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Effects of formoterol on exercise tolerance in severely disabled patients with COPD ☆

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Summary
Objective: We wished to evaluate the effects of inhaled formoterol, a long-acting β_2-adrenergic agonist, on exercise tolerance and dynamic hyperinflation (DH) in severely disabled chronic obstructive pulmonary disease (COPD) patients.
Design: In a two-period, crossover study, 21 patients with advanced COPD ($FEV_1 = 38.8 \pm 11.7\%$ predicted, 16 patients GOLD stages III–IV) were randomly allocated to receive inhaled formoterol fumarate 12 μg twice daily for 14 days followed by placebo for 14 days, or vice versa. Patients performed constant work-rate cardiopulmonary exercise tests to the limit of tolerance (Tlim) on a cycle ergometer: inspiratory capacity (IC) was obtained at rest and each minute during exercise. Baseline and transitional dyspnoea indices (BDI and TDI) were also recorded.
Results: Eighteen patients completed both treatment periods. Formoterol treatment was associated with an estimated increase of 130 s in Tlim compared with placebo ($P = 0.052$): this corresponded to a 37.8% improvement over placebo ($P = 0.012$). Enhanced exercise tolerance after bronchodilator was associated with diminished DH marked by higher inspiratory reserve and tidal volumes at isotime and exercise cessation ($P < 0.05$). There was no significant difference between formoterol and placebo on exercise dyspnoea

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ratings; however, all domains of the TDI improved ($P \leqslant 0.02$) following formoterol, compared with placebo.
Conclusion: Inhaled formoterol 12 μg twice daily is effective in ameliorating DH, daily dyspnoea and exercise intolerance even in patients with advanced COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by long-term, partially reversible, airways obstruction.[1] Exercise intolerance is a hallmark of the disease, being commonly associated with incapacitating dyspnoea, reduced quality of life and increased morbidity and mortality.[2,3] Increased end-expiratory lung volume (EELV) is commonly found during progressive exercise in flow-limited patients as ventilatory requirements increase.[4–7] This dynamic hyperinflation (DH) accommodates higher levels of airflow and therefore ventilation ($\dot{V}_E$). However, as there appears to be no associated increase in total lung capacity (TLC),[8] tidal volume (V_T) becomes elevated on to the poorly compliant upper region of the thoracic pressure–volume relationship, resulting in a substantially increased elastic work of breathing and exacerbated dyspnoeic sensation.[7,9] Reductions in DH during high-intensity constant work rate (WR) exercise can improve exercise tolerance, whether consequent to a reduction in ventilatory requirement[10,11] or to a decreased mechanical time constant of the lung.[12–15]

Formoterol is a potent β_2-adrenoceptor agonist with a rapid-onset, long-acting effect.[16] Several studies have found that formoterol treatment is associated with beneficial effects on resting pulmonary function and quality of life in patients with COPD.[17,18] However, there are few data extant regarding its effect on exercise tolerance and DH in COPD, especially in patients with more advanced disease. Aalbers et al.,[19] for instance, were unable to demonstrate any significant improvement in incremental shuttle-walking test distance following formoterol. Liesker et al.[20] reported a modest beneficial effect of formoterol on symptom-limited incremental exercise performance with peak WR increasing by only about 5 W. However, incremental exercise performance measures often prove relatively insensitive for detection of interventional changes in COPD patients, in contrast to those from symptom-limited constant WR paradigms such as time to the limit of tolerance (Tlim).[21,22]

In this context, to our knowledge, no previous study has evaluated the potential effects of inhaled formoterol in enhancing sub-maximal exercise tolerance and DH in severely disabled patients. This would seem to constitute a clinically relevant and timely research question, as few effective pharmacological alternatives are currently available for these patients.[23] Moreover, two recently published meta-analyses have concluded that there is a lack of evidence for a beneficial effect of long-acting bronchodilators in ameliorating exercise impairment in patients who are poorly responsive to a short-acting bronchodilator.[24,25]

Our aim, therefore, was to investigate whether formoterol, as compared with placebo, would improve Tlim in severely disabled COPD patients. We also evaluated whether formoterol would reduce DH and effort-related breathlessness during activities of daily living.

Methods

Subjects

Twenty-one subjects (14 males, aged 42–75, body mass index $= 24.8 \pm 5.1\,kg\,m^{-2}$) with stable COPD (forced expiratory volume in 1 s [FEV_1]/forced vital capacity [FVC] $\leqslant 60\%$, FEV_1 $<60\%$ predicted and post-bronchodilator FEV_1 change $<12\%$ predicted) were randomized (Table 1). Main exclusion criteria were: recent exacerbation, long-term oxygen therapy or arterial oxygen saturation $<85\%$ at rest, and treatment with oral corticosteroids, anticholinergics and antihistamines. All subjects gave written, informed consent (as approved by the Institutional Medical Ethics Committee).

Study design

This was a single-centre, randomized, double-blind, placebo-controlled, crossover trial. Patients were assigned to 14 days of formoterol dry powder capsules 12 μg twice daily (Foradil® Aerolizer®; Novartis Pharma AG, Basel, Switzerland) followed by 14 days of matching placebo twice daily, or vice-versa (Fig. 1), separated by a washout of at least 2 days.

Before screening, patients discontinued short- and long-acting β_2-agonists (LABAs) and inhaled anticholinergics. During the study, patients were given a Combivent® metered-dose inhaler (salbutamol 100 μg/ipratropium bromide 20 μg per actuation, Boehringer Ingelheim GmbH, Ingelheim, Germany) as rescue medication. Use of inhaled or nasal corticosteroids and oral modified-release theophylline or derivatives was allowed provided dose, schedule and formulation remained unchanged.

Protocol

After screening (visit 1), patients returned four times to the exercise laboratory at the start and end of each treatment period (visits 2–5) (Fig. 1). At visit 1, they underwent clinical evaluation, a questionnaire of activity-related breathlessness (baseline dyspnoea index: BDI),[26] pulmonary function testing, and a symptom-limited incremental cardiopulmonary exercise test (incCPX). Subjects performed a series of constant WR CPX (ctCPX) tests to the Tlim, each on a separate visit (visits 2–5). Changes in daily breathlessness