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Airway inflammation, bronchial hyperresponsiveness, and anti-asthma therapy responses in cough variant asthma and classic asthma with FEV_1% ≥80% predicted

Xue Zhang[1†], Chengjian Lv[1†], Huijuan Hao[1†], Jingwang Lin[1], Min Zhang[1*] and Xue Tian[1*]

Abstract

Objective To explore the differentiation of airway inflammation, bronchial hyperresponsiveness and anti-asthma therapy responses between the cough variant asthma (CVA) and classic asthma (CA) patients with FEV_1% ≥80% predicted.

Methods In the first monocentre retrospective cross-sectional study, 402 patients with suspicion of CA and 544 patients with chronic cough were enrolled. Further prospective monocentre study was conducted and 66 patients of suspected asthma with negative bronchial dilation test (BDT) but positive bronchial challenge (BCT) test were enrolled and followed up for 4 weeks.

Results CA patients had higher fractional exhaled nitric oxide (FENO) values than CVA patients (36.0 ppb vs. 24.0 ppb, $p < 0.0001$). The predictive value of FENO for positive BCT was significantly lower in chronic cough patients compared to those with suspicion of CA (AUC = 0.603 vs. 0.728). Following four weeks anti-asthma therapy, both the CVA and CA groups showed significant improvement in both the large and small airway function and symptom relief. There was no significant difference between the respective groups. The two most valuable spirometric variables for predicting a positive response to anti-asthma treatment were the improvements of FEV_1 (ΔFEV_1, cut-off values = 90 ml for CA and 110 ml for CVA) and FEV_1% (ΔFEV_1%, cut-off values = 3.49% for CA and 2.59% for CVA) after BDT in baseline of CA and CVA patients, respectively.

Conclusion Patients with CVA exhibited lower levels of airway eosinophilic inflammation compared to those with mild CA. Most patients with mild CA and CVA could benefit promptly from anti-asthma treatment. Additionally, an

†Xue Zhang, Chengjian Lv and Huijuan Hao contributed equally to this work and share first authorship.

*Correspondence:
Min Zhang
zhangmin@sjtu.edu.cn
Xue Tian
lwtianxue@126.com

Full list of author information is available at the end of the article

improvement in FEV_1 and FEV_1% during BDT can potentially predict positive responses to anti-asthma therapy in both groups.

Keywords Cough variant asthma, Classic asthma, Bronchial hyperresponsiveness, Airway inflammation, Anti-asthma therapy

Introduction

Mild classic asthma (CA) is the most prevalent type of asthma and typically exhibits a normal forced expiratory volume in one second (FEV_1), affecting around 50–75% of patients with CA [8]. Unfortunately, the mild symptoms and near-normal FEV_1 levels associated with mild asthma create substantial diagnostic challenges in clinical practice [18].

Cough-variant asthma (CVA), a distinct phenotype presenting with chronic cough as the cardinal symptom, shares similar diagnostic dilemmas despite its association with bronchial hyperreactivity (BHR) [4, 19, 23]. However, it is still unclear regarding phenotypic differentiation between CA and CVA in patients with FEV_1% ≥80% predicted, particularly in airway inflammation, large- and small-airway function, bronchial hyperresponsiveness, and anti-asthma therapy responsiveness.

Currently, BHR is used to detect variable expiratory airflow limitation of asthma, which is often reflected by the bronchial challenge test (BCT) [9]. However, as BCT is time-consuming, expensive, and carries bronchospasm risk, it is poorly applied in all hospitals, especially in primary hospitals [26]. Furthermore, for CA and CVA patients with $FEV_1 \geq 80\%$ predicted, due to mild and atypical symptoms, primary hospitals are often the first choice [5]. Because of the limited diagnostic utility of BCT test, many CA or CVA patients with $FEV_1\% \geq 80\%$ predicted were undiagnosed and untreated. As such, it is imperative to identify cost-effective, less hazardous, and straightforward approaches to evaluate BHR at the earliest, whether it be singularly or jointly.

Studies have shown that forced expiratory flow between 25% and 75% (MMEF), forced expiratory flow at 50% of forced vital capacity (MEF50), and forced expiratory flow at 75% of forced vital capacity (MEF25) are linked to the functional evaluation of small airway and asthma exacerbations [21, 36, 37].

Fractional exhaled nitric oxide (FENO) is a non-invasive and well-accepted biomarker of type 2 (T2) airway inflammation [22, 29]. FENO levels increase in asthma and correlate with eosinophilic inflammation [22]. Our previous investigation discovered that CVA patients exhibited elevated FENO levels, increased EOS% in blood, and reduced MMEF [1]. The combination of FENO and either MEF50 or MMEF can be used to predict BHR in asthmatic patients with normal FEV_1 [2]. However, the differences in airway inflammation characteristics and large/small airway function, along with the predictive values of such combined parameters in predicting BHR of CA and CVA, are still inconclusive, especially for asthmatic populations with $FEV_1 \geq 80\%$ predicted.

Early initiation of long-term inhaled corticosteroids (ICS) after the onset of asthma is beneficial in enhancing lung function and reducing BHR [10, 11]. The Global Initiative for Asthma (GINA) guideline recommends a diagnostic criterion for asthma as an increase in FEV_1 greater than 200 mL and more than 12% following anti-asthma therapy for a duration of one to three months [14]. In our previous study, following four weeks of anti-asthma therapy, 54.9% of suspected CA patients achieved an improvement of $FEV_1 > 200$ mL [16]. However, there is a dearth of evidence verifying which patients can benefit from diagnostic treatment. Consequently, presenting an efficient method to predict the response to anti-asthma therapy is necessary.

The aim of this study was to examine the differences in the function of central and small airways, BHR, FENO, and EOS between CVA and CA patients with $FEV_1 \geq 80\%$ predicted. In addition, we intended to compare the predictive values of small airway function variables and FENO on BHR. The secondary objective was to investigate the differences and predictive value of the response to anti-asthma therapy between CVA and CA with $FEV_1 \geq 80\%$ predicted.

Methods

Participants and study design

Part I

This monocenter retrospective cohort study was approved by the Institutional Review Board (no. [2020]30) and a waiver of informed consent was given for our study (no. 2017KY159). We included 544 patients with chronic cough who fulfilled the eligibility criteria [24], including age range of 18–75 years, normal chest CT results, and the presence of chronic cough as the main or solitary symptom for at least 8 weeks, and $FEV_1\% \geq 80\%$ predicted. We also enrolled 402 individuals with suspected classic asthma who fulfilled the same eligibility requirements as the chronic cough group, with the addition of variable respiratory symptoms including wheezing, chest tightness, and shortness of breath, with or without cough.

All patients had a detailed medical history (including allergic rhinitis and smoking history records), physical examination, and anti-asthmatic therapy responses

recorded in a standardized outpatient electronic medical record system. All patients underwent spirometry, BCT, and FENO measurements.

The exclusion criteria were as follows: current smoking or >10 pack-year smoking history; recent respiratory infection (≤8 weeks) or abnormal HRCT scan; concomitant severe systemic disorders; COPD/asthma-COPD overlap; chronic rhinosinusitis with nasal polyps (CRSwNP, confirmed by paranasal sinus CT); gastroesophageal reflux disease (GERD) with typical reflux symptoms; recent (≤4 weeks) use of montelukast, long-acting β_2-agonists (LABA), theophylline, anticholinergic agents, or inhaled or oral corticosteroids. Pregnant subjects were also excluded.

Based on the BCT results, suspected classic asthma patients and chronic cough patients were grouped as follows: CVA group vs. BCT (-) group; CA group vs. BCT (-) group.

Part II

Another monocenter prospective study was approved by the Institutional Review Board (no. [2020]30) and registered on chictr.org.cn (No. ChiCTR2000029065). Informed consent was obtained for all subjects. FENO was the main outcome index observed in this study. The difference between the test group and the control group was 15.5 ppb, and the standard deviation was 19.0 ppb. Set alpha = 0.05 on both sides, the degree of assurance (1-β) was 0.9, and the sample size ratio of the two groups was 1:1. The sample size of the CA group and CVA group was both 32 cases calculated by R language. Considering the 10% loss of follow-up rate, at least 35 cases in each group are ultimately required, with a total sample size of at least 70 cases.

A total of 118 participants were consecutively recruited via the Pulmonary Outpatient Clinic of Shanghai General Hospital (Shanghai, China) from April 1, 2020, to January 30, 2021. Patients with negative bronchodilation test (BDT) were included in this study, and the other inclusion criteria were the same as those in Part I. Correspondingly, the exclusion criteria were also those described in Part I.

- Patients who had negative BDT but had a high risk of asthma were performed asthma control test (ACT), or cough evaluation test (CET) before subjecting to BCT on the second day between 8:00–10:00 am. From the initial cohort of 118 participants, 52 demonstrating negative BDT and BCT results were excluded. The remaining 66 patients (31 CA and 35 CVA) meeting $FEV_1 \geq 80\%$ predicted, BCT-positive, and BDT-negative) underwent a standardized 4-week ICS/LABA regimen using budesonide/formoterol (160/4.5 μg per actuation, Symbicort Turbuhaler™, AstraZeneca) administered twice daily. After four weeks of treatment, follow-up measures including spirometry, ACT, or CET were performed at the same time as the initial visit (8:00–10:00 am). To ensure protocol compliance, systematic weekly monitoring (including symptom recovery time) was conducted via telephone consultations and WeChat-based communication (a widely used Chinese social media platform). It was defined as the duration from treatment initiation to improvement of symptoms, where symptom advancement was confirmed through a decrease in ACT score or an increase in CET score. Following 4-week ICS/LABA therapy, patients were stratified by spirometric response into three groups: (1) improvement-$FEV_1 > 200$ mL and improvement-$FEV_1\% > 12\%$; (2) improvement-$FEV_1 > 200$ mL and improvement-$FEV_1\% \leq 12\%$; (3) improvement-$FEV_1 < 200$ mL and improvement-$FEV_1\% < 12\%$ (Among the 66 patients analyzed, none demonstrated concurrent spirometric improvements of $FEV_1 < 200$ mL with $FEV_1\% \geq 12\%$).

Spirometry, FENO, IOS measurements, BDT, BCT, peripheral blood tests, the assessment of asthma control, cough evaluation, and symptom improvement were performed in accordance with guidelines. Details on the above measurements are provided in Supplementary Methods.

Symptom improvement was defined as an improvement of ACT or CET (ΔACT or ΔCET) of 3 or greater from baseline to 4 weeks of treatment [32].

Small-airway dysfunction (SAD) was defined as the presence of two measurements, MEF50, MEF25 or MMEF, with values lower than 65%.

ΔFEV_1 and $\Delta FEV_1\%$ indicate large airway function improvement in BDT at baseline and ΔMEF25, ΔMEF50 and ΔMMEF indicate small airway function improvement in BDT at baseline.

A positive anti-asthma treatment was defined as improved symptoms and an increase of more than 200 mL in FEV_1 after ICS/LABA treatment.

Statistical analysis

Analysis was conducted with GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA). Descriptive statistics were used to present baseline data. The Kolmogorov-Smirnov test was applied to verify the normality of the distribution. The mean and standard deviation (SD) were used to indicate the normally distributed data, while the median and interquartile range (IQR) were used to indicate non-normally distributed data. Independent samples were compared using either the Student's t-test (2-tailed) or Mann-Whitney U test. Additionally, count data were expressed as percentages, and between-group

comparisons were executed using the chi-squared test (χ^2).

The performance of each variable in predicting the outcome was assessed by measuring its area under the receiver-operating characteristic (ROC) curve. The resulting AUC of multiple logistic models of the 2 variables was used as a measure of the joint prediction performance. The Delong test was used to determine whether the multiple logistic models would significantly improve the prediction performance. We set the threshold for statistical significance at $p < 0.05$ for all analyses conducted.

Results

Part I

Baseline characteristics

Of all 946 adults with FEV_1% ≥ 80% predicted, 544 patients were suspected CVA patients (278 BCT-positive and 266 BCT-negative) and 402 patients were suspected CA patients (202 BCT-positive and 200 BCT-negative). There were no significant differences in age, height, weight, body mass index (BMI), smoking history, and allergic rhinitis in the CA with $FEV_1 \geq 80\%$ predicted vs. BCT (-) groups, and CVA vs. BCT (-) groups (Table S1). Most demographic data and clinical features did not differ between the CA and CVA groups at baseline (Table 1).

Compared with the BCT (-) group, FEV_1 (%pred), FEV_1/FVC, and PEF (%pred) were lower in the CA group ($p < 0.0001$ respectively, Table 1), although still within the normal range. As expected, MEF50 (%pred), MEF25 (%pred), and MMEF (%pred) in the CA group were lower than those in BCT (-) group ($p < 0.0001$ for all comparisons, Table 1). Similarly, a higher percentage of small airway dysfunction was found in the CA group (46.04%), compared with the BCT (-) group (13.0%) ($p < 0.0001$, Table 1). FENO was significantly elevated in the CA group compared with the BCT (-) group ($p < 0.0001$, Table 1). EOS% in peripheral blood in the CA group was higher than that in the BCT (-) group ($p < 0.0001$, Table 1).

Lower FEV_1/FVC, PEF (%pred), MEF50 (%pred), MEF25 (%pred), MMEF (%pred), and a higher ratio of

Table 1 Demographic data, spirometric variables, and values for FENO and peripheral eosinophils of patients with positive or negative bronchial provocation tests

Variables	CA patients	CVA patients	*P* values
n	202	278	-
Male, n (%)	79 (39.1%)	83 (29.86%)	0.058
Age, years	44.0 (21.25)	47.0 (22.0)	0.249
Height, m	1.61 (0.146)	1.61 (0.12)	0.324
Weight, kg	60.0 (17)	58.5 (15)	0.272
BMI, kg/m^2	23.13 (4.88)	22.77 (3.99)	0.544
Past smoking history (n / %) *	31 (15.35%)	39 (14.03%)	0.6863
Allergic rhinitis (n / %)	60 (29.70%)	67 (24.10%)	0.1695
FVC, % predicted	101.9 (15.63)	101.7 (16.12)	0.803
FEV_1, % predicted	97.85 (14.83)	97.6 (15.12)	0.786
FEV_1/FVC, %	**79.83 (8.53)**	**80.63 (9.08)**	**0.049**
PEF, % predicted	100 (17.19)	101.2 (15.59)	0.276
MEF75, % predicted	94.1 (17.52)	94.51 (17.4)	0.653
MEF50, % predicted	72.4 (23.42)	72.95 (25.15)	0.751
MEF25, % predicted	58.05 (27.52)	58.40 (29.58)	0.555
MMEF, % predicted	66.63 (22.25)	68.35 (25.48)	0.698
SAD, n (%)	93 (46.04%)	111 (39.93%)	0.1812
FENO, ppb	**36.0 (58)**	**24.0 (30.25)**	**< 0.0001**
WBC, ×10^9/L [§]	6.6 (2.207)	6.5 (2.5)	0.775
EOS in blood, cells/μl [§]	0.185 (0.26)	0.13 (0.2)	0.065
EOS in blood, % [§]	2.85 (3.575)	2.3 (3.0)	0.131
PD_{20}, mg	0.7165 (0.9409)	0.7927 (1.18)	0.231

BMI, Body mass index; FVC, Forced vital capacity; FEV_1, Forced expiratory volume in 1 s; PEF, Feak expiratory flow; MEF25, Forced expiratory flow at 75% of FVC; MEF50, Forced expiratory flow at 50% of FVC; MEF75, Forced expiratory flow at 25% of FVC; MMEF, Forced expiratory flow at 25–75% of FVC; %pred, actual measured value of spirometric indices as a percentage of predicted value; FENO, Fractional exhaled nitric oxide; ppb, parts per billion; EOS, Eosinophils; PD_{20}, Provocative dose causing a 20% fall in FEV in the first second

SAD was identified if 2 of the variables $MEF_{50\%}$, $MEF_{25\%}$ and MMEF were lower than 65%

Median (IQR) values for all

* < 10 pack-year smoking history

[§] $n = 138$ for CA group and $n = 171$ for CVA group

Bold font indicates statistical significance

small airway dysfunction were observed in the CVA group compared with the BCT (-) group ($p < 0.001$ for all). Furthermore, FENO and EOS% in peripheral blood were also dramatically increased in the CVA group compared with the BCT (-) group ($p < 0.0001$ for all) (Table 1).

Differences in lung function and FENO values between CA and CVA patients with FEV_1% ≥ 80% predicted

Baseline data (age, height, weight, BMI, smoking history, and history of allergic rhinitis) were matched between CA and CVA patients. Although there were no statistically significant inter-group differences in FVC (%pred), FEV_1 (%pred), PEF (%pred), MEF75 (%pred), MEF50 (%pred), MEF25 (%pred), and MMEF (%pred), a high ratio of small airway dysfunction was found in the CA group (13%). Interestingly, we found that the value of FEV_1/FVC was slightly lower in CA subjects compared to that of CVA patients ($p = 0.049$). FENO was significantly elevated in the CA group compared with the CVA group ($p < 0.001$), while EOS and EOS% did not differ between the two groups. Although BHR degree, which was reflected by PD_{20}, did not differ between the two groups, it showed an elevated trend in the CA group ($p = 0.231$).

Differences in diagnostic accuracy of small airway function variables and FENO used for predicting BCT between suspected CA and chronic cough patients with FEV_1% ≥ 80% predicted

ROC curves were used to evaluate the ability of the variables to predict positive BCT.

For small airway function variables, the AUCs for a positive BCT diagnosis were 0.734 (95% CI 0.688–0.776) for MEF50, 0.715 (95% CI 0.668–0.758) for MMEF, with cut-off values of 76.2% and 78.8%, respectively, in suspected CA patients with FEV_1% ≥ 80% predicted (Table 2; Fig. 1). The AUCs for a positive BCT diagnosis were 0.738 (95% CI 0.699–0.775) for MEF50, 0.716 (95% CI 0.677–0.754) for MMEF, with cut-off values of 87.1% and 73.7%, respectively, in chronic cough patients with FEV_1% ≥ 80% predicted (Table 3; Fig. 2), indicating that MEF50 and MMEF have predictive value both in CA and CVA patients with different cut-off values.

For FENO, a noninvasive biomarker of eosinophilic airway inflammation, the predictive value for BCT in chronic cough patients was much lower than that in suspected CA patients (AUC = 0.603 (95% CI 0.560–0.644) in chronic cough patients and AUC = 0.728 (95% CI 0.682–0.771) in suspected CA patients), with cut-off values of 27 ppb and 30 ppb, respectively (Tables 2 and 3; Figs. 1 and 2).

We investigated if predicting BCT could be improved by combining spirometry measurements with FENO by repeating the ROC analyses. The AUCs of MEF50 and MMEF joined with FENO in patients with CVA (AUCs = 0.834 and 0.824, respectively) were also lower than those in patients with CA (AUCs = 0.782 and 0.767, respectively), which were dramatically higher than the AUCs of single MEF50 and MMEF ($p < 0.0001$ for all) (Table S2).

Part II

Demographic and clinical characteristic data of CA patients and CVA patients with FEV_1% ≥ 80% predicted and positive BCT before ICS/LABA treatment

A total of 31 CA patients and 35 CVA patients with FEV_1 ≥ 80% predicted, positive BCT, and negative BDT underwent spirometry after ICS/LABA for 4 weeks. As shown in Table 4, demographic variables did not differ at baseline between the CA and CVA groups. Compared with the CVA group, FENO and R5-R20 were higher in the CA group at baseline ($p = 0.031$ for FENO and = 0.043 for R5-R20), although EOS% in peripheral blood, PD20,

Table 2 Optimal cut-off values and other measures of usefulness for predicting bronchial hyperresponsiveness in suspected classic asthma patients with FEV_1% ≥ 80%

Characteristic variables	AUC	95% CI of AUC	Cut-off value†	Sensitivity %	Specificity %	PPV %	NPV %	*p* value
FEV_1, %pred	0.621	0.572 to 0.669	≤ 98.8	54.95	66.5	62.4	59.4	< 0.0001
FEV_1/FVC, %	0.672	0.623 to 0.717	≤ 81.07	60.89	69	66.5	63.6	< 0.0001
PEF, %pred	0.631	0.582 to 0.678	≤ 109.83	74.75	45.5	58.1	64.1	< 0.0001
MEF75, %pred	0.688	0.641 to 0.733	≤ 94.6	54.46	76	69.6	62.3	< 0.0001
MEF50, %pred	**0.734**	**0.688 to 0.776**	**≤ 76.2**	**58.42**	**77**	**72**	**64.7**	**< 0.0001**
MEF25, %pred	0.652	0.603 to 0.698	≤ 64.1	62.38	64.5	64	62.9	< 0.0001
MMEF, %pred	**0.715**	**0.668 to 0.758**	**≤ 78.8**	**74.26**	**60.5**	**65.5**	**69.9**	**< 0.0001**
FENO, ppb	**0.728**	**0.682 to 0.771**	**> 30**	**57.92**	**81.5**	**76**	**65.7**	**< 0.0001**
EOS in blood, cell/μl	0.670	0.608 to 0.728	> 0.16	55.07	77.19	74.5	58.7	< 0.0001
EOS% in blood, %	0.673	0.611 to 0.730	> 2.8	50	80.7	75.8	57.1	< 0.0001

AUC, Area under the curve; PPV, Positive predictive values; NPV, Negative predictive values; 95% CI, 95% confidence interval of odds ratio; *P* value, the *p* value of the logistic regression test

The other abbreviations are as defined for Table 1

†The cut-off points were selected by maximizing the sum of sensitivity and specificity

Bold font indicates AUC higher than 0.70

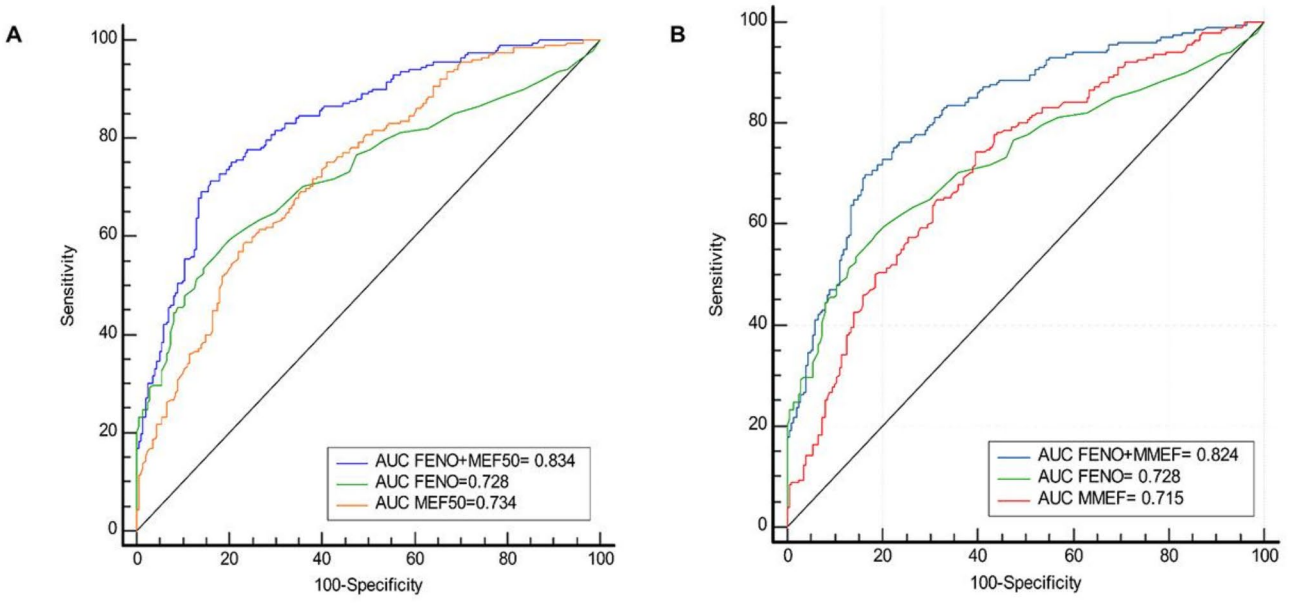

Fig. 1 ROC curves for the models of FEFs combined with FENO for predicting positive bronchial provocation tests in suspected classic asthma patients with $FEV_1\% \geq 80\%$. (**A**) MEF50 combined with FENO. $AUC_{Model} = 0.834$ (95% CI, 0.794 to 0.869); $AUC_{FENO} = 0.728$ (95% CI, 0.682 to 0.771; $p < 0.001$, compared with the model); $AUC_{MEF50} = 0.734$ (95% CI, 0.688 to 0.776; $p < 0.001$, compared with the model) (**B**) MMEF combined with FENO. $AUC_{Model} = 0.824$ (95% CI, 0.783 to 0.860); $AUC_{FENO} = 0.728$ (95% CI, 0.682 to 0.771; $p < 0.001$, compared with the model); $AUC_{MMEF} = 0.715$ (95% CI, 0.668 to 0.758; $p < 0.001$, compared with the model). Abbreviations: ROC, receiver operating characteristic; FENO, fractional exhaled nitric oxide; AUC, area under the curve; MEF50: forced expiratory flow at 50% of forced vital capacity; MEF25: forced expiratory flow at 75% of forced vital capacity; MMEF: maximum mid-expiratory flow

Table 3 Optimal cut-off values and other measures of usefulness for predicting bronchial hyperresponsiveness in chronic cough patients

Characteristic variables	AUC	95% CI of AUC	Cut-off value†	Sensitivity %	Specificity %	PPV %	NPV %	*p* value
FEV_1%pred	0.638	0.596 to 0.678	≤ 97.86	52.16	71.43	65.6	58.8	< 0.0001
FEV_1/FVC, %	0.644	0.603 to 0.685	≤ 81.06	52.88	71.80	66.2	59.3	< 0.0001
PEF%pred	0.596	0.554 to 0.638	≤ 113.4	80.22	35.47	56.6	63.1	0.0001
MEF75%pred	0.669	0.627 to 0.708	≤ 94.2	50.36	74.81	67.6	59.1	< 0.0001
MEF50%pred	**0.738**	**0.699 to 0.775**	**≤ 87.1**	**76.26**	**57.14**	**65.0**	**69.7**	**< 0.0001**
MEF25%pred	0.657	0.615 to 0.697	≤ 69.8	69.42	54.14	61.3	62.9	< 0.0001
MMEF%pred	**0.716**	**0.677 to 0.754**	**≤ 73.7**	**63.67**	**68.05**	**67.6**	**64.2**	**< 0.0001**
FENO, ppb	0.603	0.560 to 0.644	> 27	43.88	78.95	68.5	57.4	< 0.0001
EOS in blood, cell/μl	0.612	0.557 to 0.666	> 0.07	76.02	45.03	61.0	62.4	0.0004
EOS% in blood, %	0.620	0.565 to 0.674	> 2.1	53.22	70.86	67.4	57.2	0.0001

The abbreviations are as defined for Tables 1 and 2

†The cut-off points were selected by maximizing the sum of sensitivity and specificity. Bold font indicates AUC higher than 0.70

symptom duration, and improvement times did not differ between the two groups. In addition, there were no statistically significant inter-group differences in $\Delta FEV_1\%$, ΔMEF25%, and ΔMMEF%, which were still higher in the CVA group than in the CA group at baseline.

Demographic and clinical characteristic data of CA patients and CVA patients with positive BCT

Overall, both central airway (FEV_1, PEF, and MEF75) and small airway indices (MEF50, MEF25, and MMEF) were dramatically improved in both CA and CVA groups after the 4-week treatment (Table 5). All patients with CA ($n = 31$) or CVA ($n = 35$) showed no exacerbation of asthma during the 4-week follow-up period. There were 26 patients with CA and 24 patients with CVA treated with ICS/LABA that improved clinically (Δ ACT/ Δ CET > 3). Collectively, 14 subjects (45.16%) in the CA group and 18 subjects (51.43%) in the CVA group displayed an FEV_1 improvement > 200 ml and > 12%, while 26 subjects (83.87%) in the CA group and 28 subjects (80%) in the CVA group displayed an FEV_1 improvement > 200 ml.

As shown in Table 5, among CA subjects, there were 14 patients with an improvement of $FEV_1 > 200$ ml and > 12%, 12 patients with an improvement of $FEV_1 > 200$ ml, and 5 patients with an improvement of $FEV_1 < 200$ ml and

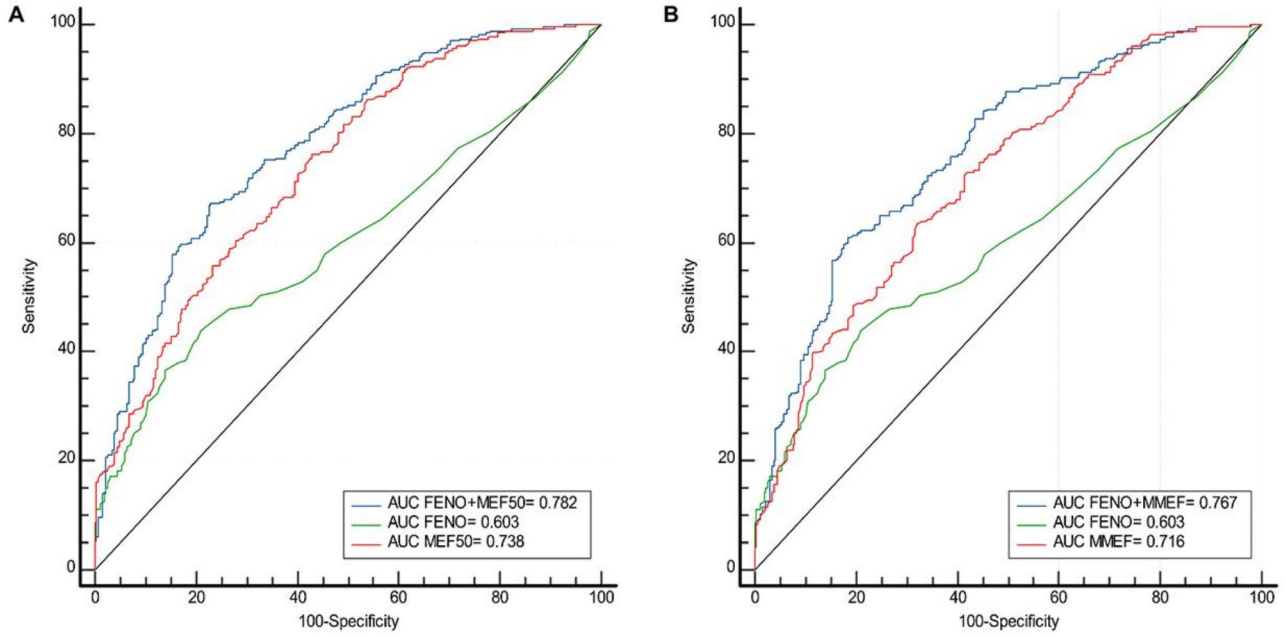

Fig. 2 ROC curves for the models of FEFs combined with FENO for predicting positive bronchial provocation tests in chronic cough patients. (**A**) MEF50 combined with FENO. AUC_{Model} = 0.782 (95% CI, 0.745 to 0.816); AUC_{FENO} = 0.603 (95% CI, 0.560 to 0.644; $p < 0.001$, compared with the model); AUC_{MEF50} = 0.738 (95% CI, 0.699 to 0.775; $p < 0.001$, compared with the model) (**B**) MMEF combined with FENO. AUC_{Model} = 0.767 (95% CI, 0.730 to 0.802); AUC_{FENO} =0.603 (95% CI, 0.560 to 0.644; $p < 0.001$, compared with the model); AUC_{MMEF} = 0.716 (95% CI, 0.677 to 0.754; $p < 0.001$, compared with the model). Abbreviations: ROC, receiver operating characteristic; FENO, fractional exhaled nitric oxide; AUC, area under the curve; MEF50: forced expiratory flow at 50% of forced vital capacity; MEF25: forced expiratory flow at 75% of forced vital capacity; MMEF: maximum mid-expiratory flow

< 12%. After the 4-week treatment, the ΔACT score was higher in patients with an improvement of $FEV_1 > 200$ ml than in patients with an improvement of $FEV_1 < 200$ ml and < 12%, while symptom recovery time was shorter in patients with an improvement of $FEV_1 > 200$ ml ($p = 0.013$). However, FENO and small airway indices were not significantly different among the three groups at baseline.

Among CVA subjects, there were 18 patients with an improvement of $FEV_1 > 200$ ml and > 12%, 10 patients with an improvement of $FEV_1 > 200$ ml, and 7 patients with an improvement of $FEV_1 < 200$ ml and < 12%. Moreover, there were significant inter-group differences in FENO, ΔFEV_1, and ΔFEV_1% before ICS/LABA treatment ($p = 0.004$ for FENO, 0.010 for ΔFEV_1, and 0.014 for ΔFEV_1%, respectively), which indicated that higher ΔFEV_1 or ΔFEV_1% predicted a better anti-asthma response. Similarly, compared with patients with an improvement of $FEV_1 < 200$ ml and < 12%, a higher ΔCET score and shorter symptom recovery time were shown in patients with an improvement of $FEV_1 > 200$ ml after ICS/LABA treatment ($p = 0.002$). However, small airway indices were not significantly different among the three groups at baseline.

Diagnostic accuracy of variables used for predicting anti-asthma therapy response in CA and CVA patients with FEV_1% ≥ 80% predicted

The prognostic value of these variables for predicting the efficacy of anti-asthma therapy was assessed by calculating the AUC (Table S3, Fig. 3). The largest AUCs in mild CA patients were the ΔFEV_1 (0.827, 95% CI 0.649 to 0.938), ΔFEV_1% (0.823, 95% CI 0.644 to 0.936), ΔMEF50 (0.812, 95% CI 0.631 to 0.929), and ΔMEF50% (0.800, 95% CI 0.618 to 0.921), taking the optimal cut-off values of 90 ml, 3.49%, 310 ml and 8.48%, respectively. The AUCs of FENO, ΔFEV_1, and ΔFEV_1% in CVA patients were 0.911, 0.842, and 0.806 with cut-off values of 19 ppb, 110 ml, and 2.59%, respectively.

Discussion

In clinical settings, clinicians are often face distinct clinical profiles between CA and CVA, particularly regarding eosinophilic inflammation, BHR and anti-asthma therapy. To understand the etiology of these asthmatic patients, we compared patients of diagnosed CVA and CA with $FEV_1 \geq 80\%$ predicted in baseline clinical characteristics, pulmonary function, FENO, eosinophilic inflammation, BCT prediction, and anti-asthma therapy responseness. Compared with CA, CVA exhibited lower FENO values (reflecting airway eosinophilic inflammation), lower EOS and EOS% in blood (reflecting systemic

Table 4 Demographic data, spirometric variables, FENO values, PD20 values, and peripheral eosinophils values of CA patients and CVA patients before ICS/LABA treatment

Variable	All subjects	CA	CVA	*p* value (CA vs. CVA)
n	66	31	35	-
Age, years	42.56 [15.14]	39.32 [14.21]	45.43 [15.55]	0.123
Height, m	1.656 [0.0831]	1.67 [0.0796]	1.643 [0.0853]	0.172
Weight, kg	63.48 [13.10]	65.42 [12.31]	61.77 [13.71]	0.173
BMI, kg/m^2	22.98 [3.354]	23.36 [3.393]	22.65 [3.333]	0.429
Symptom duration time, months	6 (6.25)	5 (8)	6 (6)	0.683
Symptom recovery time, days	7.5 (15.25)	7 (17)	8 (15)	0.738
ACT_1	-	17 (2)	-	-
CET_1	-	-	16 (3.0)	-
FENO, ppb	**32.5 (29.5)**	**38 (24)**	**26 (34)**	**0.031**
WBC, ×10^9/L	6.495 (2.335)	6.5 (2.49)	6.49 (2.08)	0.31
EOS in blood, cells/ul	0.13 (0.15)	0.14 (0.21)	0.11 (0.14)	0.137
EOS% in blood, %	1.7 (2.125)	1.9 (2.1)	1.4 (2)	0.292
FVC, L	3.395 (1.427)	3.52 (1.63)	3.22 (1.42)	0.061
FEV_1, L	2.765 (1.14)	2.84 (1.29)	2.69 (1.12)	0.096
FEV_1/FVC, %	81.28 [5.777]	80.77 [6.115]	81.73 [5.509]	0.724
PEF, L/s	6.46 (2.668)	6.47 (2.48)	6.45 (2.66)	0.857
MEF75, L/s	5.75 (2.267)	5.74 (2.35)	5.76 (1.97)	0.621
MEF50, L/s	3.065 (1.345)	3.32 (1.64)	3.06 (1.38)	0.175
MEF25, L/s	1.08 (0.908)	1.31 (0.96)	0.95 (0.71)	0.145
MMEF, L/s	2.535 (1.355)	2.68 (1.71)	2.37 (1.13)	0.117
FVC, %pred	98.32 (13.86)	98.4 (15.78)	97.38 (14.6)	0.787
FEV_1, % pred	95.07 (12.56)	95.17 (13.51)	95.02 (13.67)	0.857
PEF, %pred	94.47 (21.75)	87.45 (15.84)	96.65 (24.14)	0.067
MEF75, %pred	90.34 (24.57)	88.92 (21.38)	90.71 (25.99)	0.594
MEF50, %pred	73.23 (27.04)	75.28 (27.29)	72.3 (27.24)	0.738
MEF25, %pred	61.22 (25.32)	61.94 (21.66)	58.76 (27.24)	0.452
MMEF, %pred	68.23 (26.77)	67.6 (23.81)	68.55 (24.43)	0.468
R5*, kPa·L-1·s	4.1 (1.8)	4.2 (2)	3.965 (1.298)	0.369
R5, %pred*	120.4 (49.9)	129.7 (52.4)	108 (41.74)	0.265
R20*, kPa·L-1·s	2.9 (0.8)	2.9 (0.87)	2.915 (1.263)	0.698
R20, %pred*	104.2 (28.14)	109.7 (28.84)	103.2 (29.23)	0.904
R5-R20*, kPa·L-1·s	**0.9 (1.14)**	**1.0 (1.42)**	**0.575 (0.9025)**	**0.043**
R5-R20, %pred*	11.69 (32.55)	13.39 (39.62)	3.87 (28.15)	0.059
ΔFVC, mL	55 (200)	30 (190)	70 (210)	0.407
ΔFEV_1, mL	145 (160)	160 (160)	140 (140)	0.777
ΔPEF, mL/s	260 (890)	260 (750)	260 (920)	0.322
ΔMEF75, mL/s	355 (870)	360 (770)	350 (880)	0.594
ΔMEF50, mL/s	505 (630)	540 (520)	430 (830)	0.335
ΔMEF25, mL/s	265 (375)	290 (290)	260 (580)	0.422
ΔMMEF, mL/s	455 (395)	470 (280)	380 (820)	0.266
ΔFVC, %pred	1.535 (5.761)	0.64 (5.45)	1.66 (7.33)	0.342
ΔFEV_1, %pred	5.75 (6.577)	5.26 (5.76)	6 (5.91)	0.332
ΔPEF, %pred	3.59 (13.99)	3.25 (11.35)	3.64 (15.72)	0.253
ΔMEF75, %pred	5.87 (14.40)	5.92 (14.13)	5.82 (14.2)	0.639
ΔMEF50, %pred	15.73 (19.54)	18.06 (18.34)	12.89 (22.4)	0.358
ΔMEF25, %pred	26.85 (34.30)	26.26 (23.71)	27.91 (72.62)	0.842

Table 4 (continued)

Variable	All subjects	CA	CVA	*p* value (CA vs. CVA)
ΔMMEF, %pred	16.75 (18.75)	16.61 (14.56)	16.76 (26.23)	0.933
PD20, mg	0.1911 (0.3782)	0.2284 (0.3007)	0.1255 (0.4248)	0.559

ACT, Asthma control test; VAS, Visual analogue scale; CET, Cough evaluation test; R5, Total airway resistance at 5 Hz; R20, Central airway resistance at 20 Hz; R5-R20, Peripheral airway resistance as the difference between 5 and 20 Hz; X5, Reactance at 5 Hz; %: the improvement of spirometric indices as a percentage of baseline value. Δ: increase of spirometric indices in BDT; Δ %: the increase of spirometric indices as a percentage of baseline value in BDT

The other abbreviations are as defined for Table 1

Data expressed as Mean [SD] values and Median (IQR) values

*$n = 43$ for all subjects, 31 for CA and 12 for CVA

Bold font indicates statistical significance

eosinophilic inflammation), and milder BCT response (reflected by a lower PD_{20} of positive BCT).

Eosinophilic airway inflammation is a critical characteristic of asthma. CVA exhibits similar levels of eosinophilic airway inflammation to CA, but with less severe airway remodeling [27, 31]. Measuring EOS count and EOS% in the blood is an evidence-based standard measure of airway inflammation, as recommended by relevant guidelines [15]. EOS% were also related to asthma exacerbations and control. Similar to some previous studies [12], EOS% was increased in CVA and CA patients, compared with those in corresponding subjects negative for BCT. Our results also indicated that there was a higher EOS% and a lower PD20 values in CA patients. These suggested that the levels of eosinophil counts in blood might be a risk factor with an increased degree of BHR for the future development of asthma.

FENO is widely acknowledged as a biomarker for eosinophilic airway inflammation in the central airways, commonly elevated in asthma [20, 28]. Nevertheless, it has limited utility in detecting inflammation in the peripheral airways. Similar to previous studies [33, 35], our findings also indicated that FENO was elevated in the BCT-positive group of both chronic cough patients and suspected CA patients with $FEV_1 \geq 80\%$ predicted. On the other hand, FENO levels was obviously elevated in CA patients compared to CVA patients, which corresponds to eosinophilic airway inflammation being significantly milder in CVA than in CA.

Guidelines stipulate that spirometry and BHR are the fundamental diagnostic criteria for both CVA and CA [5]. FEV_1% predicted may reflect asthma control or symptoms of different types of asthma. In our present study, although FEV_1% predicted was normal in CA and CVA patients, it was still lower than that of corresponding subjects negative for BCT. This might indicate that declined FEV_1 existed in positive BCT patients. In addition, lower FEV_1/FVC in CA patients indicated that there was severe airflow limitation in CA rather than CVA, which is the reason that wheezing, not cough, occupied clinical symptoms in CA.

The pathobiology of asthma involves small airways, which have a significant role in certain asthmatic phenotypes. In particular, SAD is associated with a higher probability of BHR [6, 7]. Measurements of MMEF, MEF25, and MEF50 are also simpler diagnostic tools to detect SAD in asthma [34]. Here, we confirmed that MMEF, MEF25, and MEF50 in CA and CVA patients were lower than those of corresponding subjects negative for BCT, which suggested the presence of small airway injury in asthmatic subjects with $FEV_1 \geq 80\%$ predicted. However, as a previous study reported [13], MEFs did not differ between the CA and CVA groups, although there is a high ratio of SAD in CA. This suggests that while small airways cannot effectively differentiate patients with CVA from those with CA, milder SAD is more prevalent in CVA.

BHR is not only the key feature of CVA but also the main criterion for CVA diagnosis [3]. Previous studies have also suggested that the development of wheezing during the course of CVA may be induced by increasing BHR [30], and about 30% of CVA cases were likely to develop into CA [27]. While CVA shares similarities with CA in terms of BHR and eosinophilic airway inflammation, several studies have reported that CVA exhibits milder BHR and airway inflammation [33]. As expected, higher BHR and milder PD_{20} were observed in CA patients compared with those in CVA patients. However, the broad applicability of BCT to diagnose BHR is limited due to its disadvantages.

Our previous study reported that FENO and small airway indices are predictive markers, instead of BCT, in BHR of chronic cough [1]. The improvement of FEV_1% in BDR also have predictive value on CVA diagnosis and response to anti-asthma treatment in patients with chronic cough [17]. In this study, we continued to analyze the predictive value of positive BCT in CA and CVA. At first, we confirmed that FENO > 30 ppb (PPV, 76%) with an AUC of 0.728 could predict BCT of CA. However, FENO alone did not result in high AUC values for positive BCT diagnosis of CVA. This suggested that eosinophilic airway inflammation in CVA was not severe enough to predict BCT. Then, we found that the

Table 5 Demographic data, spirometric variables, FENO values, peripheral eosinophils values, improvement of clinical symptoms and lung function of CA patients and CVA patients

Variables	CA				CVA				*p* value (CA vs. CVA)
	Improvement of FEV_1 > 200 ml and FEV_1%>12%	**Improvement of FEV_1 > 200 ml and FEV_1%<12%**	**Improvement of FEV_1 < 200 ml and FEV_1%<12%**	***p* value**	**Improvement of FEV_1 > 200 ml and FEV_1%>12%**	**Improvement of FEV_1 > 200 ml and FEV_1%<12%**	**Improvement of FEV_1 < 200 ml and FEV_1%<12%**	***p* value**	
n	14	12	5	-	18	10	7	**-**	**-**
Age, years	38.29 [13.71]	38.5 [15.57]	44.2 [14.17]	0.593	48.89 [16.37]	41.8 [11.67]	41.71 [18.25]	0.545	0.123
Height, m	1.661 [0.0715]	1.679 [0.0775]	1.672 [0.1178]	0.860	1.636 [0.0903]	1.658 [0.0874]	1.643 [0.0785]	0.731	0.172
Weight, kg	63.14 [11.84]	66.0 [10.5]	70.4 [18.11]	0.510	60.72 [12.11]	62.6 [13.82]	63.29 [18.87]	0.983	0.173
BMI, kg/m^2	22.85 [3.892]	23.35 [2.878]	24.79 [3.303]	0.519	22.55 [3.17]	22.54 [3.286]	23.08 [4.246]	0.991	0.429
Symptom recovery time, days	**7 (12.5)**	**5 (11.5)**	**20 (15.50)**	**0.046**	**7 (5.25)**	**8 (18.0)**	**19 (19.0)**	**0.007**	0.738
ACT_2	**23 (2.25)**	**23 (1.5)**	**20.0 (2.5)**	**0.003**	-	-	-	-	-
ΔACT	**6.286 [2.268]**	**5.5 [1.567]**	**3.0 [1.225]**	**0.013**	-	-	-	-	-
CET_2	-	-	-	-	22.5 (3.25)	23.5 (2.25)	21 (2.0)	0.091	-
ΔCET	-	-	-	-	**6.444 [2.357]**	**5.3 [2.214]**	**2.571 [1.272]**	**0.002**	-
FENO, ppb	44.07 (26.58)	46.25 (22.33)	34 (8.602)	0.6120	**37.72 [20.59]**	**34.7 [18.34]**	**12.57 [4.756]**	**0.004**	**0.031**
> 50ppb, n	4	4	0	0.0986	5	2	0	**0.0383**	0.3980
25 ~ 50 ppb, n	7	6	1		6	5	0		0.2637
< 25 ppb, n	3	2	4		7	3	7		0.7640
SAD, (n, %)	8 (57.14%)	2 (16.67%)	1 (20%)	0.0725	11 (61.11%)	3 (30.0%)	2 (28.57%)	0.170	0.7818
WBC, ×10^9/L	6.332 [1.41]	6.104 [1.48]	6.474 [1.449]	0.884	6.473 [1.586]	6.697 [1.454]	6.877 [1.32]	0.808	0.310
EOS in blood, cell/μl	0.19 (0.2)	0.10 (0.1025)	0.31 (0.44)	0.217	0.105 (0.1225)	0.14 (0.16)	0.14 (0.17)	0.881	0.144
EOS% in blood, %	3.0 (3.0)	1.6 (1.075)	4.1 (3.7)	0.157	1.4 (1.825)	2.5 (2.4)	1.5 (2.7)	0.73	0.07
PD20, mg	0.289 (0.2116)	0.2247 (0.12)	0.3454 (0.3073)	0.734	0.0991 (0.1210)	0.1114 (0.7974)	0.4757 (0.3660)	0.059	0.559
FVC, L	3.77 (0.84)	4.605 (1.922)	3.12 (2.085)	0.184	3.365 (1.33)	3.8 (1.348)	3.42 (0.72)	0.434	0.165
FEV_1, L	3.402 [0.7188]	3.72 [0.851]	2.95 [0.9935]	0.133	3.147 [0.8757]	3.361 [0.6973]	2.939 [0.7476]	0.414	0.141
FEV_1/FVC, %	85.92 [6.348]	84.71 [4.17]	79.27 [6.142]	0.134	83.38 [6.411]	84.14 [4.783]	84.67 [7.221]	0.942	0.648
PEF, L/s	6.37 [3.32]	7.955 (3.73)	6.42 (3.475)	0.376	7.699 (2.462)	8.012 (1.423)	7.461 (2.137)	0.615	0.681
MEF75, L/s	6.16 [3.227]	6.805 (3.283)	5.92 (1.91)	0.412	6.776 (2.13)	7.359 (1.133)	6.653 (1.928)	0.415	0.847
MEF50, L/s	**4.339 [1.125]**	**4.82 [1.266]**	**3.246 [0.5428]**	**0.031**	3.826 [1.506]	4.92 [0.8352]	3.81 [1.521]	0.084	0.533
MEF25, L/s	1.696 [0.5541]	1.963 [0.6966]	1.166 [0.4962]	0.064	1.554 [0.8714]	1.55 [0.4985]	1.546 [0.8961]	0.908	0.235
MMEF, L/s	**3.595 [0.9047]**	**4.039 [1.192]**	**2.624 [0.6835]**	**0.024**	3.291 [1.301]	3.782 [0.7074]	3.211 [1.307]	0.290	0.426
FVC%pred	105.2 [10.22]	107.3 [10.69]	106.7 [16.83]	0.920	113.2 (25.49)	107.7 (17.69)	100 (14.29)	0.077	0.763
FEV_1%pred	106.6 [8.652]	108.7 [8.934]	98.82 [12.52]	0.187	108.5 (23.87)	106 (11.86)	94.83 (21.62)	0.065	0.959
PEF%pred	99.56 [25.92]	100.9 [17.75]	96.26 [13.71]	0.867	108.1 (31.98)	105.4 (15.87)	98.83 (38.73)	0.720	0.111
MEF75%pred	104.6 [27.46]	101.6 [16.03]	95.7 [16.31]	0.740	103.2 (31.99)	113.4 (27.44)	102.6 (28.87)	0.734	0.131
MEF50%pred	**97.13 [21.01]**	**103.3 [17.36]**	**76.69 [12.85]**	**0.021**	87.82 (33.71)	108.9 (28.74)	79.68 (43.65)	0.064	0.944
MEF25%pred	**87.77 [29.68]**	**94.98 [21.38]**	**62.49 [14.1]**	**0.036**	81.94 (44.33)	73.02 (48.52)	76.65 (62.96)	0.945	0.748
MMEF%pred	**93.19 [21.7]**	**100.1 [19.48]**	**72.0 [10.04]**	**0.019**	89.94 (27.43)	92.55 (32.64)	85.33 (32.16)	0.548	0.893
ΔFVC, mL	**105.0 (225.0)**	**30.0 (207.5)**	**-50.0 (100.0)**	**0.045**	85.0 (250.0)	100.0 (227.5)	10.0 (210.0)	0.095	0.407

Table 5 (continued)

Variables	CA				CVA				*p* value (CA vs. CVA)
	Improvement of FEV_1 > 200 ml and FEV_1%>12%	Improvement of FEV_1 > 200 ml and FEV_1%<12%	Improvement of FEV_1 < 200 ml and FEV_1%<12%	*p* value	Improvement of FEV_1 > 200 ml and FEV_1%>12%	Improvement of FEV_1 > 200 ml and FEV_1%<12%	Improvement of FEV_1 < 200 ml and FEV_1%<12%	*p* value	
ΔFEV$_1$, mL	**205.0 (137.5)**	**130.0 (147.5)**	**80.0 (85.0)**	**0.047**	**170.0 (180.0)**	**130 (237.5)**	**60.0 (90.0)**	**0.010**	0.777
ΔPEF, mL/s	265.0 (1007.5)	135.0 (960.0)	260.0 (790.0)	0.682	585.0 (1055.5)	290.0 (502.5)	40.0 (1470.0)	0.259	0.322
ΔMEF75, mL/s	485.0 (857.5)	405.0 (727.5)	-20.0 (825)	0.493	260.0 (1435.5)	425.0 (797.5)	270.0 (910)	0.860	0.594
ΔMEF50, mL/s	**600.0 (357.5)**	**485.0 (647.5)**	**290.0 (395.0)**	**0.046**	380.0 (760.0)	600.0 (883.0)	230.0 (830.0)	0.876	0.335
ΔMEF25, mL/s	**260.0 (197.5)**	**440.0 (452.5)**	**120.0 (360.0)**	**0.021**	385.0 (467.5)	95.0 (440.0)	190.0 (640.0)	0.276	0.422
ΔMMEF, mL/s	490.0 (167.5)	520.0 (835.0)	310.0 (415.0)	0.168	550.0 (905.0)	285.0 (475.0)	280.0 (920.0)	0.596	0.266
ΔFVC%	**3.27 (6.357)**	**0.620 (4.685)**	**-1.57 (1.83)**	**0.021**	2.1 (8.598)	2.915 (7.465)	0.29 (6.77)	0.155	0.342
ΔFEV$_1$%	**7.79 (6.162)**	**4.575 (3.648)**	**2.52 (3.66)**	**0.020**	**7.92 (3.753)**	**4.785 (7.802)**	**1.81 (5.39)**	**0.014**	0.332
ΔPEF%	4.99 (15.92)	1.68 (10.901)	5.52 (11.23)	0.938	11.54 (16.93)	3.86 (7.93)	0.86 (19.09)	0.280	0.253
ΔMEF75	8.83 (16.42)	5.97 (10.22)	-0.35 (14.64)	0.380	4.255 (23.69)	6.115 (11.47)	6.46 (14.31)	0.902	0.639
ΔMEF50%	**21.75 (10.28)**	**14.27 (18.28)**	**7.93 (12.9)**	**0.031**	12.4 (30.01)	18.04 (23.87)	9.7 (13.99)	0.794	0.358
ΔMEF25%	24.07 (16.38)	29.43 (33.03)	10.0 (42.11)	0.40	41.03 (62.9)	4.665 (48.08)	26.64 (25.32)	0.085	0.842
ΔMMEF%	18.49 (10.13)	16 (26.69)	11.97 (22.64)	0.239	24.94 (31.8)	9.5 (17.33)	16.74 (12.71)	0.266	0.933
improvement-FVC	**305.0 (277.5)**	**225.0 (125.0)**	**-30.0 (190.0)**	**0.002**	**340.0 (500.0)**	**220.0 (282.5)**	**100.0 (300.0)**	**0.008**	0.546
improvement-FEV$_1$	**505.0 (225.0)**	**270.0 (125.0)**	**30.0 (185.0)**	**< 0.0001**	**420.0 (172.5)**	**280.0 (67.5)**	**90.0 (120.0)**	**< 0.0001**	0.690
improvement-PEF	685.0 (2130.0)	650.0 (1703.0)	100.0 (745.0)	0.735	1045.0 (1070.5)	150.0 (1590.0)	330.0 (1750.0)	0.090	0.533
improvement-MEF75	1185.0 (2425.5)	610.0 (1005.5)	70.0 (630.0)	0.052	1120.0 (1433.0)	460.0 (1067.5)	650.0 (800.0)	0.062	0.159
improvement-MEF50	**1340.0 (657.5)**	**845.0 (630.0)**	**-100.0 (310.0)**	**0.002**	**895.0 (1403.0)**	**955.0 (995.0)**	**350.0 (310.0)**	**0.029**	0.933
improvement-MEF25	**440.0 (352.5)**	**375.0 (415.0)**	**0.0 (90.0)**	**0.010**	525.0 (1070.0)	130.0 (520.0)	200.0 (320.0)	0.215	0.537
improvement-MMEF	**1065.0 (642.5)**	**740.0 (405.0)**	**10.0 (315.0)**	**0.003**	**865.0 (978.0)**	**855.0 (543.0)**	**240.0 (190.0)**	**0.016**	0.964
improvement-FVC%	**8.4 (6.712)**	**5.195 (4.952)**	**-0.46 (6.3)**	**0.001**	**10.92 (19.63)**	**6.1 (10.25)**	**2.94 (11.41)**	**0.012**	0.258
improvement-FEV$_1$%	**17.03 (5.17)**	**9.745 (3.48)**	**0.64 (7.47)**	**< 0.0001**	**17.77 (4.96)**	**9.75 (2.31)**	**2.72 (6.0)**	**< 0.0001**	0.445
improvement-PEF%	**13.03 (26.36)**	**10.95 (27.89)**	**1.56 (8.465)**	**0.684**	**19.31 (14.16)**	**2.32 (20.79)**	**3.91 (23.35)**	**0.026**	0.468
improvement-MEF75%	**23.82 (39.25)**	**8.28 (15.33)**	**0.98 (11.61)**	**0.044**	**26.14 (30.95)**	**8.315 (16.01)**	**13.7 (15.83)**	**0.013**	0.122
improvement-MEF50%	**45.69 (34.07)**	**20.92 (13.8)**	**-2.56 (9.965)**	**0.001**	**35.44 (42.28)**	**28.05 (28.17)**	**11.17 (8.48)**	**0.025**	0.847
improvement-MEF25%	**42.79 (49.63)**	**27.78 (38.53)**	**0.0 (7.23)**	**0.007**	50.53 (115.6)	9.775 (43.19)	16.89 (22.37)	0.15	0.893
improvement-MMEF%	**47.39 (30.88)**	**19.27 (19.53)**	**0.29 (14.02)**	**0.001**	**42.84 (46.22)**	**29.58 (18.08)**	**8.79 (10.67)**	**0.013**	0.603

ΔACT: improvement of ACT from baseline to 4 weeks treatment (ΔACT = ACT_2 -ACT_1); ΔCET: improvement of CET from baseline to 4 weeks treatment (ΔCET = CET_2 -CET_1); improvement-: improvement of spirometric indices from baseline to 4 weeks treatment

The other abbreviations are as defined for Tables 1 and 4

Bold font indicates statistical significance

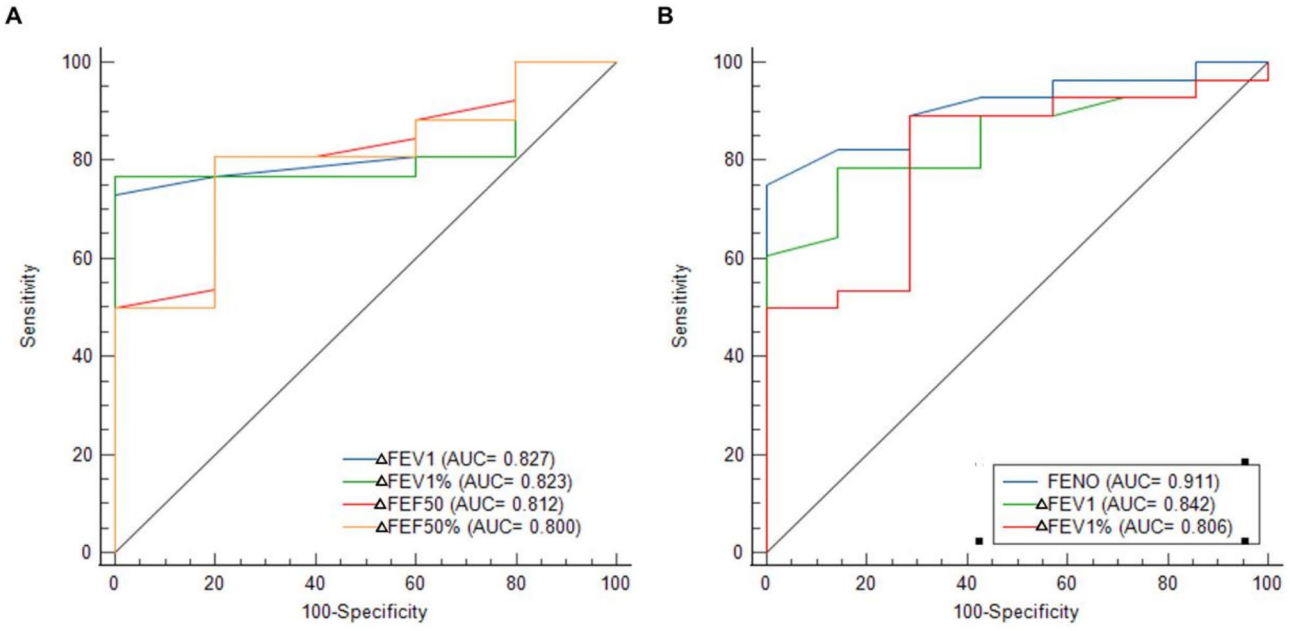

Fig. 3 ROC curves for predicting anti-asthma response in mild CA patients (**A**) and CVA patients (**B**). (**A**) $AUC_{\Delta FEV1} = 0.827$ (95% CI, 0.649 to 0.938; $p < 0.001$, compared with $AUC_{0.5}$); $AUC_{\Delta FEV1\%} = 0.823$ (95% CI, 0.644 to 0.936; $p < 0.001$, compared with $AUC_{0.5}$). $AUC_{\Delta MEF50} = 0.812$ (95% CI, 0.631 to 0.929; $p < 0.01$, compared with $AUC_{0.5}$); $AUC_{\Delta MEF50\%} = 0.800$ (95% CI, 0.618 to 0.921; $p < 0.01$, compared with $AUC_{0.5}$)(**B**) $AUC_{FENO} = 0.911$ (95% CI, 0.765 to 0.980; $p < 0.001$, compared with $AUC_{0.5}$); $AUC_{\Delta FEV1} = 0.842$ (95% CI, 0.679 to 0.943; $p < 0.001$, compared with $AUC_{0.5}$); $AUC_{\Delta FEV1\%} = 0.806$ (95% CI, 0.638 to 0.920; $p < 0.001$, compared with $AUC_{0.5}$). Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; ΔMEF50: increase of forced expiratory flow at 50% of forced vital capacity in one second in BDT; ΔMEF50%: increase of forced expiratory flow at 75% of forced vital capacity as a percentage of baseline value in BDT; FENO, fractional exhaled nitric oxide; ΔFEV_1: increase of forced expiratory volume in one second in BDT; $\Delta FEV_1\%$: increase of forced expiratory volume in one second as a percentage of baseline value in BDT

two most valuable spirometry variables for predicting BCT were MEF50 (AUCs = 0.734 and 0.738) and MMEF (AUCs = 0.715 and 0.716) in CA and CVA patients, respectively.

Since all the generated AUC values were below 0.80, utilizing only these parameters would be inadequate to foretell BHR among patients with CA or CVA. Therefore, we combined the MEFs with FENO or EOS counts to enhance their predictive value for BCT diagnosis. Here, we verified that positive BCT in CA was associated with FENO > 30 ppb and MMEF%predicted < 78.8% or MEF50%predicted < 76.2%. On the other hand, the joint model of FENO > 27 ppb and MMEF%predicted < 73.7% or MEF50%predicted < 87.1% predicted positive BCT in CVA. Correspondingly, the AUCs of MEFs combined with FENO were much higher than those of single AUCs, both in CA and CVA. Therefore, similar to our previous study [2], MEF50 and MMEF predicted BCT in patients with CA or CVA, but whether FENO has a predictive value depends on the type of asthma. In addition, our finding that the PPV of MEFs combined with FENO was higher in CA patients than in CVA patients suggested that MEFs combined with FENO were more likely to improve the prediction of BCT diagnosis in CA. Such measurement may provide economic substitutes for predicting BCT in suspected CA patients with $FEV_1 \geq 80\%$ predicted, especially in primary hospitals.

ICS is regarded as the first-line therapy for CVA, which not only alleviates cough but also minimizes the likelihood of advancing to CA [10]. Patients administering ICS showed a decline in CA onset rate, providing evidence that long-term ICS use can act as an intervention against CA originating from CVA [11]. In addition, long-term ICS attenuated BHR to inhaled methacholine in patients with CVA. Here, we selected patients with BCT of CA and CVA to assess anti-asthma response after four weeks of ICS/LABA treatment. We also observed that all patients showed improvement in central and small airway function after four weeks of ICS/LABA therapy, while there were no significant differences between the two groups. Thereby, this finding verified that both CA patients and CVA patients were likely to benefit from initial anti-asthma therapy. Our findings, showing that patients with a higher improvement of FEV_1 in BDT were more likely to achieve a better response to anti-asthma therapy and shorter time of symptom recovery, confirmed that patients with lower improvements of FEV_1 in BDT were less likely to achieve an anti-asthmatic response. In brief, this finding, which indicated that BCT has a high false-negative rate, confirmed that even if BDT has a high ratio of being negative, it has a

better anti-asthma response predictive value. On the other hand, previous studies reported that both MMEF value and FENO can predict the anti-asthma course or response in CA and CVA [25]. However, in our present study, FENO > 19 ppb (PPV, 100%) with an AUC of 0.911 could only predict CA, while ΔMEF50 > 310 ml (PPV, 95.5%) with an AUC of 0.812 only predicted CVA. Furthermore, the two most valuable spirometric variables for predicting better anti-asthma responses were ΔFEV_1 (AUC = 90 ml and 110 ml) and ΔFEV_1% (AUC = 3.49% and 2.59%) in CA and CVA patients, respectively. Such results implied that ΔFEV_1 and ΔFEV_1% at baseline were the most stable parameters in predicting anti-asthma response, both in CA patients and CVA patients. Consequently, we are able to carry out on-demand anti-asthma therapy according to different asthma subtypes, FEV_1%, MMEF%, or FENO. This idea needs to be further verified in the near future.

There are some limitations to our current study. First, due to the difficulty of clinical operation, the sample size of CA and CVA patients with 4 weeks of ICS/LABA treatment was small, the follow-up time was relatively short, and the single inhaled device/molecular may also be a limitation of our study. Our finding's credibility should be affirmed by conducting additional national multicenter clinical research with a larger sample size, longer follow-up period, and various inhaled devices. Second, the history of atopy was important for asthma diagnosis, but only allergic rhinitis history was collected in this retrospective study. Therefore, the inquiry of atopy needed to be followed up in our study. Third, sputum eosinophil count is a better assessment of airway inflammation rather than eosinophils in blood. Further data on sputum eosinophils will be applied in the evaluation of airway inflammation in our future research.

Conclusions

In conclusion, CVA patients show less airway eosinophilic inflammation (FENO) values than CA patients with $FEV_1 \geq 80\%$ predicted. FENO combined with MEF50% or MMEF% could be an economically favorable method to forecast hyperresponsiveness in CA patients with normal FEV_1. Moreover, both CA and CVA patients with $FEV_1\% \geq 80\%$ predicted were likely to benefit promptly from anti-asthma therapy, and improvement of FEV_1 and FEV_1% in BDT predicted a better anti-asthma response in asthmatic patients.

Abbreviations

ACT	Asthma control test
ACT_1	Asthma control test at the first visit
ACT_2	Asthma control test at the second visit
ATS	American Thoracic Society
AUC	Area under the curve
BHR	Bronchial hyperresponsiveness
BCT	Bronchial challenge tests
BDT	Bronchodilation test
BMI	Body Mass Index
CA	Classic asthma
CRSwNP	Chronic rhinosinusitis with nasal polyps
CVA	Cough variant asthma
EOS	Eosinophils counts in blood
EOS%	Eosinophils percentages in blood
ERS	European Respiratory Society
FENO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in one second
FEV_1/FVC	Ratio of the FEV_1 to the forced vital capacity
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
ICS	Long-term inhaled corticosteroids
ICS/LABA	Inhaling corticosteroids and longacting β agonists
IOS	Impulse oscillometry
ROC	Receiver-operating characteristic
MEF75	Forced expiratory flow at 25% of forced vital capacity
MEF50	Forced expiratory flow at 50% of forced vital capacity
MEF25	Forced expiratory flow at 75% of forced vital capacity
MMEF	Forced expiratory flow between 25% and 75%
NO	Nitric oxide
NPV	negative predictive values
PEF	Peak expiratory flow
PPV	positive predictive values
Pred	Predictive value
SD	Standard deviation
VAS	visual analogue scale
WBC	White blood cell

Supplementary Information

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Supplementary Material 1

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Author contributions

X.T. and M.Z. conceived of and designed the entire study.X.Z. enrolled the patients.H.H. contributed to data collection.C.L. and J.L. was involved in interpreting spirometric assessments, bronchodilation tests, bronchial challenge tests and FENO data.X.Z and C.L. performed statistical analysis.X.T. wrote the manuscript supervised by M.Z.All authors critically reviewed and approved the final version.All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability

The data that support the fundings of this study are available from corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the Shanghai General Hospital (no. [2020]30). The prospective study in PART II was registered on chictr.org.cn (No. ChiCTR2000029065). Informed consent in PART II was obtained for all subjects. As PART I in our study was a retrospective study, the requirement for obtaining informed consent from participants was waived

by the ethics committee (no. 2017KY159). The research was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Respiratory and Critical Care Medicine, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, No. 100, Haining Road, Shanghai 200080, China

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