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Effect of tiotropium on neural respiratory drive during exercise in severe COPD

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ABSTRACT

Background: Studies have shown that tiotropium once daily reduces lung hyperinflation and dyspnea during exercise and improves exercise tolerance in patients with COPD. Mechanisms underlying the effects of the muscarinic receptor antagonist tiotropium on COPD have not been fully understood.
Objective: In this study, we investigated whether improvement in neural respiratory drive is responsible for reducing dyspnea during exercise and improving exercise tolerance in COPD.
Methods: Twenty subjects with severe COPD were randomized into two groups: no treatment (Control, $n = 10$, 63.6 ± 4.6 years, FEV_1 29.6 ± 13.3%pred) or inhaled tiotropium 18 μg once daily for 1 month ($n = 10$, 66.5 ± 5.4 years, FEV_1 33.0 ± 11.1%pred). All subjects were allowed to continue their daily medications other than anti-cholinergics during the study. Constant cycle exercise with 75% of maximal workload and spirometry were performed before and 1 month after treatment. Diaphragmatic EMG (EMGdi) and respiratory pressures were recorded with multifunctional esophageal catheter. Efficiency of neural respiratory drive, defined as the ratio of minute ventilation (VE) and diaphragmatic EMG (VE/EMGdi%max), was calculated. Modified British Medical Research Council Dyspnea Scale (mMRC) was used for the evaluation of dyspnea before and after treatment.
Results: There was no significant difference in spirometry before and after treatment in both groups. Diaphragmatic EMG decreased significantly at rest (28.1 ± 10.9% vs. 22.6 ± 10.7%, $P < 0.05$) and mean efficiency of neural respiratory drive at the later stage of exercise increased (39.8 ± 2.9 vs. 45.2 ± 3.9, $P < 0.01$) after 1-month treatment with tiotropium. There were no remarkable changes in resting EMGdi and mean efficiency of neural respiratory drive post-treatment in control group. The score of mMRC decreased significantly (2.5 ± 0.5 vs. 1.9 ± 0.7, $P < 0.05$) after 1-month treatment with tiotropium, but without significantly difference in control group.
Conclusion: Tiotropium significantly reduces neural respiratory drive at rest and improves the efficiency of neural respiratory drive during exercise, which might account for the improvement in exercise tolerance in COPD.

Abbreviations: IC, inspiratory capacity; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FRC, functional residual capacity; TLC, total lung capacity; VE, minute ventilation; RMS, root mean square; BMI, body mass index; mMRC, Modified British Medical Research Council Dyspnea Scale; EMG, electromyogram; EMGdi, diaphragm electromyogram; NRD, neural respiratory drive; Pes, esophageal pressure; Pga, gastric pressure; Pdi, transdiaphragmatic pressure; P0.1, occlusion pressure.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive and partially reversible airflow obstruction. The diagnosis and assessment of COPD primarily depend on spirometry, for instance, the ratio of Forced expiratory volume in one second (FEV_1) and Forced vital capacity (FVC) [1]. Based on the 2011 GOLD guideline [2], the maintenance therapy for moderate to severe COPD is consisted of bronchodilators, i.e. β_2-adrenergic receptor agonists, or muscarinic receptor antagonist, including tiotropium, which have been demonstrated to alleviate dyspnea and improve exercise tolerance in COPD [3–6]. However, compared with asthma, bronchodilators result in a relatively minor magnitude of improvement in lung function in patients with COPD despite their improved exercise tolerance and minor dyspnea. The inconsistent post-bronchodilator changes between spirometry and patient-reported dyspnea might necessitate more objective parameters to assess the therapeutic outcomes. It has also been reported that neural respiratory drive (NRD) might be a physiological biomarker for monitoring the changes during acute exacerbations of COPD [7].

The major pathophysiologic change of COPD is airflow obstruction and hyperinflation which impair exercise capacity. It has been recognized that inhaled bronchodilators, for instance, salbutamol, significantly lengthened the duration of exercise and six-minute walk distance. The effects of inhaled β_2-adrenergic receptor agonists on improvement of exercise tolerance may be attributed to the reduction in dynamic hyperinflation during exercise [8]. However, dynamic hyperinflation during submaximal exhaustive exercise might not be achieved in all COPD patients [9], miscellaneous factors, for instance, neural respiratory drive, might have also implicated in the pathophysiology of COPD.

We have recently shown [10] that the efficiency of neural respiratory drive, expressed as the ratio of Minute ventilation (VE) and diaphragmatic EMG (EMGdi) in COPD, differed from that in healthy subjects during exercise. The efficiency of NRD remained stable in healthy subjects but decreased substantially during the exercise in COPD at a submaximal constant load. We hypothesized that the decrease in the efficiency of NRD may be responsible for exercise limitation. In this study, we tested the hypothesis that the better exercise tolerance after inhalation of tiotropium in COPD was associated with an improved the efficiency of NRD.

2. Methods

2.1. Subjects

Twenty subjects with severe COPD who remained clinically stable were recruited from the out-patient clinics of the First Affiliated Hospital of Guangzhou Medical University, and were randomized to tiotropium group ($n = 10$, 66.5 ± 5.4 years, FEV_1 33.0 ± 11.1%pred) and control group ($n = 10$, 63.6 ± 4.6 years, FEV_1 29.6 ± 13.3%pred). Subjects in tiotropium group received tiotropium (Spiriva™, 18ug once daily) in addition to usual therapy for 1 month, whereas subjects in control group continued their daily medications other than anti-cholinergics. Daily medications included oral methylxanthines, inhaled glucocorticosteroids and oral mucolytics in our study. Short-acting β_2-adrenergic receptor agonists, including salbutamol, were allowed if necessary.

The study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University, and all subjects gave informed consent.

2.2. Esophageal electrode and positioning

A multifunctional esophageal catheter (a balloon-electrode combined catheter with 10 metal coils and two balloons), as describe previously [11], was used to record the esophageal pressure (Pes), gastric pressure (Pga), EMGdi and the transdiaphragmatic pressure (Pdi) which was calculated by subtracting the Pes from the Pga. The multifunctional esophageal catheter was passed through the nose into the stomach and carefully positioned based on the magnitude of EMGdi recorded simultaneously from the catheter. The catheter was securely taped at the nose at an optimal position characterized by the greatest magnitude of EMGdi in electrode pairs 1 and 5, and lowest in electrode pair 3, as described previously [12]. The balloon at the esophagus contained 0.5 ml of air and the balloon in the stomach was filled with 1.0 ml of air. The EMGdi signals were amplified and band-pass filtered between 20 Hz and 1 kHz (RA-8, Yinghui Medical Technology Co., Ltd., Guangzhou, China).

2.3. Measurement of maximal EMGdi

The maximal EMGdi was recorded from different maneuvers, including maximal inspiration to the total lung capacity (TLC maneuver), maximal inspiration against a closed valve at the functional residual capacity (FRC) (MIP maneuver) and maximal sniff from the FRC (sniff maneuver) [13]. Each maneuver was repeated for at least three times, with an interval of 30 s or greater. All EMGdi data were normalized by the maximal EMGdi derived either from the above-mentioned maneuvers or during exercise. The efficiency of NRD was defined as the ratio of VE and EMGdi%max and measured during exercise.

2.4. Study protocol

All subjects visited the laboratory for three times. In the initial visit, subjects underwent spirometry, measurement of mMRC scale and the maximal workload based on incremental cycle ergometry [14]. A constant cycle ergometry at 75% of the maximal workload, derived from visit 1, was performed on visits 2 and 3 at least 1 month apart. The cycle ergometry on visits 2 and 3 included a 3-minute resting stage, 1-minute warm-up of unloaded exercise and constant loaded exercise. The EMGdi, Pes, Pga and Pdi were recorded on visits 2 and 3. Minute ventilation (VE), oxygen consumption (VO_2), carbon dioxide consumption (VCO_2), tidal volume (VT), respiratory rate (RR) and heart rate (HR), oxygen saturation (SpO_2) during exercise were also measured by using the K4b2 system (COSMED Co., Ltd., Milan, Italy). The mMRC scale was also assessed on visit 3.

2.5. Data analysis and processing

Data were analyzed off-line. The raw signals were converted to the root mean square (RMS) by using the Chart 5.4.2 software (Powerlab, ADInstruments Co, Australia) with the time constant of 100 ms. To avoid the influence of electrocardiogram on EMGdi, the RMS was measured from the segments between QRS complexes. A peak of RMS selected from five pairs of electrodes was measured on a breath-by-breath basis. Statistical analyses were conducted using SPSS 12.0 (SPSS Inc., Chicago, Ill., USA). Data were expressed as mean ± standard deviation. Comparisons between groups (Tiotropium versus Control) and within a group (before and after treatment) were made using one-way analysis of variance (ANOVA). $P < 0.05$ was considered to be statistically significant.