Energy expenditure and impact of bronchodilators in COPD patients

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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. Increased oxygen cost of breathing probably contributes to the increased total daily EE due to increased...
Hyperinflation during exercise,\textsuperscript{2,3} and the thermogenic effects of bronchodilating agents\textsuperscript{4} and systemic inflammation\textsuperscript{5} are other suggested contributors to the elevated EE. Long-acting bronchodilators are now central to the symptomatic management of COPD,\textsuperscript{6} but there is no documentation on their impact on EE, although there is evidence that these agents can reduce lung hyperinflation during exercise.\textsuperscript{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 b-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.\textsuperscript{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 \(\mu\)g or tiotropium 18 \(\mu\)g, respectively. The washout period between the test days was at least 96 h to avoid any carryover effect of tiotropium\textsuperscript{9} or formoterol.

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).

<table>
<thead>
<tr>
<th></th>
<th>Formoterol</th>
<th>Tiotropium</th>
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</thead>
<tbody>
<tr>
<td>FEV(_1)</td>
<td>FVC</td>
<td>TLC</td>
</tr>
<tr>
<td>Basal</td>
<td>1.42 ± 0.10</td>
<td>2.73 ± 0.13</td>
</tr>
<tr>
<td>2 h</td>
<td>1.62 ± 0.10***</td>
<td>3.10 ± 0.14***</td>
</tr>
<tr>
<td>4 h</td>
<td>1.60 ± 0.09***</td>
<td>3.02 ± 0.13***</td>
</tr>
<tr>
<td>6 h</td>
<td>1.55 ± 0.09***</td>
<td>3.00 ± 0.13***</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01; ***p < 0.001.
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
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 \(\beta_1\)-adrenoceptor (AR) antagonist atenolol,\(^{15}\) and also during selective \(\beta_2\)-AR stimulation with salbutamol.\(^{16}\) This finding clearly indicates that the \(\beta_2\)-AR subtype contributes significantly to \(\beta\)-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\(^{21}\) 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 \(\beta\)-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 \(\beta\)-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


