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Effect of Fluticasone Propionate/Salmeterol on Lung Hyperinflation and Exercise Endurance in COPD*

Denis E. O’Donnell, MD; Frank Sciurba, MD; Bartolome Celli, MD; Donald A. Mahler, MD; Katherine A. Webb; Chris J. Kalberg, PhD; and Katharine Knobil, MD

Study objective: To examine the effect of fluticasone propionate, 250 µg/salmeterol, 50 µg combination (FSC 250/50) twice daily on lung hyperinflation and associated measures of exercise performance in patients with COPD.

Design: This was a randomized, double-blind, parallel-group study.

Patients: Eligible patients were ≥ 40 years old with a diagnosis of COPD, prealbuterol FEV₁ < 70% of predicted, FEV₁/FVC ratio ≤ 0.70, and functional residual capacity (FRC) ≥ 120% of predicted normal.

Interventions: Patients were randomized to FSC 250/50; salmeterol, 50 µg; or placebo twice daily for 8 weeks. Predose and postdose spirometry, plethysmography, and constant-load cycle cardiopulmonary exercise test evaluations were compared. The primary comparison was FSC 250/50 with placebo. The salmeterol group was included for exploratory comparisons with FSC 250/50.

Results: A total of 185 patients (mean baseline FEV₁ of 41% predicted) were enrolled. At rest, FSC 250/50 significantly reduced postdose FRC and increased inspiratory capacity (IC) compared with placebo (differences of -0.35 ± 0.12 L and 0.33 ± 0.06 L [mean ± SE], respectively, at week 8; p ≤ 0.003) and increased exercise endurance time (difference, 132 ± 45 s; p = 0.004). At a standardized time during exercise (isotime), FSC 250/50 increased postdose IC by 0.20 ± 0.05 L over placebo with associated improvements in tidal volume and minute ventilation (p < 0.05 vs placebo at week 8). Improvement in exercise time was significantly correlated with the increase in IC (r = 0.45, p < 0.001) but not FEV₁ (r = 0.23, p = 0.08). Predose comparisons of FSC 250/50 with salmeterol and placebo favored FSC 250/50.

Conclusion: We conclude that FSC 250/50 decreases lung hyperinflation at rest and during exercise with an associated increase in exercise endurance time when compared with placebo.

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Key words: COPD; exercise; fluticasone propionate; inhaled corticosteroid; long-acting β₂-agonist; lung hyperinflation; salmeterol

Abbreviations: BDI = baseline dyspnea index; CPET = cardiopulmonary exercise test; FP = fluticasone propionate; FRC = functional residual capacity; FSC 250/50 = fluticasone propionate, 250 µg/salmeterol, 50 µg combination; IC = inspiratory capacity; PFT = pulmonary function test; RV = residual volume; TLC = total lung capacity; V̇CO₂ = carbon dioxide production; V̇E = minute ventilation; V̇O₂ = oxygen consumption; VT = tidal volume

COPD is defined as a preventable and treatable disease characterized by airflow limitation that is not fully reversible. The airflow limitation is progressive and is associated with an abnormal inflammatory response of the lungs primarily caused by cigarette smoking.¹ Expiratory airflow limitation in COPD leads to air trapping (hyperinflation) when there is insufficient time for adequate lung emptying. The impact of lung hyperinflation on symptoms and impairment at rest and during exertion is increasingly recognized in COPD. The consequences of hyperinflation include a shortened diaphragm with less efficient neuromechanical coupling, and constraints on inspiratory reserve volume within the
limitations of the thoracic cage expansion. During exercise, as ventilation increases and expiratory time diminishes, further dynamic hyperinflation occurs as reflected by the progressive increase in end-expiratory lung volume and a reciprocal decrease in inspiratory capacity (IC). Dynamic hyperinflation is a primary mechanism for the exertional dyspnea and reduced exercise capacity associated with COPD.

Reduced exercise capacity and activity limitation are commonly experienced by patients with COPD, with > 60% of patients reporting limitation in sports and recreation activities, and > 50% reporting limitation in normal physical exertion. Further, exercise intolerance is a major determinant of impaired quality of life for COPD patients, and improvement in exercise capacity is a key goal of COPD disease management.

Both short-acting and long-acting bronchodilators have been shown to reduce lung hyperinflation at rest and during exercise with associated improvements in exercise endurance time. Studies have shown that bronchodilator-mediated improvements in hyperinflation allow flow-limited patients to achieve greater increases in tidal volume and ventilation during exercise that contribute to improvement in exercise capacity. In fact, measures of hyperinflation such as IC are generally more predictive of bronchodilator-mediated improvement in exercise endurance than FEV1, demonstrating the relevance of lung hyperinflation outcome measures for the evaluation of COPD treatments.

The use of the long-acting β2-agonist salmeterol and the inhaled corticosteroid fluticasone propionate (FP) in a single device improves airway obstruction in patients with COPD as measured by FEV1. The improvement with FP/salmeterol is larger than that achieved by salmeterol or FP alone, demonstrating a beneficial contribution from both components of FP/salmeterol. To further evaluate the benefit of FP, 250 μg/salmeterol, 50 μg combination (FSC 250/50) for the treatment of COPD, a multicenter, randomized, double-blind, parallel-group, placebo-controlled study was conducted to evaluate efficacy in the reduction in lung hyperinflation and improvement in exercise endurance.

The primary comparison was between FSC 250/50 and placebo. A salmeterol group was included to allow for initial evaluation of the contribution of FP to improvements in hyperinflation.

**Materials and Methods**

**Subjects**

Subjects included clinically stable patients ≥ 40 years old with a diagnosis of COPD; a cigarette smoking history ≥ 10 pack-years; a prealbuterol FEV1 < 70% of predicted; an FEV1/FVC ratio ≤ 0.70; a functional residual capacity (FRC) ≥ 120% of predicted normal; a baseline dyspnea index (BDI) score ≤ 7; and the ability to complete a work rate of 20 W during an incremental cycle cardiopulmonary exercise test (CPET) at the screening visit. Exclusion criteria included a current diagnosis of asthma; clinically significant medical disorder (other than COPD); supplemental use of oxygen for exertion; concurrent use of some respiratory medications (including inhaled corticosteroids, long acting β2-agonists, tiotropium, theophylline, leukotriene modifiers, or systemic corticosteroids); and initiation of pulmonary rehabilitation within 6 months of screening. Concurrent use of albuterol, and ipratropium and ipratropium/albuterol combinations was permitted.

**Study Design**

This was a multicenter, randomized, double-blind, parallel-group study (protocol number SCO40030) conducted at 21 research centers in the United States and Canada. For each site, an institutional review board or ethics committee approved the study, and all patients provided written informed consent prior to the conduct of study procedures. Study visits were conducted at screening, during run-in (two visits), at randomization (day 1), and after 4 weeks and 8 weeks of treatment (Fig 1).

At screening, patients performed pulmonary function tests (PFTs) [body plethysmography and spirometry] and completed an incremental cycle CPET. During run-in, subjects received single-blind placebo twice daily (morning and evening) and performed constant-load cycle ergometer exercise tests on two separate visits. The constant-load tests were performed at 75% of the maximal work rate achieved during the incremental exercise test at screening. The purpose of the run-in exercise tests was to familiarize the study subjects with the constant-load exercise test procedures and reduce possible learning effects. After run-in, subjects were randomized to treatment with either FSC 250/50; salmeterol, 50 μg; or placebo via dry powder inhaler twice daily for 8 weeks. At the day 1 and week 8 visits, PFTs performed before dose and 2 h after dose were followed by a constant-load cycle CPET conducted at 75% maximal work rate (Fig 1). The postdose exercise test was initiated 3 h after dosing. At the week 4 visit, predose PFTs were performed.
Procedures

Spirometry and constant-volume plethysmography were conducted according to recognized standards. Predicted normal values for FEV₁, FRC, and total lung capacity (TLC) were from Crapo et al. Predicted normal values for IC were determined by subtracting predicted FRC from predicted TLC. BDI scores were obtained from an interviewer-administered dyspnea questionnaire.

Cycle CPETs were conducted using standardized methodology as previously described. Cardiopulmonary test equipment was provided by the sites and included systems manufactured by the following companies: SensorMedics (Yorba Linda, CA), MedGraphics (St. Paul, MN), and VIASYS Healthcare (Hoechberg, Germany). Electronically braked cycle ergometers were used. Physiologic calibration of the systems was performed at study start and every 6 months thereafter, and consisted of an incremental cycle exercise test performed by a healthy volunteer at work rates of 20 and 70 W with a pedaling frequency of 60 revolutions per minute. Breath-by-breath data were averaged over 10 s. Physiologic calibration data were transmitted to a central laboratory for review, and the cardiopulmonary test equipment was considered adequately calibrated if a 10 mL/W increase in oxygen consumption ($\dot{V}O_2$) was achieved across the transition from 20 to 70 W.

Incremental and constant-load exercise tests consisted of the following sequence of stages: rest, unloaded pedaling, loaded pedaling, and recovery. During rest, subjects performed tidal breathing for at least 3 min while seated on a cycle ergometer and no pedaling was performed. This was followed by 1 min of pedaling without a load, after which loaded pedaling was initiated; pedaling frequencies were maintained at 50 to 70 revolutions per minute. For the incremental test, the initial work rate was 10 W and the work rate was increased by 10 W every minute until symptom limitation. During recovery, pedaling without a load was performed for at least 2 min. Maximal work rate was defined as the highest work rate maintained for at least 30 s. Exercise tests were terminated for the following reasons: symptom limitation, inability to maintain pedaling frequency, or safety reasons. Procedures for the constant-load tests were similar, except immediately following the unloaded pedaling, and the work rate was increased to 75% of the maximum work rate. Cycle endurance time was defined as the duration of loaded pedaling. Breath-by-breath measurements were recorded as 30-s averages at rest, during exercise at 2-min intervals, and at end-exercise (peak). Pulse oximetry, ECG, and BP were monitored at rest, during exercise, and at recovery. IC measurements were obtained at rest, every 2 min during exercise, and at end-exercise. Borg ratings of dyspnea were obtained at rest, every minute during exercise, and at end-exercise. The Borg scale ranged from 0 (nothing at all) to 10 (maximal). Following completion of the exercise tests, the reason for exercise discontinuation was recorded.

Statistical Methods

The primary efficacy measure was postdose FRC at week 8 for the comparison of FSC 250/50 and placebo. The sample size provided > 90% power to detect a treatment difference of 0.4 L in postdose FRC between FSC 250/50 and placebo using a two-sample t test with a significance level of 0.05, assuming a SD of 0.6 L. Analyses were conducted on the intent-to-treat population, defined as all patients randomized to blinded study medication. Step-down rules for testing of efficacy end points were implemented to account for multiple significance testing. Primary analyses were performed on week 8 postdose measurements. Exercise measures were compared both at peak exercise and at isotone, defined as the highest common time achieved across the day 1 and week 8 exercise tests. Statistical tests were conducted at the two-sided 0.05 significance level. Differences between treatment groups were estimated and tested using
Results

Subject Characteristics

A total of 185 patients were randomized to treatment with FSC 250/50 (n = 62), salmeterol (n = 59), or placebo (n = 64), and 176 patients completed the study. Five of the nine patients who withdrew were in the placebo group, with one patient and three patients in the salmeterol and FSC 250/50 groups, respectively. Demographic, smoking history, dyspnea, lung function, and exercise values at screening are shown in Table 1. Patients had moderate-to-severe COPD, with mean FEV₁ values of 39.5 to 42.5% of predicted (range, 14 to 77%) and resting lung hyperinflation as demonstrated by mean FRC values of 154 to 157% of predicted. Mean BDI scores were indicative of moderate impairment due to dyspnea, and peak work rate values were low across groups indicating severe exercise limitation.

Pulmonary Function at Rest

Postdose spirometry and plethysmography measures at day 1 and week 8 improved significantly with FSC 250/50 and salmeterol as compared with placebo (Fig 2). At week 8 (Fig 2, right, B), postdose treatment differences between FSC 250/50 and placebo for FRC, residual volume (RV), FEV₁, IC, and FVC were \(-0.35 \pm 0.12\) L, \(-0.35 \pm 0.13\) L, \(0.24 \pm 0.04\) L, \(0.33 \pm 0.06\) L, and \(0.28 \pm 0.07\) L, respectively \((p \leq 0.005)\) [mean ± SE], with treatment differences between salmeterol and placebo of \(-0.26 \pm 0.12\) L, \(-0.30 \pm 0.13\) L, \(0.17 \pm 0.04\) L, \(0.27 \pm 0.06\) L, and \(0.28 \pm 0.07\) L, respectively \((p \leq 0.028)\). Predose pulmonary function values at week 4 and week 8 are shown in Figure 3. At week 8 (Fig 3, right, B), the treatment difference between FSC 250/50 and placebo was significant \((p \leq 0.008)\) for FEV₁ \((0.17 \pm 0.03\) L), IC \((0.23 \pm 0.05\) L), and FVC \((0.17 \pm 0.06\) L) but not FRC \((-0.23 \pm 0.12\) L) and RV \((-0.23 \pm 0.14\) L). For salmeterol, treatment differences were significant \((p \leq 0.041)\) for FEV₁ \((0.08 \pm 0.04\) L) and FVC \((0.13 \pm 0.06\) L) but not IC \((0.11 \pm 0.06\) L), FRC \((-0.08 \pm 0.12\) L), and RV \((-0.12 \pm 0.14\) L). Between FSC 250/50 and salmeterol, significant treatment differences were observed for predose FEV₁ and IC \((p \leq 0.029)\).

Exercise Endurance Time

For postdose assessments, FSC 250/50 significantly increased exercise time compared with placebo, with treatment differences of 131 ± 36 s and 132 ± 45 s at day 1 and week 8, respectively.
(p ≤ 0.004; Fig 4), representing a 22% difference at both visits. Before dose, the increase in exercise time with FSC 250/50 was significantly larger compared with placebo at week 8 (treatment difference of 104 ± 43 s, p = 0.017; Fig 4). For comparisons of salmeterol to placebo, postdose differences of 49 ± 37 s and 86 ± 46 s at day 1 and week 8, respectively, and the predose difference of 37 ± 44 s at week 8 were not statistically significant (Fig 4).

In all groups, the change from baseline in postdose exercise time was less at week 8 compared with day 1. However, between-group differences were maintained. With FSC 250/50, the postdose exercise time increased from baseline by 104 ± 29 s and 49 ± 36 s at day 1 and week 8, respectively. With salmeterol, postdose exercise time increased from baseline by 23 ± 30 s and 3 ± 36 s, respectively, at day 1 and week 8, and decreased by −27 ± 28 s and −84 ± 35 s, respectively, with placebo. Before dose, change from baseline values for FSC 250/50, salmeterol, and placebo at week 8 were 63 ± 35 s, −3 ± 35 s, and −41 ± 33 s, respectively.

The majority of subjects discontinued exercise due to respiratory symptom limitation. At predose baseline, 74% of subjects discontinued due to respiratory symptoms, with the remaining subjects discontinuing due to leg discomfort (24%) or other reasons (3%) such as “dry mouth or throat,” “fatigue,” and “bike seat discomfort.” Similar results were observed at subsequent evaluations, with between 68% and 72% of subjects stopping due to dyspnea limitation across exercise tests.

**Physiologic and Dyspnea Responses During Exercise**

Predose and postdose treatment differences with placebo are shown in Tables 2 and 3, respectively. In the FSC 250/50, salmeterol, and placebo groups, the mean exercise times for isotime comparisons were 5.5 ± 3.1 min, 4.4 ± 2.7 min, and 4.5 ± 3.2 min, respectively. At both day 1 and week 8, FSC 250/50 significantly increased postdose IC at isotime and peak exercise compared with placebo, with treatment differences ranging from 0.13 to 0.20 L (Table 2). Similarly, IC values from exercise tests conducted before dose at week 8 were significantly increased with FSC 250/50 as compared with placebo (Table 3; Fig 5). Before dose, FSC 250/50 significantly increased IC at isotime and peak exercise compared with salmeterol (p = 0.031 with treatment differences 0.11 ± 0.05 L and 0.12 ± 0.05 L at week 8, respectively).

FSC 250/50 significantly improved postdose evaluations of VT, minute ventilation (VE), and carbon dioxide production (VCO₂) at both isotime and peak exercise compared with placebo, while postdose VO₂ was increased at peak exercise. Borg
dyspnea scores for FSC 250/50 during exercise were significantly lower at day 1 but not at week 8 (Table 2). Before dose, FSC 250/50 significantly increased $V_t$ at isotime and peak compared with placebo (Table 3).

Salmeterol significantly increased postdose IC over placebo at isotime but not at peak exercise and improved postdose $V_t$, $V_e$, and $V_{CO_2}$ compared with placebo (Table 2). There were no statistical differences for evaluations of $V_{O_2}$ and Borg scores. Predose differences between salmeterol and placebo for IC at week 8 were not significantly different (Table 3).

**Correlates of Exercise Endurance Time**

With FSC 250/50 treatment, postdose improvement in exercise time at week 8 was significantly correlated with the increase in IC at rest ($r = 0.45$, $p < 0.001$) but not with FEV$_1$ ($r = 0.23$, $p = 0.08$).

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**Table 2—Postdose Treatment Differences for Exercise Measures at Day 1 and Week 8***

<table>
<thead>
<tr>
<th>Variables</th>
<th>FSC 250/50-Placebo</th>
<th>Salmeterol-Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Week 8</td>
</tr>
<tr>
<td>$IC$, L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotime</td>
<td>$0.18 \pm 0.04^{\dagger}$</td>
<td>$0.20 \pm 0.05^{\dagger}$</td>
</tr>
<tr>
<td>Peak</td>
<td>$0.13 \pm 0.05^{\dagger}$</td>
<td>$0.17 \pm 0.06^{\dagger}$</td>
</tr>
<tr>
<td>$V_t$, L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotime</td>
<td>$0.12 \pm 0.02^{\dagger}$</td>
<td>$0.10 \pm 0.03^{\dagger}$</td>
</tr>
<tr>
<td>Peak</td>
<td>$0.10 \pm 0.02^{\dagger}$</td>
<td>$0.14 \pm 0.03^{\dagger}$</td>
</tr>
<tr>
<td>$V_e$, L/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotime</td>
<td>$1.6 \pm 0.7^{\dagger}$</td>
<td>$2.3 \pm 1.0^{\dagger}$</td>
</tr>
<tr>
<td>Peak</td>
<td>$3.1 \pm 0.7^{\dagger}$</td>
<td>$4.2 \pm 1.0^{\dagger}$</td>
</tr>
<tr>
<td>$V_{O_2}$, L/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotime</td>
<td>$0.03 \pm 0.02$</td>
<td>$0.04 \pm 0.02$</td>
</tr>
<tr>
<td>Peak</td>
<td>$0.05 \pm 0.02^{\dagger}$</td>
<td>$0.15 \pm 0.08^{\dagger}$</td>
</tr>
<tr>
<td>$V_{CO_2}$, L/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotime</td>
<td>$0.04 \pm 0.02^{\dagger}$</td>
<td>$0.05 \pm 0.02^{\dagger}$</td>
</tr>
<tr>
<td>Peak</td>
<td>$0.07 \pm 0.02^{\dagger}$</td>
<td>$0.09 \pm 0.02^{\dagger}$</td>
</tr>
<tr>
<td>Dyspnea, Borg score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotime</td>
<td>$-0.5 \pm 0.2^{\dagger}$</td>
<td>$-0.5 \pm 0.4$</td>
</tr>
<tr>
<td>Peak</td>
<td>$-0.4 \pm 0.2^{\dagger}$</td>
<td>$-0.4 \pm 0.3$</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SE.

$^{\dagger} p < 0.001$.

$^{\ddagger} p < 0.01$.

$^{\ast} p < 0.05$. 

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**Figure 4.** Treatment differences in constant-load cycle exercise endurance time as compared with placebo. *$p \leq 0.017$.**
Additionally, the predose change in IC at isotime significantly correlated with the increase in predose exercise endurance time ($r = 0.44$, $p < 0.001$) at week 8.

**Safety**

Adverse events were reported for 26 patients (42%), 28 patients (47%), and 24 patients (38%) in the FSC 250/50, salmeterol, and placebo groups, respectively. Of these, six patients (10%), one patient (2%), and five patients (8%) receiving FSC 250/50, salmeterol, and placebo, respectively, had adverse events that were considered “possibly” related to study medication by the reporting investigator, and none of these events were considered serious. Serious adverse events (eg, events resulting in hospitalization) were reported for one patient (2%), four patients (7%), and two patients (3%) in the FSC 250/50, salmeterol, and placebo groups. There were no deaths during the study. In the FSC 250/50, salmeterol, and placebo groups, COPD exacerbations were reported for two patients (3%), one patient (2%), and six patients (9%), respectively.

**Discussion**

The results of this study demonstrate that treatment with FSC 250/50 twice daily for 8 weeks resulted in reduced lung hyperinflation at rest, as shown by significant reductions in postdose evaluations of FRC and RV; a reduction in hyperinflation during exercise, as shown by a significant increase in resting and exercise IC, and in VT and VE; and a significant improvement in exercise endurance time when compared with placebo.

The magnitude of decrease in static lung volumes observed with FSC 250/50 was comparable to results reported for the long-acting anticholinergic bronchodilator tiotropium in a similar study population. It is noteworthy that significant exercise

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**Table 3—Predose Treatment Differences for Exercise Measures at Week 8**

<table>
<thead>
<tr>
<th>Variables</th>
<th>FSC 250/50-Placebo</th>
<th>Salmeterol-Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC, L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotime</td>
<td>0.19 ± 0.05†</td>
<td>0.08 ± 0.05</td>
</tr>
<tr>
<td>Peak</td>
<td>0.16 ± 0.05‡</td>
<td>0.05 ± 0.05</td>
</tr>
<tr>
<td>VT, L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotime</td>
<td>0.08 ± 0.03†</td>
<td>0.05 ± 0.03</td>
</tr>
<tr>
<td>Peak</td>
<td>0.07 ± 0.03§</td>
<td>0.05 ± 0.03</td>
</tr>
<tr>
<td>VE, L/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotime</td>
<td>1.3 ± 0.9</td>
<td>0.4 ± 0.9</td>
</tr>
<tr>
<td>Peak</td>
<td>2.1 ± 0.9‡</td>
<td>1.4 ± 0.9</td>
</tr>
<tr>
<td>V\textsubscript{O\textsubscript{2}}, L/min</td>
<td>0.03 ± 0.02</td>
<td>0.01 ± 0.02</td>
</tr>
<tr>
<td>Isotime</td>
<td>0.04 ± 0.02</td>
<td>0.02 ± 0.02</td>
</tr>
<tr>
<td>Peak</td>
<td>0.05 ± 0.02§</td>
<td>0.02 ± 0.02</td>
</tr>
<tr>
<td>V\textsubscript{CO\textsubscript{2}}, L/min</td>
<td>0.04 ± 0.02</td>
<td>0.01 ± 0.02</td>
</tr>
<tr>
<td>Isotime</td>
<td>0.05 ± 0.02§</td>
<td>0.02 ± 0.02</td>
</tr>
<tr>
<td>Peak</td>
<td>−0.9 ± 0.3‡</td>
<td>−0.5 ± 0.3</td>
</tr>
<tr>
<td>Dyspnea, Borg score</td>
<td>−0.3 ± 0.3</td>
<td>−0.3 ± 0.3</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SE.
†$p < 0.001$.
‡$p < 0.01$.
§$p < 0.05$.

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**Figure 5.** Predose (trough) changes in isotime exercise measurements at week 8. *$p < 0.05$ vs difference from baseline (before dose day 1). IRV = inspiratory reserve volume.
volume deflation occurred after first dosing with FSC 250/50, confirming rapid improvements in airway function and lung emptying.

Reductions in IC during exercise are associated with a reduced ability to augment VE through recruitment of Vt in response to increased respiratory drive. Conversely, an increase in IC is a measurement of improved ventilatory capacity associated with increased exercise tolerance.12 17 It has been suggested that such volume-deflating responses reflect dilation of peripheral airways, such that improved time constants of extremely slow lung units allow deflation, and that the consequent filling of relatively more normal units in the constraints of a limited thorax allow improvements in expiratory flow both at rest and during exertion.30–32 In the present study, FSC 250/50 significantly improved exercise IC both at isotime and peak compared with placebo. Significant improvements over placebo were observed at both postdose and predose exercise tests. Improvements in exercise IC were associated with significantly greater increases in Vt, VE, and exercise endurance time for postdose and predose comparisons of FSC 250/50 and placebo. Significantly larger increases in V̇O₂ and VO₂ with FSC 250/50 compared with placebo were indicative of these improvements in ventilation during exercise and increased exercise time.

Comparison of FSC 250/50 and salmeterol at predose (trough) allows for evaluation of the contribution of FP to the beneficial effects of FSC 250/50. Consistent with previous studies,18–20 FSC 250/50 treatment resulted in a significantly greater improvement in predose FEV₁ compared with salmeterol alone. Thus, multiple studies have shown FP contributes to the improvement in forced expiratory flow observed with FSC 250/50. Results from this study demonstrating greater reductions in predose FRC with consequent reciprocal findings for IC further indicate that FP contributes to the sustained reduction in lung hyperinflation over 12 h observed with FSC 250/50. Direct β₂-receptor–mediated bronchodilator effects of salmeterol and antiinflammatory actions of FP are most likely the primary mechanisms for the improvements in FEV₁ and lung hyperinflation measures observed with FSC 250/50.33–35 Additionally, complementary interactions between corticosteroids and β₂-agonists may also contribute. These include both corticosteroid-mediated modulation of β₂-receptor function and β₂-receptor modulation of glucocorticoid receptor function.

A variety of exercise tests have been developed to evaluate functional status, establish prognosis, and determine response to treatment. These tests include timed walk tests, incremental walk tests, and incremental and submaximal constant-load CPETs.22 Standardized CPETs allow for evaluation of physiologic (metabolic and ventilatory) measures, symptoms, and exercise endurance time at a controlled work rate. Constant-load cycle CPETs are reproducible and responsive to bronchodilator therapy.13,14,16,17 Several studies13,14,16,17,40,41 have evaluated bronchodilator effects using standardized constant-load cycle CPET procedures across similar patient populations; ipratropium, ipratropium/albuterol, oxitropium, tiotropium, and salmeterol were all found to significantly increase exercise time compared with placebo in subjects with COPD. Across the studies,13,14,16,17,40,41 baseline exercise times were relatively short, ranging from approximately 3 to 9 min; and treatment differences between bronchodilator medications and placebo ranged from 34 s to approximately 2.5 min. In the present study, the treatment difference between FSC 250/50 and placebo was evident at day 1 (131 ± 36 s) and maintained at week 8 (132 ± 45 s), despite a decrease in week 8 exercise time relative to day 1 across treatment groups. The treatment difference over placebo was maintained due to a substantially greater decrease from baseline in exercise time in the placebo group. These findings suggest that the study subjects were not able to perform two exercise challenges on the same day with equal consistency, likely due to advanced age and disease severity. Similar findings were observed in a previous study16 in which two cycle constant-load CPETs were performed on the same day.

The impact of salmeterol on exercise endurance time and dyspnea was modest and inconsistent in this study compared with a previous study14 in which consistent positive effects were seen. The difference in results likely reflects differences in study design: the crossover design used in the former study14 (with patients acting as their own controls) may have been more sensitive for the purpose of detecting a significant difference in exercise endurance. Additionally, the current study was not designed to provide definitive clinical and statistical comparisons of FSC 250/50 and salmeterol on exercise and lung volume measures. While a comparison of the predose (trough) exercise tests showed numerically superior effects on operating lung volumes, breathing pattern, and ventilation in the FSC 250/50 group compared with the salmeterol group (Fig 5), these findings should be considered exploratory and future study will be required to determine their clinical relevance.

The effect of FSC 250/50 on lung hyperinflation and exercise endurance time is similar in magnitude to the improvement in these parameters previously reported in association with tiotropium therapy in a
similar COPD population in two multicenter clinical trials. However, differences in study design, particularly in the exercise testing protocol, confound any direct comparison of the clinical benefits of these two medications.

In keeping with the results of previous bronchodilator studies, improvement in isotime IC correlated better with improved exercise endurance time after FSC 250/50 than did the change in resting FEV1. This suggests that, in the evaluation of therapeutic efficacy, measures of lung hyperinflation during exercise can provide additional, functionally relevant information about the impact of the investigational drug on dynamic airway function.

Ratings of exertional dyspnea at a standardized time during exercise were not significantly diminished with either of the active medications compared with placebo. However, patients receiving FSC 250/50 accomplished higher levels of ventilation over a greater exercise duration without experiencing greater dyspnea, confirming a beneficial effect.

Safety results from this study indicate that short-term use of FSC 250/50 or salmeterol in a hyperinflated study population with moderate-to-severe COPD did not result in any new or unexpected safety concerns. In addition, no significant safety concerns were associated with the conduct of cycle CPETs at maximal and submaximal work loads in this population or with the concurrent use of FSC 250/50 and salmeterol during exercise testing.

In summary, in patients with poor exercise tolerance as a result of moderate-to-severe COPD, treatment with FSC 250/50 was shown to decrease lung hyperinflation at rest as measured by FRC, RV, and IC. Further, FSC 250/50 reduced lung hyperinflation throughout exercise and increased exercise endurance time. It is important to note that the impact of FSC 250/50 on volume reduction and exercise improvement was evident 3 h after the first dose. Improvement in respiratory mechanics through a reduction in hyperinflation with an associated increase in VT expansion and ventilation during exercise provide a likely mechanism for the increase in exercise time observed with FSC 250/50. This study extends findings from previous studies that evaluated the effect of FP/salmeterol on lung function using FEV1 and adds to the clinical evidence supporting the use of FSC 250/50 as an effective treatment option for patients with COPD.

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