

# Clinical significance of airway mucus hypersecretion in chronic obstructive pulmonary disease

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## ABSTRACT

Airway mucus hypersecretion is one of the most important features of chronic obstructive pulmonary disease (COPD). Airway mucus hypersecretion in COPD patients results in outcomes such as rapid decline of lung function, poor quality of life, and high rate of acute exacerbation, hospitalization and mortality. Nonpharmacologic treatments for airway mucus hypersecretion in COPD include smoking cessation and physical rehabilitation. Pharmacologic therapies include expectorants, mucolytics, methylxanthines, beta-adrenergic receptor agonists, anticholinergics, glucocorticoids, phosphodiesterase-4 inhibitors, antioxidants, and antibiotics. Novel drugs with promising prospects are currently under clinical trials.

**Key words:** pulmonary disease, chronic obstructive; mucus hypersecretion

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD), mainly characterized by constant and progressive airflow obstruction, is chronic inflammation of the airways and lungs exposed to harmful granules or air. It is estimated by WHO that over 200 million people worldwide are suffering from COPD and it might rank third among killer diseases by 2030<sup>[1]</sup>. Airway mucus hypersecretion is one of the most important features of COPD, clinically manifested as repeated cough and expectoration. It is more than a symptom; rather, it is an independent risk factor for COPD progression and prognosis<sup>[2]</sup>. COPD complicated with airway mucus hypersecretion has become a hot topic in the field of pulmonary diseases, because the treatment of airway mucus hypersecretion is of vital clinical significance for COPD patients.

## PATHOGENESIS OF AIRWAY MUCUS HYPERSECRETION

The pathogenesis of airway mucus hypersecretion in COPD is complicated, involving inflammation, oxidative stress,

proteinase balance, and signal transduction pathways. In chronic inflammatory disorder of the airways, long-term and repeated inflammatory stimuli cause extensive metaplasia of bronchial epithelial goblet cells, and hypertrophy and hyperplasia of submucosal bronchial glands, which result in blockage of the respiratory tract, obstruction of airflow, and accelerated decline of lung function, leading to deterioration and increase of acute exacerbation rate<sup>[3]</sup>; in the meantime, inflammatory reactions make cilia unable to function normally, lose surfactants, and biochemical properties of mucus change so that mucus retains within the airways and forms plugs, which worsens blockage of narrowed airway and pathogen colonization, leading to constant infection, obstruction, and reconstruction of respiratory tract.

## EFFECTS OF AIRWAY MUCUS HYPERSECRETION ON COPD PATIENTS

### *Lung function*

Chronic airway mucus hypersecretion can cause progressive decline in pulmonary

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function among COPD patients. A 12-year follow-up study of 1,757 males and 2,191 females reveals the relation between chronic phlegm and FEV<sub>1</sub> decline after adjustment for age and cigarette smoking<sup>[4]</sup>. In the study, men and women with chronic phlegm show FEV<sub>1</sub> decline of (4.5±2.0) ml/yr and (1.7±1.5) ml/yr, respectively<sup>[4]</sup>. Vestbo and others made a 5-year follow-up study on 5,354 women and 4,081 men and found that chronic airway mucus hypersecretion was significantly associated with FEV<sub>1</sub> decline among COPD patients<sup>[5]</sup>. The study shows that chronic airway mucus hypersecretion is associated with an excess FEV<sub>1</sub> decline of 22.8 ml/yr, compared with men without airway mucus hypersecretion after adjusting for age, height, weight, and smoking; in women, the excess decline was 12.6 ml/yr.

### **Quality of life**

Several large-scale clinical research studies indicate that chronic phlegm is closely associated with limitation of activity and worsening quality of life. Kim and others have found that chronic bronchitis (CB) in patients with COPD is associated with modified medical British research council (mMRC) and St George Respiratory Questionnaire (SGRQ) scoring<sup>[6]</sup>. ECLIPSE investigators have found that CB in patients with various degrees of COPD (GOLD II ~ IV grades) is associated with mMRC and SGRQ score decline<sup>[7]</sup>. The PLATINO study has found that COPD patients with CB had worse general health status and physical activity limitation<sup>[8]</sup>.

### **Acute exacerbation and hospitalization**

Vestbo and others have found that chronic airway mucus hypersecretion in patients with COPD is associated with a significant increase in risk for acute exacerbation and hospitalization: In men, the risk increased 2.4 times and in women, 2.6 times<sup>[5]</sup>. A multi-center clinical observational study on 433 COPD patients shows that in those with chronic cough and phlegm, the risk for acute exacerbation increased 4.15 times and that for the following hospitalization increased 4.08 times<sup>[9]</sup>. However, not all the relevant studies have similar findings. ECLIPSE and PLATINO studies have not detected any association between chronic cough and phlegm among COPD patients and rate of acute exacerbation<sup>[7-8]</sup>.

The differences in research results should be analyzed objectively, because they are caused by multiple factors including setting, subjects (such as race, severity, and smoking), and design. Therefore, more large-scale prospective studies are needed to determine whether chronic cough and phlegm are related to acute exacerbation and hospitalization.

### **Mortality**

Chronic cough and phlegm significantly increase death risk. In a clinical study, 1,711 middle-aged men were followed up for up to 40 years; the statistical analysis shows that persistent cough and phlegm increased death risk related to respiratory disorders by 2.54 times and total death risk by 1.64 times after adjusting for lung function<sup>[10]</sup>. Prescott and others followed up 14,223 COPD patients for 10 to 12 years and found that chronic airway mucus hypersecretion increased death risk related to lung infections by 3.5 times<sup>[11]</sup>. Speizer and others followed up 8,427 COPD patients for 12 years and found that chronic cough and phlegm significantly increased death risk: In men, the risk increased by 3.75 times and in women, 11.04 times<sup>[12]</sup>.

## **TREATMENTS FOR AIRWAY MUCUS HYPERSECRETION**

The treatments should counteract each factor contributing to the pathogenesis of airway mucus hypersecretion, for example, to decrease excessive mucus production, inhibit inflammation, clear mucus by increasing cilia transport, reduce mucus viscosity, enhance airway shear stress, to relieve cough and phlegm. Generally, the treatments are divided into two categories: pharmacologic and nonpharmacologic.

### **Nonpharmacologic treatments**

#### **Smoking cessation**

Smoking cessation can relieve cough in patients with chronic cough and phlegm. It can improve mucus cilia functions, inhibit goblet cell hyperplasia, and repair airway injuries. The sputum of those who quit smoking contains less mucus than that of persistent smokers. A large-scale clinical research by Pelkonen and others shows that the incidence of chronic cough and phlegm among smokers (42%) is significantly higher than that of nonsmokers (26%)<sup>[10]</sup>.

#### **Physical rehabilitation**

Cough and increased minute ventilation may help to clear airway mucus. With the increase in minute ventilation, airflow production and mucus shear stress increase. Physical therapy can moisten airways and regulate mucus hydration. Thus, forced expirations (directed cough or huff), or shaking might benefit patients with chronic cough and phlegm<sup>[13]</sup>. However, physical therapy has not been proved in large-scale clinical research.

### **Pharmacologic treatments**

#### **Expectorants and mucolytics**

Guaifenesin can stimulate the vagus nerve and increase respiratory secretion to promote the discharge of sputum.

Yet, COPD patients cannot benefit from long-term use of guaifenesin. A clinical research on COPD patients shows that hypertonic saline could absorb the water within airway epithelial cells, hydrate mucus and induce cough, and also improve breathing and exercise tolerance<sup>[14]</sup>.

#### Methylxanthines and beta-adrenergic receptor agonists

Methylxanthines and beta-adrenergic receptor agonists can remove mucus. Such medications can augment airway lumen diameter, promote cilia motion by increasing cyclic adenosine monophosphate in cells, and activate transmembrane regulators to induce chloride ion secretion and mucus hydration, resulting in airway cilia transport. Long-acting beta-adrenergic receptor agonists can promote mucociliary function and increase peak expiratory flow rate, thus relieving cough. In vitro studies suggest that salmeterol could promote cilia motion and increase ciliary beat frequency. Similarly, formoterol could improve mucociliary function of COPD patients<sup>[15]</sup>.

#### Anticholinergics

Anticholinergics, muscarinic receptor antagonists, can increase airway lumen diameter and decrease mucus secretion, thus removing mucus. Yet, they can reduce airway surfactant fluid and make airway secretions dry and difficult to remove. Clinical studies suggest that ipratropium bromide could reduce cough frequency and severity and enhance lung functions, but could not improve mucociliary function<sup>[16]</sup>.

#### Glucocorticoids

In vitro studies show that glucocorticoids can alleviate inflammation and reduce mucus production. In vivo studies suggest that dexamethasone can downregulate the expression of MUC5AC, a mucin gene in human airway epithelial cells, and enhance mucociliary function. Inhaled glucocorticoids could lower the rate of acute exacerbation and improve quality of life among COPD patients. However, whether they can relieve chronic cough and phlegm is still unknown<sup>[17]</sup>.

#### Phosphodiesterase-4 (PDE4) inhibitors

PDE4, a major cAMP-metabolizing enzyme in inflammation, plays an important mediating role in the synthesis and release of airway nonadrenergic, noncholinergic neurotransmitters. PDE4 inhibitors can relieve inflammation and relax airway smooth muscle. A systemic review of 23 randomized clinical trials on roflumilast or cilomilast versus placebo shows that PDE4 inhibitors could increase FEV<sub>1</sub> by 45.59 ml (95%CI 39.1~52.03) and reduce rate of acute exacerbation (OR 0.78, 95%CI 0.72~0.85)<sup>[18]</sup>. Two clinical studies evaluated the effects of roflumilast on patients with moderate to

severe COPD, most of whom (78%~100%) had chronic cough and phlegm before entering the studies. In one study, the subjects were randomly divided into roflumilast combined with salmeterol and salmeterol groups<sup>[19]</sup>, while in another, the subjects were randomly divided into roflumilast combined with tiotropium bromide and tiotropium bromide groups<sup>[20]</sup>. Both studies prove that roflumilast can significantly increase FEV<sub>1</sub> and reduce rate of acute exacerbation. The studies indicate that PDE4 inhibitors can benefit COPD patients with chronic cough and phlegm.

#### Antioxidants

Drugs targeting oxidative stress, an important part of COPD pathogenesis, can benefit the patients. Sulfhydryl compounds including N-acetyl-L-cysteine (NAC), carbocysteine, erdosteine, and fudosteine are effective antioxidants, among which NAC and carbocysteine are studied in detail. NAC, the N-acetyl derivative of L-cysteine, can decrease reduced glutathione, cellular oxidative stress, and reactive oxygen species (ROS) production. It can also reduce disulfide and thiol bonds associated with mucin polymer and lower mucus viscosity. In vitro studies show that carbocysteine, the mercaptan derivative of L-cysteine, can remove free radicals, inhibit inflammation, and reduce mucus viscosity by acting on fucose and sialic acid. In a multi-center study, 523 patients with COPD, whose average baseline FEV<sub>1</sub> accounted for 57% of expected value, were randomly assigned to NAC or placebo and followed for 3 years. It was found that the average number of exacerbations per year among all the subjects was 2.4~2.5. The number did not differ between groups; neither did the yearly rate of decline in FEV<sub>1</sub>. Yet, subgroup analysis suggested that the exacerbation rate of patients treated with NAC reduced significantly compared with that of those not treated with inhaled corticosteroids (accounting for 30% of all the subjects) or those treated with placebo<sup>[21]</sup>. In a double-blind randomized placebo-controlled study in 34 centers in China, 1,006 patients with moderate to severe COPD aged from 40 to 80 were randomly assigned to 600 mg NAC twice a day or placebo. After one year follow-up, it was found that the number of acute exacerbation per year of NAC group was 1.16 and that of placebo group was 1.49, suggesting that the exacerbation rate of NAC group was reduced significantly (RR 0.78, 95%CI 0.67~0.90, *P* < 0.05). However, the study does not evaluate the effects of NAC on chronic cough and phlegm among COPD patients<sup>[22]</sup>.

#### Antibiotics

Macrolide antibiotics may alleviate chronic cough and phlegm among COPD patients. Macrolide antibiotics can inhibit pro-inflammatory factors, decrease neutrophil influx, impair neutrophil migration, induce apoptosis, relieve

eosinophilic inflammation, increase cilia transport, reduce goblet cell secretion, and alleviate bronchial contraction. In a clinical study, 109 COPD patients were randomly assigned to 250 mg erythromycin twice a day or placebo. After one year, the exacerbation rate of erythromycin group was significantly lower than that of placebo group<sup>[23]</sup>. In a large-scale prospective placebo-controlled study published in *NEJM* in 2011, COPD patients were randomly divided into 250 mg azithromycin and placebo groups. After one year follow-up, it was found that the exacerbation rate was significantly decreased and quality of life was improved in the azithromycin group<sup>[24]</sup>.

### Novel drugs

Our research team has found that myristoylated alanine-rich C kinase substrate (MARCKS) is an important factor in airway mucus secretion and inflammation regulation; MARCKS-related peptide promotes the release of inflammatory mediators within airway epithelial cells in a rat model of airway mucus hypersecretion induced by acrolein, a toxic component of cigarettes<sup>[25]</sup>. BIO-11006, a new inhalation drug targeting patients with chronic cough and phlegm, is under Phase II study (BREATH 1 trial)<sup>[26]</sup>. BIO-11006 can inhibit MARCKS. Preliminary studies have shown that the new medication can improve lung function and relieve symptoms such as cough and phlegm in COPD patients, which suggests that it may benefit COPD patients with chronic cough and phlegm.

### Conflicts of Interest

None declared.

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