Effect of salmeterol on respiratory muscle activity during exercise in poorly reversible COPD

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Background: Some patients with irreversible chronic obstructive pulmonary disease (COPD) experience subjective benefit from long acting bronchodilators without change in forced expiratory volume in 1 second (FEV1). Dynamic hyperinflation is an important determinant of exercise induced dyspnoea in COPD. We hypothesised that long acting bronchodilators improve symptoms by reducing dynamic hyperinflation and work of breathing, as measured by respiratory muscle pressure-time products.

Methods: Sixteen patients with “irreversible” COPD (<10% improvement in FEV1, following a bronchodilator challenge; mean FEV1 31.1% predicted) were recruited into a randomised, double blind, placebo controlled, crossover study of salmeterol (50 μg twice a day). Treatment periods were of 2 weeks duration with a 2 week washout period. Primary outcome measures were end exercise isotime transdiaphragmatic pressure-time product and dynamic hyperinflation as measured by inspiratory capacity.

Results: Salmeterol significantly reduced the transdiaphragmatic pressure-time product (294.5 vs 348.6 cm H2O/s/min; p = 0.03), dynamic hyperinflation (0.22 vs 0.33 litres; p = 0.002), and Borg scores during endurance treadmill walk (3.78 vs 4.62; p = 0.02). There was no significant change in exercise end time. Improvements in isotime Borg score were significantly correlated to changes in tidal volume/oesophageal pressure swings, end expiratory lung volume, and inspiratory capacity, but not pressure-time products.

Conclusions: Despite apparent “non-reversibility” in spirometric parameters, long acting bronchodilators can cause both symptomatic and physiological improvement during exercise in severe COPD.

B ronchodilators are the mainstay of treatment in chronic obstructive pulmonary disease (COPD). Inhaled long acting β2 agonists improve control of symptoms and health status and reduce the need for rescue medications and the frequency of exacerbations.

Traditionally, improvement in forced expiratory volume in 1 second (FEV1) has been used to measure the bronchodilator response in COPD. However, some COPD patients with little or no change in FEV1 experience improvement in symptoms with long acting β2 agonists. The response of an individual patient to a bronchodilator challenge on a single occasion does not predict whether or not the patient will benefit subsequently from that agent. Furthermore, some investigators have found no correlation between improvements in exertional dyspnoea and changes in FEV1. These findings could be explained if other physiological mechanisms operated in the absence of a change in FEV1.

Dynamic hyperinflation is an important determinant of exertional dyspnoea. During exercise, increased airways resistance and expiratory airflow limitation increase end expiratory lung volume (EELV). The resulting intrinsic positive end expiratory pressure (PEEPI) acts as an inspiratory threshold load that increases the work of breathing as well as placing the diaphragm and other inspiratory muscles at a mechanical disadvantage. It is conceivable that reducing airways resistance and subsequent dynamic hyperinflation with bronchodilators would unload the respiratory muscles by reducing the inspiratory load and work of breathing.

Work of breathing is a complex variable to measure, and many investigators use the pressure-time product (PTP) as an indicator of respiratory muscle activity. The PTP correlates well with measurements of oxygen consumption of contract-
Study design and medications
The study was of a randomised, double blind, placebo controlled, crossover design with a run in period of 2 weeks and consisted of five outpatient visits. On visit 1, subjects performed full baseline lung function tests, including formal bronchodilator reversibility, and incremental shuttle walks to determine predicted peak oxygen consumption (\( V_{\text{O2peak}} \)). Patients stable on inhaled corticosteroids remained on this medication throughout the trial. All other medications apart from rescue short acting \( \beta_2 \) agonists were stopped at the start of the run in period between visits 1 and 2; patients with a symptomatic exacerbation or spirometric deterioration during the run in period were withdrawn from the study and re-started on their usual medication. During both visits 1 and 2 subjects were familiarised with treadmill walking and the performance of inspiratory capacity manoeuvres at rest and during treadmill walking. At the end of visit 2 subjects were randomised to receive either placebo followed by salmeterol (50 \( \mu \)g) twice a day or salmeterol followed by placebo using a computer generated randomisation schedule, the Patient Allocation for Clinical Trials. Treatments were given via matching metered dose inhalers and spacer for 2 weeks with a 2 week washout period between visits 3 and 4. Post-treatment measurements were made on visits 3 and 5 at the same time of day for each patient. The study medication (salmeterol or placebo) was taken 2 hours before lung function tests and 3 hours before the exercise tests. In terms of “rescue therapy”, patients were allowed short acting \( \beta_2 \) agonists during treatment periods, but these were stopped for at least 8 hours before measurements were made.

Exercise tests
On visits 3 and 5 an endurance treadmill test was performed, as well as spirometry and total lung capacity (TLC) obtained from body plethysmography. The chosen walking speed was that producing 80% of predicted \( V_{\text{O2peak}} \), and the exercise test consisted of five outpatient visits. On visit 1, subjects performed full baseline lung function tests, including formal bronchodilator reversibility, and incremental shuttle walks to determine predicted peak oxygen consumption (\( V_{\text{O2peak}} \)). Patients stable on inhaled corticosteroids remained on this medication throughout the trial. All other medications apart from rescue short acting \( \beta_2 \) agonists were stopped at the start of the run in period between visits 1 and 2; patients with a symptomatic exacerbation or spirometric deterioration during the run in period were withdrawn from the study and re-started on their usual medication. During both visits 1 and 2 subjects were familiarised with treadmill walking and the performance of inspiratory capacity manoeuvres at rest and during treadmill walking. At the end of visit 2 subjects were randomised to receive either placebo followed by salmeterol (50 \( \mu \)g) twice a day or salmeterol followed by placebo using a computer generated randomisation schedule, the Patient Allocation for Clinical Trials. Treatments were given via matching metered dose inhalers and spacer for 2 weeks with a 2 week washout period between visits 3 and 4. Post-treatment measurements were made on visits 3 and 5 at the same time of day for each patient. The study medication (salmeterol or placebo) was taken 2 hours before lung function tests and 3 hours before the exercise tests. In terms of “rescue therapy”, patients were allowed short acting \( \beta_2 \) agonists during treatment periods, but these were stopped for at least 8 hours before measurements were made.

Data and statistical analysis
Based on previous PTP data during exercise in COPD patients, a minimum of 15 patients were required to show a reduction of 50 cm H2O in PTPdi with 80% power. Primary outcome measures were PTPdi and IC at end exercise isotime (ISO). ISO was the highest equivalent exercise endurance time between the two treadmill walks.

Statistical analysis was performed using SPSS 11.1 for Windows. Patients were divided into two groups according to the treatment sequence. Since this was a crossover trial, treatment effect was assessed after both period effect and treatment-period interactions had been assessed using two sample \( t \) tests. In the absence of period effect and treatment-period interaction, treatment effect was assessed with paired \( t \) tests or non-parametric equivalent depending on whether the groups were normally distributed. If a significant treatment-period interaction was found at the 10% significance level, the treatment effect was assessed with a two sample \( t \) test, disregarding data from the second period. Univariate and multivariate regression analysis was used to determine which patients were most likely to have a significant change in static lung volumes, dynamic hyperinflation, respiratory muscle activity and mechanics, as well as changes in static lung function.

RESULTS
Sixteen of the 20 patients completed the study; two were withdrawn because of worsening of symptoms during the run in period and two developed infective exacerbations during the treatment periods (one while on placebo and the other on salmeterol). Ten of the 16 patients received salmeterol as the first intervention. Baseline characteristics of the remaining participants are shown in table 1. Of note,
mean change in FEV$_1$ was only 10 ml following a bronchodilator reversibility test.

**Lung function and respiratory muscle strength**
Salmeterol had no significant effect on spirometric measurements or TLC, although resting hyperinflation appeared to be reduced as evidenced by a reduced RV:TLC ratio and an increased IC (tables 2 and 3). There were no changes in inspiratory muscle strength (table 2).

**Endurance treadmill exercise**
Salmeterol did not have a significant effect on tidal volume, respiratory frequency, minute ventilation, inspiratory/expiratory time, inspiratory duty cycle, or transcutaneous oxygen saturation. However, there was a significant reduction in breathlessness as measured by mean ISO Borg score following salmeterol (-1.54 (1.14); mean difference -0.84 (95% CI -1.54 to -0.14)), and change in Borg score from rest to isotime (table 3). In addition, salmeterol led to a significant reduction in the primary outcome measure (ISO IC), accompanied by improvements in operational lung volumes (table 3). Mean (SD) ISO IC was 0.98 (0.44) l following placebo and 1.27 (0.51) l after salmeterol (mean difference 0.29 (95% CI 0.11 to 0.44); p = 0.002).

**Respiratory muscle pressure time products (PTPs)**
Figure 1 shows the effects of salmeterol on ISO PTPs. Salmeterol led to a significant reduction in the primary outcome measure, mean (SD) ISO PTPdi (294.5 (99.6) cm H$_2$O/s/min; mean difference -54.2 (95% CI -102.5 to -5.9); p = 0.03), and also in mean ISO PTPga (544.8 (291.3) cm H$_2$O/s/min; mean difference -115 (95% CI -225.7 to -3.5); p = 0.04).

**Improvements in isotime Borg score**
There was no significant linear relationship between improvements in ISO Borg score and changes in respiratory muscle PTP, breathing pattern, minute ventilation, or baseline lung function. However, significant linear correlations were found between changes in ISO tidal volume/oesophageal pressure (r = 0.60; p = 0.01), EELV/TLC% (r = 0.58; p = 0.02) and IC (r = 0.56; p = 0.02) and ISO Borg score (fig 2). On backwards multivariate analysis, only tidal volume/oesophageal pressure and EELV/TLC% remained significant independent factors.

**DISCUSSION**
Using a randomised, placebo controlled, double blind, cross-over design, we assessed the effects of a long acting $\beta_2$ agonist, salmeterol, on inspiratory and expiratory muscle activity as well as dyspnoea, exercise capacity, and dynamic hyperinflation in patients with poorly reversible COPD. The principal finding is that, in the absence of a spirometric response to a bronchodilator challenge, this treatment can reduce dynamic hyperinflation and respiratory muscle activity in patients with severe COPD, suggesting a physiological basis for a reduction in symptoms.

**Significance of findings**
Recent work has emphasised the role of dynamic hyperinflation as a key determinant of exercise induced dyspnoea. Bronchodilators have also previously been shown to reduce dynamic hyperinflation during exercise in COPD. Belman and colleagues showed that a single dose of albuterol significantly reduced breathlessness and end expiratory/end inspiratory lung volumes during incremental cycle ergometry, while similar findings were described by O’Donnell and colleagues during endurance cycling following a 3 week period of nebulised ipratropium bromide. Broni and colleagues have shown a relationship between changes in resting IC following inhaled salbutamol and dyspnoea during light exercise in COPD patients with expiratory flow limitation. Apart from obvious differences in design, exercise test, and therapeutic drug, our study offers important additional information compared with these previous studies. Our patients were markedly more severe (FEV$_1$ 0.76 l compared with 1.20, 1.05 and 1.75 l) and none of our patients had any spirometric response to bronchodilator challenge (mean FEV$_1$ change 10 ml compared with 110, 230 and 390 ml). Despite this, our patients showed comparable improvements in operating lung volumes during exercise with salmeterol.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of study patients</th>
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<tbody>
<tr>
<td>Sex (M:F)</td>
<td>10:6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.1 (7.6)</td>
</tr>
<tr>
<td>Smoking history (pack years)</td>
<td>35.3 (13.8)</td>
</tr>
<tr>
<td>Pre-BD FEV$_1$ (l)</td>
<td>0.77 (0.17)</td>
</tr>
<tr>
<td>Pre-BD FVC (%)</td>
<td>72.3 (10.8)</td>
</tr>
<tr>
<td>Post-BD FEV$_1$ (l)</td>
<td>0.77 (0.15)</td>
</tr>
<tr>
<td>FEV$_1$ (l)</td>
<td>0.77 (0.17)</td>
</tr>
<tr>
<td>FEV$_1$/FVC (%)</td>
<td>32.8 (14.8)</td>
</tr>
<tr>
<td>TLC (%)</td>
<td>115 (14.5)</td>
</tr>
<tr>
<td>RV (%)</td>
<td>139 (14.8)</td>
</tr>
<tr>
<td>PaO$_2$ (PaO$_2$)</td>
<td>3.6 (0.9)</td>
</tr>
<tr>
<td>PaCO$_2$ (PaCO$_2$)</td>
<td>5.3 (0.6)</td>
</tr>
<tr>
<td>ISW distance (m)</td>
<td>275 (7.2)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Effect of salmeterol on lung function and respiratory muscle strength</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>Salmeterol</td>
</tr>
<tr>
<td>FEV$_1$ (l)</td>
<td>0.74 (0.22)</td>
</tr>
<tr>
<td>VC (l)</td>
<td>2.26 (0.78)</td>
</tr>
<tr>
<td>FEV$_1$/FVC (%)</td>
<td>35.0 (11.5)</td>
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<tr>
<td>TLC (l)</td>
<td>6.56 (1.47)</td>
</tr>
<tr>
<td>RV (l)</td>
<td>4.30 (0.82)</td>
</tr>
<tr>
<td>RV/TLC (%)</td>
<td>62.6 (20.5)</td>
</tr>
<tr>
<td>Sniff Pdi</td>
<td>99.9 (10.7)</td>
</tr>
<tr>
<td>Sniff Poes</td>
<td>79.6 (12.4)</td>
</tr>
</tbody>
</table>

Values are mean (SD) or mean treatment differences with 95% confidence intervals. Respiratory muscle strength tests are measured in cm H$_2$O. FEV$_1$ = forced expiratory volume in 1 second; VC = vital capacity; TLC = total lung capacity; RV = residual volume; Pmax = maximum inspiratory pressure; Pdi = diaphragmatic pressure; Poes = oesophageal pressure.

*Significant period vs treatment interaction.
O’Donnell and colleagues demonstrated a mean improvement of 390 ml in ISO IC in their patients following acute nebulised ipratropium, similar to the improvement seen in our study.7 Similarly, Belman et al reported a mean reduction of 4% in isotime EELV/TLC% and a 2% reduction in ISO EELV/TLC% following single dose albuterol,6 compared with the 5% and 4.7% reduction seen, respectively, in our group. The only other study in patients with COPD of comparable severity22 found a mean improvement in resting IC of 210 ml with 5 mg nebulised salbutamol, but the observations were not extended into exercise.

This study is also the first to investigate the effects of bronchodilation on pressure time products during treadmill exercise, demonstrating a reduction in PTPdi and PTPga with salmeterol. For a given neural output, transdiaphragmatic pressure increases as lung volumes fall; the reduction in PTPdi is particularly striking given that operating lung pressure increases as lung volumes fall; the reduction in oesophageal pressure swings, surface diaphragm electromyogram activity, and total lung resistance in patients with severe COPD at rest following a high dose of fenoterol.

Dynamic hyperinflation during exercise increases EELV, leading to adverse mechanical sequelae including breathing on a higher and less steep portion of the compliance curve, as well as a positive pressure within the alveoli at the end of expiration. PEEPi acts as an inspiratory threshold load that increases the work of breathing and also places the diaphragm at a mechanical disadvantage. Although PTPdi was reduced at isotime with salmeterol, there was no significant change in PTPoes. This is not altogether surprising, given that hyperinflation is more detrimental to the diaphragm than the rib cage or accessory inspiratory muscles.23 The effect on PTPga corroborates previous findings that expiratory muscle activity increases with progressive airflow obstruction and dynamic hyperinflation.24

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expiratory muscle activity cannot contribute to greater expiratory flow, and it remains unclear what role this abdominal muscle activity plays as it should be detrimental in energy terms.

Although salmeterol reduced isotime PTPdi and PTPga, there was no significant linear relationship with improvements in dyspnoea. The best correlates of reduced breathlessness were changes in operational lung volumes, particularly EELV/TLC and IC, and in tidal volume/oesophageal pressure. Current hypotheses on the origin of dyspnoea emphasise the role of neuromechanical dissociation (a disparity between the respiratory drive or motor output and the mechanical response of the system) rather than work of breathing per se.27 This is supported by recent work which found a progressive mismatch between diaphragm electromyogram activity and transdiaphragmatic pressure swings during exercise in patients with COPD.28 A reduction in dynamic hyperinflation would improve the mechanical response and hence decrease neuromechanical uncoupling. One potential explanation for our findings could be improved inspiratory muscle contractility with salmeterol as β2 agonists may increase the maximal force generated by the diaphragm.29 However, this is unlikely to play a major role given that no change was seen in the inspiratory muscle volumes, in the absence of changes in FEV1 or breathing in energy terms.

Abdominal muscle activity. A poor physiological improvements in patients with severe COPD.30 and quadriceps fatigue may con-
demonstrated in COPD30 and quadriceps fatigue is probably a less important to note that quadriceps fatigue is probably a less significant factor during walking.12 This study has shown that, despite “non-reversibility” in spirometry, a long acting bronchodilator can lead to physiological improvements in patients with severe COPD. A 2 week treatment period of salmeterol improves exertional dyspnoea and operational lung volumes, and reduces diaphragmatic and abdominal muscle activity. A poor spirometric response to a bronchodilator challenge in COPD patients does not preclude symptomatic and physiological improvements during exercise with a long acting β2 agonist.

ACKNOWLEDGEMENTS

The authors thank Tracey Fleming, Claire Wood and the Lung Function Department of King’s College Hospital for performing the lung function tests and Toni Maslen and Anne Chessbrough of GlaxoSmithKline UK for their help in planning the study and for statistical advice.

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WDCM is a Clinical Research Training Fellow of the Medical Research Council (UK).

This study was funded in part by a project grant from GlaxoSmithKline UK (protocol no SMS40312) who provided study drugs and placebo. They were involved in the initial design of the study but had no input in the writing of the final protocol, patient recruitment, data acquisition or analysis, or in the preparation of the manuscript.

WDCM has received assistance for travel to international conferences from Schering-Plough, GlaxoSmithKline, Allen & Hanbury, Boehringer-Ingelheim, and Bayer pharmaceutical companies. SK has received lecture fees from GlaxoSmithKline, Astra Zenera and Boehringer-Ingelheim. NH has received assistance for travel to international conferences from Bayer BREAS, 3M, Glaxo Wellcome, Cephalon and MedicAid. MIP has received lecture fees from Astra Zenera, GlaxoSmithKline, Nutricia and Cephalon, and assistance for travel to international conferences from Glaxo Wellcome, Astra Zenera, Cephalon, 3M and Ciba. JM has received assistance for travel to international conferences from Schering-Plough and Pfizer. NM, DN, GFR and ND have no conflicts of interest.

WDCM was involved in the design of the protocol, recruitment of patients, collection and analysis of data, and wrote the first draft of the manuscript. NM, DN, and SK were involved in recruitment of patients, collection of data, and preparation of the final manuscript. NH and GFR were involved in the design of the study, analysis of the data, and preparation of the final manuscript. ND gave statistical support and was involved in the analysis of data and the preparation of the final manuscript. MIP and JM were the senior investigators with the original idea for the study. They designed the study protocol, helped to write the first draft of the manuscript, supervised the conduct of the study and preparation of the final manuscript.

REFERENCES


Budesonide/formoterol may be used for adjustable maintenance dosing in asthma

This randomised, double blind/open two phase multicentre study, sponsored by Astra Zeneca, was conducted over 7 months to find out if asthma control was better when patients adjusted the maintenance dose of inhaled budesonide/formoterol (Symbicort Turbuhaler) according to asthma symptoms than when fixed dose (FD) regimens were used.

Eligible patients were randomised to one of three groups: (1) Symbicort FD 160/4.5 µg, two inhalations twice daily (bd); (2) Symbicort adjustable maintenance dose (AMD) 160/4.5 µg, two inhalations bd; or (3) salmeterol/fluticasone FD (Seretide Diskus) 50/250 µg, one inhalation bd. The study consisted of three treatment periods: run in (10–14 days), double blind (1 month with either Symbicort FD or Seretide FD), and open extension (6 months). In the open extension phase, those in the Symbicort AMD arm were advised to reduce the number to one inhalation bd or to increase the number of inhalations to four bd for at least 7 days according to the frequency of reliever usage and nocturnal awakenings due to asthma.

Symbicort FD significantly increased FEV₁ compared with Seretide FD (p<0.05). Comparable improvements in FEV₁ were observed with Symbicort AMD and Seretide FD. Patients in the Symbicort AMD group had significantly fewer exacerbations/hospital attendances/oral steroid courses (p<0.018) and lower use of reliever medication (p<0.01) than those in the Seretide FD group. There was no difference in the number of “well controlled asthma weeks” (WCAW) between the two FD groups, but Symbicort AMD increased the odds of achieving a WCAW compared with Symbicort FD (p = 0.049).

The results suggest that FD regimens with Symbicort and Seretide provide similar levels of asthma control. Total drug usage was lower with Symbicort AMD than FD. This study reinforces the need for home management plans and empowerment of patients to manage their asthma at home.

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