ORIGINAL RESEARCH

Small Airways Dysfunction and Bronchial Hyper-Responsiveness in Cough Variant Asthma

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Background: Cough variant asthma (CVA) is one kind of atypical asthma. The study was to compare spirometric parameters of small airways and the degree of bronchial hyper-responsiveness (BHR) between CVA and classic asthma (CA), and examine the relationship between BHR and small airways to determine the accuracy of these markers as indicators of CVA.

Methods: A total of 825 asthmatic patients were screened for the study, and 614 were included. All patients performed spirometry and underwent a bronchial challenge with methacholine.

Results: The number of small airways dysfunctions in the CVA group was less than those of the CA group with MMEF% predicted (70% vs 80.91%, P=0.002) and $FEF_{50\%}$ predicted (62.71% vs 73.5%, P=0.004). The degree of small airways dysfunction was less in the CVA group compared with the CA group (P<0.001). Significant positive correlations were observed between the FEV_1 level below 20% of the baseline value (PD_{20}) and MMEF% predicted (r=0.282, P<0.001), $FEF_{50\%}$ predicted (r=0.2522, P<0.001), and $FEF_{75\%}$ predicted (r=0.2504, P<0.001) in patients with CVA. The area under curve (AUC) of MMEF, FEF_{50}, and FEF_{75} (% predicted) was 0.615, 0.621, and 0.606, respectively. In addition, 0.17 mcg of PD_{20} was the best diagnostic value for CVA, with an AUC of 0.582 (P=0.001).

Conclusion: Small airway dysfunction is milder in CVA. The value of BHR combined with small airways in CVA prediction, which was significant, but not enough to be clinically useful.

Keywords: small airways, bronchial hyper-responsiveness, cough-variant asthma, classic asthma

Background

Asthma is a heterogeneous disease with chronic airway inflammation of bronchial hyper-responsiveness (BHR) to a variety of stimuli, and variable expiratory airflow limitation that is often reversible either spontaneously or as a result of therapy.[1,2] The definition of "classic asthma (CA)" is based on the characteristics and intensity of the respiratory symptoms (wheeze, shortness of breath, tightness, and cough).[1]

The original definition of cough variant asthma (CVA) was described by Glauser[3–5] in 1979. They described patients with asthma with cough as their sole presenting symptom, but whose symptoms improved with bronchodilators alone. The European and American guidelines do not discuss specific diagnostic criteria, but they do highlight the diagnostic value of BHR and recommend that the CVA diagnosis should be determined according to the therapeutic response.[1] The 2016 Chinese Cough guidelines take the detailed diagnostic criteria and treatment of

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CVA, which is the BHR, and successful treatment of bronchodilators and/or inhaled corticosteroids as the basic diagnostic criteria.[6]

Small airways were defined as the bronchial being less than 2 mm in internal diameter.[7] The assessment of small airways dysfunction is a challenging matter, because the distal airway is relatively inaccessible to assess. More specialized tests have been developed, such as spirometry, impulse oscillometry (IOS), breath nitrogen washout (BNW), and body plethysmography, No assessment method is universally and directly representative of small airways function. The value and limitations of each test have been extensively reviewed.[8–11] Small airways played a role in the pathobiology of asthma and have a distinct role in specific disease phenotypes, although they are involved in half of all cases of asthma.[12–14] The severity of asthma was also associated with inflammatory changes and functional alterations in the small airways.[11,15] The role of the small airways in asthma is increasingly recognized as a potential target in optimal control of the disease. Therefore, this study aims to explore the validity of small airways and BHR in the diagnosis of CVA.

Methods
Study Design and Participants
In this retrospective and observational study, we conducted a series of 614 patients with CVA and CA visiting the Third People's Hospital of Guangzhou Medical College in Huizhou from January 2018 to April 2019.

CA patients were diagnosed according to 1) a clinical record of recurrent wheezing, dyspnea, or/and cough episodes, chest tightness; 2) pulmonary function tests demonstrate variable airflow limitation by means of BHR testing or airway reversibility testing; and 3) a positive to the therapeutic response, which satisfied those of the Chinese national Guidelines on Diagnosis and Management of Asthma (2016).[16]

CVA patients were described as 1) chronic cough (lasting more than 8 weeks without specific cause) as the only symptom; 2) the cough was usually dry or productive with minimal amounts of clear sputum, and was mainly nocturnal; 3) Normal baseline lung function, some might actually include normal small airway function, and positive test for BHR; 4) No other cause of chronic cough; and 5) a positive to the therapeutic response.[6]

Inclusion criteria were: age greater than 14 years; no smoking or quitting smoking for more than 1 year; diagnosis

of CA and CVA was made according to the guidelines criteria of China;[6,16] received initial diagnosis of CA or CVA and were uncontrolled stage; no other apparent causes of cough were present; not used any oral or/and inhaled corticosteroid (ICS) in the previous 4 weeks.

Exclusion criteria were: a history of chronic obstructive pulmonary disease (COPD) or asthma-COPD overlap (ACO), bronchitis, bronchiectasis, lung cancer, cystic fibrosis, or pneumonia; do not continue treatment because of some reasons or diagnosed as other diseases after treatment were excluded.

Ethics Statement
The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Huizhou Third People's Hospital, which absolved the need for written informed consent because of the retrospective study. All personal identification data were anonymized and de-identified before analysis.

Assessments and Spirometry
Pulmonary function tests, induced sputum cell differentials, and CT of the chest were performed on the same day.

Variable airflow limitation was performed by a spirometer (MS-pneumo + APS; JAEGER, Germany). In accordance with recommendations of the Chinese National Guidelines of Pulmonary Function Test (2014): rapid rise in flow/volume curve, duration of expiration more than or equal to six seconds, and visualization of peak expiratory flow (PEF) were required. Repeat at least three times (a reproducible way), the best spirometric values were measured prior to the methacholine challenge. Patient with a percent predicted forced expiratory volume in first second (FEV_1%pred) $\geq$ 60% continued to the BHR test (at baseline). The procedure was terminated when the FEV_1 level fell below 20% of the baseline value. The positive response was defined as PD_{20} $\leq$2.504 mcg (between NS and 2.504 mcg). The cumulative dose of PD_{20} was used to assess the degree of BHR.[17,18]

Small airways dysfunction is the early expression of airway obstruction. FVC, FEV_1, and FEV_1/FVC are still in normal range, but MMEF, $FEF_{50\%}$, and $FEF_{75\%}$ can be significantly decreased. When two of the three indicators were lower than LLN (lower limits of normal), it could be judged as small airway dysfunction.[17]

Statistical Analysis

All statistical variables were analyzed using SPSS version 22 (IBM Corporation, Armonk, NY, USA). Data were presented as mean±standard deviation (SD), frequencies, and percentages, as appropriate. A *t*-test for independent samples or a Chi square test was used to observe two groups of CVA and CA patients. The relationship between PD_{20} and spirometry was detected with the Pearson correlation coefficient. Correlation between tests was assessed by constructing a receiver operating characteristic (ROC) curve. A *P*-value<0.05 was considered statistically significant.

Results

Characteristics and Pre-Challenge Spirometry of the Patients

A total of 825 asthmatic outpatients attended the diagnosis by pulmonary and critical care medicine physicians and underwent a detailed lung function test. In total, 614 asthmatic patients were eligible and analyzed. Reasons for exclusion were 1) aged <14 years (n=53); 2) combined diagnosis of COPD or ACO (n=8 and n=5, respectively); 3) diagnosis of CA or CVA in the previous (n= 67); and 4) performed by bronchodilator reversibility test (n=78). The strategies of flow-chart are illustrated in Figure 1.

There were a total of 825 samples with asthmatic patients to be collected in the retrospective study and 211 were excluded. Demographic parameters of included patients are presented in Table 1. Significant but weaker

Table 1 Baseline Characteristics and Pre-Challenge Spirometry of Patients with CVA and CA (N=614)

Demographic Parameters	CVA (n=263)	CA (n=351)	P
Age, years	46.06±16.43	48.64±15.85	0.051
Females, n (%)	164 (62.36%)	190 (54.13%)	0.041
BMI, kg/m^2	23.54±3.62	23.5±3.56	0.902
FVC (L)	3.16 (0.83)	3.15 (0.84)	0.937
FVC% predicted	97.55 (13.48)	96.47 (12.92)	0.317
FEV$_1$ (L)	2.41 (0.65)	2.29 (0.63)	0.023
FEV$_{1\%}$ predicted	89.21 (11.84)	85.02 (12.36)	<0.001
FEV$_1$/FVC (%)	76.46 (8.62)	73.12 (9.77)	<0.001
PEF (L/min)	6.18 (1.63)	6.07 (1.73)	0.393
PEF% predicted	89.89 (15.15)	87.1 (16.75)	0.028

Notes: N refers to the total patients; n refers to the sub-group population; data are presented as mean±SD (standard deviation), or number (%). Significant *P*-value<0.05.
Abbreviations: CVA, cough variant asthma; CA, classic asthma; BMI, body mass index; FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1 second; PEF, peak expiratory flow.

differences were found in sex ratio between CVA and CA patients (*P*=0.041).

According to the results of spirometry, FEV$_1$% predicted, FEV$_1$/forced expiratory vital capacity (FVC)(FEV$_1$/FVC), and PEF% predicted were higher in CVA compared to CA (*P*<0.05). We did not find any difference in age, BMI, or history of smoking between the two groups.

Table 2 reflects small airway function. Patients with CVA showed less small airway dysfunction (<65%) than the CA group in MMEF% predicted (70% vs 80.91%, *P*=0.002) and FEF$_{50\%}$ predicted (62.71% vs 73.5%, *P*=0.004). The degree of small airways dysfunction was
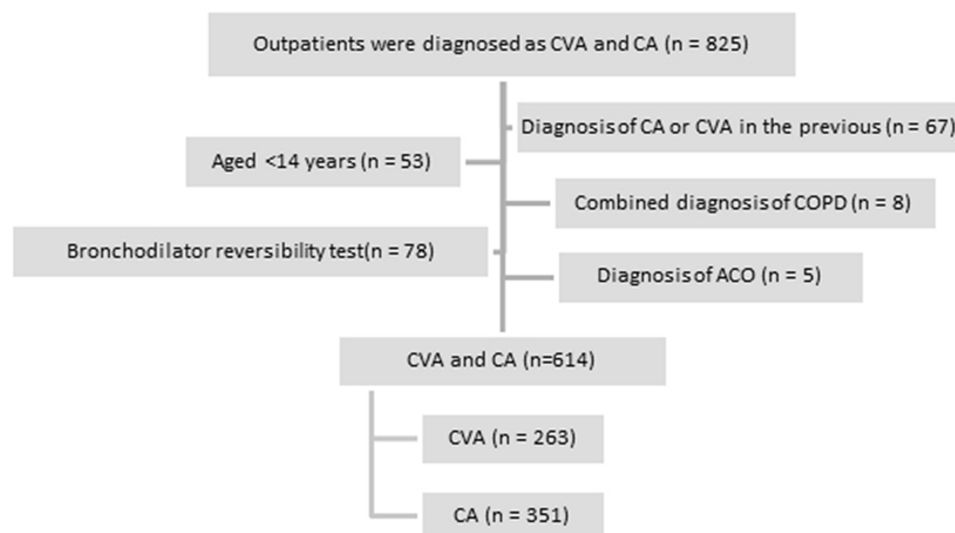

Figure 1 The strategies of flow-chart with asthmatic patients. n: number of subjects.

Table 2 Baseline Spirometry of Small Airways in Patients with CVA and CA (N=614)

Demographic Parameters	CVA (n=263)	CA (n=351)	P
MMEF% predicted (<65%), n (%)	184 (70%)	284 (80.91%)	0.002
FEF$_{50\%}$ predicted (<65%), n (%)	165 (62.74%)	258 (73.5%)	0.004
FEF$_{75\%}$ predicted (<65%), n (%)	199 (75.67%)	277 (78.92%)	0.379
MMEF (L/s)	2 (0.85)	1.76 (0.86)	0.001
MMEF% predicted	56.1 (18.26)	49.52 (19.57)	<0.001
FEF$_{50}$ (L/s)	2.5 (0.97)	2.15 (0.93)	<0.001
FEF$_{50\%}$ predicted	60.54 (19.46)	52.76 (20.16)	<0.001
FEF$_{75}$ (L/s)	0.92 (0.49)	0.78 (0.49)	0.001
FEF$_{75\%}$ predicted	53.37 (20.18)	47.1 (22.92)	<0.001

Notes: Data are expressed as the mean±SD or frequencies; the difference between groups was analyzed by Student's *t*-test or Chi square. *P*<0.05 vs the control.
Abbreviations: n, sub-group population; MMEF, maximum mid-expiratory flow; FEF, forced expiratory flow.

significantly milder in the CVA group compared with the CA group (*P*<0.001).

BHR of the Patients

Responses to bronchial challenge tests with methacholine in CVA and CA patients are shown in Table 3. Significantly higher BHR was found in CA patients compared to in CVA patients (*P*=0.005). Compared to CVA, CA showed more sensitivity in the degree of FEV$_1$ fall (%) (*P*=0.002 and *P*=0.001, respectively).

Associations between PD$_{20}$ and FEV$_1$/FVC, Small Airway Function of the Patients

Figure 2 gives an overview of all correlations between PD$_{20}$ and small airways (MMEF%, FEF$_{50\%}$, FEF$_{75\%}$) with CVA and CA. Significant positive correlations were observed for MMEF% predicted (r=0.282, *P*<0.0001), FEF$_{50\%}$ predicted (r=0.2522, *P*<0.0001), and FEF$_{75\%}$

Table 3 BHR of CVA and CA Patients (N=614)

Parameters	CVA (n=263)	CA (n=351)	P
PD$_{20}$ (mcg)	0.89 (0.79)	0.71 (0.8)	0.005
FEV$_1$ fall (L)	1.7 (1.4, 2.05)	1.62 (1.25, 1.95)	0.002
FEV$_1$ fall (%)	26.95 (7.92)	29.65 (11.48)	0.001

Notes: Data are presented as mean±SD (standard deviation); N refers to the total patients; BHR, bronchial hyper-responsiveness. Significant *P*-value<0.05.
Abbreviations: CVA, cough variant asthma; CA, classic asthma.

predicted (r=0.2504, *P*<0.0001) in patients with CVA (Figure 2A). We also found significant correlations between PD$_{20}$ and small airways (r=0.2861, r=0.2917, and r=0.2476, respectively) with CA patients (*P*<0.001) (Figure 2B).

PD$_{20}$ and proportion parameters in spirometry as predictors to identified CVA from CA were analyzed using the ROC curve (Figure 3). The optimum cut-point for FEV$_1$% predicted was 82.65% with an area under the curve (AUC) of 0.602 (*P*<0.001), and the AUC of MMEF, FEF$_{50}$, and FEF$_{75}$ (% predicted) was 0.615, 0.621, and 0.606, respectively. In addition, 0.17 mcg of PD$_{20}$ was the best diagnostic value for CVA with an AUC of 0.582 (*P*=0.001). Data of sensitivity and specificity are shown in Table 4. The AUC of PD$_{20}$ combined with MMEF (% predicted) was 0.616, and that combined with MEF$_{50}$ (% predicted) and MEF$_{75}$ (% predicted) was 0.625 and 0.606, respectively (Figure 4).

Discussion

The retrospective study showed that more patients with CVA were associated with differences in levels of sex, FEV$_1$% predicted, FEV$_1$/FVC, compared to patients with CA. Milder BHR and small airway dysfunction are shown in CVA, and the correlation between them were observed weak but significant differences. BHR and small airways were poor to distinguish patients with CVA, respectively. We also evaluated the value of BHR combined with small airways in CVA prediction, which was reflected as significant, but not enough to be clinically useful.

Chronic cough is the sole presenting symptom of CVA. Previous literatures have studied that chronic persistent non-productive cough is more frequent in females, and females are more easily troubled by the symptom.[19,20] Females exceed males in number among patients attending specialist respiratory clinics.[21] The cough threshold is lower in females than in males, illustrating that the cough sensitivity is heightened in females.[22,23] In our study, the difference of gender is weak. The numbers of females was a little frequent in CVA (*P*=0.041). The mechanism of the gender differences is still unclear, and additional studies are needed to better understand gender differences.

Spirometry is the fundamental diagnostic method and the most widely non-invasive, easy to assess the airflow limitation associated with asthma. Parameters such as FEV$_1$ and PEF are frequently used to evaluate proximal airway obstruction. In the study, we found that patients with CVA were more
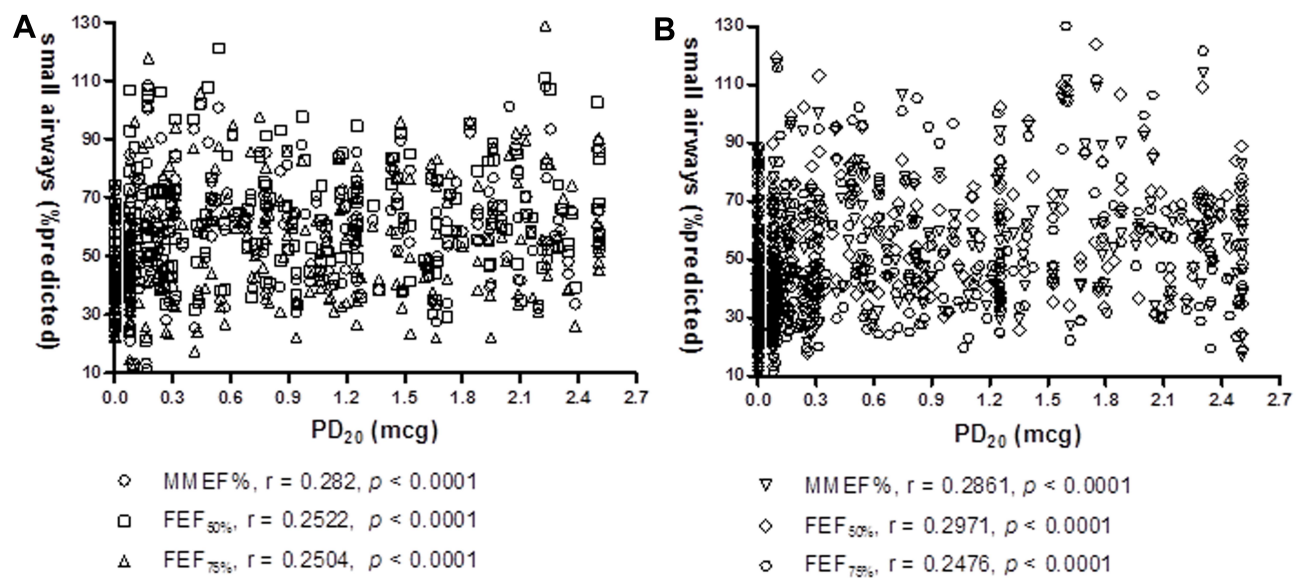
Figure 2 Scatter plots of correlation between PD_{20} (mcg) and small airways. (**A**) Correlation between PD_{20} (mcg) and small airways (MMEF%, $FEF_{50\%}$, $FEF_{75\%}$) in CVA. (**B**) Correlation between PD_{20} (mcg) and small airways (MMEF%, $FEF_{50\%}$, $FEF_{75\%}$) in CA.
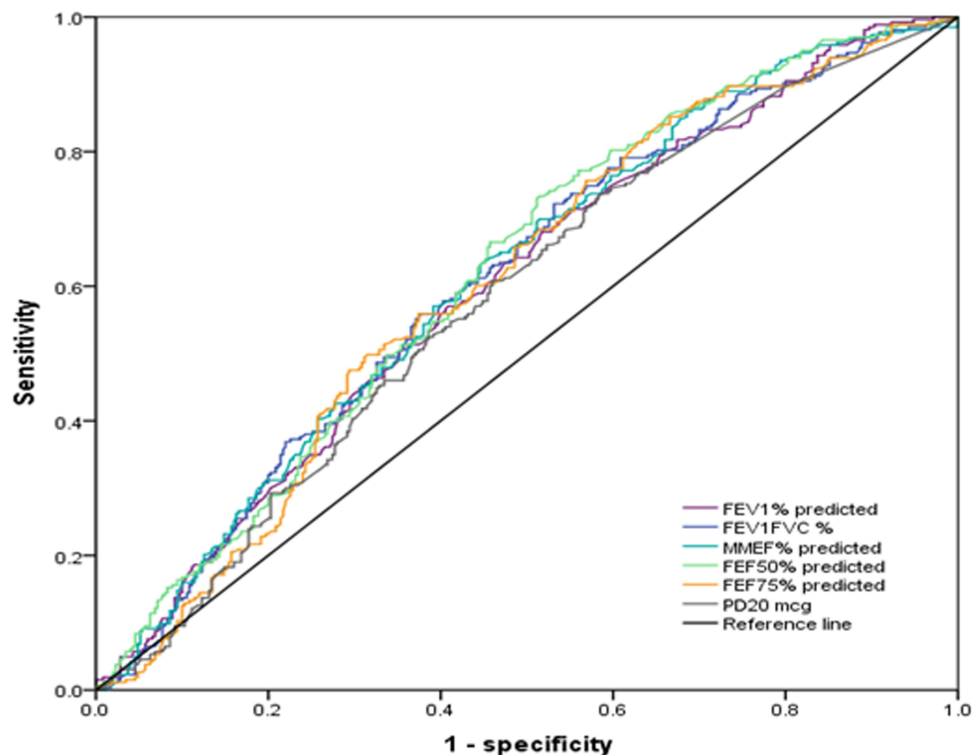

Figure 3 ROC curve analysis of PD_{20}, FEV_1, MMEF, FEF_{50}, and FEF_{75} (%predicted) for CVA diagnosis.

likely to have a better FEV_1 and FEV_1% predicted (89.21% vs 85.02, $P<0.001$). Spirometric values indices are almost independent of patient's activity if the expiration is forced; they depend only on the properties of the respiratory system because of the airflow limitation phenomenon.[24–26]

Evaluation of forced spirometry results begins with analysis of whether bronchial airflow capacity quantified by means of the FEV_1.

Previously, asthma was understood to be a disease primarily of the central airways. However, surgical lung

Table 4 Results of ROC Analysis of PD$_{20}$ and Spirometry

Parameters	PD$_{20}$ (mcg)	FEV$_1$% Predicted	MMEF% Predicted	FEF$_{50\%}$ Predicted	FEF$_{75\%}$ Predicted
CVA vs CA					
AUC (95% CI)	0.582	0.603	0.615	0.621	0.606
Cut-off	0.17mcg	82.65%	47.85%	47.95%	38.2%
Sensitivity/specificity (%)	73.8/41.4	68.1/48.3	63.9/54.9	73.4/48.6	75.7/43.1
P-value	0.001	<0.001	<0.001	<0.001	<0.001

Note: Significant P-value<0.05.
Abbreviations: CVA, cough variant asthma; CA, classic asthma; PD$_{20}$, dose of methacholine induce a 20% decrease in FEV$_1$ (PD$_{20}$).

specimens with living chronic asthma and autopsy specimens with fatal asthma reveal mucus plugging and inflammatory involvement of both the small and large airways.[27,28] It is an inflammatory characterized by increased T cells, activated eosinophils, and major basic protein in the small airways, which was similar to the inflammation of the central airways.[28] The intensity of the inflammation may be even higher in the small airways compared with central airways.[29] These observation confirm that the chronic inflammation of asthma involves the entire lung, from the large proximal to the small distal airways. Assessment of small airways pathology can be subdivided in tests measuring flow, airway resistance, inhomogeneity of ventilation distribution, and hyperinflation or air trapping by pulmonary function machines. Flow measures of small airways commonly used in forced expiratory flow at 50% (FEF$_{50\%}$), at 75% (FEF$_{75\%}$), and

Figure 4 Predictive value for CVA by combining PD$_{20}$ and small airway resistance; combination 1: PD$_{20}$+FEF$_{50}$ (%predicted); combination 2: PD$_{20}$+FEF$_{75}$ (% predicted); combination 3: PD$_{20}$+MMEF (% predicted).

at 25–75% (FEF$_{25–75\%}$/MMEF) of FVC. Among these parameters, FEF$_{25–75\%}$ is the most commonly adopted, although the literature supporting its reliability is not conclusive.

The pathophysiological features of CVA are similar to those of CA. CVA shows similar levels of eosinophilic airway inflammation and a milder degree of airway remodeling, such as sub-epithelial thickening, goblet cell hyperplasia, and vascular proliferation.[30–32] The maximal airway response on the dose–response curve is a clinically relevant component of BHR because it reflects the potential degree of airway obstruction. BHR of CVA is caused by the type of airway inflammation and airway structural changes, which are shown to be similar to CA.[31–34] Nearly 30% of CVA patients eventually develop CA, sometimes severe enough to require continuous treatment.[5,35] Some researches indicate that increasing BHR has a pathogenetic role in the development of wheezing during the course of CVA on exposure to an allergic or a non-allergic stimulus.[36,37] Given these studies, CVA is considered to be the initial stage of asthma.[37] Some patients with CVA will evolve into continuous CA. Therefore, the early diagnosis and treatment is recommended to attenuate the inflammation and remodeling. In our study, the spirometric parameters for small airways (FEF$_{50\%}$, FEF$_{75\%}$, and MMEF) with the CVA group were better than those with the CA group. Small airway dysfunction was present in a large proportion of asthma patients at baseline, and the number of small airways dysfunction in the CVA group was less than those of the CA group. Our study has provided a positive relationship between PD$_{20}$ and small airways in both CVA and CA. The optimum cut-point for MMEF, FEF$_{50}$, and FEF$_{75}$ (% predicted) were 47.85%, 47.79%, and 38.2%, and the AUC of them were 0.615, 0.621, and 0.606, respectively. It has been shown that 0.17 mcg of PD20 may help identify CVA with an AUC of 0.582 (P=0.001). The correlation and ROC analyses demonstrated a relatively poor,
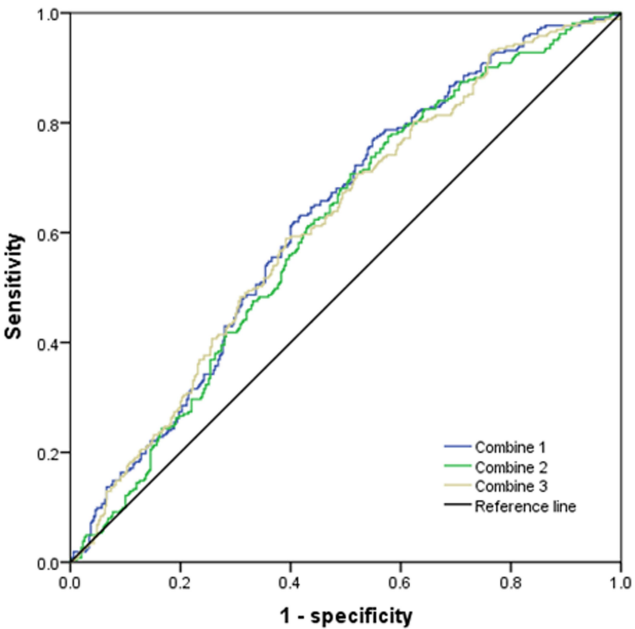
although significant relationship for PD$_{20}$ and small airways to predict CVA in statistics. Thus, it is difficult to use BHR and small airways to predict CVA.

Limitation of the Study

Our study reported on a clinical study with 825 patients with asthma to investigate the diagnostic validity of small airways and BHR in cough-variant asthma. A positive relationship showed between PD20 and small airways. However, overall the association appeared weak with low AUCs for the prediction of BHR and small airways to CVA. While these correlations might show statistical significance, none of these appear convincing and potentially clinically relevant judged. Also, the low AUC values are very unreliable and, very likely, not helpful to inform clinical decision-making. Statistically significant does not always imply clinical significance, but the level of association needs to be considered as well.

Another major limitation was the smoking cigarettes factor. In addition to the possibility that this could be a cause of the cough, smoking is associated with small airway dysfunction which (except for non-causally related cough) is usually asymptomatic until values are very obstructed. Further investigation of smoking or no smoking factor in CVA would also benefit from bigger sample sizes.

Conclusions

This study demonstrates that small airway dysfunction and BHR are milder in patients with CVA, and the relationship of them is weak. Small airways and BHR may not be potentially useful as diagnostic measures to CVA patients. Based on these weak correlations and poor prediction values, further investigations would be required.

Abbreviations

BHR, bronchial hyper-responsiveness; GINA, the Global Initiative for Asthma; FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1 s; PEF, peak expiratory flow; MMEF, maximum mid expiratory flow; MEF, maximal expiratory flow. CVA, cough-variant asthma; CA, classic asthma.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Huizhou Third People's Hospital, which absolved the need for written informed consent because of the retrospective study. All personal identification data were anonymized and de-identified before analysis.

Author Contributions

All authors contributed to the data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

These authors contributed equally to this work and should be considered co first authors: Jie Gao and Haigui Wu.

Disclosure

The authors report no conflicts of interest for this work.

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