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• BRIEF REPORTS •

Effects of antireflux treatment on bronchial hyper-responsiveness and lung function in asthmatic patients with gastroesophageal reflux disease

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Abstract

AIM: To investigate the effects of antireflux treatment on bronchial hyper-responsiveness and lung function in asthmatic patients with gastroesophageal reflux disease (GERD).

METHODS: Thirty asthmatic patients with GERD were randomly divided into two groups (group A and group B). Patients in group A (n=15) only received asthma medication including inhaled salbutamol 200 μg four times a day and budesonide 400 μg twice a day for 6 weeks. Patients in Group B (n=15) received the same medication as group A, and also antireflux therapy including oral omeprazole 20 mg once a day and domperidone 10 mg three times a day for 6 weeks. Pulmonary function tests and histamine bronchoprovocation test were performed before and after the study.

RESULTS: There was no significant difference in the baseline values of pulmonary function and histamine $PC_{20\text{-}FEV1}$ between the two groups. At the end of the study, the mean values for VC, VC%, FVC, FVC%, FEV_1, FEV_1%, PEF, PEF%, $PC_{20\text{-}FEV1}$ were all significantly improved in group B, compared with group A.

CONCLUSION: Antireflux therapy may improve pulmonary function and inhibit bronchial hyper-responsiveness in asthmatic patients with GERD.

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INTRODUCTION

Bronchial asthma is likely to be associated with gastroesophageal reflux disease (GERD). Bronchial hyper-responsiveness is one of the characteristics of asthma. Numerous observations have suggested that GERD may be causally related to the reactive airways condition, and may at least be a trigger causing airways to react[1-4]. Our study was carried out to determine the effects of antireflux treatment on bronchial hyper-responsiveness and lung function in asthmatic patients with GERD.

MATERIALS AND METHODS

Thirty asthmatic patients with GERD were included in our study. All patients were recruited in the Second Affiliated Hospital Sun Yat-Sen University from December 2000 to December 2001. The diagnosis of asthma was established according to the Global Initiative for Asthma issued by the National Heart, Lung, and Blood Institute. The presence of GERD was determined in accordance with below standards[5]: typical clinical symptom of GERD such as postprandial chest pain and sour regurgitation, signs of erosive esophagitis shown by barium esophagogram and/or lower esophageal erosions shown by endoscopic examination and mucosal biopsy.

The patients were randomly divided into two groups. Group A included 15 patients (7 men, 8 women; range of age 23-60 years, mean 34.9±19.2 years), with duration of asthma ranging from 1-19 years (mean 8.2±6.3 years). Group B included 15 patients (6 men, 9 women; range of age 20-65 years, mean 35.6±17.4 years), with duration of asthma ranging from 1-25 years (mean 7.8±6.1 years). There was no significant difference in age, sex, and duration of asthma between these two groups.

Patients in group A only received asthma medication which included inhaled salbutamol 200 μg four times a day and budesonide 400 μg twice a day for 6 weeks. Patients in Group B received the same medication as group A, and also antireflux therapy which included oral omeprazole 20 mg once a day and domperidone 10 mg three times a day for 6 weeks. Pulmonary function tests and histamine bronchoprovocation test were performed before and at the end of the medications.

Pulmonary function tests included vital capacity (VC), forced vital capacity (FVC), forced expiratory volume at the first second (FEV_1), and the peak expiratory flow rate (PEF), and the percentage of the above parameters over the predicted values (i.e. VC%; FVC%; FEV_1% and PEF%). Bronchial hyper-responsiveness was detected by histamine bronchoprovocation test (HIT). Briefly, the patients were asked to orderly inhale a series of histamine solutions with increasing concentrations ranging from 0.03, 0.06, 0.12, 0.24, 0.48, 1, 2, 4 to 8 g/L for two minutes with an interval of 5 minutes. Every 30 seconds and 90 seconds after each inhalation, FEV_1 was detected. The test was stopped when FEV_1 fell by 20 % from baseline value. Histamine-$PC_{20\text{-}FEV1}$, the concentration of histamine required to produce a 20 % fall from baseline in FEV_1, calculated from Cockcroft formula[6], represented the degree of bronchial responsiveness. Pulmonary function tests and inhaled histamine bronchoprovocation test were performed with the Spiroanalyzer ST-300, Fukuda Sangyo, Japan.

Statistical analysis

The differences of mean values ±SD were determined by *t* test. The distribution of frequency of histamine $PC_{20\text{-}FEV1}$ was skewed distribution. When the values were expressed as geometric mean, it became a normal distribution. A *P* value of < 0.05 was considered statistically significant.

RESULTS

There was no significant difference in the baseline values of pulmonary function and histamine $PC_{20\text{-}FEV1}$ between the two groups. At the end of the study, the mean values for VC, VC%, FVC, FVC%, FEV_1, FEV_1%, PEF, PEF%, $PC_{20\text{-}FEV1}$ did not change significantly in group A, while in group B the mean values for VC, VC%, FVC, FVC%, FEV_1, FEV_1%, PEF, PEF%, $PC_{20\text{-}FEV1}$ all significantly increased. Also, at the end of the study, the mean values for above indices were all significantly higher in group B than in group A. The changes in pulmonary function and bronchial responsiveness were showed in Table 1.

Table 1 Changes in pulmonary function and bronchial responsiveness in asthmatic patients with GERD (mean values ±SD)

Index	Group A *n*=15		Group B *n*=15	
	Before therapy	After therapy	Before therapy	After therapy
VC(L)	2.9±0.4	2.7±0.9	2.8±0.7	3.7±0.7[ab]
VC%	86.3±14.6	85.9±1.9	84.9±18.9	111.2±13.6[ab]
FVC(L)	2.9±0.6	2.7±0.8	2.8±0.4	3.6±0.9[ab]
FVC%	88.4±19.2	85.1±23.6	86.3±21.7	102.6±16.1[ab]
FEV_1(L)	2.3±0.9	2.4±0.6	2.2±0.8	2.8±0.5[ab]
FEV_1%	76.8±11.6	77.5±16.3	75.6±14.5	84.6±12.7[ab]
PEF(L/S)	4.4±1.5	4.8±1.7	4.6±1.2	5.9±1.6[ab]
PEF%	74.8±19.6	75.±16.3	70.5±20.4	85.1±23.1[ab]
$PC_{20\text{-}FEV1}$ (g/L)	0.31±0.11	0.28±0.16	0.33±0.14	0.84±0.22[ab]

[a]$P<0.05$ *vs.* group A after therapy, the *t* values were 2.34, 2.59, 2.31, 2.55, 2.49, 2.26, 2.63, 2.22, and 2.68, respectively. [b]$P<0.01$ *vs.* group B before therapy, the *t* values were 3.93, 4.16, 3.87, 4.04, 3.95, 3.62, 4.46, 3.98, and 4.33, respectively.

DISCUSSION

It has been indicated that there is a causal relationship between asthma and GERD: asthma may cause or precipitate GERD and vice versa, and so much as a vicious cycle[11-13]. On one hand, asthma may be the cause of GERD in some patients. Prolonged period of cough, wheezing and greater respiratory muscle effort in asthma increase abdominal pressure, and facilitate the movement of gastric secretions towards the lower esophageal sphincter (LES). Moreover, the diaphragm's contribution to sphincter tone is decreased in asthma. Furthermore, bronchodilator therapies (both beta-agonists and theophylline) appear to reduce LES pressure[7]. It has become clear that the pressure gradient across the LES is increased in asthma, which promotes the development of GERD.

On the other hand, GERD may cause or facilitate asthma. Mechanisms of bronchospasm inspired by reflux include[8,9]: (1) acid in the inflamed esophagus may stimulate exposed acid sensitive receptors which act through vagal afferents to the airways to cause an increase in bronchial hyper-responsiveness which leads to bronchoconstriction; (2) microaspiration, with stimulation of upper-airway vagal receptor, causes bronchoconstriction; and (3) microaspiration of gastric contents into the lung results into exudative mucosal reaction.

GERD has been found to occur in 30-80 % of asthmatic patients. Kiljander *et al* found that the prevalence of GERD in asthmatic patients is 53 %[11]. Dal Negro *et al* reported that GERD was found in 78.9 % of atopic asthmatic patients[12]. Sontag *et al* demonstrated that more than 80 % of asthmatic patients had abnormal GERD[13]. A number of authors have suggested that some factors may be associated with an increased risk for the development of GERD in asthmatic patients, and thus further diagnostic tests should be proposed to evaluate the presence of GERD in such patients. These factors include[10]: (1) asthma of adult onset; (2) asthmatic symptoms that are largely or predominantly nocturnal; (3) large meals, which might cause or worsen cough and wheezing; (4) asthma of non-smokers; (5) sour dietary and drinks that can cause cough and wheezing; (6) non-allergic (it may be changed to no allergen identified); (7) responders to antacid therapy; and (8) steroid resistant asthma.

Many diagnostic tests have been used to prove the presence of GERD, including barium esophagogram, endoscopic examination and mucosal biopsy, measurement of the LES pressure, esophageal acid perfusion tests, gastroesophageal scintiscan, and twenty-four-hour esophageal PH monitoring.

In 1985, Barish *et al* established a series of procedures to determine the prevalence of GERD in asthmatic patients[5] including barium esophagogram, endoscopic examination, mucosal biopsy and measurement of the LES pressure. It was suggested that GERD be definitely diagnosed if there are two positive results from above examinations. Otherwise, ambulatory 24-hour esophageal PH monitoring can be used as the gold standard to determine the prevalence of GERD[14,15]. However, Barish *et al* emphasized that this test should only be used in cases with diagnostic difficulties because of long time of catheter inserting or shortage of equipment[5]. David *et al* established that in patients with predominant reflux symptoms and supportive evidence from endoscopy, the diagnosis of GERD was straightforward[10]. Allescher *et al* suggested that in patients with persistent reflux problems and erosive reflux esophagitis indicated by endoscopy, the diagnosis of GERD was certain[17]. Hollenz *et al* also proposed that gastroesophageal reflux was diagnosed when endoscopy revealed typical esophageal lesions[16]. In some uncertain cases, 24-hour pH monitoring can be used to verify and objectify an acid gastroesophageal reflux[17].

All the thirty cases in our study had classic symptoms of GERD and positive signs by both barium esophagogram and endoscopic examination. Therefore, the presence of GERD is certain.

A variety of different treatments aiming at the improvement of reflux symptoms have been used in adult asthmatic patients with GERD. Most investigators[10,18] have suggested the three-step procedures. The first step includes elevation of the head of the beds 15-20 cm, no eating or drinking for three hours before sleeping, avoidance of large meals, weight loss, restricted consumption of caffeine, alcohol, spicy foods and chocolate and no smoking. The second step consists of medical management including antacids, H_2-receptor antagonists, proton pump inhibitors, pro-kinetic agents and cytoprotective agents. The third step consists of surgical management. In asthmatic patients with GERD, many studies have indicated that medical antireflux therapy can improve the symptoms of asthma. Harding *et al* reported improvements in both symptoms and pulmonary function in asthmatic patients with GERD after antireflux therapy[19]. Levin *et al* demonstrated that omeprazole improved PEF and quality of life in asthmatic patients with GERD[20]. Teichtahl *et al* found that omeprazole therapy significantly increased evening PEF in asthmatic patients with GERD[21]. Meier *et al* indicated that medical antireflux therapy by omeprazole might predispose to improve respiratory function in asthmatics with GERD[22]. Our observation also

demonstrated that antireflux medications could make an obvious favor in the improvement of pulmonary function and inhibition of bronchial hyper-responsiveness in asthmatic patients with GERD. These results provide strong evidence that GERD can precipitate asthma. Therefore, in such subset of patients, elimination of GERD may be proven to be especially beneficial.

In patients with GERD, esophageal acid exposure is reduced by up to 80 % with H_2-receptor antagonists and up to 95 % with proton pump inhibitors[10]. So, proton pump inhibitors are superior to H_2-receptor antagonists. In addition, pro-kinetic agents also decrease GERD by improving gastric emptying.

In conclusion, our observations indicate that antireflux therapy by proton pump inhibitors and pro-kinetic agents is beneficial to asthmatic patients with GERD.

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