Thermogenic effect of bronchodilators in patients with chronic obstructive pulmonary disease

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Abstract
Background — Patients with chronic obstructive pulmonary disease (COPD) are frequently malnourished and have increased resting energy expenditure (REE). An increase in the work of breathing is generally considered to be the main cause of this hypermetabolism, but other factors may also be implicated. Bronchodilators may decrease the work of breathing by reducing airway obstruction, but β₂ adrenergic agents have a thermogenic effect. The aim of this study was to determine the effect of salbutamol and ipratropium bromide administration on REE in patients with COPD.

Methods — Thirteen patients (10 men) of mean (SD) age 68.3 (7.3) years and forced expiratory volume in one second (FEV₁) 39.0 (17.0)% predicted were studied on three consecutive days. The REE was measured by indirect calorimetry at 30, 60, 120, and 180 minutes after double blind nebulisation of either salbutamol, ipratropium bromide, or placebo in random order.

Results — FEV₁ increased both after salbutamol and after ipratropium. The difference in the mean response between salbutamol and placebo over 180 minutes was +199 ml (95% CI +104 to +295). The difference in mean response between ipratropium and placebo was +78 ml (95% CI +2 to +160). REE increased after salbutamol but was not changed after ipratropium. The difference in mean response between salbutamol and placebo was +4.8% of baseline REE (95% CI +2.2 to +7.4). Heart rate increased after salbutamol but not after ipratropium. The difference in the mean response between salbutamol and placebo was +5.5 beats/min (95% CI +2.6 to +8.4).

Conclusion — Salbutamol, but not ipratropium bromide, induces a sustained increase in the REE of patients with COPD despite a reduction in airway obstruction.

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Keywords: chronic obstructive pulmonary disease, energy expenditure, bronchodilating drugs.

Weight loss may be a feature in some patients with chronic obstructive pulmonary disease (COPD) and is associated with an increased mortality. As the nutritional state is a balance between energy and substrate intake and energy expenditure and substrate utilisation, any factor which alters this balance may have detrimental effects. Using standard methods of indirect calorimetry, previous studies have found an increased resting energy expenditure (REE) in patients with COPD. This has been attributed mainly to an increased cost of breathing, but several other factors have been suspected including drugs. Inhaled anticholinergic drugs are not known to induce a thermogenic effect, but in normal subjects oral theophylline and oral and inhaled β₂ adrenergic drugs increase REE. A similar thermogenic effect can be expected in patients with chronic airflow limitation. On the other hand, bronchodilating drugs may decrease the work of breathing by reducing airway obstruction, and thereby the REE. Thus, the net thermogenic effect of bronchodilators is unknown in COPD and may differ according to the type of pharmacological agent.

This study was undertaken to examine whether bronchodilators had a thermogenic effect in patients with stable COPD. To test this hypothesis we measured the effects on REE of three substances administered by nebulisation — a β₂ adrenergic bronchodilator (salbutamol), an anticholinergic bronchodilator (ipratropium bromide), and placebo.

Methods

Thirteen patients with stable COPD were studied at the end of a stay in the Pulmonary Rehabilitation Centre of the Rolle Hospital. Functional criteria for inclusion were defined as a ratio of forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC) of <70% of the predicted value and reversibility of <10% of predicted FEV₁ after inhalation of 400 mg salbutamol. All patients could tolerate withdrawal of bronchodilators for 16 hours and all were appraised at the time of the study. None of the patients had evidence of diabetes, cancer, digestive or renal disease. The protocol was approved by the ethical committee of our institution and all patients gave their written informed consent.

NUTRITIONAL STATUS

Each patient was weighed and measured at the beginning of the study. The body weight was expressed as percentage of ideal body weight (IBW), as defined by the mid point of the
weight range for height in the table of the Metropolitan Life Insurance Company.19 The body mass index (BMI) was calculated by dividing the body weight (kg) by the height squared (m²). Body fat content was estimated by measuring skinfold thickness at four sites – bicipital, tricipital, subscapular, and supra-iliac16 17 ± with a caliper (Lange Caliper, Cambridge Scientific Industries Inc, Cambridge, Massachusetts, USA). All measurements were made in triplicate by the same investigator. Fat-free mass (FFM) was calculated by subtracting the fat content from the body weight. The fat-free mass was also assessed by bioelectrical impedance analysis by measuring the whole body resistance (Z-mètre, Division Autonome d’Electronique Médicale CHUV, Lausanne, Switzerland) to a low alternating current passing between the right wrist and the right ankle.18 The impedance was measured in triplicate and the fat-free mass calculated using the equation of Schols et al.19

PULMONARY FUNCTION TESTS
Forced expiratory flow rates were measured by a mass flow anemometer (SensorMedics 2200 Pulmonary Function Laboratory, Sensor-Medics Corp, California, USA), and carbon monoxide transfer factor (TLco) by the single breath method (SensorMedics). Arterial blood gas tensions were measured by a blood gas analyser (AVL Blood Gas Analyser 995 S, AVL Medical AG, Schaffhausen, Switzerland). During the experimental sessions forced expiratory flow rates were measured by a pneumotachometer (Multispiro SA/100, Medical Equipment Design Inc, California, USA). Reference values were those proposed by Quanjer et al.20

ENERGY EXPENDITURE
REE was measured by indirect calorimetry with a transparent ventilated hood placed over the head of the patient. A constant fraction of the air flowing through the hood was collected for analysis in an indirect calorimetry device (Deltatrac, Datex Instrumentarium Corp., Helsinki, Finland). Oxygen concentration was measured by a paramagnetic oxygen sensor and carbon dioxide concentration by an infrared sensor. The energy expenditure (EE) was calculated from these values according to the method of Bursztein et al.21 The calorimetric measurements were continuously integrated over consecutive one minute intervals. The accuracy and precision of the calorimeter were assessed by an infusion test using nitrogen and carbon dioxide over a period of one hour and 48 minutes. The mean (SD) measured oxygen consumption was 100.6 (1.7)% of the actual value and measured carbon dioxide production was 101.3 (1.4)% of the actual value. The device was calibrated immediately before each measurement with a reference gas mixture.

HEART AND RESPIRATORY RATES
Heart rate was measured continuously during the test by a portable device (Baumann Construction Electronique Médicale, Fleurier, Switzerland) and the mean value was calculated in the last 10 minutes of each calorimetry period. The respiratory rate was counted by the attending physician looking at the patient’s respiratory movements during three periods of two minutes in each calorimetry period.

THEOPHYLLINE LEVELS
On the first day of the study the theophylline concentration was measured with a polarisation fluorescence system (TDx, Abott Laboratories, North Chicago, Illinois, USA) in the serum of patients who were treated with xanthine derivatives. Blood samples were taken in the morning at the predicted trough levels of theophylline.

EXPERIMENTAL PROTOCOL
The study was performed in three sessions on three consecutive mornings after an overnight fast. For the six patients taking xanthine drugs the dose was unchanged for at least three days before the study and during the study. All patients were requested to stop any oral β₂ adrenergic drugs for at least 10 hours before the study and during the study. All measurements were continuously integrated over consecutive one minute intervals. The mean (SD) measured oxygen consumption was 101.3 (1.4)% of the actual value. The device was calibrated immediately before each measurement with a reference gas mixture.
The time at the end of nebulisation was taken as T0. EE was then measured for three periods of at least 15 minutes, ending at 30, 60, 120, and 180 minutes after T0. Since it was not possible to ensure that the steady state period would end exactly on time, a maximal 10 minute delay was allowed. After each calorimetry period the hood was removed and spirometric tests were performed (T30, T60, T120, T180). Between periods of measurement the patients were allowed to sit on a chair next to the bed but without exerting themselves. They did not receive any other medication or food during the course of each morning of testing. In the afternoons and evenings they could eat normally, follow the rehabilitation programme, and take their usual treatment other than the drugs mentioned above.

The REE was expressed in kcal/24 hours and compared with predicted basal metabolic rate (BMR) according to Harris and Benedict. Each day the change in REE after the treatment was expressed as a percentage of the baseline value measured on the same day.

### Statistical Analysis

The mean baseline REE values during the three measurement sessions were compared by repeated measures ANOVA. Post-tests were then performed with a Bonferroni t test as described by Glantz. For each parameter (FEV1, REE, heart rate, respiratory rate) the effect of each treatment (salbutamol, ipratropium, placebo) was assessed by calculating the difference in mean response between ipratropium and placebo was divided by the duration of the study (180 minutes) to obtain the mean response as the summary measure. Differences between treatments were then compared using repeated measures ANOVA, followed by paired t tests to compare salbutamol and ipratropium with placebo. The relationship between the maximal change in REE after bronchodilator and the baseline REE was analysed by linear regression. The baseline REE was compared between patients receiving theophylline and those not receiving theophylline by a two-tailed unpaired t test. The increase in REE 60 minutes after salbutamol in patients receiving theophylline was compared with the increase measured in patients who did not receive theophylline by a two-tailed unpaired t test. Significance was determined at the 5% level. All reported values are means (SD).

### Results

#### Nutritional Status

Two patients were obese (body weight 148.5% and 158.0% of IBW) and two were underweight (85.6% and 89.0% of IBW). The mean weight of the remaining nine patients was 109.4% of IBW and their mean BMI was 24.4 kg/m² (table 1).

### Pulmonary Function Tests

The mean FEV1 was 39% predicted (range 24–76). Seven patients were emphysematous on the basis of a Tlco of <60% of predicted values. Four patients were hypoxaemic (Pao 2 ≤ 8 kPa or 60 mmHg) and three were hypercapnic (Paco 2 ≥ 6 kPa or 45 mmHg) (table 2).

| Table 1 Mean (SD) physical characteristics of the patients (n=13) |
|-----------------|----------------|
| M:F             | 10:3           |
| Age (years)     | 68.3 (7.3)     |
| Height (cm)     | 169 (10)       |
| Weight (kg)     | 72.8 (18.5)    |
| BMI (% of IBW)  | 113 (20)       |
| BMI (kg/m²)     | 25.2 (4.8)     |
| FFMSF (kg)      | 55.2 (15.9)    |
| FFMBIA (kg)     | 57.9 (11.9)    |

IBW = ideal body weight; BMI = body mass index; FFMSF = fat-free mass calculated by bioelectrical impedance analysis.

| Table 2 Mean (SD) results of pulmonary function tests (n=13) |
|-----------------|----------------|
| FEV1 (%)        | 103 (0.40)     |
| FEV1 (% predicted) | 39.6 (17.0)   |
| FEV1/FVC (% predicted) | 45.9 (13.1) |
| Tlco (%)        | 61.5 (17.6)    |
| Paco2 (kPa; mmHg) | 9.0 (1.3)    |
| Paco2 (kPa; mmHg) | 67.6 (9.5)    |
| Paco2 (kPa; mmHg) | 5.5 (0.4)     |
| Paco2 (kPa; mmHg) | 41.6 (3.3)    |

FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; Tlco = carbon monoxide transfer factor; Paco2 = arterial oxygen and carbon dioxide tensions. All measures made at 400 m above sea level.

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**Figure 1** Mean change in forced expiratory volume in one second (FEV1) after nebulisation (n=12). Bars = SE.
ENERGY EXPENDITURE
Before nebulisation the mean REE of the three sessions was 1456 (260) kcal/24 hours which represented 100.2 (4.9)% of the predicted value or 25.3 (1.9) kcal/24 hours/kg of FFM measured by bioelectrical impedance (fig 2). There was no difference between the baseline REE on placebo (1460 (265) kcal/24 hours), ipratropium (1453 (257) kcal/24 hours), or salbutamol (1456 (266) kcal/24 hours). However, the baseline REE was 3.5% higher in the first measurement session than in the last (p<0.01).

REE increased after salbutamol but there was no change after ipratropium. The difference in the mean response between salbutamol and placebo was +4.8% of baseline REE (95% CI +2.2 to +7.4 %; p<0.002). The difference in the mean response between ipratropium and placebo was −0.4% of the baseline REE (95% CI −2.3 to +1.5%; NS).

HEART AND RESPIRATORY RATES
The mean heart rate before nebulisation was 74.5 (14.9) beats/minute. This increased after salbutamol but no change occurred after ipratropium (fig 3). The difference in the mean response between salbutamol and placebo was +5.5 beats/min (95% CI +2.6 to +8.4; p<0.002). The difference in the mean response between ipratropium and placebo was −1.5 beats/min (95% CI −3.1 to 0.1; NS). Neither salbutamol nor ipratropium had any effect on respiratory rate. The difference in the mean response between salbutamol and placebo was −0.1 breaths/min (95% CI −1.4 to +1.1; NS). The difference in the mean response between ipratropium and placebo was 0.0 breaths/min (95% CI −0.7 to +0.8; NS).

THEOPHYLLINE LEVELS
The mean serum level of the six patients receiving theophylline was 50.2 (15.1) mmol/l (therapeutic range 45–110 mmol/l). This was not correlated with baseline REE which was 100.3 (5.8)% predicted in patients receiving theophylline and 100.0 (4.1)% in those not receiving theophylline (p>0.9). There was no difference in maximal REE after salbutamol (1456 (266) kcal/24 hours) which represented 100.2 (4.9)% of the predicted value or 25.3 (1.9) kcal/24 hours/kg of FFM measured by bioelectrical impedance (®g 2). There was no difference between the baseline REE on placebo (1460 (265) kcal/24 hours), ipratropium (1453 (257) kcal/24 hours), or salbutamol (1456 (266) kcal/24 hours). However, the baseline REE was 3.5% higher in the first measurement session than in the last (p<0.01).

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Discussion
Theoretically, bronchodilators could have two opposite effects on REE in patients with airway obstruction – firstly an increase in REE due to a direct thermogenic effect28 and secondly a decrease in REE due to diminished work of breathing because of bronchodilation.

Our results are consistent with a thermogenic effect of b2 adrenergic drugs. Compared with placebo, we found a maximal 7.3% increase in REE 30 minutes after the nebulisation of salbutamol (fig 2) which was sustained with the mean response between salbutamol and placebo was +4.8% of baseline REE (95% CI +2.2 to +7.4%; p<0.002). The difference in the mean response between ipratropium and placebo was −0.4% of the baseline REE (95% CI −2.3 to +1.5%; NS).

Drug tolerance has not been found with the chronic use of ipratropium,30 but it develops with chronic use of b agonists.31 All our patients were treated with salbutamol on a regular basis. For ethical reasons and in order to study these patients in their usual clinical condition, this
treatment was continued except for 10 hours before and during the measurement sessions. Despite this regular \( \beta_2 \) adrenergic treatment we were able to measure an increase in \( \text{REE} \) after salbutamol. This is in agreement with the study cited above\(^1\) in which an increase in \( \text{REE} \) in response to an infusion of isoprenaline was still present, although blunted, after two weeks of treatment with terbutaline. In patients with cystic fibrosis\(^2^\) nebulisation of salbutamol also increased \( \text{REE} \) in the subgroup chronically treated with \( \beta_2 \) agonists, but to a lesser extent than in those not receiving \( \beta_2 \) agonists. This contrasts with a study in normal subjects in which treatment with salbutamol for 13 days prevented an acute thermogenic effect occurring after inhalation of the drug.\(^3\) Because a certain degree of drug tolerance was likely to be present in our patients, the increase in \( \text{REE} \) measured after salbutamol could be expected to have been larger if they had not been receiving regular treatment with \( \beta_2 \) agonists or if we had interrupted this treatment earlier.

The relative increase in heart rate and in \( \text{REE} \) followed a similar time course (peak at 30 minutes) but was of a different magnitude (figs 2 and 3). This could be explained by two distinct effects of salbutamol – a chronotropic effect mediated by \( \beta_2 \) receptors of the heart and a thermogenic effect whose mechanism is not fully elucidated but which is likely to be related to skeletal muscle.\(^4\) The measured increase in heart rate is probably not clinically relevant, but it confirms a metabolic effect of salbutamol by a method independent of calorimetry. The fact that the heart rate increased despite chronic treatment with \( \beta_2 \) agonists argues against a dissociation between the downregulation of the thermogenic and cardiac effects of the drug.\(^5\)

In contrast, ipratropium bromide has no thermogenic effect and, as expected, we found no increase in energy expenditure after ipratropium.

We chose the doses of salbutamol and ipratropium according to the literature. In the three studies comparing the wet nebulisation of these drugs in COPD\(^2^ \) the degree of bronchodilation produced by 5 mg of salbutamol or 0.5 mg of ipratropium was equivalent. In our study both drugs induced bronchodilation but with a different time course (fig 1). This is not surprising since the pharmacokinetic properties of the two drugs differ. In view of the total absence of a thermogenic effect of ipratropium the different time course of bronchodilation is not likely to affect our results.

Theophylline causes an increase in \( \text{REE} \) in normal subjects.\(^6\) The dose of theophylline prescribed was unchanged three days before the study and during the study and we assumed that the plasma level of the drug was stable. Besides, theophylline does not modify the acute thermogenic response to inhaled salbutamol.\(^7\) No difference was found in the baseline \( \text{REE} \) or in the maximal increase in \( \text{REE} \) after salbutamol between the patients who received theophylline and those who did not.

\( \text{REE} \) of our patients was not increased. In some studies\(^8^\)-\(^10\) patients had received bronchodilators before the measurement of \( \text{REE} \), possibly leading to an overestimation of true basal metabolism. In addition, the reported baseline \( \text{REE} \) of our patients was calculated as the mean of the three sessions. \( \text{REE} \) was 3.5% higher in the first measurement session than in the last. Taking values from a single measurement session could therefore lead to a slight overestimate of the \( \text{REE} \). Finally, there is no evidence that the effects of the bronchodilators on \( \text{REE} \) would have been different with a higher baseline \( \text{REE} \). In our patients there was no correlation between the baseline \( \text{REE} \) and the maximal increase in \( \text{REE} \) after salbutamol. Furthermore, the baseline \( \text{REE} \) values during the measurement sessions with salbutamol, ipratropium, or placebo were the same.

The increase in \( \text{REE} \) measured in patients with COPD is particularly relevant in underweight patients because it has been cited as the main cause of their malnutrition.\(^10\) The mean weight of our patients was normal, but among them were two patients who were obese and two who were underweight. The effects of the bronchodilators on \( \text{FEV}_1 \), \( \text{REE} \), and heart rate were similar in the obese subgroup, the overweight subgroup, and in the remaining patients (data not shown). This suggests that the thermogenic effect of salbutamol is independent of nutritional status, although the small number of patients in each group does not allow one to draw definite conclusions.

Are our results clinically relevant? The increase in \( \text{REE} \) after the nebulisation of 5 mg salbutamol was maximal at 30 minutes but was sustained with a mean change of 4.8% over 180 minutes. Assuming that the patients take this high dose every six hours and that the mean increase in \( \text{REE} \) over this period is 3%, this excess in energy expenditure would represent about 16 000 kcal over a year, or the energy equivalent of 1.8 kg of fat. It should be noted, however, that the increase in \( \text{REE} \) due to bronchodilator treatment could be compensated by changes in other factors contributing to the total energy balance such as a decrease in activity induced energy expenditure or an increase in food intake. As the thermogenic effect of salbutamol is dose-dependent,\(^11\) a smaller dose would induce a lesser increase in \( \text{REE} \). In addition, it is difficult to compare the dose delivered by wet nebulisation with that by other methods of administration such as metered dose inhalers.

In conclusion, the nebulisation of salbutamol, but not ipratropium bromide, induced a sustained increase in the \( \text{REE} \) of patients with COPD treated with bronchodilators on a chronic basis. The observed thermogenic effect of \( \beta_2 \) agonists does not explain the hypermetabolism frequently present in COPD because hypermetabolism has also been reported after withdrawal of \( \beta_2 \) agonists. However, when added to other factors, it may further disrupt the energy balance.

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