ORIGINAL ARTICLE

Chronic bronchitis leads to accelerated hyperinflation in COPD patients during exercise

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ABSTRACT

Background and objective: It is not known whether patients with chronic obstructive pulmonary disease (COPD) have a different exercise capacity with (CB+) or without accompanying chronic bronchitis (CB−). Methods: We conducted spirometry, a 6-min walk distance test and cardiopulmonary exercise test in 50 age-matched healthy control subjects, 45 COPD patients without CB (CB−) and 37 COPD patients with CB (CB+). A multiple regression model was established to identify factors independently associated with peak oxygen consumption (VO2peak).

Results: Patients with and without CB had similar forced expiratory volume in 1 s (FEV1). CB+ patients had a lower VO2peak. CB+ and CB− participants had similar increases in tidal volume at peak exercise; however, CB+ patients had an increased respiratory rate (RR). These patients reached the peak value for ratio of end-expiratory lung volume to total lung capacity (TLC) at a lower work load. A stepwise multiple linear regression analysis identified chronic bronchitis, FEV1, diffusing capacity for carbon monoxide, the ratio of residual inspiratory capacity to TLC and serum tumour necrosis factor-α as independent predictors of peak VO2peak.

Conclusions: CB significantly lowers exercise capacity in COPD patients because of dynamic hyperinflation during exercise. The accelerated dynamic hyperinflation may contribute to increased airway and systemic inflammation in COPD patients.

Key words: cardiopulmonary exercise test, chronic bronchitis, chronic obstructive pulmonary disease, dynamic hyperinflation, exercise capacity.

Abbreviations: %pred, per cent of predicted; 6MWD, 6-min walk distance; BMI, body mass index; CB, chronic bronchitis; CB−, COPD patient without chronic bronchitis; CB+, COPD patients with chronic bronchitis; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise test; DLCO, diffusing capacity for carbon monoxide; EELV, end-expiratory lung volume; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; IC, inspiratory capacity; Rm, airway resistance; RR, respiratory rate; RV, residual volume; TLC, total lung capacity; TNF-α, tumour necrosis factor-α; VCO2, carbon dioxide output; VE, minute ventilation; VO2peak, oxygen consumption; Vt, tidal volume.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder with variable clinical, functional and radiologic presentations. The forced expiratory volume in 1 s (FEV1) alone cannot be used for assessing or managing COPD. COPD patients are often classified into subgroups based on phenotype, and a common form of subgrouping distinguishes between COPD patients with and without accompanying chronic bronchitis (CB+ or CB−). The incidence of accompanying CB in patients with COPD is estimated between 14% and 74%,.

Compared with CB− patients, CB+ patients tend to have more severe dyspnoea, accelerated FEV1 decline, a poorer quality of life, more frequent disease exacerbations and higher mortality rates. The pathology of CB is mucous metaplasia. Mucous metaplasia harms ciliary function and leads to...
epithelial thickening, altered airway surface tension, expiratory airway collapse and occlusion, ineffective cough and difficulty clearing secretions.12–15 The Latin American Project for the Investigation of Obstructive Lung Disease study showed that CB+ patients had more severe exercise limitations as measured by the physical and pulmonary function domains of a 12-question Medical Outcomes Study Short Form questionnaire.16 In contrast, the Genetic Epidemiology of COPD study found no difference in exercise capacity between CB+ and CB− patients as measured by a 6-min walk distance (6MWD).17 The inconsistency between those findings might be partly due to different patient inclusion criteria and methods for evaluating exercise capacity.16 Additionally, the value of data obtained from a 6MWD test and the physical domain score on the Medical Outcomes Study Short Form questionnaire used to evaluate exercise capacity is limited when compared with data obtained from a cardiopulmonary exercise test (CPET).

Exercise increases air trapping and dynamic hyperinflation in COPD patients and thus lowers their exercise capacity.17 No previous study has investigated possible mechanisms responsible for the different exercise capacities in COPD patients with and without accompanying CB. Dynamic hyperinflation may be accelerated in CB+ patients due to a rapid and shallow breathing pattern during exercise. In this study, we compared the exercise capacities of CB+ and CB− patients by CPET and then determined the effects of incremental increases in exercise on dynamic hyperinflation.

**METHODS**

**Subjects**

The study protocol was approved by the Human Research Ethics Board of Beijing Chao-Yang Hospital (study 10-ke-65). Written informed consent was obtained from each participant.

The patient inclusion criteria for this study were: stable COPD with post-bronchodilator FEV1/forced vital capacity (FVC) values <70%. Exclusion criteria included a COPD exacerbation within 4 weeks, severe cardiovascular or cerebrovascular disease or other diseases that might contribute to dyspnoea or limit exercise. CB was defined as a chronic cough with sputum production at least 3 months per year for 2 consecutive years.2 Age-matched healthy volunteers were recruited as normal control subjects. A flow chart for the study is provided in Figure 1.

**Measurements**

Demographic data, including the subject’s age, gender, body mass index (BMI) and smoking history were collected. Dyspnoea was measured using a modified Medical Research Council dyspnoea score. Health-related quality of life was measured using the COPD Assessment Test.18 The patient’s score on the Hospital Anxiety and Depression Scale (HADS) was assessed,19 and a 6MWD test was conducted according to American Thoracic Society guidelines.20

**Statistical analysis**

Categorical data were assessed with the chi-square test. Normally distributed continuous variables were assessed with the unpaired two-tailed t-test or a one-way analysis of variance. Non-normally distributed data were further analysed using the Mann–Whitney or Kruskal–Wallis H test. To explore the determinants of peak %pred VO2, variables possibly associated with peak %pred VO2 were evaluated by a simple correlation analysis; after which, multiple stepwise linear regression was used to identify the independent determinants of peak %pred VO2.
regression models including potential confounding factors were established to identify factors independently associated with the peak VO₂. P-values < 0.05 were considered statistically significant.

RESULTS

Subject characteristics
A total of 181 subjects were recruited between 1 September 2011 and 31 January 2013, and 82 stable COPD patients and 50 healthy control subjects completed the study (Table 1). Thirty-seven (45%) of the COPD patients had CB. There were no significant differences in age or gender among subjects in the CB⁺, CB⁻, and control groups. Additionally, the CB⁺ and CB⁻ groups showed no significant differences in BMI, comorbidities, smoking history or disease exacerbation history during the previous year.

When compared with the control group, both the CB⁺ and CB⁻ groups had a lower mean BMI, a greater pack-year smoking history (P < 0.05) (Table 1), more severe dyspnoea at rest, a worse quality of life, a higher ratio of residual volume (RV) to total lung capacity (TLC), higher airway resistance (Raw), a lower %pred IC, a lower IC/TLC value, a lower %pred FEV₁, and a lower %pred DLCO (P < 0.05) (Table 2).

More subjects in the CB⁺ and CB⁻ groups had anxiety or depression compared with the percentage in the control group (P < 0.05); however, the CB⁺ and CB⁻ cohort had similar level of anxiety and/or depression (Table 1). The CB⁺ and CB⁻ groups showed no significant differences in IC/TLC, RV/TLC, %pred FEV₁ or %pred DLCO. Compared with the CB⁺ group, the CB⁻ group had a poorer quality of life, higher Raw (0.94 ± 0.42 kPa/L/s vs 0.69 ± 0.37 kPa/L/s, P < 0.05), a shorter mean 6MWD (459 ± 68 m vs 501 ± 73 m, P < 0.01) and a higher mean serum TNF-α concentration (3.08 ± 0.94 pg/mL vs 2.72 ± 0.89 pg/mL, P = 0.057) (Table 2).

Table 1 Characteristics of the subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy controls (n = 50)</th>
<th>COPD without chronic bronchitis (n = 45)</th>
<th>COPD with chronic bronchitis (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD (years)</td>
<td>61.8 ± 6.3</td>
<td>64.3 ± 7.5</td>
<td>63.1 ± 7.4</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>41/9</td>
<td>41/4</td>
<td>32/5</td>
</tr>
<tr>
<td>BMI, mean ± SD (kg/m²)</td>
<td>26.2 ± 3.6</td>
<td>24.4 ± 3.2*</td>
<td>24.7 ± 3.1*</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>6.0</td>
<td>6.7</td>
<td>5.4</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>10.0</td>
<td>11.1*</td>
<td>10.8*</td>
</tr>
<tr>
<td>HADS-anxiety (%)</td>
<td>4.0</td>
<td>11.1*</td>
<td>10.9*</td>
</tr>
<tr>
<td>HADS-depression (%)</td>
<td>6.0</td>
<td>11.1*</td>
<td>13.5*</td>
</tr>
<tr>
<td>Smoking history, median (IQR) (pack years)</td>
<td>5 (20)</td>
<td>20 (53.8)*</td>
<td>37 (40)*</td>
</tr>
<tr>
<td>Exacerbations in the previous year, median (IQR)</td>
<td>NA</td>
<td>0 (1)*</td>
<td>0 (1)*</td>
</tr>
</tbody>
</table>

* P < 0.05 versus controls.

Values are expressed as the mean ± standard deviation (SD). HADS score ≥8 signifies a ‘possible case’.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; NA, not applicable.

**CPET results**

A total of 132 subjects successfully completed the symptom-limited CPET, and no subject reported an adverse reaction. Compared with the control group, both the CB⁺ and CB⁻ groups had lower peak values for VO₂, VCO₂ and VE, and higher mean values for EELV and EELV/TLC at peak exercise. The two subgroups also showed greater changes (Δ) in values for EELV and EELV/TLC from rest to peak exercise (Table 3). Compared with the CB⁻ group, the CB⁺ group had lower peak values for VO₂ (P < 0.05), VCO₂ (P < 0.05) and VE (P < 0.01), which reflect a more limited exercise capacity of the CB⁺ group.

Compared with the CB⁺ group, the CB⁻ group had higher mean values for EELV/TLC (P < 0.05), and lower values for IC (P < 0.001) and IC/TLC (P < 0.05) at peak exercise. In the CB⁺ group, the inspiratory reserve volume (defined as TLC minus the end-inspiratory lung volume) decreased to the limit at a lower work load. During exercise, there was a more rapid rise in EELV/TLC in the CB⁺ group (P < 0.05) as that group had a lower work rate (Fig. 2a). However, there was no significant difference in ΔEELV/TLC between the CB⁺ and CB⁻ groups (Table 3; Fig. 2b).

The CB⁺ group showed a trend towards lower mean values of Vt (P = 0.06) and expiratory flow (P < 0.05) compared with the CB⁻ group at peak exercise, as did the COPD group versus the control group (Table 3). However, the CB⁺ and CB⁻ groups showed no differences in Vt at each work load (Fig. 3a).

At work loads of 30 watts and 60 watts but not at 90 watts, the CB⁺ group had a higher mean RR compared with the CB⁻ group (P < 0.05) (Fig. 3b).

**Association of exercise capacity with other variables in COPD**

The values for peak %pred VO₂ in COPD patients showed a good correlation with values for EELV/TLC.
(r = −0.536, P < 0.001) at peak exercise (Fig. 4). Additionally, values for %pred peak \( V_{O2} \) were significantly related to several other variables including age, gender, BMI, CB, %pred FEV\(_1\), %pred IC, RV/TLC, %pred DLCO, \( R_{aw} \) and TNF-\( \alpha \) (Table 4). A stepwise multiple linear regression analysis identified CB, %pred FEV\(_1\), %pred DLCO, RV/TLC and TNF-\( \alpha \) as independent predictors of peak %pred \( V_{O2} \) (\( R^2 = 0.775 \); adjusted \( R^2 = 0.754 \)) (Table 5). Other variables including age, gender, BMI, comorbidity and the number of disease exacerbations were not independent predictors.

**DISCUSSION**

The major finding of this study is that COPD patients with CB have a shorter 6MWD and lower peak \( V_{O2} \).
compared with those without CB. Both the CB+ and CB− groups showed a significant increase of ΔEELV during exercise compared with the control group. However EELV and EELV/TLC increased at a lower work load in the CB+ group, indicating that increases in EELV and EELV/TLC during exercise occurred earlier in the CB+ group.

As Lu et al. described, the lower exercise capacity of COPD patients with CB was not completely accounted for by their more impaired lung functions and other factors play a role in the pathological mechanism. It is generally agreed that dynamic hyperinflation is the primary cause of exercise limitation in COPD patients. Exercise requires a patient to increase their VT and/or RR. A faster RR worsens dynamic hyperinflation by less complete lung emptying, which further constrains VT increases, thus creating a vicious circle that limits both exercise capacity and at-rest lung function.

In the present study, both the CB+ and CB− groups showed a significant increase of ΔEELV during exercise compared with the control group, and this finding is consistent with previous reports. However, in our study, the mean increases in EELV and EELV/TLC from rest to peak exercise in the CB+ and CB− groups were not significantly different, suggesting that both groups experienced the same extent of dynamic hyperinflation during exercise. However, the values for EELV and EELV/TLC increased to peak limit values at a lower work load in the CB+ group, indicating that increases in EELV and EELV/TLC during exercise occurred more rapidly in the CB+ group. In addition to showing accelerated dynamic hyperinflation during exercise, the CB+ group also had a higher mean RR than the CB− group at work loads of 30 watts and 60 watts, suggesting that dynamic hyperinflation during exercise was accelerated by tachypnoea in the CB+ patients. The observation that this was not
observed at 90 watts can be explained by the fact that only a few CB+ patients reached the 90-watt work load.

Currently, we can offer several speculative explanations for our observed phenomena. The first explanation is that increasing degrees of pathologic changes (e.g. mucous metaplasia, mucus hypersecretion) in the peripheral airways of CB+ patients may have increased Raw. It is known that certain increases in Raw may not be shown by measurements of FEV1 and values for FEV1/FVC, which mostly reflect proximal airway status. From an energetic point of view, rapid shallow breathing in subjects with higher Raw might decrease the amount of work required to breathe.26,27

Another possible explanation is that the worse airway inflammation in CB+ patients stimulated non-myelinated bronchial and/or alveolar vagal C-fibre afferents, which cause rapid and shallow breathing during exercise.28 Although we did not compare the severity of airway inflammation in CB+ and CB− patients, mucus hypersecretion itself might suggest the status of airway inflammation. On the other hand, Gatta et al.29 observed that reduced IC was associated with higher serum levels of C-reactive protein in stable COPD patients. Although the CB+ patients in the current study did not display significantly higher serum TNF-α levels (P = 0.057), a
significant negative correlation between exercise capacity and serum TNF-α implied that systemic inflammation might affect breathing patterns during exercise and induce a dynamic hyperinflation in COPD patients.

Finally, it is also possible that anxiety and depression may have affected breathing patterns. Increasing numbers of studies show that anxiety and depression are common comorbidities of COPD, suggesting these factors may directly impact a patient’s health status, exercise capacity and chances of experiencing an exacerbation of COPD. Additionally, several studies have reported that anxiety may influence respiratory behaviour during periods of exercise and mental stimulation. In the present study, our HADS results did not indicate a higher degree of anxiety or depression in the CB group compared with the CB+ group. However, it should be recognized that the HADS results by themselves cannot be used make a clinical diagnosis of generalized anxiety or a depression disorder, and may not be able to evaluate changes in anxiety and depression which occur during exercise.

The results of our current study are limited by the small number of patients enrolled. In addition, no subject was examined by chest high-resolution computed tomography; therefore, no information was available concerning differences in per cent emphysema and air trapping areas in the two subgroups. Further studies are needed to obtain this additional information.

In conclusion, CB+ demonstrated a significantly lower exercise capacity compared with CB, primarily due to their accelerated dynamic hyperinflation during exercise. This accelerated dynamic hyperinflation might have partially contributed to the airway and systemic inflammation. The main clinical implication of our findings is that CB+ is a phenotype of COPD with respect to a patient’s breathing pattern during exercise.

Acknowledgements

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REFERENCES


### Table 5

<table>
<thead>
<tr>
<th>Variables</th>
<th>β</th>
<th>SE</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB+ group</td>
<td>-2.268</td>
<td>1.072</td>
<td>(-4.419) to (-0.117)</td>
<td>0.039</td>
</tr>
<tr>
<td>%pred FEV₁</td>
<td>0.281</td>
<td>0.093</td>
<td>0.093 to 0.468</td>
<td>0.004</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>-0.396</td>
<td>0.132</td>
<td>(-0.660) to (-0.131)</td>
<td>0.004</td>
</tr>
<tr>
<td>%pred DLco</td>
<td>0.194</td>
<td>0.062</td>
<td>0.069 to 0.319</td>
<td>0.003</td>
</tr>
<tr>
<td>TNF-α</td>
<td>-5.810</td>
<td>1.328</td>
<td>(-8.474) to (-3.146)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Variables included in the analysis were those previously described as being associated with % pred peak VO₂, β, estimated coefficient; CB, chronic bronchitis; CI, confidence interval; DLco, diffusing capacity for carbon monoxide; FEV₁, forced expiratory volume in 1 s; RV/TLC, the ratio of residual volume to total lung capacity; SE, standard error; TNF-α, tumour necrosis factor-α.*