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Effect of tiotropium on spontaneous expiratory flow–volume curves during exercise in GOLD 1-2 COPD

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ABSTRACT

This substudy of a large, randomized, controlled trial (NCT01072396) examined tiotropium (18 μg qd) effects on dynamic hyperinflation during constant work rate treadmill exercise. Areas-under-the-spontaneous expiratory flow-volume (SEFV)-curves were compared in 20 COPD patients and 16 age-matched untreated controls, using rectangular area ratio (RAR) between peak intrabreath and end-expiratory flow.

Seven patients exhibited SEFV curve concavity with RAR ≤ 0.5 (RAR_{low}) in ≥1 test without tiotropium; (mean ± SD FEV_1: 1.60 ± 0.59 L; 63.4 ± 14.0%predicted). In RAR_{low} patients, tiotropium increased end-exercise inspiratory capacity (IC, 2.10 ± 0.05 vs. 1.89 ± 0.05 L, tiotropium vs. placebo; $p = 0.045$) and RAR (0.57 ± 0.02 vs. 0.53 ± 0.02; $p < 0.001$). Patients without SEFV curve concavity with RAR > 0.5 ($n = 13$; RAR_{high}), had higher screening FEV_1 (2.15 ± 0.47 L; 79.6 ± 10.1%predicted) versus RAR_{low} patients and no difference in end-exercise IC and RAR between tiotropium and placebo (IC: 2.24 ± 0.03 vs. 2.17 ± 0.03 L; RAR: 0.63 ± 0.005 vs. 0.62 ± 0.005). RAR and%predicted IC at peak exercise were positively correlated in RAR_{low} patients ($R^2 = 0.43$, $p = 0.0002$).

Tiotropium increased exercise RAR in GOLD 1-2 patients with SEFV curve concavity.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and morbidity, affecting millions of people worldwide (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2017). Currently, the accepted classification standard for grading the spirometric severity of COPD is set out in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2017), and is based on post-bronchodilator forced expiratory volume in 1s (FEV_1). However, this spirometric variable correlates poorly with clinical variables such as exercise tolerance (Puente-Maestu et al., 2016), and may provide an oversimplified representation of COPD severity.

It has been well recognized that there is information embedded in the spontaneous flow–volume loop beyond that reflected in spirometric values, but the task of analyzing the geometry of flow–volume loop shapes in a meaningful manner remains difficult. Traditionally, expiratory flow limitation is said to occur when the tidal flow–volume loop encroaches on the maximal expiratory flow–volume curve (Johnson et al., 1999). During exercise in COPD, as hyperinflation develops, the elastic recoil decreases lengthening the expiratory time constants of these lung units, necessitates increased intrathoracic

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pressure to maintain flow. Greater expiratory pressures augment gas compression and dynamic airway compression, leading to a progressive fall in expiratory flow, which manifests as concavity in the spontaneous expiratory flow–volume (SEFV) curve (Lee et al., 2016; Ma et al., 2010; Varga et al., 2016). Expiratory flow limitation contributes to dynamic hyperinflation during exercise, whereby the end-expiratory lung volume progressively increases and inspiratory capacity (IC) and inspiratory reserve volume are reduced, and which is associated with dyspnea and exercise intolerance in COPD (O'Donnell et al., 2004). In case of these events, the following is our working hypothesis: i) the shape of the flow–volume loop becomes concave; ii) the concavity reflects increased airway resistance; iii) reduced elastic recoil in COPD (particularly in emphysema) increases expiratory time constants, which necessitates increased intrathoracic pressure to maintain flow; this should further worsen the concavity of the flow–volume loop; iv) bronchodilation should improve this situation and, as such, it should reflect in analysis of the concavity of the flow–volume loop which could then be useful to evaluate the effects of bronchodilators. Breath-by-breath quantification of SEFV curve concavity has been used to describe progressive shape changes denoting expiratory flow limitation during incremental exercise in patients with COPD (Ma et al., 2010; Varga et al., 2016).

Tiotropium, a once-daily, long-acting muscarinic antagonist (LAMA) bronchodilator, approved for COPD management, is associated with significant improvement in lung hyperinflation and exercise tolerance in COPD patients with GOLD spirometric grades 2–4 (Maltais et al., 2005; O'Donnell et al., 2004; Verkindre et al., 2006). In GOLD 1 COPD patients, tiotropium significantly reduced dynamic hyperinflation, but this did not translate into significant exercise tolerance improvement (Casaburi et al., 2014). The authors postulated this lack of improvement may be due to exercise limitation from leg muscle fatigue rather than from dyspnea. Another possibility is that there is a heterogeneous response to tiotropium within GOLD 1 patients. The differences in response to tiotropium between patients with GOLD 1 and 2 COPD may represent fundamental differences in the nature and extent of abnormalities of peripheral airway dynamics and propensity to dynamic hyperinflation, which are directly explored in this current study. While the GOLD classification system broadly categorizes patients with COPD based on their FEV_1 and FEV_1/forced vital capacity (FVC), there is growing evidence that considerable clinical heterogeneity exists within groups with similar spirometric values (Gagnon et al., 2015).

The aim of this study was to examine how tiotropium versus placebo influences the shape of the SEFV curve during constant work rate (CWR) treadmill exercise in patients with mild and moderate COPD (GOLD grades 1 and 2) and determine the association of any treatment-related change in the SEFV curve with change in dynamic hyperinflation. We emploYed the strategy of dividing the patient group between those who did or did not demonstrate flow-volume concavity during exercise. We reasoned that those who demonstrated flow-volume concavity would be more likely to respond to bronchodilation with reduction in dynamic hyperinflation and improvement in exercise tolerance.

2. Materials and methods

2.1. Study design

This substudy constituted an exploratory analysis of a large multicenter trial (ClinicalTrials.gov identifier: NCT01072396). The main study was conducted over 22-weeks, and was a multicenter (11 US and four Canadian sites), randomized, double-blind, two-period, crossover study (Fig. 1), which assessed the effects of once-daily tiotropium vs. placebo on dynamic hyperinflation and exercise tolerance in patients with symptomatic GOLD 1 and 2 COPD (Casaburi et al., 2014; O'Donnell et al., 2014). Patients who completed a 2-week Characterization Phase (Visits 1–3) (O'Donnell et al., 2014) and were eligible for further study participation were entered into the Treatment Phase (Visits 4–6) (Casaburi et al., 2014). Patients were randomized 1:1 to 6 weeks of 18 μg tiotropium or placebo (oral inhalation capsule) administered once daily via a HandiHaler® (Boehringer Ingelheim, Ingelheim, Germany). Following a 4-week washout, patients switched over treatments. After completion of the last 6-week treatment period patients were followed up for 30 days (Visit 7). Patients who discontinued, were followed up for 30 days after the final dose of study medication. In addition, a reference group of healthy, age-matched, control participants were enrolled in the Characterization Phase.

The main study and the substudy were approved for all participating institutions by local or central Independent Review Boards and were conducted in accordance with the principles of the Declaration of Helsinki (October 1996) and the International Conference on Harmonisation Tripartite Guidelines for Good Clinical Practice. Written informed consent was obtained from all participants before entering the study.

2.2. Study participants

The patients in this substudy were those recruited at two sites each in the US and Canada that were equipped for data collection for the substudy: the patients were not subjected to any further selection criteria. Study participants were males and females, aged ≥40 years, body mass index 18–35 kg/m^2, current or ex-smokers (smoking history ≥10 pack-years) with a post-bronchodilator $FEV_1/FVC < 70\%$, and FEV_1 ≥50% predicted (Quanjer et al., 1993) at Visit 1. Patients were categorized according to the 2014 GOLD spirometric classification scheme (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2014): GOLD grade 1 (post-bronchodilator $FEV_1/FVC < 0.7$ and FEV_1 ≥80% of predicted) and GOLD grade 2 (post-bronchodilator $FEV_1/FVC < 0.7$ and 50% ≤FEV_1 < 80% predicted). Patients were required to demonstrate dynamic hyperinflation during exercise manifested by a > 100 mL IC decrease during exercise from mean resting values in two out of three baseline exercise tests (Visits 1 through Visit 3; Fig. 1). Participants were symptomatic, as determined by a Baseline Dyspnea Index focal score ≤9 (Mahler et al., 1984) and/or daily cough with production of sputum for 3 months/year during at least two consecutive years. Patients with significant disease other than COPD were excluded if it was likely that the study results, patient welfare, or ability of patients to participate in the study would be affected. Healthy, age-matched control subjects, with normal lung function and minimal smoking history (i.e., no cigarettes in the preceding 2 years and < 1-pack year smoking history) participated in the Characterization Phase of the study only (Visits 1–3).

2.3. Study procedures

During screening (−30 to −14 days from the start of treatment) participants provided a medical history and demographic data, and pre-exercise pulmonary function assessed by spirometry. Spirometry values were obtained 60 min before the exercise tests and 80 min after dosing (placebo or tiotropium). All spirometry was carried out according to American Thoracic Society/European Respiratory Society recommendations (Miller et al., 2005). The predicted values of Quanjer et al. (Quanjer et al., 1993) were used for FVC and FEV_1. A symptom-limited treadmill incremental exercise test (IET) was performed on Visit 1 using a linearized protocol (Porszasz et al., 2003). To achieve an optimal exercise time between 8 and 12 min, for patients with COPD, the IET was carried out using a 10 W/min protocol; which was repeated at 15 W/min if peak work rate was ≥150 W. For the control subjects, a 15 W/min protocol was used, which was repeated at 20 W/min if the peak work rate was ≥200 W. Results of the IET were used to set the treadmill speed and inclination for subsequent CWR tests to produce a work rate that was equivalent to 80% peak work rate in the IET. The target exercise duration for the CWR tests was 4–10 min; if this target