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Small airway function changes and its clinical significance of asthma patients in different clinical phases

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ABSTRACT

Objective: To observe the small airways function changes of asthmatic patients in different clinical phases and to discuss its clinical significance. **Methods:** A total of 127 patients diagnosed as asthma were selected randomly and pulmonary function (PF) of them was determined by conventional method. Then they were divided into A, B and C group based on PF results. All 34 patients in A group suffered from acute asthma attack for the first time. All 93 patients in B group had been diagnosed as asthma but in remission phase. C Group was regarded as Control group with 20 healthy volunteers. Then FEV_1, $FEF_{50\%}$, $FEF_{75\%}$ levels of patients in each group were analyzed, and FEV_1, $FEF_{75\%}$ and $FEF_{50\%}$ levels of patients in each group were compared after bronchial dilation test. **Results:** It was found that most patients in group A and B had abnormal small airways function, and their small airways function was significantly different compared with that of group C (P<0.01). In addition, except for group C, $FEF_{75\%}$, $FEF_{50\%}$ levels in A and B group were improved more significantly than FEV_1 levels (P<0.01). **Conclusions:** Asthma patients in acute phase all have abnormal small airways function. Most asthma patients in remission phase also have abnormal small airways function. After bronchial dilation test, whether patients in acute phase or in remission phase, major and small airways function of them are improved, but improvement of small airways function is weaker than that of major airways. This indicates that asthma respiratory tract symptoms in different phases exists all the time and so therapeutic process is needed to perform step by step.

1. Introduction

GINA guide points out in 2009 that inflammation of asthma exists in different parts of airways irregularly, including small airways and pulmonary alveoli. Small airways refers that airway diameter is less than 2 millimeters, which is calculated from the 8th branch of trachea branches, and is closely connected with pulmonary alveoli and vesicles through many levels of braches. When branches are increased unceasingly, diameter of airway becomes thinner accordingly from 2 mm to 0.35 mm. Total cross sectional area of tracheal wall is increased gradually[1]. Small airway walls consists of epithelial cells, smoothness tissues and connective tissues. Due to cartilaginous supporting points loss, submucosal glands are less and are even lacked severely. Cilium numbers in the surface of epithelial tissues are decreased unceasingly and then are disappeared finally, and occupied ratio of smooth muscles within tracheal walls is increased unceasingly. Between pulmonary alveoli and pulmonary alveoli and also terminal peripheral small airways and pulmonary alveoli, bypass branches exists for ventilation. Gas formation mode in small airways is laminar flow, and its flow rate is closely related with the viscosity of gas. When things go wrong in small airways, airflow resistance especially viscous airflow is increased constantly[2]. Under normal conditions, airflow resistance in small airways only accounts for one-tenth of the total lung airflow resistance, which is often regarded as "stable region". Small airway lesions in the early stage do not show any symptoms or physical signs. As reported by Chen *et al*, small airway function of mild asthma patients in the early stage is poorer than normal people[3]. Because sample drawn of systematic small airways is difficult, and specific respiratory function tests on small airways are relatively rare, under normal conditions, small airways function gets no

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attention. In recent years, some scholars overseas discuss deeply on the small airways function and physiological response intensity of airways, and tracheal wall lesions. However, similar scientific research projects in our country are relatively rare. Therefore, we have performed pulmonary function study on 127 asthma patients (including in acute attack phase and in remission phase) to evaluate their small airways function and the reversibility of small airways after bronchial dilation test, in addition, their pulmonary function is compared with healthy people, in order to provide basis for asthma treatment.

2. Materials and methods

2.1. Data

A total of 127 asthma patients who were confirmed by our outpatient service and then were admitted between February 2012 and March 2014 were selected , with male 44 cases, female 83 cases, age 16-64 years old, average age as 42 years old. Cases selection was in accordance with the asthma diagnostic standard established by Asthma Group, Respiratory Society, Chinese Medical Association[1]. Among whom, asthma patients in acute attack phase were 34 cases, with male 14 cases, female 20 cases, age 22-64 years old, average age as 47 years old; patients in remission phase were 93 cases, with male 30 cases, female 63 cases, age 16-56 years old, average age as 38 years old. In addition, 20 cases of healthy people were selected as Control group, with male 12 cases, female 8 cases, age 20-37 years old, average age as 26 years old. All participants had no drinking and smoking history, and within 2 months before experiments, they had no any the upper respiratory tract diseases. Auditing indexes of clinical asthma in chronic phase were that when patients were not given treatment in the healing process, related symptoms and physical signs were no longer in existence, respiratory organ function returned to the state before asthma attack, and this state lasted for over one month[4]. All participants were divided into A, B and C group based on PF results; 34 patients in A group were in asthma acute attack phase for the first time, 93 patients in B group were in asthma remission phase, C group was regarded as Control group with 20 healthy people.

Instruments: Vmax 229 (Sensormedics Inc. USA) type pulmonary function detector was adopted, and testing instrument was checked by standardization, which was in accordance with American Thoracic Society (ATS) standard.

Medical materials: salbutamol sulfate inhalation aerosol, product name was called Wantuoling, with 100 μg 200 times.

2.2. Study methods

According to ATS standard, each determination was repeated for 3 times, the best 2 variations <5%, then the max value was obtained. Pulmonary function determination was under the charge of fixed professionals.

Bronchial dilation test (BDT) method were as follows: firstly the minimum FEV_1 value of participants was judged, then participants were inhaled with 200μg of salbutamol aerosol through dose-dependent inhaler, therewith, within 15 minutes after this step, the remaining FEV_1 was determined.

FEV_1 determination were as follows: The most agile breathing numbers of the first second after peak value of respiratory gases reached to TLC level, it was not only the dosage determination but also the balanced air velocity determination, which was regarded as the only certification mark of respiratory organ function damages.

FEV_1/FVC% determination were as follows: The percentage of forced expiratory volume at the first second accounted for forced vital capacity, which was regarded as the important indicator of airway obstruction judgement.

$FEV_{1\%}$: FEV_1 measured value/FEV_1predicted value.

$FEF_{75\%}$: The instant airflow rate of the expiratory three-quarters of the total vital capacity as best one can, which showed the later period expiratory flow rate standard, and was also regarded as $MEF_{25\%}$.

$FEF_{50\%}$: The instant airflow rate of the expiratory 50% of the total vital capacity as best one can, which showed the last phase flow velocity indicator of expiration, and was also called $MEF_{50\%}$.

$FEF_{75\%}$: The difference value between the measured $FEF_{75\%}$ after bronchial dilation test and the measured $FEF_{75\%}$ before bronchial dilation test and the specific value between both values.

$FEF_{50\%}$: The difference value between the measured $FEF_{50\%}$ after bronchial dilation test and the measured $FEF_{50\%}$ before bronchial dilation test and the specific value between both values.

FEV_1: The difference value between the measured FEV_1 after bronchial dilation test and the measured FEV_1 before bronchial dilation test and the specific value between both values.

Table1

Pulmonary function of patients in A, B, C group.

Pulmonary function indicators	A group	B group	C group
FEV_1/FVC%	64.03±12.35	84.05±14.74	82.30±9.48
Pre FEV_1	69.68±10.54	87.24±16.82	99.80±11.67
Pre $FEF_{75\%}$	59.62±16.68	64.51±18.14	101.20±8.74
Pre $FEF_{50\%}$	50.21±17.44	59.77±15.04	98.70±11.10
Post FEV_1	77.85±12.13	92.26±10.85	99.30±12.87
Post $FEF_{75\%}$	67.79±20.04	70.44±9.98	101.00±16.42
Post $FEF_{50\%}$	58.09±10.09	68.52±14.25	99.70±10.86
FEV_1/preFEV_1 (%)	15.32±11.99	10.02±15.94	0.80±14.16
$FEF_{50\%}$/pre$FEF_{50\%}$ (%)	11.44±15.54	9.12±14.56	0.65±12.11
$FEF_{75\%}$/pre$FEF_{75\%}$ (%)	9.76±14.75	6.52±13.09	0.40±12.79

2.3. Statistical analysis

SPSS13.0 software was adopted, and mean±SD was adopted for statistical data expression, and t test and *Chi*-square test were adopted for data statistics solution. $P<0.05$ showed the statistical significant difference.

3. Results

3.1. Pulmonary function of patients in each group

Detection results of pulmonary function of patients in A, B, C group showed that small airway function of patients with asthma acute attack for the first time (A group) and patients with asthma in remission stage (B group) was abnormal, and compared with healthy people in C group, differences were statistical significance ($P<0.05$), as shown in Table 1.

3.2. Small airway function comparison between asthma group and healthy group

Predicted value of $FEF_{50\%}\leqslant 70\%$ in A, B, C group was 34, 85, 0, respectively, and continuous corrected *chi*-square test showed difference in $FEF_{50\%}\leqslant 70\%$ predicted value distribution in each group was statistical significant ($\chi^2=67.096$, $P<0.01$); and difference in $FEF_{75\%}\leqslant 70\%$ predicted value distribution in each group was also statistical significant ($\chi^2=118.979$, $P<0.01$).

3.3. Small airway function improvement rate and major airway function improvement rate comparison after bronchial dilation test

Differences in $FEF_{75\%}$/preFEF$_{75\%}$ and FEV_1/preFEV$_1$ were significant within A group ($t=1.731$, $P=0.029$), and differences in $FEF_{50\%}$/preFEF$_{50\%}$ and FEV_1/preFEV$_1$ were also significant ($t=4.122$, $P<0.01$). Differences in $FEF_{75\%}$/preFEF$_{75\%}$ and FEV_1/preFEV$_1$ were significant within B group ($t=19.924$, $P<0.01$), and differences in $FEF_{50\%}$/preFEF$_{50\%}$ and FEV_1/preFEV$_1$ were also significant ($t=1.515$, $P=0.013$), as was shown in Table 2.

Table 2

Airway improvement rate of patients in A, B group (%).

Pulmonary function indicators	A group	B group
FEV_1/preFEV$_1$	15.32±11.99	10.02±15.94
$FEF_{50\%}$/preFEF$_{50\%}$	11.44±15.54	9.12±14.56
$FEF_{75\%}$/preFEF$_{75\%}$	9.76±14.75	6.52±13.09

4. Discussion

Through this study we found that small airway function of asthma patients in acute phase and remission phase was reduced. What is the reason? Chen *et al* points out that asthmatic lesions occurrs in small airway at the earliest, but small airway is the latest remittent structure of lesions[3]. Small airway lesions could result in the thickness of tracheal inner walls and the thinness of tracheal lumens, in addition, surrounding airflow resistance is increased in a conditioned reflex with tracheal walls; however, due to the larger total cross-sectional area and smaller airway resistance, although airflow resistance is increased significantly, total resistance of air passage would not have great differences. Therefore, in asthma remission phase, there are no any symptoms in the clinic, but small airway inflammation persists and is in spasticity state[5]. In addition, many achievements in scientific research show that lesion types of tracheal walls of asthma patients are often located in all-sided unchoked air passages involving in muscle tissues and non-muscle tissues, and minitype tracheal walls with tracheal diameter <2 mm are thickened in the meanwhile, which is recognized as "reconstruction" of minitype tracheal walls of asthma patients. Moreover, in recent years, some researchers have found that airway epithelium of children with asthma have already damages under the condition of no significant eosinophilic granulocyte infiltration, and even children with asthma have airway remodeling history several years before asthma attack. Research results show that airway remodeling is not necessarily the result of airway inflammation[6]. Hereby, Holgate and Davies point out airway inflammation and airway remodeling parallel development theory. This theory thinks that as for each link in the airway remodeling, Th2 cytokines and EMTU play effects mutually, which promote and enlarged these effects and exacerbate the process of airway inflammation and airway remodeling. Some researches point out that airway remodeling is involved in major and small airways, and occurre in the early stage of asthma[7-9]. Small airway formal changes cover the thickness of the bottom membrane of epithelial cells, regeneration of smoothness tissue structures, thickness of outer membrane fine fiber structure tissues, expansion and hyperplasia of surrounding blood capillaries and continuous generation of new blood vessels. Experimental results show that proteoglycan ratio in small airways of asthma patients have significant distinction with that of healthy people; that is to say, main proteoglycan and LUMICAN of asthma patients around tiny airways are reduced, while versican within tiny airways is increased, which is the possibility of airway remodeling[10-12]. Hereby we have a depth knowledge of the inevitability of tiny airways in the process of tiny airway remodeling of patients. Through several studies, our experts point out that in fatal asthma attacks, toughness tissues of outer walls of small airways are reduced, and pulmonary alveoli affiliated damaged numbers are increased, thus they reach to a conclusion that formal changes of thinner trachea branches have effects on lung dysfunction[13]. And that, small airway forms are different from major airway's: muscular layer was thicker, smooth muscle tissues development is very fast. Small airway of asthma patients is compared with major airway, we find that occupied ratio of smooth muscle tissues is more significant. Smooth muscle tissues area of major airway is about 2.6% of the total cross-sectional area, while small airway is only 14%. Smooth muscle tissues in small airway not only have hyperplasia but also have thickness performance. Theory proving that even patients without any symptoms suffer from airway blocking in a certain degree, in addition, small airway walls of whom are thickened accordingly. With the help of relevant treatment, radical changes without recovery of major and small airway forms possibly occurr at the same time[14]. CT (HRCT) experiments with better resolution ratio prove that as for patients with abnormal airway

branches, under the help of treatments in many ways, parts of them could be relieved.

This experiment also point out that as for asthma patients in acute phase or remission phase, after bronchial dilation test, major and small airway function is improved, but small airway function improvement rate is smaller than major airway's, which indicates that reversibility of small airway is poorer than major airway's. So, why could appear such result? The following two reasons could be included: (1) Drug factors: bronchodilators for bronchial dilation test is salbutamol, but salbutamol formed into solid aerosols with tracheal diameter of 2-4 μm when in fog state, the remaining 10%-20% of dosage reaches to lower respiratory system after respiration and treatment. When tracheal diameter of small airway is less than 2 mm, diastole relieving solvents directly reaching to small airway branches are the lowest. (2) Airway remodeling: irreversible structure changes occurr within airway, so effects of bronchodilators are not better.

The extant prevention and cure for asthma in books point out that the surviving hospital indications and physical indications, and whether or not FEV_1, PEF are over 80% of planned value, and PEF variables are often regarded as the judgment of disease severity and drug strategies; but the remission of blocking symptoms and the FEV_1, PEF reaching the standard do not show the radical disappearance of symptoms of tracheal walls. However, scientific gains in recent years find that untraditional asthma patients and asthma patients in chronic phase in the earlier stages suffer from small airway dysfunction in succession. Such achievements in scientific research show that asthma patients in chronic phase also suffer from airway conditioned reflex and small airway dysfunction, which indicates symptoms of tracheal walls in chronic phase would continue to exist, and a long-time therapeutic process is needed urgently. Therefore, as for patients in chronic phase, when relevant symptoms and major airway standards such as FEV_1, PEF are examined, at the same time, small airway function changes are also need to be taken into consideration together for showing the glucocorticoid effects. We must strictly prevent from respiratory airway remolding caused by inappropriate treatments.

In conclusion, asthma patients in acute phase all suffer from small airway dysfunction, while most asthma patients in remission phase also have abnormal small airway function. After bronchial dilation test, whether patients in acute phase or in remission phase, major and small airways function of them are improved, but improvement of small airway function is weaker than that of major airway, which is related with the fact that bronchodilators do not reach to small airway and airway remodeling occurrs in small airway. This indicates that asthma airway inflammation in different phases exists all the time, long-time anti-inflammatory treatment is needed, and administration route in treatment is needed to pay attention, ensuring that drugs played effects in small airway to the greatest extent

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