
FeNO value	>24 ppb	82.67	81.33
FeNO value	>25 ppb	81.33	84.00
FeNO value	>26 ppb	77.33	85.33
FeNO value	>27 ppb	73.33	86.67
FeNO value	>28 ppb	71.33	88.00
FeNO value	>29 ppb	66.67	89.33
FeNO value	>30 ppb	64.00	90.33

Abbreviations: FeNO, fractional exhaled nitric oxide; ppb, part per billion.

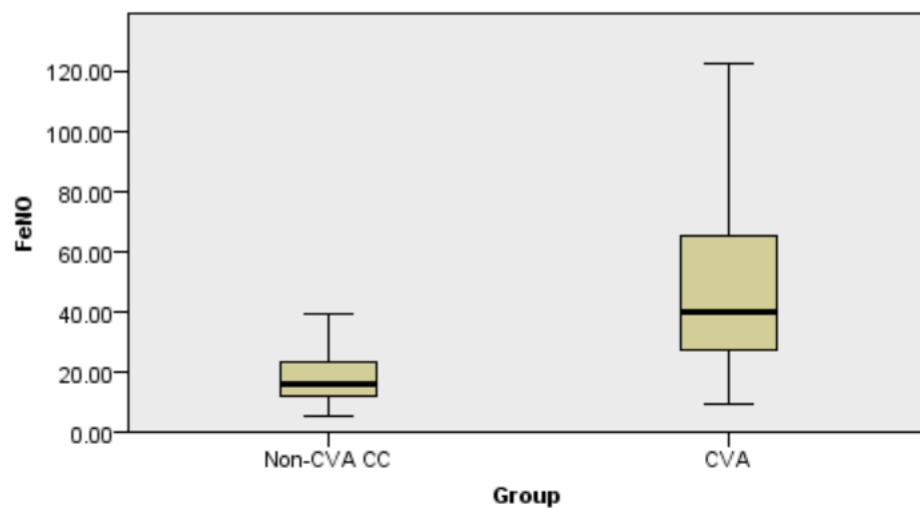


Figure 1. Comparison of FeNO level between the CVA group and NCVA group

Abbreviations: FeNO, fractional exhaled nitric oxide; ppb, part per billion; CVA, Cough variant asthma

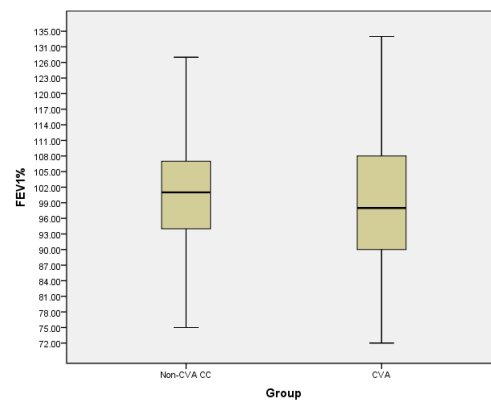


Figure 2a. Comparison of FEV1 (% predicted) between the two groups

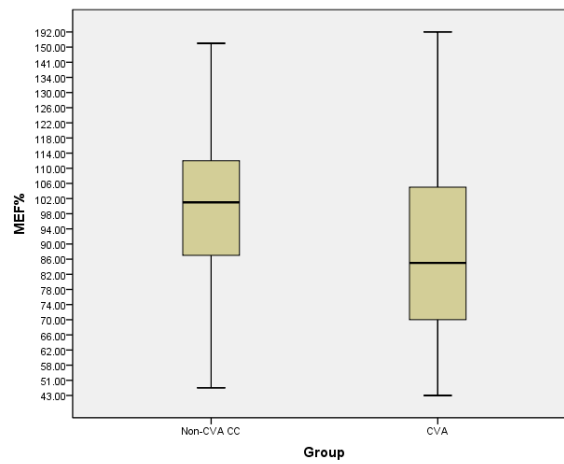


Figure 2b. Comparison of MEF (% predicted) between the two groups

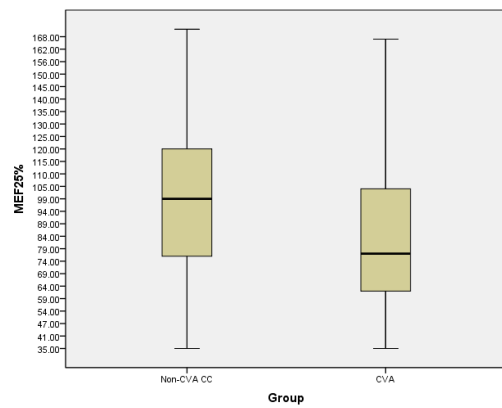


Figure 2c. Comparison of MEF25 (% predicted) between the two groups

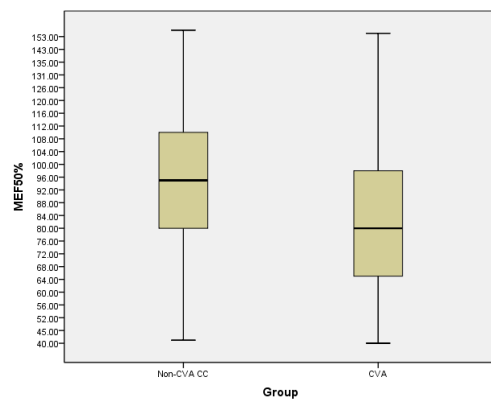


Figure 2d. Comparison of MEF50 (% predicted) between the two groups

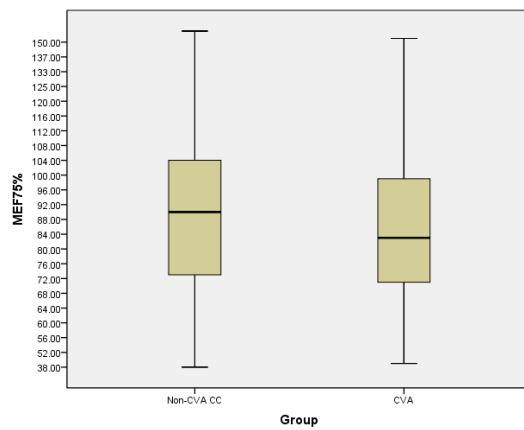


Figure 2e. Comparison of MEF75 (% predicted) between the two groups

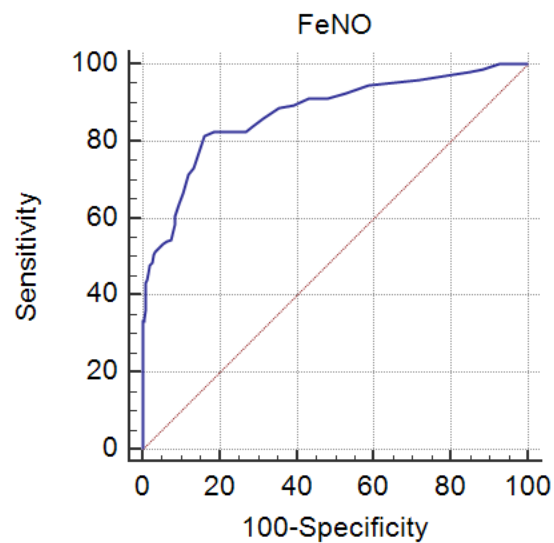


Figure 3. Receiver Operator Curves (ROC) analysis of the sensitivity and specificity of FeNO for the diagnosis of CVA. **Abbreviations:** FeNO, fractional exhaled nitric oxide

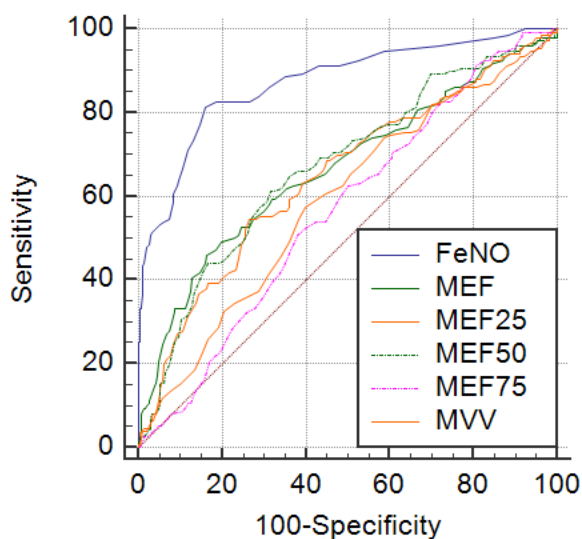


Figure 4. ROC curve analysis of FeNO, MEF, MEF25, MEF50, MEF75, and MVV (% predicted) for CVA diagnosis. **Abbreviations:** ROC, receiver operating characteristic; FeNO, fractional exhaled nitric oxide; MEF, maximal midexpiratory flow; MEF25, forced expiratory flow at 25% of the FVC; MEF50, forced expiratory flow at 50% of the FVC; MEF75, forced expiratory flow at 75% of the FVC; MVV, maximum voluntary ventilation; AUC, area under the curve

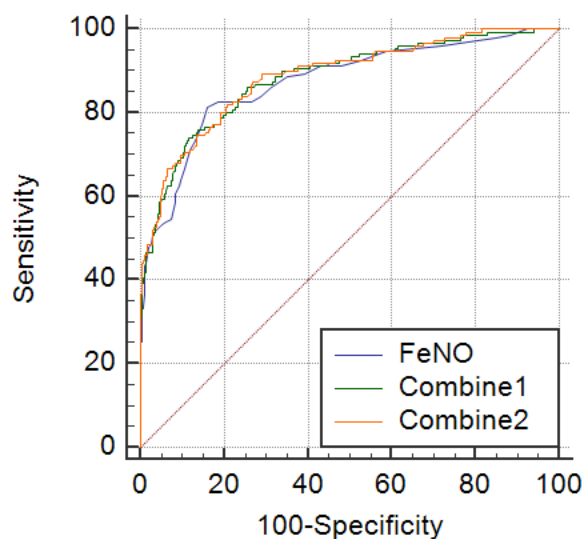


Figure 5. Predictive value for CVA by combining FeNO and small airway resistance; combination 1: FeNO+MEF (% predicted); combination 2: FeNO+MEF50 (% predicted).

Abbreviations: ROC, receiver operating characteristic; FeNO, fractional exhaled nitric oxide; MEF, maximal midexpiratory flow; MEF50, forced expiratory flow at 50% of the FVC; AUC, area under the curve