Respiratory Medicine (2010) **104**, 1490–1494

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Energy expenditure and impact of bronchodilators in COPD patients

Mario Cazzola [a,b,*], Andrea Segreti [a], Emanuele Stirpe [a], Massimiliano Appodia [a], Lucia Senis [a], Maria G. Matera [c]

[a] *Division of Respiratory Diseases, Department of Internal Medicine, University of Rome 'Tor Vergata', Rome*
[b] *Rehabilitation Group, IRCCS, San Raffaele Pisana, Rome*
[c] *Unit of Pharmacology, Department of Experimental Medicine, Second University of Naples, Naples, Italy*

Received 5 February 2010; accepted 5 April 2010
Available online 14 May 2010

KEYWORDS
COPD;
Energy expenditure;
Bronchodilators;
SenseWear® Armband

Summary
28 Consecutive COPD patients performed four 6-minute walking tests (6-MWTs) in 2 different days before and 2, 4 and 6 h after the inhalation of formoterol 12 μg or tiotropium 18 μg, respectively. Physical activity during each 6-MWT was assessed by the SenseWear® Armband. At each time also spirometry was performed. Both formoterol and tiotropium induced a significantly sustained bronchodilation and influenced hyperinflation. Formoterol significantly increased distance walked in 6 min at 2 h and at 4 h, whereas tiotropium significantly increased it at all time points. There was a trend to an increase in calories and metabolic equivalents of task (METs) after formoterol and a decrease after tiotropium, but changes were not statistically significant. Total energy expenditure for each 6-MWT was not changed by formoterol, but decreased in significant manner 6 h after the inhalation of tiotropium. Active energy expenditure at physical activity level of more than 3 METs decreased significantly after tiotropium at each 6-MWT, but not after formoterol. We did not find any significant correlation between the changes in lung function and those of parameters recorded with SenseWear® Armband. Our study seems to indicate that tiotropium, but not formoterol, is able to reduce energy expenditure in COPD patients, although both drugs elicit significant bronchodilation and are able to increase the distance walked in 6 min.

Introduction

Energy expenditure (EE) may be elevated in COPD patients due to increased basal metabolic rate, increased activity expenditure, or an increase in nutrient-induced thermogenesis.[1] Increased oxygen cost of breathing probably contributes to the increased total daily EE due to increased

* Corresponding author. Dipartimento di Medicina Interna, Via Montpellier 1, 00133 Rome, Italy, Tel.: +39 062090 3615.
E-mail address: mario.cazzola@uniroma2.it (M. Cazzola).

0954-6111/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2010.04.002

hyperinflation during exercise,[2,3] and the thermogenic effects of bronchodilating agents[4] and systemic inflammation[5] are other suggested contributors to the elevated EE.

Long-acting bronchodilators are now central to the symptomatic management of COPD,[6] but there is no documentation on their impact on EE, although there is evidence that these agents can reduce lung hyperinflation during exercise.[7,8]

The apparent discrepancy between the favourable action of bronchodilators on exercise-induced hyperinflation and their potential thermogenic effects, has led us to undertake the present study for assessing the influence of tiotropium and formoterol, two long-acting bronchodilators with different pharmacological mechanisms of action, being the first an anticholinergic agent and the second a β-agonists, on EE during physical activity in patients with COPD.

Patients and methods

We enrolled 28 consecutive COPD outpatients as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) position paper.[6] All had a baseline $FEV_1 < 60\%$ predicted. Exclusion criteria included: unstable respiratory status within the previous four weeks, a known history of asthma or chronic respiratory disease other than COPD, any clinically significant concurrent disease, and a change in medication for COPD within the four weeks prior to the screening visit.

The protocol was approved by the ethics committee, and written informed consent was obtained from all subjects.

All patients were ex-smokers, older than 60 years, and all had experience of walking tests. They performed four 6-minute walking tests (6-MWTs) in each of 2 separate test days, before and 2, 4 and 6 h after the inhalation of formoterol 12 μg or tiotropium 18 μg, respectively. The washout period between the test days was at least 96 h to avoid any carryover effect of tiotropium[9] or formoterol. During this period, the patients could use salbutamol 200 μg as needed as "rescue" drug. The sequence of treatments was randomized.

The 6-MWTs were conducted according to current guidelines on a 30-m corridor.[10]

EE was assessed during all walking tests by the SenseWear® Armband (BodyMedia Inc., Pittsburgh, PA, USA), a physiologic activity monitor worn on the upper right arm over the triceps muscle, which contains a biaxial accelerometer (longitudinal and transverse). It also uses sensors that continuously gather data (i.e. movement, heat flux, skin temperature, galvanic skin response) estimating the wearer's caloric expenditure, duration of physical activity and number of steps taken. Early research, which tested COPD patients with this device and with indirect calorimetry during two 6-MWTs as well as during two incremental shuttle walking tests, showed that it tracked very well to indirect calorimetry with very high session correlations (0.93).[11] During each test day, patients wore the SenseWear® Armband for 7 h. The first hour was not used for analysis because the sensors require 30—40 min to reach thermal equilibrium.

At each time, soon before each 6-MWT, also spirometry was performed according to ATS/ERS guidelines.[12]

The results of the study are expressed as mean and 95% CI unless otherwise stated. The extent to which the two bronchodilators were able to induce changes in the measured variables was examined using a paired *t* test. The end-exercise values for the measured variables obtained during 6-MWT were compared using paired *t* tests and Bland and Altman analyses. A $p < 0.05$ level of significance was used for all analyses. Since the variables from the physical activity assessment were non-normally distributed, correlations between pulmonary function and physical activity were performed using the Spearman correlation coefficient.

Results

All 28 subjects completed the study and there were no missing data.

Both formoterol and tiotropium induced a significant ($p < 0.05$) bronchodilation and reduced pulmonary hyperinflation (Table 1).

Formoterol significantly ($p < 0.05$) increased distance walked in 6 min at 2 h and at 4 h, whereas tiotropium significantly ($p < 0.05$) increased it at all time points (Fig. 1).

There was a trend toward an increase in calories after formoterol (maximum increase: +0.89 kcal, 95% CI: 2.70—0.91 at 2 h) and decrease after tiotropium (maximum decrease: −1.61 kcal, 95% CI: 0.60—3.82), but changes were always statistically non-significant ($p > 0.05$). Also metabolic equivalents of task (METs) increased after formoterol (maximum increase: +0.18, 95% CI: 0.44—0.08, at 2 h) and decreased after tiotropium (maximum decrease: −0.22, 95% CI: 0.09—0.52, at 4 h) in a non-significant manner ($p > 0.05$) (Fig. 1).

Total energy expenditure (TEE) for each 6-MWT was not changed by formoterol, but decreased in significant manner ($p = 0.02$) 6 h after the inhalation of tiotropium.

Table 1 Changes in lung function before each 6-MWT. Values are mean ± S.E.

	Formoterol				Tiotropium			
	FEV_1	FVC	TLC	RV	FEV_1	FVC	TLC	RV
Basal	1.42 ± 0.10	2.73 ± 0.13	7.25 ± 0.23	4.30 ± 0.18	1.40 ± 0.08	2.72 ± 0.11	7.30 ± 0.24	4.37 ± 0.19
2 h	1.62 ± 0.10***	3.10 ± 0.14***	7.16 ± 0.23	3.82 ± 0.15***	1.52 ± 0.09**	2.88 ± 0.14*	7.14 ± 0.22*	3.98 ± 0.16***
4 h	1.60 ± 0.09***	3.02 ± 0.13***	7.16 ± 0.22	3.90 ± 0.17**	1.53 ± 0.09**	2.95 ± 0.14*	7.09 ± 0.23**	3.95 ± 0.14***
6 h	1.55 ± 0.09***	3.00 ± 0.13***	7.11 ± 0.23	3.84 ± 0.15***	1.49 ± 0.09**	2.95 ± 0.13**	7.16 ± 0.25*	4.01 ± 0.15***

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

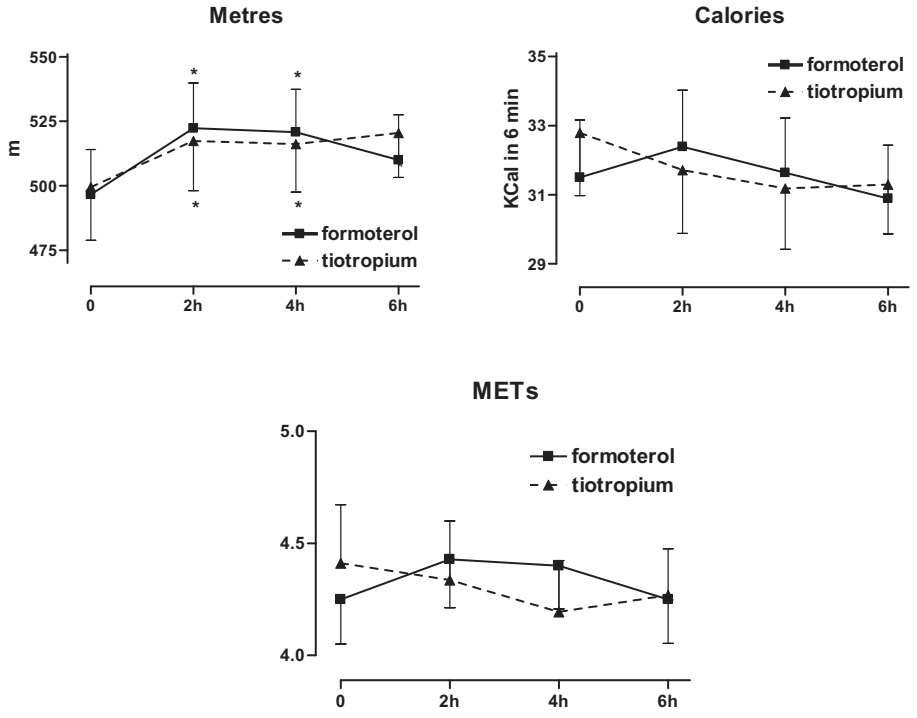

Figure 1 Impact of formoterol and tiotropium on distance walked in 6 min, calories and METs. Values are mean ± S.E. *$p < 0.05$ vs baseline.

Active energy expenditure (AEE) at physical activity level of more than 3 METs during each 6-MWT decreased significantly after tiotropium (−2.32 kcal/6 min, 95% CI: −0.25 to 4.39, $p = 0.03$ at 2 h; −3.04 kcal/6 min, 95% CI: −0.49 to 5.58, $p = 0.0211$ at 4 h; −2.68 kcal/6 min, 95% CI: −0.30 to 5.05, $p = 0.03$ at 6 h) but not after formoterol (Fig. 2). It must be highlighted that formoterol induced a slight increase in TEE and AEE, at least in the early hours after its administration, but the recorded increases were never statistically significant ($p > 0.05$).

We did not find any significant correlation between the changes in lung function and those of parameters recorded with SenseWear® Armband.

Discussion

Our study seems to indicate that tiotropium but not formoterol is able to reduce EE in COPD patients although both drugs elicit significant bronchodilation and are able to increase the distance walked in 6 min. This finding fits rather well with the results of a previous study who documented that salbutamol, a β-agonist, but not ipratropium bromide, an anticholinergic agent, induced a sustained increase in the EE of patients with COPD despite a reduction in airway obstruction obtained with both drugs.[13]

The effect of tiotropium on EE appeared to be independent of its impact on lung function. This is an unexpected finding. There is documentation of a reduction in EE following lung volume reduction surgery in subjects with COPD and it was suggested that it was related to an improvement in work of breathing.[14] In our patients, both formoterol and tiotropium were able to induce a pharmacologic lung volume reduction but formoterol did not

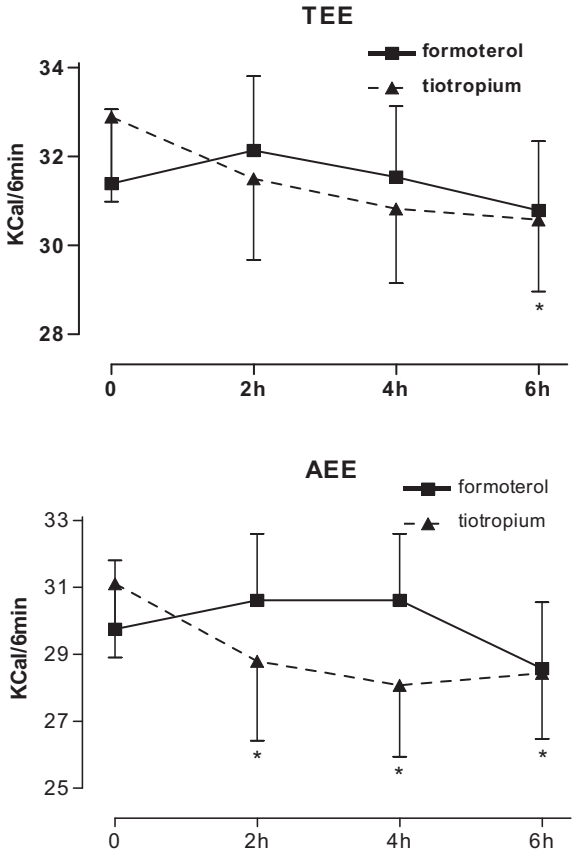

Figure 2 Impact of formoterol and tiotropium on total energy expenditure (TEE) and active energy expenditure (AEE). Values are mean ± S.E. *$p < 0.05$ vs baseline.

reduce EE. This finding leads us to hypothesize that the reduction in pulmonary hyperinflation is not enough to also induce a reduction in EE.

Theoretically, bronchodilators could have two opposite effects on EE in patients with airway obstruction — firstly an increase in EE due to a direct thermogenic effect and secondly a decrease in EE due to diminished work of breathing because of bronchodilation.[13]

The peripheral sympathetic nervous system is a key factor in the regulation of energy balance in humans. Appreciable increases in EE were observed during administration of isoproterenol with co-infusion of the selective β_1-adrenoceptor (AR) antagonist atenolol,[15] and also during selective β_2-AR stimulation with salbutamol.[16] This finding clearly indicates that the β_2-AR subtype contributes significantly to β-AR-mediated thermogenesis. Consequently also formoterol has the potential for increasing EE. In effect, in our patients it induced by trend a slight increase in TEE and AEE, at least in the early hours after its administration, with a modest reduction at the sixth hour, but changes were without statistic significance, likely because of the lack of statistical power (e.g., from small sample size). On the contrary, tiotropium, being an anticholinergic drug, is a non-thermogenic bronchodilator[13] and, as expected, it did not elicit an increase in EE after its administration but only its significant progressive reduction. The trend that we detected seems to be comparable to what has been observed in horses with the similar disease, recurrent airway obstruction. Salbutamol resulted in a $<10\%$ decrease in EE,[17] whereas ipratropium bromide resulted in a far more striking reduction in EE, with all horses experiencing $>10\%$ change in EE.[18]

It is difficult to determine how important the different impact of formoterol and tiotropium on EE may be in the clinical setting. We must admit that there are several study limitations that need to be addressed. We recognize that the relatively small sample size of patients enrolled in this study could be regarded as a limitation, but it must be considered that this study was conducted in a single centre as a pilot investigative trial. One could argue that a 6-MWT, with uncontrolled speed and distance, is inappropriate to test the hypothesis implied. It is possible that the 6-MWT is unlikely to replace an objective measurement of physical activity when the whole range of COPD severity is investigated.[19] However, a preliminary investigation, which evaluated reliability, validity, and stability of an accelerometer in the measurement of activity during 6-MWT, reported a highly linear association between accelerometer activity and distance walked during three walk tests, suggesting that the accelerometer is a valid measure of physical movement during walking in functionally-limited patients.[20]

SenseWear® Armband provides a reasonable approach to estimate EE in healthy subjects and in patients with COPD over a longer period of time in a setting, where no other technology is available (i.e. at home). Whether it is able to capture such very small differences in EE of about 1—2 kcal in 6 min is lacking validation so far and our study is the first attempt to examine this possibility.

Although all patients enrolled in our study had previous experience of walking tests, our findings do not allow excluding that the supposed impact of a learning experience when repetitive tests are performed has influenced the results that we have obtained.

We must also mention that our data have been generated after the acute administration of the two bronchodilators, whereas it is possible that their chronic use may have a different impact, at least with respect to formoterol. It is well known that the continuous long-term exposure of β-ARs to agonists results in the downregulation of mRNA and receptor protein with the rapid onset of tolerance to their effects.[21] Therefore, the thermogenic effect of formoterol would be expected to be transient in nature and it likely that the regular use of this drug does not affect the EE in COPD patients.

In any case, it must be mentioned again that in our patients both formoterol and tiotropium reduced pulmonary hyperinflation although all patients underwent several 6-MWTs in the same day and it is well known that in patients with COPD, dynamic hyperinflation can occur during activities such as walking,[22] but only tiotropium reduced EE. It is clear that large and prolonged studies focused on this outcome are now mandatory if we want to understand whether there is a real advantage in using anticholinergic agents instead of β-agonists in these patients.

Conflict of interest

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References

1. Goldstein S, Askanazi J, Weissman C, Thomashow B, Kinney JM. Energy expenditure in patients with chronic obstructive pulmonary disease. *Chest* 1987;**91**:222—4.
2. Donahoe M, Rogers RM, Wilson DO, Pennock BE. Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989;**140**:385—91.
3. Sridhar MK, Carter R, Lean ME, Banham SW. Resting energy expenditure and nutritional state of patients with increased oxygen cost of breathing due to emphysema, scoliosis and thoracoplasty. *Thorax* 1994;**49**:781—5.
4. Creutzberg EC, Schols AMWJ, Bothmer-Quaedvlieg FCM, Wouters EFM. Prevalence of an elevated resting energy expenditure in patients with chronic obstructive pulmonary disease in relation to body composition and lung function. *Eur J Clin Nutr* 1998;**52**:396—401.
5. Schols AM, Buurman WA, Staal van den Brekel AJ, Dentener MA, Wouters EF. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. *Thorax* 1996;**51**:819—24.
6. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;**23**:932—46.
7. O'Donnell DE, Flüge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, Make B, Magnussen H. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004;**23**:832—40.
8. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA. Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. *Eur Respir J* 2004;**24**:86—94.
9. Littner MR, Ilowite JS, Tashkin DP, Friedman M, Serby CW, Menjoge SS, et al. Long-acting bronchodilation with once daily

dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;**161**:1136–42.
10. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;**166**:111–7.
11. Patel SA, Benzo RP, Slivka WA, Sciurba FC. Activity monitoring and energy expenditure in COPD patients: a validation study. *COPD* 2007;**4**:107–12.
12. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;**26**:319–38.
13. Burdet L, de Muralt B, Schutz Y, Fitting JW. Thermogenic effect of bronchodilators in patients with chronic obstructive pulmonary disease. *Thorax* 1997;**52**:130–5.
14. McKeough ZJ, Alison JA, Bayfield MS, Bye PT. Reduction in resting energy expenditure following lung volume reduction surgery in subjects with chronic obstructive pulmonary disease. *Chron Respir Dis* 2004;**1**:197–202.
15. Blaak EE, Saris WH, van Baak MA. Adrenoceptor subtypes mediating catecholamine-induced thermogenesis in man. *Int J Obes Relat Metab Disord* 1993;**17**(Suppl. 3):S78–S81.
16. Oomen JM, van Rossum CT, Hoebee B, Saris WH, van Baak MA. β_2-Adrenergic receptor polymorphisms and salbutamol-stimulated energy expenditure. *J Clin Endocrinol Metab* 2005;**90**:2301–7.
17. Mazan MR, Hoffman AM, Kuehn H, Deveney EF. Effect of aerosolized albuterol sulfate on resting energy expenditure determined by use of open-flow indirect calorimetry in horses with recurrent airway obstruction. *Am J Vet Res* 2003;**64**: 235–42.
18. Mazan MR, Deveney EF, DeWitt S, Bedenice D, Hoffman A. Energetic cost of breathing, body composition, and pulmonary function in horses with recurrent airway obstruction. *J Appl Physiol* 2004;**97**:91–7.
19. Steele BG, Holt L, Belza B, Ferris S, Lakshminaryan S, Buchner DM. Quantitating physical activity in COPD using a triaxial accelerometer. *Chest* 2000;**117**:1359–67.
20. Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. *Eur Respir J* 2009;**33**:262–72.
21. Newnham DM, Grove A, McDevitt DG, Lipworth BJ. Subsensitivity of bronchodilator and systemic β_2 adrenoceptor responses after regular twice daily treatment with eformoterol dry powder in asthmatic patients. *Thorax* 1995;**50**: 497–504.
22. Marin JM, Carrizo SJ, Gascon M, Sanchez A, Gallego B, Celli BR. Inspiratory capacity, dynamic hyperinflation, breathlessness, and exercise performance during the 6-minute-walk test in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;**163**:1395–9.