Original articles

Acute effects of inhaled salbutamol on the metabolic rate of normal subjects

P Amoroso, S R Wilson, J Moxham, J Ponte

Abstract

***Background*—This study was designed to investigate the contribution of inhaled salbutamol to the increase in resting metabolic rate found in patients with chronic airflow limitation who were receiving bronchodilator therapy.**

***Methods*—The resting metabolic rate of 10 normal subjects (age 20-47 years, weight 42–105 kg, seven men) was studied after inhalations of salbutamol or placebo. An open canopy method of indirect calorimetry was used to measure resting oxygen consumption ($\dot{V}O_2$) and resting carbon dioxide production ($\dot{V}CO_2$). Subjects inhaled two, four, eight, or 12 puffs (100 μg/puff) of salbutamol or placebo in a double blind manner. Recordings of $\dot{V}O_2$ and $\dot{V}CO_2$ were made after inhalation of the four doses of salbutamol or placebo, integrated over one hour, and compared.**

***Results*—$\dot{V}O_2$ and $\dot{V}CO_2$ increased in a dose dependent manner after inhaled salbutamol with a maximum effect at five minutes after inhalation. After four puffs, $\dot{V}O_2$ was 203 and 188 ml/kg/h for salbutamol and placebo respectively. After eight puffs, $\dot{V}O_2$ was 207 and 185 and $\dot{V}CO_2$ was 167 and 155 ml/kg/h. After 12 puffs, $\dot{V}O_2$ was 220 and 190 with a $\dot{V}CO_2$ of 181 and 168 ml/kg/h. Twelve puffs of salbutamol increased the mean (SE) respiratory quotient from 0·85 (0·01) to 0·93 (0·04) at five minutes indicating an increase in ventilation in excess of metabolic demand. Mean heart rate increased in parallel with $\dot{V}O_2$.**

***Conclusion*—Inhaled salbutamol significantly increases resting metabolic rate in a dose dependent manner.**

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Previous studies have shown that patients with chronic airflow limitation have a raised resting oxygen consumption ($\dot{V}O_2$).[1] There are several possible explanations for this increase including greater respiratory muscle work. The effect of drug treatment cannot be discounted as all these patients were treated with β agonists, methyl xanthines, and corticosteroids. Adrenergic agonists such as adrenaline and dobutamine are known to increase resting metabolic rate when administered acutely,[2 3] but the effect of inhaled salbutamol in doses used clinically has not been reported. In this paper we report the acute metabolic response of normal subjects to a range of doses of inhaled salbutamol.

Methods

Ten healthy non-smoking volunteers (seven men) aged 20-47 years and weighing 42–105 kg were studied. All subjects were studied early in the morning, having fasted and abstained from caffeine for six hours. The study was approved by the hospital ethics committee and all subjects gave informed consent.

Resting $\dot{V}O_2$ and resting carbon dioxide production ($\dot{V}CO_2$) were measured by an open canopy technique with a mass spectrometer (Airspec Ltd) linked to a microcomputer. Subjects reclined on a comfortable couch in a clear plastic whole body chamber (600 l) from which air and expired gases were exhausted at a constant rate of between 85 and 110 l/min via a 5 l mixing box (fig 1). The flow of gases through the chamber was measured with argon as a tracer gas injected at an accurately measured rate (about 220 ml/min) into the inlet of the mixing box. The mass spectrometer continuously measured concentrations of O_2, CO_2, N_2, and argon at the outlet of the mixing box, except for one minute interruptions every 10 minutes when the concentration of these gases in room air was measured. During a run concentrations of O_2, CO_2, N_2, and argon were transferred every two seconds via an RS232 interface to a computer. Six consecutive values were averaged over 12 seconds and subtracted from the most recently measured (<10 minutes) room air values. The air chamber difference in argon concentration (about 0·3%) was used to calculate flow through the chamber which, when multiplied by the air chamber differences in O_2 and CO_2 (0·25–0·98%), gave $\dot{V}O_2$ and $\dot{V}CO_2$ respectively; from these the respiratory quotient (RQ) was calculated. The dilution effect of adding argon was taken into account in these calculations. Every 12 seconds, $\dot{V}O_2$, $\dot{V}CO_2$, and RQ were printed.

The mass spectrometer was calibrated daily (two points) with 100% nitrogen and a gas mixture containing precisely known concentrations of O_2 (15·63%), CO_2 (1·02%),

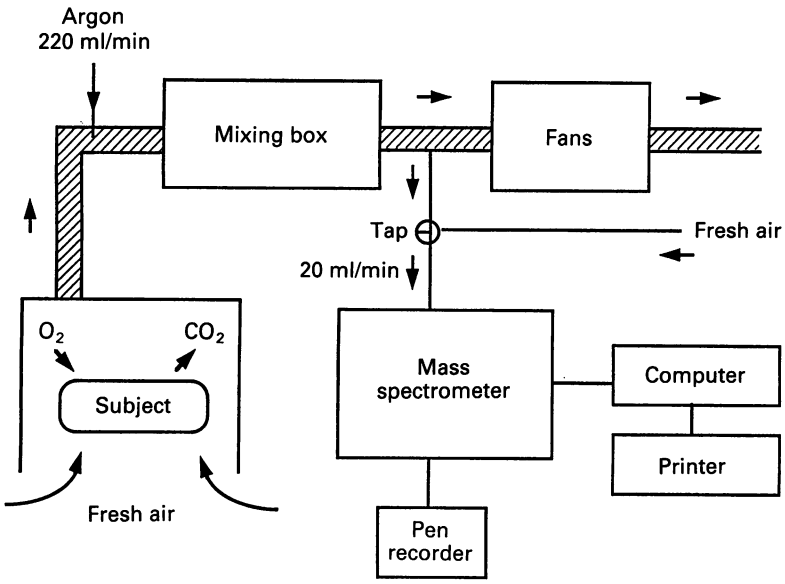

Figure 1 Indirect calorimetry system. Flow though the system (hatched) ranged between 85 and 110 l/min. The "tap" switching the mass spectrometer inlet between air and mixing box was replaced by a software operated solenoid valve. A combined temperature and humidity sensor was placed within the pipe between the mixing box and the fans.

argon (1·98%) and N_2 (81·37%). The whole system was then tested by burning methanol at a constant rate of 0·161 ml/min through a burner that ensured complete combustion. Measured $\dot{V}O_2$ and $\dot{V}CO_2$ were compared with the predicted values from the combustion equation for methanol ($\dot{V}O_2$ = 144·3 ml/min, $\dot{V}CO_2$ = 96·2 ml/min) and a correction factor was derived daily. The correction factor was applied to the results of the day when it exceeded 2% of the predicted values. These small corrections reduced the day to day variation of absolute values of $\dot{V}O_2$ and $\dot{V}CO_2$, but did not affect comparisons between baseline and postinhalation values taken on the same day.

All studies were of a double blind cross over design. Measurements began with the subject reclining comfortably on a couch listening to quiet music. After 30 minutes in the chamber 25 to 30 readings of $\dot{V}O_2$, $\dot{V}CO_2$, and RQ were averaged over five to six minutes. These preinhalation readings are defined in this study as baseline values. The subject then inhaled from an unmarked dispenser with a spacer device (Volumatic, Allen and Hanburys Ltd) to improve the delivery of the drug to the small airways and reduce the amount absorbed orally.[4] The inhaler delivered salbutamol (100 μg per puff) or placebo. Subjects were studied on eight separate days and received either two, four, eight, or 12 puffs of salbutamol or placebo in random order. Each inhalation was taken with a maximal slow inspiration held for two seconds and followed by two normal breaths before the next inhalation. Twelve inhalations took about three minutes to complete. One subject (42 kg) received half these doses and one other subject (65 kg) omitted 12 puffs because of lightheadedness occurring after eight puffs of salbutamol. Measurements of resting $\dot{V}O_2$, $\dot{V}CO_2$, and RQ were made continuously for one hour after inhalation and 10 consecutive readings (two minutes) were averaged starting at five, 15, 30, and 60 minutes. The electrocardiogram (Datascope) and blood pressure (Accutorr) were monitored every five minutes throughout each experiment. The subject's age, height, weight, and sex were entered into the computer, as were the day's barometric pressure, and room and chamber temperature and humidity.

Subjects were observed by the experimenter after inhalations for the presence of tremors of the fingers. They were also asked at the end of the experiment and throughout the day for subjective feelings.

Table 1 Mean (SE) values for $\dot{V}O_2$ integrated over one hour (ml/kg/h) after inhalation of salbutamol or placebo by 10 subjects (nine for 12 puffs)

	No of puffs			
	2	*4*	*8*	*12*
Placebo	186(7·89)	188(7·87)	185(6·42)	190 (7·03)
Salbutamol	193(5·13)	203(9·56)	207(7·03)	220 (6·65)
p value	NS	<0·02	<0·005	<0·005

TEST OF THE METHOD

The mean (SE) of 10 measurements (10 readings over two minutes) of $\dot{V}O_2$ and $\dot{V}CO_2$, taken on different days during the burning of 0·161 ml/min of methanol, were 143·8 (2·9) and 100·8 (3·2) ml/min respectively, compared with predicted values of 144·3 and 96·2 ml/min. The daily correction factor derived from methanol burning was applied to 41 of a total of 78 measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ in the 10 subjects.

ANALYSIS OF DATA

Subjects acted as their own controls. In each test, values for $\dot{V}O_2$ and $\dot{V}CO_2$ were obtained at five, 15, 30, and 60 minutes after inhalation and the area under the curve was calculated giving results in ml/kg/h. Comparisons for $\dot{V}O_2$ and $\dot{V}CO_2$ were made between salbutamol and placebo at each dose. There were 10 subjects for all the tests except for the 12 puffs, when there were nine. The RQ was expressed in absolute values. The frequency distribution of 80 $\dot{V}O_2$ and $\dot{V}CO_2$ baseline measurements showed a normal distribution and therefore statistical analysis was performed with Student's paired *t* test. Heart rate and blood pressure were compared with the same method as that used for $\dot{V}O_2$.

Results

The pattern of the responses to inhalations was similar between subjects with maximal changes occurring five to 15 minutes after inhalation.

Inhalation of salbutamol gave significant increases in $\dot{V}O_2$ and $\dot{V}CO_2$ (integrated over one hour after inhalation) compared with placebo (tables 1 and 2). Figures 2 and 3 show the time course of the effects of salbutamol and placebo. The maximal transient increases in $\dot{V}O_2$ and $\dot{V}CO_2$ were about 20% above baseline

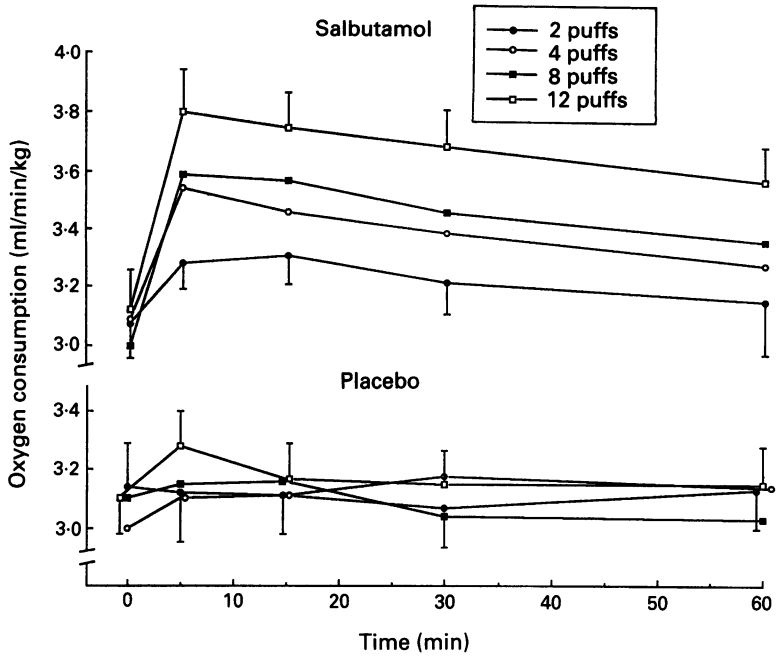

Figure 2 Time course of the changes in $\dot{V}O_2$ after the inhalation of two to eight puffs of salbutamol or placebo in 10 subjects and 12 puffs in nine subjects. Bars = SE.

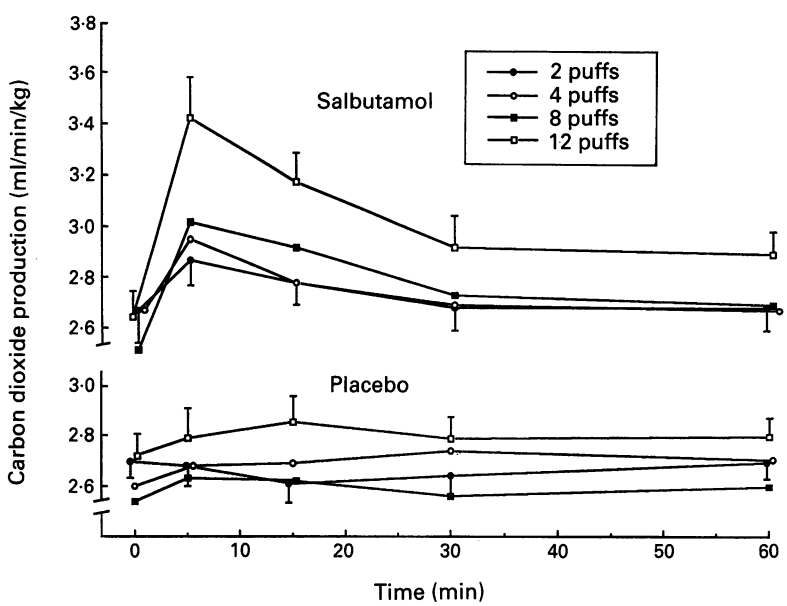

Figure 3 Time course of the changes in $\dot{V}CO_2$ after the inhalation of two to eight puffs of salbutamol or placebo in 10 subjects and 12 puffs in nine subjects. Bars = SE.

and were found five minutes after inhalation of 12 puffs of salbutamol. Most placebo inhalations caused negligible transient effects on $\dot{V}O_2$ and $\dot{V}CO_2$; only 12 puffs caused a small increase (figs 2 and 3).

The RQ changed after 12 puffs of salbutamol only. A large increase occurred at five minutes after inhalation followed by a slight fall below baseline at 30 and 60 minutes (fig 4).

The changes in heart rate followed the pattern of changes in $\dot{V}O_2$ after inhalations of salbutamol and placebo (fig 5). Table 3 shows the comparison between salbutamol and placebo for the results integrated over one hour after inhalation. Mean blood pressure fell slightly and transiently only after the highest dose of salbutamol and the change was not significant when compared with placebo. During the measurements there was no visible or objective tremor, but some subjects reported a fine tremor and a feeling of agitation starting two to three hours after the experiment, when they resumed normal activity.

Table 2 Mean (SE) values for $\dot{V}CO_2$ integrated over one hour (ml/kg/h) after inhalation of salbutamol or placebo in 10 subjects (nine for 12 puffs)

	No of puffs			
	2	4	8	12
Placebo	159 (4·63)	162 (5·21)	155 (5·42)	168 (5·76)
Salbutamol	164 (5·34)	164 (6·80)	167 (5·44)	181 (6·34)
p value	NS	NS	<0·02	<0·005

Table 3 Mean (SE) values for heart rate (beats/min) averaged over one hour after inhalation of salbutamol or placebo in 10 subjects (nine for 12 puffs)

	No of puffs			
	2	4	8	12
Placebo	61·6(0·32)	59·9(0·35)	61·4 (0·45)	59·1(5·76)
Salbutamol	62·1(0·41)	64·2(0·37)	70·0(0·48)	75·2(6·34)
p value	NS	<0·05	< 0·001	<0·001

Discussion

Our results clearly show that inhaled salbutamol increases resting energy expenditure in a dose dependent manner. The standard therapeutic dose of two puffs of salbutamol caused only a small increase in $\dot{V}O_2$, which did not reach significance. Eight puffs, however, produced a clear and rapid effect on $\dot{V}O_2$ and $\dot{V}CO_2$ comparable with an intravenous infusion of 50 ng/kg/min adrenaline.[2]

Recent guidelines of the British Thoracic Society[5] suggest that in severe acute bronchospasm patients may be given up to 5 mg (50 puffs) of inhaled salbutamol. Transient increases in $\dot{V}O_2$ and $\dot{V}CO_2$ in excess of 25% could occur at these high dosages.

The increases in $\dot{V}O_2$ and $\dot{V}CO_2$ after placebo were very small and rule out an important placebo component in the $\dot{V}O_2$ and $\dot{V}CO_2$ changes after salbutamol. It was not surprising to find a placebo effect at five to 15 minutes after 12 puffs because of the apprehension experienced by the subjects inhaling such a high dose. As well as the effect of apprehension, the increased work of breathing associated with 12 near maximal inspirations may have had an effect lasting more than five minutes.

The results do not necessarily imply that chronic six hourly inhalation of two to four puffs of salbutamol will always increase $\dot{V}O_2$ and $\dot{V}CO_2$, as there may be tachyphylaxis as previously found with terbutaline.[6] The effects of prolonged inhalation of salbutamol are reported in an accompanying paper.[7]

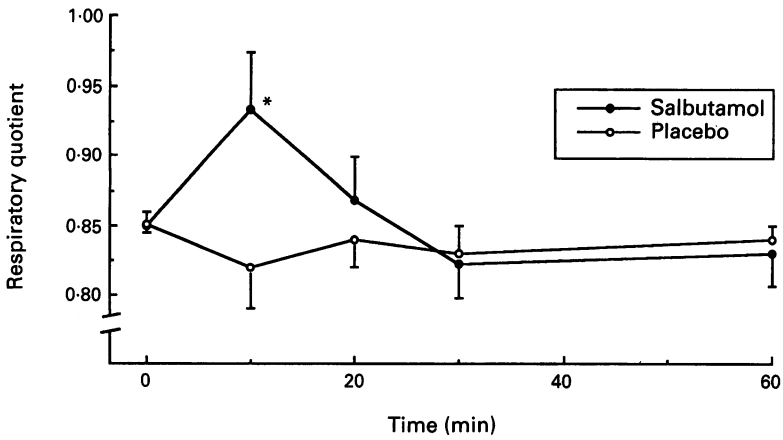

Figure 4 Time course of the changes in respiratory quotient (RQ) during 60 minutes after inhalation of 12 puffs of salbutamol or placebo in nine subjects. Bars = SE; comparisons between salbutamol and placebo were made at the four time intervals. The difference was only significant at five minutes ($p = <0·01$ uncorrected and $<0·05$ applying the Fisher-Bonferroni correction for multiple comparisons).

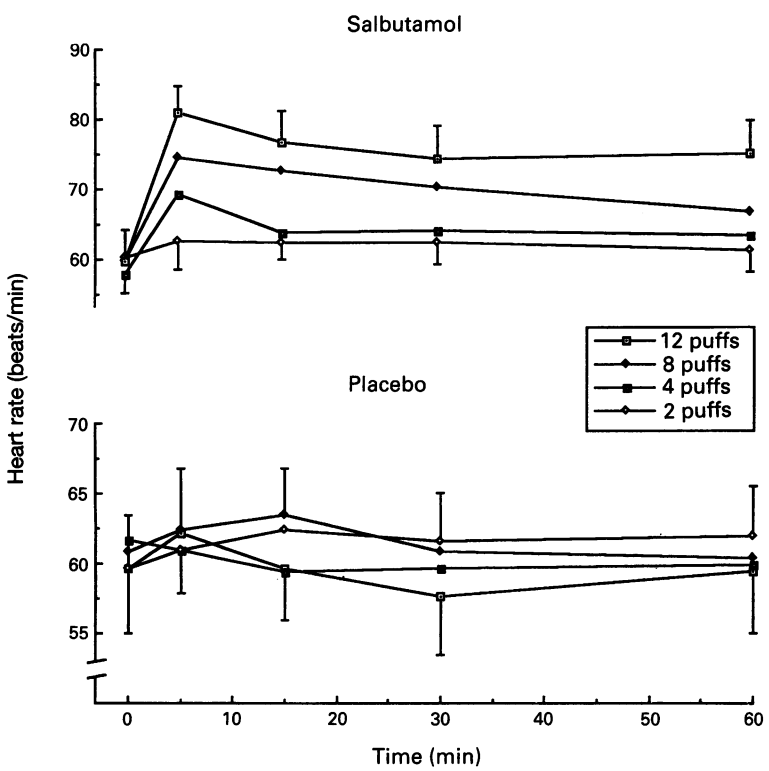

Figure 5 Time course of the changes in heart rate after the inhalation of two to eight puffs of salbutamol or placebo in 10 subjects and 12 puffs in nine subjects. Bars = SE.

There is a recent trend away from the regular use of β_2 agonists for the treatment of asthma in favour of their acute, intermittent, use solely for symptomatic relief,[8] which gives the results of this study a practical application, especially if large doses of salbutamol are used. In another context, the large potential increases in $\dot{V}CO_2$ should also be taken into account when salbutamol is nebulised during intermittent positive pressure ventilation in the intensive care unit.

Several mechanisms may account for the increase in $\dot{V}O_2$ and $\dot{V}CO_2$ with salbutamol in our study. There may have been increased muscular activity in the form of raised muscle tone or undetected tremor, although none of the subjects reported tremor and it was not objectively seen during measurements. The data clearly suggest that cardiac work was increased as indicated by the changes in heart rate, which probably contributed to the rapid increase in $\dot{V}O_2$. Finally, β agonists have a direct thermogenic effect, possibly mediated via a distinct population of receptors (β_3) described in brown fat and skeletal muscle.[9] Because little is known about the time course of these specific β_3 effects in humans, we cannot be certain of the contribution of such mechanisms to the rapid changes in $\dot{V}O_2$ and $\dot{V}CO_2$ in our experiments.

One interesting finding in this study was the change in RQ that occurred with the highest dose of salbutamol. The initial increase from 0·85 to 0·93 (fig 3) and subsequent fall to below the baseline indicates that salbutamol increased minute ventilation in excess of the increased $\dot{V}CO_2$. This suggests that respiratory drive may have been transiently increased by salbutamol at the highest dose as previously shown for intravenous delivery.[10] Possible mechanisms for such an increase include direct stimulation of the medullary respiratory neurones or an effect on the peripheral chemoreceptors as previously reported for isoprenaline in animal studies.[11]

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