ORIGINAL ARTICLE

Clinical and Airway Inflammation Features of COPD Patients with Positive Bronchodilator Test

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ABSTRACT

Objective: To explore the difference in clinical characteristics and airway inflammation in chronic obstructive pulmonary disease (COPD) patients on the positive bronchodilator tests.

Study Design: Descriptive study.

Place and Duration of Study: Affiliated Hospital of Shaoxing University, Shaoxing, China, from January to December 2017.

Methodology: A total of 200 COPD patients were subjected to COPD Assessment Test (CAT), modified Medicine Research Council (mMRC) score, 6-minute walk distance, Rating of Perceived Exertion Scale (Borg), pulmonary function, serum IgE, and cell count in induced sputum. They were divided into a positive group and a negative group according to the response to the bronchodilator test, and the results were compared.

Results: There were 46 cases (23.00%) in the positive group, and 154 cases (77.00%) in the negative group. There were evident differences in the history of smoking and serum IgE. The positive group had better outcomes than those of the negative group regarding forced expired volume in one second to total predicted value ratio (FEV1% pred), forced vital capacity to total predicted value ratio (FVC% pred), improvement rate of maximum expiratory flow of 75% of lung capacity (MEF75%), and MEF50%. CAT score, mMRC score, Borg score, meters in 6-minute walking test (all $p<0.05$). There was no significant difference in cell count in induced sputum between the two groups.

Conclusion: COPD patients having a positive response to the bronchodilator had better lung function, better CAT score, better mMRC score, and Borg scale score. They also had further 6-minute walking distance. It suggests that a positive bronchodilator response might be a clinical phenotype of COPD.

Key Words: *Chronic obstructive pulmonary disease, Bronchodilator test, Lung function, Serum IgE.*

INTRODUCTION

COPD is a common disease characterised by continuous limited airflow which becomes progressively worse but can be prevented and treated. Some patients have high airway reaction and partial reversible airflow limitation. It seriously endangers the human health and the prognosis of the patients. The fatality rate is relatively high.[1] Pulmonary function examination is important to determine airflow limitation. After inhalation of bronchodilators, FEV1/FVC <70% indicates that the airflow is restricted and is not completely reversible. FEV1 is an important indicator of the severity of the airway obstruction, and FEV1% pred is the classification basis of the chronic obstructive lung.[1] According to the diagnostic criteria of the American Thoracic Society/ European Respiratory Association, the improvement rate of FEV1 was higher than 12%, and its absolute value was higher than 200 mL, which was positive for a bronchodilator test.[2] In recent years, studies have shown that the bronchodilator test in some patients with COPD is positive.[3,4] It is sometimes difficult to distinguish COPD from bronchial asthma. Therefore, some scholars suggest that COPD patients with positive bronchodilator test should be combined with asthma patients.[5]

The aim of this study was to evaluate the clinical characteristics of patients with COPD who were positive for bronchodilator test, regarding gender, age, smoking history, body mass index, mMRC, CAT, Borg score, pulmonary function, serum IgE, and the eosinophilia granulocyte count of induced sputum. This may provide a basis for the evaluation of diagnosis and prognosis.

METHODOLOGY

This study was conducted at the Affiliated Hospital of Shaoxing University, Shaoxing, China, from January to December 2017. Two hundred patients with COPD from outpatients and inpatients were selected as the research object. Inclusion criteria were patients who met the initiative of 2017 GOLD Update;[1] with dyspnea, chronic cough or expectoration; airway obstruction defined as having a forced expiratory volume in 1 second (FEV1)/ forced vital capacity (FVC) <70%; with smoking, occupational factors, early respiratory infection, low body mass and other risk factors. Exclusion criteria were patients with massive hemoptysis, pneumothorax, huge pulmonary vesicles, cavitary tuberculosis; combined

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with other systemic disease; with the history diagnosis of asthma. The study was approved by the Hospital Ethical and Research Committee, and all patients signed the informed consent.

Studied variables included general characteristics (gender, age, course of illness, cough and sputum time, occurrence frequency, smoking history, allergic disease history, body mass index, *etc*.), mMRC, CAT, Borg in questionnaire survey, and a 6-minute walk distance.[6] Lung function detection and bronchodilator tests were made by the QuarkPFT lung function instrument. Lung function detection included FEV1, FVC, FEV1/FVC, FEV 1%, FVC%, RV, TLC, PEF, MEF 75%, MEF 50%, and MEF 25%. The bronchodilator test result was used to divide the subjects into two groups: bronchodilator test positive group and bronchodilator test negative group. According to the literature,[1] patients with COPD were classified as GOLD 1-4 and A B C D. IgE was measured by BN ProSpec. The sputum of patients was collected. The cell was counted with Rui's dyeing.[7]

All statistical analyses were performed using computer software SPSS version 17.0. Descriptive statistics were presented for measurement variables as mean ± standard deviation and were tested by an independent sample. Categorical variables were presented as percentages along with frequency and were tested by the χ^2 test. A $p<0.05$ was accepted as the level of statistical significance for all tests.

Table I: Comparison of general conditions of patients in the two groups ($\bar{x}$ ± s or %).

General Conditions	Bronchodilator test positive group	Bronchodilator test negative group	p-value
Number of cases [n (%)]	46 (23.00)	154 (77.00)	
Age (years)	71.3 ±6.9	75. 8 ±7. 2	0.068
Male [n (%)]			
Yes	22 (47.83)	96 (62.34)	0.079
No	24 (52.17)	58 (37.66)	
Current smoking and former smokers [n(%)]			
Yes	22 (47.83)*	120 (77.92)	<0.001
No	24 (52.17)	34 (22.08)	
Recurrent cough, sputum time (year)	18.3 ±9.1	19.6 ±10.8	0.457
History of allergic diseases [n (%)]			
Yes	12 (26.09)	36 (23.38)	0.706
No	44 (95.65)	148 (96.10)	
Body mass index	22.4 ±4.3	21.4 ±3.5	0.100

Table II: Comparison of clinical symptoms of the two groups ($\bar{x}$ ± s).

Scores	Bronchodilator test positive group	Bronchodilator test negative group	p-value
CAT score	11.6 ±2.8*	19.4 ±3.2	<0.001
MMRC score	1.4 ±0.7*	1.9 ±0.9	<0.001
Borg score	2.6 ±2.3*	3.7 ±1.8	0.012
Six minutes walking distance (m)	428.18 ±99.55*	365.27 ±102.66	0.001
Number of hospitalisations in the past 1 year	0.3 ±0.8*	1.6 ±2.2	<0.001

RESULTS

Among the 200 patients, 118 (59.00%) were males and 82 (41.00%) were females; the age ranged from 47 to 90 (74.4 ±6. 5) years. There was no statistically significant difference between the two groups in age, gender, duration of disease, history of allergic diseases, family history of allergic diseases, or body mass index. History of smoking in the negative group was significantly higher than that in the positive group (p<0.001, Table I).

For the positive group of bronchodilator test, mMRC score, CAT score, and the number of hospitalisation in the past one year were statistically significant compared with those of the negative bronchodilator test group (p<0.001). Thirty-six patients in the positive group completed the 6-minute walking distance measurement. A total of 134 patients in the negative group completed the measurement. The patients with positive bronchodilator test results had a longer walking distance of 6 minutes and a lower Borg score (p=0.001, and 0.012 respectively, Table II).

In the bronchodilator test positive group, FEV 1% Pred, FEV1 improvement, FEV1 improvement rate, FVC% pred, MEF 75% improvement rate, and MEF 50% after inhalation of bronchodilators were higher than in bronchial test negative group (p<0.001). The difference

Table III: Comparison of lung function between positive and negative group patients ($\bar{x}$ ± s).

Groups	FVC% pred (%)	FEV1 pred (%)	FEV1 Improvement (mL)	FEV1 Improvement rate (%)	FEV1/ FVC (%)	RV (L)	TLC (L)	RV/TLC (%)	PEF (L/s)
Positive Group (46 cases)	75.15 ±11.04*	53.04 ±11.81*	278.38 ±59.88*	25.55 ±8.19*	54.66 ±8.57	1.66 ±0.33	3.67 ±0.77	53.05 ±8.82	2.14 ±0.23
Negative Group (154 cases)	63.63 ±13.45	43.84 ±12.99	95.35 ±24.60	8.47 ±2.88	52.69 ±10.31	1.56 ±0.65	3.70 ±1.01	52.05 ±9.98	1.93 ±0.90
p-value	<0.001	<0.001	<0.001	<0.001	0.243	0.313	0.873	0.541	0.062
Groups	PEF Improvement rate (%)	MEF 75% (L/s)	MEF75 Improvement rate (%)	MEF50% (L/s)	MEF50 Improvement rate (%)	MEF25% (L/s)	MEF25 Improvement rate (%)	DLCO [mL/(min. mmHg)]	DLCO% pred (%)
Positive Group (46 cases)	23.61 ±12.42	1.53 ±0.66	66.26 ±18.50*	0.68 ± 0.26	38.25 ±4.77*	0.28 ±0.02	43.41 ±10.49	11.55 ±2.98	45.78 ±11.86
Negative Group (154cases)	20.84 ±4.75	1.47 ±0.48	5.54 ±1.17	0.63 ±0.22	9.87 ±0.38	0.29 ±0.06	46.64 ±5.03	11.22 ±3.75	42.39 ±12.08
p-value	0.170	0.856	<0.001	0.086	<0.001	0.848	0.469	0.079	0.096

Table IV: The cellular count in induced sputum and IgE in the two groups ($\bar{x} \pm s$).

Groups	Acidophils (/100 cells)	Macrophages (/100 cells)	Lympho- cytes (/100 cells)	Neutrophils (/100 cells)	Squamous epithelial cells (/100 cells)	IgE (KU/L)
Positive	3.45 ±1.72	18.78 ±7.80	4.14 ±2.12	70.66 ±13.88	6.64 ±7.80	25.5 ±4.4*
Negative	2.66 ±2.27	20.64 ±8.99	3.74 ±1.88	68.51 ±14.49	5.78 ±6.36	20.4 ±3.8
p-value	0.095	0.260	0.345	0.490	0.557	<0.001

was statistically significant. There was no statistical difference in RV, TLC, RV/TLC, FEV1/FVC (%), PEF, PEF improvement rate, MEF 75%, MEF 50%, MEF 25%, MEF 25% improvement rate, DLCO, or DLCO% pred between the two groups (Table III).

One hundred and eighteen (59.00%) patients completed the induced sputum detection. There were 28 (23.73%) cases from the bronchodilator test positive group and 90 (76.27%) cases from the bronchodilator test negative group. There was no statistically significant difference in squamous epithelial cells, macrophages, neutrophils, acidophilic granulocytes, and lymphocytes percentage of sputum induction between the two groups ($p>0.05$). The serum IgE levels in the positive test group were significantly higher than those in the negative group ($p<0.001$). The results are shown in Table IV.

There were 96 patients with GOLD1 and GOLD2 COPD (A 71 cases, B 25 cases of them). Among them, 43 cases were positive on the bronchodilator test, and the percentage was 44.79%. There were 104 patients with GOLD3 and GOLD4 COPD. Nine cases were positive on the bronchodilator test, and the percentage was 8.65%. The positive rate on the bronchodilator test in patients with GOLD1 and GOLD2 COPD was significantly higher than that in patients with GOLD3 and GOLD4 COPD ($p<0.01$).

DISCUSSION

There is a certain percentage of COPD patients with positive results on the bronchodilator test. Zhiqiang *et al*. reported that 16.7% of patients with COPD have positive results on the bronchodilator test.[3] Han *et al*. conducted a study of 544 patients with COPD and found that 22.2% of patients had positive results.[4] In this study, there were 200 patients with COPD, of which 46 patients (23.00%) had a positive test, which is similar to previous study.

The positive group exhibited partially reversible airflow and their smoking history was less than the negative group. Smoking is the most important risk factor for COPD. This shows that smoking history is a factor that impacts reversible airflow of COPD patients. Inflammation caused by smoking plays an important role in the pathology of COPD. Lung and small airway inflammation is a key indicator of COPD.[8] Quitting smoking may be the best treatment for COPD patients.[9]

FEV 1% pred, FVC % pred, MEF 75% improvement rate, and MEF 50% improvement rate of positive broncho-dilator test patients were better after using a bronchial bronchodilator. However, there was no significant difference in DLCO % pred, RV/TCL, or PEF among others between the two groups. FEV1, FVC, and MEF are sensitive indicators of airflow limitation in lung function measurement. DLCO % pred and RV/TCL can reflect the degree of emphysema. The use of bronchodilator can relieve the spasm of the smooth muscle of the respiratory tract, but it has no obvious effect on the respiratory tract that has been reshaped. In this study, FEV 1% pred, FVC % pred, MEF 75% improvement rate, and MEF 50% improvement rate were all better than those in the negative group on the bronchodilator test. This indicates that there were differences in airway reconstruction and airway spasm in both groups. Patients with COPD who are positive on the bronchodilator test may have limited airflow in large and medium airways, resulting in an increase in the functional residual capacity of patients. Therefore, patients with COPD who are positive on the bronchodilator test can be treated with drugs such as anticholinergic drugs, which can be used to relieve spasms.

The positive rate on the bronchodilator test in patients with GOLD1 and GOLD2 COPD was significantly higher than that in patients with GOLD3 and GOLD4 COPD. This indicates that the more severe the degree of COPD, the greater the destruction degree of pulmonary parenchyma. The elasticity of the lung will be reduced, the airway will become less reversible, and the positive rate of bronchodilator test will be lower. This is consistent with other reports.[10] Therefore, the bronchodilator test may indicate the severity of COPD. Of course, the severity of COPD is also related to symptoms and risk of future acute exacerbations.[1]

Renkema *et al*. found that serum IgE increased in the early phase of COPD.[11] Lewis *et al*. found that serum IgE was negatively correlated with the FEV1 in COPD, and was positively correlated with high airway reaction.[12] In this study, the serum IgE level was significantly increased in COPD patients on the positive bronchodilator test. This suggests that COPD patients who are positive on the bronchodilator test may have a high airway reactivity. These patients may be treated with hormones and atomised inhalation medications to relieve symptoms, reduce the number of recurrent episodes of COPD, and the high airway reactivity.

In this study, CAT and mMRC scores were better in patients with a positive bronchodilator test, and the 6-minute walking distance was longer. Brog scores were better, and the number of hospitalisations was less for

the past year. It was suggested that the patients with positive bronchodilator tests were mild. Other studies in China have indicated that the eosinophils induced by bronchial positive test patients were significantly higher than those induced by bronchial negative test patients.[13] However, the results of the study showed that there was no statistically significant difference between the patients with different bronchodilator test results in eosinophil classification of induced sputum cells. The differences in the airway inflammatory cells and cytokines in patients with different bronchodilator tests required further study. In recent years, both domestic and foreign research studies have put forward the syndrome of bronchial asthma with chronic obstructive pulmonary syndrome (ACOS).[14-16] The reference diagnostic criteria of ACOS were also presented. Positive results for the bronchodilator test were obtained as one of the diagnostic criteria for ACOS.[14] ACOS has the characteristics of asthma and COPD at the same time. With ACOS, frequent aggravation is more common, the quality of life is worse, the lung function is decreased faster, the mortality rate is higher, and the medical expense is higher.[17,18] To the contrary, in this study, patients with positive bronchodilator test results had no difference in family history of allergic diseases or allergic diseases compared with the negative group of bronchodilator test. These patients also have no clinical characteristics of bronchial asthma in clinical manifestations. There was no significant increase in the number of eosinophils in induced sputum. Patients had better daily life, less breathing difficulties, and less degree of disease. All of the above were not consistent with ACOS.

In recent years, there have been many phenotypic studies on COPD. Throughout the world, the clinical phenotype, imaging phenotype, respiratory physiologic phenotype, and pathogenetic phenotype were mainly reported.[19] The clinical phenotype can be divided into chronic bronchitis and emphysema, acute exacerbation of frequent onset, slow obstructive pulmonary and asthmatic overlap, and chronic obstructive pulmonary and bronchial dilatation.[14,19-22] It is suggested that patients with positive bronchodilator test results may be a clinical phenotype of patients with COPD.

CONCLUSION

COPD patients with positive bronchodilator test results, have better pulmonary function than those patients with negative bronchodilator test results. CAT scores, mMRC scores, and Brog scores for these patients are better. Their walking distance is longer for the 6 minutes duration, with a less acidophil in induced sputum. Therefore, COPD patients with positive bronchodilator tests may be a clinical phenotype.

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