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Original Article

The diagnostic value of Astograph test for patients with chest tightness variant asthma

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Abstract: In this work, we aim to evaluate the diagnostic value of Astograph methacholine bronchial provocation test (AMBPT) for chest tightness variant asthma (CTVA). A total of 443 patients complained of chest tightness as the sole or major clinical manifestation were finally included in this work. The cases were divided into two groups: the CTVA group (n = 111) and the control group without asthma (n = 332). All subjects were received a series of examinations, including pulmonary ventilation function, peak expiratory flow (PEF) average daily diurnal variation rate or PEF week variation rate, AMBPT (the baseline value of forced expiratory volume in one second (FEV1) ≥ 70% of the expected value) as well as related-examinations of chest tightness caused by various diseases. The sensitivity, specificity, positive predictive value, negative predictive value, Yunden index and accuracy of AMBPT for the diagnosis of CTVA were 0.8108, 0.6958, 0.4712, 0.9167, 0.5066 and 0.7246 respectively. There are high sensitivity, negative predictive value, Youden index and diagnostic accuracy of AMBPT for CTVA, whereas the specificity and positive predictive value are low, suggesting that there is a higher diagnostic value of AMBPT for CTVA with low false negative and high false positive.

Keywords: Astograph, bronchial provocation test, chest tightness variant asthma, diagnosis, clinical cases

Introduction

The typical clinical manifestations of asthma include recurrent wheezing, chest tightness, breathlessness and coughing, and these symptoms are more serious at night or early in the morning [1-3]. However, in 2013, *Shen* et al. described several patients who complained of chest tightness as their sole presenting manifestation without other symptoms such as breathlessness, wheezing, or recurrent cough for the first time. Therefore, they defined this atypical symptom as chest tightness variant asthma (CTVA), which is a new clinical subtype of asthma [4, 5]. These investigators have proposed that asthma can present with variant as well as classic symptoms, and physiological testing for bronchial hyperresponsiveness is important to evaluate the possibility of symptomatic asthma [5, 6].

Airway responsiveness refers to the degree that the airway responses to a variety of stimulating factors including physical and chemical stimulation, allergen and exercise [7]. These micro-stimulations can't cause smooth muscle contraction, or only induce a slight contraction of human airway in the physiological state, but some asthma patients suffer a strong or premature airway contraction in response to the same stimulations following by the airway inflammation [8-10]. Airway hyper reactivity (AHR) occurs along with the increase of eosinophil inflammatory cells in the airway, and it results in intermittent reversible airflow limitation [11, 12]. Therefore, AHR directly reflect the severity of bronchial asthma as an important phenomenon in the occurrence and development of asthma [13]. The determination of airway reactivity (AR) can provide a strong objective basis for supporting or excluding the diagnosis of asthma, and it is of great value for the judgment of asthma and the evaluation of efficacy [14]. This is similar to the typical bronchial asthma in that AHR is also the classic pathophysiological characteristic of CTVA [15]. Thus, AHR determination has been developed into an important objective basis for the CTVA diagnosis [16].

Currently, the bronchial provocation test (BPT) is usually used to detect AR level basing on the principle that a certain stimulus can cause bronchial smooth muscle contraction. Furthermore, lung function indicators are used for determining the degree of bronchial stenosis [17]. BPT mainly includes the following three inhalation methods: (1) Moisture method (Cockroft method, also known as cumulative excitation concentration method); (2) Metrological method (Chai, Yan or Klein method, also known as cumulative excitation dose method); (3) Astograph method (forced shock continuous tracing breathing resistance method) [18, 19]. The first two methods are the traditional detection methods of BPT with more uniform international standards and operating procedures. However, the subjects are required to undergo repeated pulmonary ventilation tests for 6-14 times. These two methods are not only time-consuming but also often show false positive because of the respiratory muscle fatigue.

Astograph bronchial provocation test was successfully developed and applied to clinical practice in 1977 [20]. It can assess airway responsiveness via forced oscillatory techniques as a continuous monitor of respiratory resistance; and it's maneuverable and time-saving to reduce the time for entire test to only 15 min. This method is implemented through the real-time monitoring of respiratory resistance, and the short-acting bronchodilator was inhaled immediately if a significant increase in respiratory resistance was detected [21, 22]. Although Astograph method has been widely applied in clinical practice because of its high security, but the uniform international evaluation criteria still has not yet reached a consensus at present [23]. This study was conducted in the Department of Respiratory Medicine, the affiliated Kailuan general hospital of North China University of Science and Technology. From May 2013 to July 2017, 111 patients complained of recurrent chest tightness as their only symptom were exposed to Astograph methacholine bronchial provocation test (AMBPT) in order to assess the diagnostic value of this method for the patients with CTVA.

Materials and methods

Cases

A total of 495 patients from the Department of Respiratory Medicine, the affiliated Kailuan general hospital of North China University of Science and Technology from May 2013 to July 2017 were initially included in the present research; and they were complained of chest tightness as the sole or major clinical manifestation. Then, 52 undiagnosed cases were excluded from data analysis according to the exclusion criteria.

Inclusion criteria

CTVA diagnosis was primarily based on the diagnostic guidelines released by *Shen* et al. [4]: (1) The sole or typical clinical manifestation is recurrent chest tightness particularly at night or early in the morning induced by the contact with cold air, allergen, and physical or chemical stimulus, exercise, and emotional changes; and the disease progress lasts more than eight weeks without symptoms of breathlessness, wheezing, or recurrent cough; (2) There is no wheeze on auscultation during the onset of the chest tightness; (3) There is no significant organic pathological change based on the X-ray and computed tomography (CT) observation of chest examination; (4) The subjective inspections associated with variable airflow limitation: peak expiratory flow (PEF) average daily diurnal variation rate (lasts for seven days, the sum of daily PEF diurnal variation rate/7) > 10%, or PEF week variation rate {within two weeks, (PEF_{max} value - PEF_{mix} value)/[(PEF_{max} value + PEF_{mix} value × 1/2] × 100%} > 20%; (5) The treatments with bronchodilator and inhaled glucocorticoid are effective; (6) Exclude all other diseases that cause chest tightness, such as COPD, ILD, CHD, HHD, cardiomyopathy, pulmonary thromboembolism, Graves disease with hyperthyroidism, autonomic dysfunction and so on.

Exclusion criteria

The exclusion criteria used in this study were as follows: (1) acute upper respiratory tract infection in the past 1 month; (2) baseline FEV1 < 70% of the expected value; (3) methacholine allergy; (4) inability to tolerate pulmonary ventilation function, PEF mutation rate test and AMBPT.

Groups

All subjects were divided into two groups: the CTVA group and the control group. There were 111 cases in the CTVA group, 52 males and 59

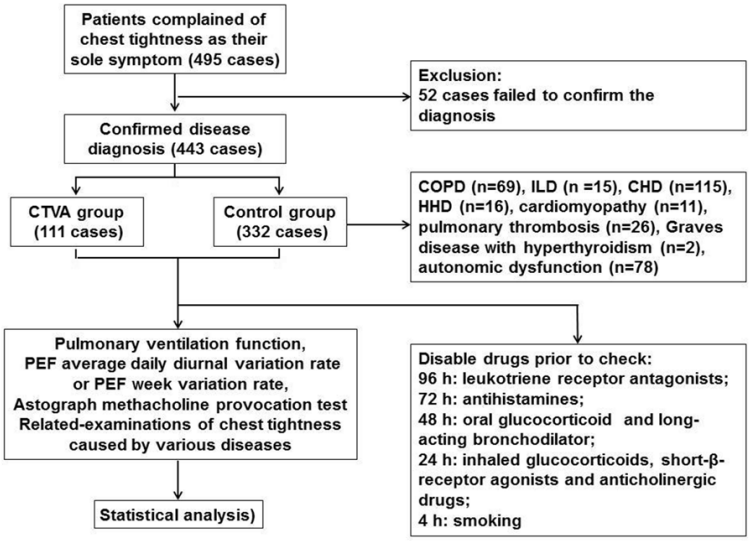

Figure 1. Flow diagram of this study. CTVA, chest tightness variant asthma; COPD, Chronic obstructive pulmonary disease; ILD, interstitial lung disease; CHD, coronary heart disease; HHD, hypertensive heart disease; PEF, peak expiratory flow rate.

females with age ranging from 16-81 years old and the mean age was 44.27 ± 11.99 years. There were 332 cases in the control group that composes of patients discharge with chronic obstructive pulmonary disease (COPD, n = 69), interstitial lung disease (ILD, n = 15), coronary heart disease (CHD, n = 115), hypertensive heart disease (HHD, n = 16), cardiomyopathy (n = 11), pulmonary thrombosis (n = 26), Graves disease with hyperthyroidism (n = 2) and autonomic dysfunction (n = 78), 146 males and 186 females with age ranging from 17-80 years old and the mean age was 46.54 ± 10.15 years. The differences in number of subjects, gender, age, height, body weight and body mass index (BMI) between these two groups all had no statistical significance. This study was approved by the medical ethical committee for the affiliated Kailuan General Hospital of North China University of Science and Technology and informed consent by all subjects (or parent or guardian). The experiment described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) (**Figure 1**).

Methods

All subjects underwent a series of examinations including pulmonary ventilation function, PEF average daily diurnal variation rate or PEF week variation rate, AMBPT (the baseline value of forced expiratory volume in one second (FEV1) ≥ 70% of the expected value) as well as related-examinations of chest tightness caused by various diseases. Pulmonary function test was conducted by using HI-801 pulmonary function analyzer (Chest, Japan); PEF average daily diurnal variation rate or PEF week variation rate was detected with PEF-3 peak speed meter (PARI, Germany); AMBPT was performed by Astograph J-21 Airway Reactivity Analyzer (Chest, Japan), and the positive criteria of AMBPT is that the respiratory resistance increased to more than two times of the basal level after the inhalation of drugs [24]. Subjects were asked to disable leukotriene receptor antagonists, antihistamines, oral glucocorticoid and long-acting bronchodilator 96 h, 72 h, 48 h prior to checks, respectively. Administration of inhaled glucocorticoids, short-β-receptor agonists and anticholinergic drugs were stopped 24 h before the examination, and patients were asked not to smoke for at least 4 h before examination (**Figure 1**).

Statistical analysis

SPSS19.0 statistical software (SPSS Inc, Chicago, IL) was used for data analysis. The measurement data consistent with the normal distribution presented as mean ± standard deviation (SD), and the count data presented as the composition ratio. Comparison between the two groups was performed using the two independent samples t test, while count data were examined using the x^2 test or Fisher's exact probability method. The diagnostic value of AMBPT for patients with CDVA was evaluated using diagnostic test evaluation indicators (sensitivity, specificity, positive predictive value, negative predictive value, Yunden index, and diagnostic accuracy). $\alpha = 0.05$ is the inspection level, and $P < 0.05$ declared that the difference was statistically significant (**Figure 1**).

Table 1. Comparison of general conditions between the CTVA and control groups

Item	CTVA group	Control group	t/X^2	*P*
Number of case (male/female)	52/59	156/176	0.001	0.979
Age, y	44.27 ± 11.99	46.54 ± 10.15	-1.79	0.076
Height (cm)	168.13 ± 7.74	166.78 ± 6.07	1.67	0.096
Body weight (kg)	70.67 ± 14.09	67.89 ± 10.25	1.91	0.057
BMI (kg/m^2)	24.85 ± 3.70	24.38 ± 3.23	1.19	0.237

Table 2. Comparison of lung function index between the CTVA and control groups

	FVC	FEV1	FEV1%	FEV1/FVC	PEF
CTVA group	3.74 ± 0.83	3.00 ± 0.70	98.30 ± 11.34	102.65 ± 7.25	7.01 ± 1.85
Control group	3.63 ± 0.70	2.94 ± 0.57	99.61 ± 10.76	106.11 ± 33.70	6.72 ± 1.44
t	1.26	0.74	-1.11	-1.07	1.49
P	0.171	0.463	0.270	0.285	0.139
	PEF%	FEF25%	FEF50%	FEF75%	
CTVA group	77.70 ± 11.85	6.08 ± 1.61	3.46 ± 0.95	1.19 ± 0.45	
Control group	79.99 ± 12.32	5.99 ± 1.37	3.59 ± 1.03	1.33 ± 0.50	
t	-1.72	0.56	-1.19	-2.78	
P	0.087	0.579	0.236	0.006	

Results

Comparison of general conditions between the CTVA and control groups

There were 111 cases in the CTVA group, 52 males and 59 females; the mean age, height, body weight, and BMI were 44.27 ± 11.99 years old, 168.13 ± 7.74 cm, 70.67 ± 14.09 kg, and 24.85 ± 3.70 kg/m^2, respectively. There were 332 cases in the control group, 156 males and 176 females; the mean age, height, body weight, and BMI were 46.54 ± 10.15 years old, 166.78 ± 6.07 cm, 67.89 ± 10.25 kg, and 24.38 ± 3.23 kg/m^2, respectively. The differences in age, height, body weight, and BMI between these two groups all lacked statistical significance ($P > 0.05$, **Table 1**).

Comparison of lung function indexes between the CTVA and control groups

The pulmonary ventilation function is commonly measured by the volume of lungs inhaled or exhaled per unit of time. The determination of lung function indexes has important guiding significance for the early detection of lung or airway disease and the prediction of the disease severity. As shown in **Table 2**, 75% decreased forced expiratory flow (FEF) was observed in the CTVA group compared with the control group (P = 0.006), however, other lung function indexes including forced vital capacity (FVC), FEV1, FEV1%, FEV1/FVC, PEF, PEF%, FEF 25%, FEF 50% exhibited no significant differences between the CTVA and control groups ($P > 0.05$).

The diagnostic value of AMBPT for patients with CTVA

The positive criteria of AMBPT is that the respiratory resistance increased to more than two times of the basal level after drugs inhalation. The diagnostic value of this method for patients with CTVA was assessed through calculating the sensitivity, specificity, positive predictive value, negative predictive value, accuracy and Yunden index of AMBPT for CTVA patient diagnosis. As shown in **Table 3**, the true positive and false negative cases of AMBPT in the CTVA group were 90 and 21 respectively, while the counts of false positive and true negative in the control group were 101 and 231 cases, respectively. In addition, the sensitivity, specificity, positive predictive value, negative predictive value, Yunden index and diagnostic accuracy of AMBPT for CTVA were 0.8108, 0.6958, 0.4712, 0.9167, 0.5066 and 0.7246, respectively (**Table 4**). These results indicate that AMBPT has a high diagnostic value for

Table 3. Relative Calculation Formula for the diagnostic value evaluation of Astograph methacholine provocation test

	CTVA group (111 cases)		Control group (332 cases)	
	True positive (A)	False negative (B)	False positive (C)	True negative (D)
Astograph methacholine provocation test	90	21	101	231

FVC, forced vital capacity; FEV1, forced expiratory volume in one second; PEF, peak expiratory flow rate; FEF, forced expiratory flow. Note: sensitivity = A/(A+B) × 100%, specificity = D/(C+D) × 100%, positive predictive value = A/(A+C) × 100%, negative predictive value = D/(B+D) × 100%, Yunden index = sensitivity+specificity-1, consistency = (A+D)/(A+B+C+D) × 100%.

Table 4. The diagnostic value of Astograph methacholine provocation test for patients with CTVA

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Yunden index	Consistency
CTVA group	0.8108	0.6958	0.4712	0.9167	0.5066	0.7246

patients with CTVA, but the false positives should be paid more attention to distinguish.

Discussion

CTVA is a newly reported asthma subtype that the only or major clinical symptom is recurrent chest tightness lasting more than eight weeks without the typical bronchial asthma features that mainly include recurrent wheezing, cough and shortness of breath; and the symptom particularly aggravates at night or early in the morning [4]. CTVA frequently occurs when the patients contact with cold air, allergen, and physical or chemical stimuli, or exercise, and emotional changes. There is no wheeze on auscultation during the onset of the chest tightness, and no significant organic pathological changes in the X-ray and/or CT examination of chest; whereas, patients with CTVA behave consistent pathologic features including AHR, reversible air flow limitation and typical bronchial asthma pathology; and they are sensitive to inhaled glucocorticosteroid (ICS) or ICS/long-acting 32-agonists (LABA) therapy [5]. Patients with CTVA are often misdiagnosed as other diseases, such as COPD, CHD, pulmonary thromboembolism and autonomic dysfunction [6]. Therefore, it's urgent to investigate new diagnostic methods of CTVA with high sensitivity and specificity for the effective treatment of this disease.

Since the invention in 1977, Astograph bronchial provocation test has been widely used in Japan, China, Southeast Asia and other countries and regions because of its property of high accuracy, good security, time-saving and maneuverable [25]. Unfortunately, the lack of uniform criterions and rare literatures about AMBPT results in the accumulation of the bronchial stimulant amount during the examination, so that it's difficult to compare the method with other methods such as moisture method and metrological method.

Recent research have demonstrated that the diagnostic sensitivity, specificity, and accuracy of AMBPT for asthma were 92.9%, 42.7% and 43.4% respectively; and the positive criteria was defined that the respiratory resistance after inhalation of methacholine is greater double than the basic resistance in the test [26]. Moreover, one research included 80 patients with asthma and 125 patients without asthma was executed to evaluate the diagnostic value of AMBPT, and the positive criteria was consistent with previous studies. The results showed that the sensitivity, specificity, and accuracy of AMBPT for asthma diagnosis was corresponding to 100.00%, 53.60% and 71.71%, respectively [27].

In this study, we compared the pulmonary function indexes of the CTVA group to the control group. The results showed that the FEF 75% in the CTVA group was significantly lower than that in the control group, yet other pulmonary function indexes between the two groups had no significant difference ($P > 0.05$). These results suggested that no significant pulmonary function abnormality was observed in patients with CTVA in addition to the presence of small airway obstruction and airflow limitation. Furthermore, we obtained the sensitivity and negative predictive value of AMBPT was up to

0.8108 and 0.9167 respectively after making extensive effort on the diagnostic value evaluation of AMBPT for CTVA, which indicates that it's beneficial to reduce the false negative of CTVA diagnosis by using AMBPT. In addition, the Youden index and the accuracy of AMBPT that used to diagnose CTVA were 0.5066 and 0.7246, respectively. Thus, we can easily conclude that the diagnostic accuracy for CTVA may be increased by AMBPT. However, the specificity and the positive predictive value of this method in our study were 0.6958 and 0.4712 separately, which illustrated that AMBPT for CTVA diagnosis presents a high false positive.

Furthermore, compare with other studies [21, 24, 26], AMBPT has lower sensibility but higher specificity, which may be associated with the differences between research subjects. In the present work, we only collected the CTVA patients. Currently, there are still few reports on the diagnostic value of the AMBPT for CTVA despite the 30-40 years of development, which reminds us that it's urgent to perform the clinical research about the AMBPT.

In conclusion, our study found that the lung functions of CTVA patients present almost normal except for the presence of small airway obstruction; the high sensitivity, negative predictive value, Youden index and diagnostic accuracy but low specificity and positive predictive value of AMBPT for CTVA prompt that AMBPT may be an important diagnostic tool for CTVA due to its low false negative, however, its high false positive cannot be ignored. In addition, in the cases of AMBPT with positive symptoms, smoking, diet, drugs, acute respiratory tract infection and other influencing factors should be paid special attention to avoid misdiagnosis.

Disclosure of conflict of interest

None.

Abbreviations

AMBPT, Astograph methacholine bronchial provocation test; CTVA, chest tightness variant asthma; PEF, peak expiratory flow; FEV1, forced expiratory volume in one second; AHR, airway hyper reactivity; AR, airway reactivity; BPT, bronchial provocation test; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; CHD, coronary heart disease; HHD, hypertensive heart disease; BMI, body mass index; CT, computed tomography; FEF, forced expiratory flow; FVC, forced vital capacity.

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