

Bronchodilation improves endurance but not muscular efficiency in chronic obstructive pulmonary disease

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Abstract: We hypothesized that bronchodilator treatment not only improves hyperinflation and endurance capacity but also muscular efficiency in stable chronic obstructive pulmonary disease (COPD). We aimed to demonstrate that tiotropium and salmeterol improve muscular efficiency compared with placebo. Twenty-five COPD patients were studied, including 20 males of mean (standard deviation) age 62 years (7 years) with baseline forced expiratory volume in 1 second of 41% (10%) predicted, and maximal workload of 101 Watt (36 Watt). Subjects were randomized for 6-week treatment with tiotropium 18 µg once daily, salmeterol 50 µg twice daily, or placebo using a double-blind, crossover design. Muscular efficiency and endurance time were measured during cycling at 50% of maximal work load. Resting energy expenditure was measured using a ventilated hood. Muscular efficiency after tiotropium, salmeterol, and placebo treatment was 14.6%, 14.4%, and 14.4%, respectively ($P > 0.05$), and resting energy expenditure was 1485 kcal/24 hours, 1709 kcal/24 hours, and 1472 kcal/24 hours ($P > 0.05$), respectively. Endurance time after tiotropium treatment was significantly higher than that after placebo (27.0 minutes versus 19.3 minutes [$P = 0.02$]), whereas endurance time after salmeterol treatment was not higher than that after placebo (23.3 minutes [$P = 0.22$]). In this small study, we were not able to demonstrate that bronchodilator therapy improved muscular efficiency. Apparently, reduced costs of breathing relative to total energy expenditure were too small to be detected.

Keywords: bronchodilation, chronic obstructive pulmonary disease, energy expenditure, muscle energetics, muscular exercise

Introduction

Patients with chronic obstructive pulmonary disease (COPD) often have impaired exercise tolerance, leading to reduced physical activity and low quality of life. Impaired exercise tolerance is due to a complex interplay between limitations in ventilatory capacity, gas exchange, cardiovascular capacity, and peripheral muscle metabolism. Static and dynamic hyperinflation during exercise plays an important role and may initiate a vicious circle of decline that includes physical deconditioning and worsening of dyspnea.¹ Lung deflation by means of bronchodilators reduces hyperinflation and improves submaximal exercise endurance, as was shown for both the long-acting- β -2 agonist salmeterol and the long-acting anticholinergic agent tiotropium.^{2,3} One study demonstrated that both agents were equally effective at improving functional residual capacity (FRC) and inspiratory capacity (IC) at rest and at increased breathing frequencies (15 breaths/minute, 30 breaths/minute, and 45 breaths/minute).⁴ No published direct comparison between the two agents' effect on submaximal exercise tolerance exists.

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Energy expenditure at a constant submaximal workload is another way to investigate hyperinflation and its consequences for exercise tolerance. “Muscular efficiency” of movement is frequently used to express the efficacy of skeletal muscles to transfer biochemical energy into external work or movement.⁵ Calculations of muscular efficiency during steady-state situations are based on open-circuit indirect calorimetry (oxygen uptake [VO_2], carbon dioxide output [VCO_2]) and the assumption that energy requirements in the muscles are met by respiration. Baarends et al⁶ showed that after correction for resting energy expenditure (REE), the net muscular efficiency in 33 patients with mild-to-moderately severe COPD ranged from 8.5% to 22.7% (median 15.5%). Interestingly, patients with a low net muscular efficiency (<17%) demonstrated enhanced ventilatory responses to exercise and higher airway resistance at rest. This suggests that decreased muscular efficiency is related to increased costs of breathing, probably due to hyperinflation.

We speculated that measurement of muscular efficiency in COPD can detect improvements in costs of breathing induced by tiotropium or salmeterol. We hypothesized that both treatments improve muscular efficiency, along with endurance capacity, in clinically stable patients with COPD who demonstrated ventilatory limitation during maximal exercise.

Methods

Patients

Outpatients with stable COPD were recruited from pulmonary departments of hospitals in the north of The Netherlands. Patients had to be ≥ 40 years old with a diagnosis of moderate-to-severe COPD (forced expiratory volume in 1 second [FEV_1] $\leq 60\%$ predicted; $\text{FEV}_1/\text{forced vital capacity [FVC]} \leq 70\%$) and a smoking history of >10 pack-years. $\text{FEV}_1\%$ predicted had to increase by $>5\%$ after inhalation with 480 μg salbutamol and 80 μg ipratropium (Combivent®, Boehringer Ingelheim, Ridgefield, CT, USA). The use of inhaled and oral steroids (maximally 10 mg a day) was allowed during the study. Patients who needed supplemental oxygen and who had three or more exacerbations per year were excluded. Ventilatory limitation of maximal exercise capacity was required (defined by an increase in oxygen tension in arterial blood [PaCO_2] and/or an increase in minute ventilation [VE] $> 80\%$ [$\text{FEV}_1 \times 37.5$]). Additionally, patients required a maximal workload (Wmax) of ≥ 40 Watt during an incremental cycle test. The main exclusion criteria for the study included a 10 mmol/L increase in blood lactate during peak exercise or 2.5 mmol/L at $\geq 50\%$ of Wmax and oxygen saturation $<90\%$ at 50% of Wmax .

Study design

This was a randomized, double-blind, double-dummy, placebo-controlled, crossover study, conducted over three 6-week periods. The effects of tiotropium, salmeterol, and placebo on muscular efficiency were compared. The primary endpoint was change in gross muscular efficiency following 6 weeks of randomized treatment. Secondary endpoints included REE, endurance capacity at 50% Wmax , net muscular efficiency, FEV_1 , FVC, peak expiratory flow (PEF) variability over 1 week, specific airway conductance (sGaw), FRC, and symptoms determined using the Clinical COPD Questionnaire (CCQ). The study was approved by the local independent ethics committee, and informed consent was obtained from all individuals.

Study protocol

Following screening and a 4-week run-in period, 25 patients were randomized to one of six treatment sequences (Figure 1). During each 6-week treatment period, patients received either tiotropium 18 μg once daily, salmeterol 50 μg twice daily, or placebo twice daily. Salbutamol was taken as required, using a metered dose inhaler, but not during the 8 hours prior to testing. Testing occurred after each 6-week period between 8 a.m. and 10 a.m., 1 hour after drug administration. Visits were delayed for maximally 2 weeks in case of an exacerbation. PEF was measured twice daily during the 6-week periods.

Incremental bicycle ergometer test

Maximal exercise capacity was measured using an incremental symptom-limited cycle ergometer test. Patients inhaled four puffs of ipratropium/salbutamol 20/120 μg (Combivent) via an AeroChamber® (Boehringer Ingelheim, Ingelheim, Germany) 30 minutes before commencing the test. A brachial or radial artery catheter was inserted, and samples were drawn at rest and then every 2 minutes. VE , VO_2 , and VCO_2 were

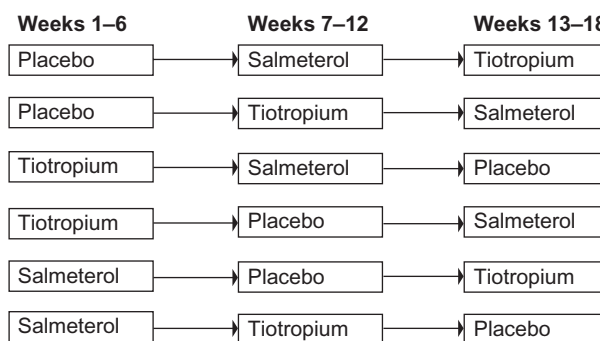


Figure 1 The six possible treatment sequences to which patients were randomly assigned. There was no washout period between successive treatment sequences.

measured from breath-by-breath analysis every 30 seconds (EOS Sprint; Jaeger, Würzburg, Germany). Dyspnea was assessed every minute using a modified Borg scale.⁷

The test required 2 minutes of seated rest on the ergometer when baseline measurements were collected. Patients were then instructed to pedal at 60–70 revs/minute. After 5 minutes, unloaded cycling power was increased every minute by work rate of 10% of the estimated W_{max} (according to the European Respiratory Society criteria), until the patient was unable to maintain the pedaling frequency. Reasons for stopping were recorded. Peak values were the average over the last 20 seconds of the maximum completed work. Peak VO₂ was predicted using equations for healthy subjects older than 55 years of age.⁸ Peak VE was predicted from the Carter et al's⁹ equation: $37.5 \times FEV_{1,}$

Muscular efficiency and REE

Gross muscular efficiency (%) was assessed by measuring energy expenditure (EE) during cycling at 50% of W_{max}. Immediately after reaching steady state, EE was averaged over a period of at least 5 minutes. In addition, steady-state EE was measured at isotime, a time point that was determined by the shortest exercise time of each subject. After reaching the constant workload of 50% W_{max}, patients were asked to continue cycling for as long as possible. Gross muscular efficiency (%) was calculated using the equation $\text{load (Watt) of exercise} \times 0.01433 \text{ kcal/min/EE kcal/min} \times 100\%$. REE was measured using an open-circuit indirect calorimetry system using a ventilated hood (Oxycon Beta®, Jaeger). Measurements were taken in the early morning, following an overnight fast, with patients in a supine position. Net muscular efficiency (%) was calculated using the values obtained for the gross muscular efficiency and REE using the equation¹⁰ $\text{load (W) of exercise} \times 0.01433 \text{ kcal/min/EE} - \text{REE kcal/min} \times 100\%$. In a pilot study, mean (standard deviation [SD]) differences of two measurements (interval of 1–2 weeks) of gross muscular efficiency, net muscular efficiency, and REE were 0.011% (0.82%), 0.035% (1.76%), and 7 kcal/24 hours (228 kcal/24 hours).

Lung function

Lung function tests were performed according to the guidelines of the European Respiratory Society¹¹ and included FEV₁ and FVC. Screening FEV₁ was measured before and 40 minutes after 480 µg salbutamol and 80 µg ipratropium (Combivent). Total lung capacity, FRC, airway resistance, and sGaw were measured by body plethysmography (Masterlab®, Jaeger Würzburg, Germany). PEF values (MiniWright®, Clement

Clarke International, Harlow, UK) were recorded twice daily during the treatment periods, immediately after waking up and just before going to sleep, and always before study medication. PEF day-to-day variability was defined by $(\text{highest morning PEF} - \text{highest morning PEF of the day before}) \times 100\%$, averaged over 7 successive days. PEF within-day variability was defined by $(\text{highest PEF} - \text{lowest PEF})/(\text{mean value of 2}) \times 100\%$, averaged over 7 successive days.

Disease-specific symptoms were assessed using the CCQ. This is a self-administered questionnaire specifically developed to measure clinical control in patients with COPD.¹² CCQ score <1 = no limitation, ≥1 and <2 = mild limitation, ≥2 and <3 = moderate limitation, and ≥3 = severe limitation. Adverse events occurring during the study period were monitored and recorded.

Statistical analysis

Statistics were computed using SAS® Version 8.02 (SAS Institute Inc., Cary, NC, USA). Characteristics of the study group are given as mean (SD). Statistical analysis was performed using a full analysis set and analysis of variance. Twenty-four patients were required in order to detect an absolute difference of 1% in mean gross muscular efficiency between the two treatments at the 5% significance level with 90% power. $P < 0.05$ was considered significant.

Results

Patients had moderate-to-severe COPD (Table 1). Four patients had an exacerbation during the study. One exacerbation led to discontinuation of the study. No hospitalizations occurred during the study period.

Of the 25 patients randomized, 23 received tiotropium, 24 salmeterol, and 24 placebo. Both tiotropium and salmeterol improved FEV₁, FVC, FRC, and sGaw compared with placebo (Table 2). Differences between tiotropium and salmeterol were not statistically significant.

Compared with placebo, neither tiotropium nor salmeterol significantly improved the primary endpoint of mean gross muscular efficiency after 6 weeks of treatment (Table 3). Active treatment did not significantly changed mean net muscular efficiency, VO₂, VCO₂, VE, and tidal volume. Mean (SD) REE values after tiotropium, salmeterol, and placebo treatment were 1485 kcal/24 hours (112 kcal/24 hours), 1709 kcal/24 hours (105 kcal/24 hours), and 1472 kcal/24 hours (120 kcal/24 hours), respectively.

Irrespective of the absence of change in the primary outcome, a significant improvement above placebo in exercise endurance was observed after 6 weeks with tiotropium but

Table 1 Screening characteristics (n = 25)^a

Screening characteristics	N (mean [SD])
Clinical characteristics	
Age (years)	62.0 (7.1)
Sex (% males)	20 (80)
Smoking history (pack-years)	45.3 (26.9)
Current smoker/exsmoker (%)	40/60
Number of corticosteroid users, inhaled/oral	19/2
Duration of COPD (years)	7.4 (5.9)
Body mass index (kg/m ²)	24.6 (3.4)
Prebronchodilator FEV ₁ (% predicted)	40.7 (10.4)
Postbronchodilator FEV ₁ (% predicted)	48.1 (10.1)
FEV ₁ /FVC × 100 (%)	39.1 (8.8)
FVC (% predicted)	3.9 (0.7)
Maximal incremental bicycle test	
Maximal workload (Watt)	99.6 (37.2)
VO ₂ at maximum (L/minute)	1128.9 (394.7)
PaO ₂ at rest (mmHg)	50.6 (198.4)
PaO ₂ at maximum (mmHg)	54.5 (181.5)
PaCO ₂ at rest (mmHg)	25.0 (96.3)
PaCO ₂ at maximum (mmHg)	34.5 (115.3)
Lactate rest (mmol/L)	1.5 (1.2)
Lactate at maximum (mmol/L)	6.5 (2.5)
Subjective reason for stopping exercise	
Discomfort with legs (%)	2 (8)
Discomfort with breathing (%)	19 (76)
Both discomfort with legs and breathing (%)	3 (12)
Pain in the chest (%)	0 (0)
Other (%)	1 (4)
Dyspnea Borg before exercise	0.2 (0.4)
Dyspnea Borg at end of exercise	7.0 (1.9)

Note: ^aValues are means (SD) or numbers (% proportion).

Abbreviations: BMI, body mass index; CO₂, carbon dioxide; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; O₂, oxygen; SD, standard deviation; VO₂, oxygen uptake.

not with salmeterol (Figure 2). After 6 weeks, mean (SD) endurance time was 26.96 minutes (2.26 minutes) with tiotropium compared with 19.30 minutes (2.34 minutes) with placebo ($P = 0.02$). Mean (SD) endurance time after salmeterol was 23.33 minutes (2.26 minutes) ($P = 0.22$ versus placebo).

No correlations were present between changes in endurance time and FEV₁, FRC, or gross muscular efficiency.

Assessment of patients' symptoms and functional state by total CCQ scores suggested a significant reduction with both tiotropium ($P = 0.011$) and salmeterol ($P = 0.0003$) (Figure 3, Table 4). This was mainly due to significant changes in the symptoms and functional state domains. Differences between tiotropium and salmeterol were not statistically significant ($P = 0.20$).

Weekly mean (SD) number of puffs of rescue medication over the last 3 weeks on treatment were 11.9 (18.5), 12.0 (17.2), and 15.5 (18.5) for tiotropium, salmeterol, and placebo, respectively.

Table 2 Pulmonary function values after 6 weeks of treatment^a

Function	Tiotropium	Salmeterol	Placebo
FEV ₁ (L)	1.32 (0.03)*	1.27 (0.03)**	1.14 (0.03)
FVC (L)	3.27 (0.06)*	3.12 (0.06)*	2.81 (0.06)
FEV ₁ /FVC (%)	40.70 (0.7)	40.81 (0.7)	41.20 (0.73)
TLC (L)	7.72 (0.09)***	7.85 (0.09)**	8.13 (0.09)
RV (L)	3.97 (0.10)*	4.37 (0.10)***	4.90 (0.11)
FRC (L)	5.13 (0.12)**	5.13 (0.12)**	5.61 (0.13)
Raw (kPa sec/L)	0.49 (0.03)*	0.54 (0.03)***	0.68 (0.03)
sGaw 1/(kPa sec)	0.51 (0.03)*	0.45 (0.03)*	0.31 (0.03)
Diary data			
Morning PEF ^b (L/min)	248.91 (3.63)*	250.24 (3.52)*	229.98 (3.63)
Evening PEF (L/min)	260.24 (3.26)*	253.63 (3.14)*	231.91 (3.26)
Day-to-day PEF variability	5.55 (0.53)	5.45 (0.53)	6.72 (0.56)
Within-day PEF variability	11.25 (1.40)	7.91 (1.34)	10.92 (1.44)

Notes: ^aValues are means (standard deviation [SD]) adjusted for patient and cycle using analysis of covariance; ^bPEF values were assessed in the 6-week treatment periods, whereas the other lung functions were assessed 1 hour after drug administration and 1 hour in advance of the submaximal bicycle tests; * $P < 0.001$ versus placebo; ** $P < 0.05$ versus placebo; *** $P < 0.01$ versus placebo.

Abbreviations: FEV₁, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; PEF, peak expiratory flow; Raw, airway resistance; RV, residual volume; sGaw, specific airway conductance; TLC, total lung capacity.

Discussion

This study investigated the effects of two long-acting bronchodilators on working energy expenditure and REE in COPD. The mean gross muscular efficiency and REE did not differ significantly from placebo with either tiotropium or salmeterol treatment. Only tiotropium significantly improved exercise endurance. Consistent with the results of other studies,

Table 3 Constant-load exercise after 6 weeks of treatment^a

	Tiotropium	Salmeterol	Placebo
Immediately after reaching steady state			
Gross muscular efficiency (%)	13.01 (0.32)*	13.17 (0.30)*	14.14 (0.34)
Net muscular efficiency (%)	16.03 (0.57)	17.15 (0.51)	17.12 (0.65)
EE (Kcal/min)	5.43 (0.24)	5.32 (0.22)	5.40 (0.25)
VO ₂ (mL/min)	1018.05 (18.22)	1019.30 (17.38)	1015.51 (19.59)
VCO ₂ (mL/min)	897.65 (13.80)	898.20 (13.16)	888.32 (14.84)
At isotime (shortest exercise time)			
Gross muscular efficiency (%)	14.55 (0.31)	14.35 (0.30)	14.42 (0.33)
Net muscular efficiency (%)	19.34 (0.54)	18.51 (0.51)	19.07 (0.62)
EE (Kcal/min)	5.02 (0.10)	5.07 (0.09)	5.01 (0.10)
VO ₂ (mL/min)	1026.30 (20.72)	1037.91 (19.75)	1026.18 (21.96)
VCO ₂ (mL/min)	898.40 (15.83)	904.32 (15.08)	893.35 (16.77)

Notes: ^aValues are means (standard error); * $P < 0.05$ versus placebo; ** $P < 0.01$ versus placebo; *** $P < 0.001$ versus placebo.

Abbreviations: EE, energy expenditure; VCO₂, carbon dioxide production; VO₂, oxygen consumption.

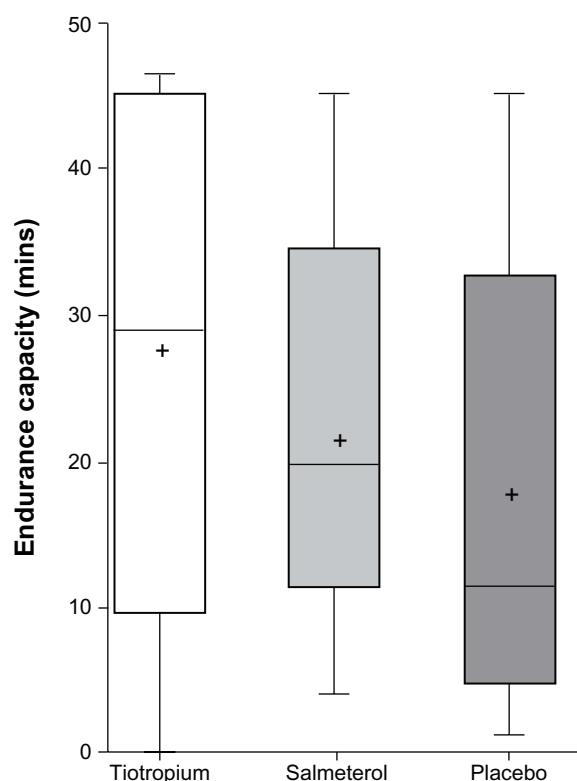


Figure 2 Endurance time at 50% maximal workload after 6 weeks of treatment.

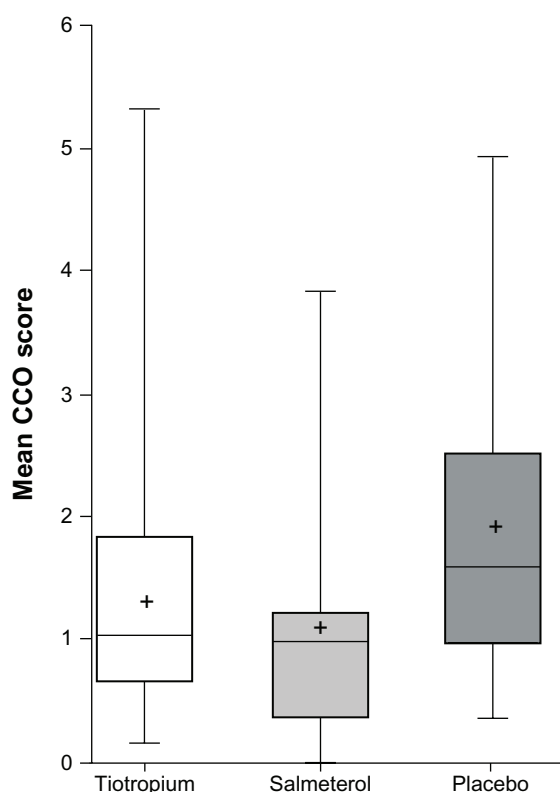


Figure 3 Clinical COPD Questionnaire after 6 weeks of treatment.

Table 4 Clinical COPD Questionnaire items after 6 weeks of treatment^a

	Tiotropium	Salmeterol	Placebo
Symptom domain			
Short of breath at rest	0.69 (0.18)*	0.47 (0.18)*	1.69 (0.18)
Short of breath during physical exercise	2.63 (0.21)**	2.18 (0.21)*	3.67 (0.22)
Did you cough?	1.77 (0.19)	1.69 (0.19)	2.02 (0.20)
Did you produce phlegm?	1.59 (0.21)	1.32 (0.21)	1.76 (0.22)
Mental state domain			
Concerned about getting a cold/exacerbation	0.50 (0.14)	0.28 (0.14)	0.65 (0.15)
Depressed due to breathing problems	0.68 (0.19)	0.65 (0.19)	0.92 (0.19)
Functional state domain			
Daily activities at home	1.10 (0.21)	0.73 (0.21)**	1.53 (0.21)
Social activities	0.77 (0.20)	0.64 (0.20)	1.21 (0.21)
Moderate physical activities	2.54 (0.24)***	2.09 (0.24)**	3.27 (0.25)
Strenuous physical exercises	1.59 (0.22)	1.24 (0.22)**	2.22 (0.23)

Notes: ^aValues are means (standard error) adjusted for patient and cycle using analysis of covariance; * $P < 0.001$ versus placebo; ** $P < 0.01$ versus placebo; *** $P < 0.05$ versus placebo.

both drugs significantly improved symptoms, functional state, and lung function, including parameters of hyperinflation.

Cost of breathing during maximal exercise may rise to 35%–40% of the maximal oxygen consumption and contribute significantly to the limited physical performance of patients with COPD.¹³ Assuming that effective bronchodilator therapy reduces the work of breathing during submaximal cycling by 25%, total energy expenditure during exercise would be anticipated to be reduced by 8%–10%. This study was statistically powered to detect a change in gross muscular efficiency of 1%, which reflects a relative change of approximately 7%. With a sample size of 24 subjects, we feel 95% confident that both salmeterol and tiotropium improved total energy expenditure by no more than 7%. Our results are in line with a study investigating the effects of pressure support ventilation in severe COPD patients who cycled at a mean constant work load of 33 Watts.¹⁴ Despite significantly improved VE and inspiratory effort, no changes were found in oxygen consumption. The authors concluded that the anticipated reduction in oxygen cost of breathing relative to total oxygen consumption was too small to be detected.

Recently, the underlying mechanisms of decreased muscular efficiency in COPD have been examined and may explain, at least in part, our findings. Arterial and venous blood flow in the legs during a two-leg cycle exercise and single knee-extensor exercise was compared between COPD patients and age-matched healthy controls.¹⁵ At a given workload, local oxygen consumption in leg muscles was significantly higher in COPD patients than in healthy controls. In addition, a higher

proportion of type II muscle fibers in the vastus lateralis muscle from COPD patients suggested that the reduced muscular efficiency of the leg muscles was due to the contribution of less effective muscle fibers. In contrast, respiratory muscles in COPD are suggested to have an elevated proportion of very efficient type I fibers.¹⁶ This suggests that, in exercising COPD patients, the contribution of peripheral muscle dysfunction to pathologically increased total energy expenditure might be more important than the increased work of breathing.

Tiotropium significantly improved airway conductance ($\pm 60\%$) and FRC ($\pm 9\%$) as well as endurance time ($\pm 40\%$), yet without significant correlations between these parameters. Other studies demonstrated modest correlations between changes in endurance capacity and changes in FEV₁ or IC induced by ipratropium¹⁷ and tiotropium,¹⁸ whereas 20% of patients failed to improve endurance time despite positive effects on lung function.¹⁷ Consequently, bronchodilators may alter rate-limiting factors other than lung function. In this respect, a rate-limiting blood flow has been demonstrated in the lower limbs of some COPD patients during cycling exercise.¹⁹ In healthy subjects, a local reflex vasoconstriction due to the increased work of breathing has been suggested to reduce leg blood flow and to promote quadricep fatigue during cycling at relatively high work loads.^{20,21} Unloading of the respiratory muscles improved time to exhaustion and exercise-induced quadricep muscle fatigue.^{20–23} Similar mechanisms may have improved the endurance time in our tiotropium-treated COPD patients. Redistribution of blood to the legs after tiotropium inhalation may also be the result of an improved cardiac performance. Travers et al²⁴ demonstrated that heart rate was lower with tiotropium at rest and during exercise, with a corresponding increase in oxygen pulse (surrogate measure of cardiac stroke volume) and decrease in the rate pressure product (surrogate measure of myocardial work). Together, these findings give rise to a new research question: is tiotropium-improved endurance capacity in COPD the consequence of reduced hyperinflation as well as increased leg blood flow?

We anticipated that patients with modest reversibility after Combivent would improve notably, as one study demonstrated that work of breathing improved by $>25\%$ after inhaling a single dose of formoterol in COPD patients with a mean reversibility in FEV₁ of 5% predicted.²⁵ Retrospectively, it may have been better to have selected patients on the basis of volume (hyperinflation) instead of flow (FEV₁) response, although both frequently occur together.²⁶ Additionally, we selected COPD patients with a proven ventilatory limitation at maximal work load, assuming that reduced muscular efficiency due to dynamic hyperinflation is more common

in patients with a cardiovascular limitation or oxygen uptake disorder. However, muscular efficiency was tested at 50% of W_{max}, at which breathing frequency may have been too low to significantly increase hyperinflation and the work of breathing. Finally, we excluded subjects with oxygen desaturation and/or lactate production at 50% of W_{max}, as energy release due to anaerobic combustion is not measured by indirect calorimetry. However, arterial blood samples may not reflect local anaerobic combustion in the leg and respiratory muscles.

Net muscular efficiency in our study was somewhat higher than the 15.5% (8.5%–22.7%) values of Baarends et al.⁶ Their study took place in a pulmonary rehabilitation center and included COPD patients with similar age (61 years) and FEV₁ (37% predicted), yet with a lower W_{max} (58 Watt). Muscular efficiency in their study was measured during submaximal cycling at a work load of (on average) 30 Watt versus (on average) 50 Watt in our study, suggesting that the lower values of net muscular efficiency reported by Baarends et al⁶ reflect methodological differences and more severe disease. Interestingly, Perrault et al²⁷ demonstrated similar delta muscular efficiency in COPD patients (FEV₁ 36% predicted) and age-matched controls; however, COPD patients and controls did not cycle at the same workloads. To our knowledge, no studies compared net muscular efficiency of COPD patients and age-matched healthy controls during cycling at similar workloads.

We hypothesized that salmeterol would increase REE and therefore decrease gross muscular efficiency. This was based on the finding of a 5% increase in REE after inhaling 5 mg salbutamol in patients with COPD.²⁸ Another study showed a positive correlation between 24-hour total energy expenditure and the daily dose of inhaled β -2-agonists.²⁹ Such findings have not been demonstrated for the anticholinergic drug ipratropium bromide.³⁰ Our nonsignificant finding ($P = 0.15$ for salmeterol versus placebo) may be due to insufficient statistical power or may reflect adaptation in resting metabolism after 6-week treatment with salmeterol.

Conclusion

We conclude that muscular efficiency and REE do not improve after 6-week treatment with tiotropium or salmeterol in clinically stable COPD. This lack of effect occurs despite significant improvements in lung function, including parameters of hyperinflation, and, in cases of tiotropium treatment only, significant improvements in exercise endurance. We assume that the reduced costs of breathing relative to total energy expenditure were too small to be detected. Future studies should focus on the effects of bronchodilators on cardiovascular and local leg performance during submaximal exercise.

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Disclosure

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