Eur Respir J, 1994, 7, 1978–1984
DOI: 10.1183/09031936.94.07111978
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European Respiratory Journal
ISSN 0903 - 1936

Does single dose salmeterol affect exercise capacity in asthmatic men?

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Does single dose salmeterol affect exercise capacity in asthmatic men? W. Robertson, J. Simkins, S.P. O'Hickey, S. Freeman, R.M. Cayton. ©ERS Journals Ltd 1994.

ABSTRACT: The aim of this study was to investigate whether the long-acting beta-agonist salmeterol affects athletic performance in patients with asthma.

The effect of 50 µg salmeterol on the cardiorespiratory responses to a progressive maximal cycle exercise test and on endurance capacity (defined as the exercise duration at 70% maximum oxygen uptake), was compared with 200 µg salbutamol and a matched placebo in eight asthmatic men.

Both salmeterol and salbutamol improved pre- and postexercise forced expiratory volume in one second (FEV_1) for maximal and endurance exercise. Following active treatment, patients exercised from a significantly high baseline FEV_1, with both salmeterol (3.58(1.16) *l*) (mean (SD)) and salbutamol (3.55(1.24) *l*) compared with placebo (3.29(1.35) *l*). Similar improvements preceded endurance exercise. Cardiorespiratory, haemodynamic or subjective responses to the progressive maximum exercise tests were not different with salmeterol, salbutamol or placebo, nor did endurance capacity change with any treatment modality. Blood lactate levels, after 15 min exercise, were significantly higher with salbutamol (3.64 (1.83) mM), but not with salmeterol (3.03 (1.64) mM), compared with placebo (2.95 (1.69) mM).

These results demonstrate the absence of significant cardiorespiratory or metabolic effects during exercise after a single dose of salmeterol, together with a lack of ergogenic effect, as measured by maximal or endurance exercise performance, in patients with asthma.

Eur Respir J., 1994, 7, 1978–1984.

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Keywords: Asthma
exercise
salmeterol
salbutamol

Received: September 7 1993
Accepted after revision July 19 1994

Salmeterol has been shown to be effective in preventing exercise-induced asthma (EIA) for up to 12 h [1, 2], and may, thus, play an important role in controlling EIA. However, for an anti-asthma drug to be permitted for use in high performance sport it must only minimize the effect of the asthma and EIA and not otherwise augment athletic performance [3]. Salmeterol is not currently permitted for use by asthmatics in international sport [4]. The effect of this drug on exercise capacity, apart from its effect in exercise-induced asthma, has not been evaluated either in an asthmatic or a nonasthmatic group, and thus merits attention.

We have previously examined the effect of nebulized salbutamol on the cardiorespiratory, subjective and metabolic responses, in asthmatic and nonasthmatic men during maximum exercise performance [5], on submaximal exercise akin to aerobic exercise [6], and on endurance exercise capacity [7]. This showed no effect of 5 mg nebulized salbutamol on endurance capacity in asthma. However, the same dose of salbutamol reduced endurance in normal subjects [7].

The present study compares the maximum exercise capacity and the endurance capacity at 70% maximum oxygen uptake ($\dot{V}O_2$ max) on a cycle ergometer with the pre-exercise administration of 50 µg salmeterol, 200 µg salbutamol and a matched placebo given by dry powder inhaler, in asthmatic men.

Methods

Subjects

Eight nonsmoking, asthmatic men, each participating in regular physical activity (though not elite athletes), who had previously been shown to have a documented 20% or more increase in the forced expiratory volume in one second (FEV_1) either spontaneously or with treatment, were investigated (table 1). The subjects were aged 21–49 yrs (mean 33 yrs). Mean (SD) height was 1.73 (0.07) m, and weight 75 (15) kg. They were all taking inhaled β_2-agonists (seven salbutamol, one terbutaline), with five taking them as required and the other three regularly. All patients were receiving regular inhaled corticosteroids (seven beclomethasone dipropionate, one budesonide). Treatment had been unchanged for at least four weeks. Subjects gave informed consent, and the protocol was approved by the Hospital Ethics Committee.

Protocol overview

The study involved a double-blind, cross-over comparison of the pre-exercise administration of 50 µg salmeterol, 200 µg salbutamol and a matched placebo on progressive maximal exercise tests and on endurance exercise capacity at 70% maximal oxygen consumption ($\dot{V}O_2$max). Each patient initially performed maximum and endurance tests without treatment modification to allow familiarization with the equipment and protocols. All exercise tests were performed on an electromagnetically braked cycle ergometer (Rodby Elektronik 820, Sweden). Treatments were delivered by dry powder disk-inhalers 30 min before exercise, with the order of treatment determined by a balanced randomization code. The tests were performed a week apart and at the same time of day. $Beta_2$-agonists and disodium cromoglycate were withdrawn 6 and 24 h before the tests, respectively; inhaled steroids were continued.

Maximum tests

The progressive maximum exercise tests started from a workload (WL) of 50 W, increasing by 20 W each minute until exhaustion. Using the computerized exercise testing system (Magna 88, P.K. Morgan, Rainham, Kent, UK) described previously [5], the expired minute ventilation ($\dot{V}E$), breathing frequency (fR),oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and heart rate (HR) were measured at rest (pre- and post-inhaler), at 5 s intervals throughout the progressive maximal exercise test, and after 10 min of recovery. The respiratory exchange ratio ($\dot{V}CO_2$ /$\dot{V}O_2$), ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$), tidal volume (VT) and oxygen pulse ($\dot{V}O_2$/HR) were derived. To obtain the maximum response to exercise, the highest consecutive readings for $\dot{V}O_2$ over 60 s were averaged ($\dot{V}O_2$max) and the mean values for the coincident physiological measurements obtained. The $\dot{V}O_2$max, maximum workload (W), and maximum heart rate (HRmax) were expressed as a percentage of normal, and the maximum expired ventilation ($\dot{V}E$max) compared with maximum voluntary ventilation (MVV) [8].

Blood pressure was measured using an automatic monitor (Infrasonde D4000, Puritan Bennett) and the perceived ratings of breathlessness and exertion were obtained using a modified Borg scale from 0 to 10 [9, 10] at rest (pre- and post-inhaler), at 2 min intervals during exercise, at the end of the maximal test, after 10 min of recovery.

Endurance tests

The endurance capacity tests involved cycling for as long as possible at a workload calculated to elicit 70% of the average $\dot{V}O_2$max from the three progressive maximal exercise tests. In order to calculate the workload equivalent to 70% $\dot{V}O_2$max, a submaximal cycle exercise test for 4 min, at steady-state for each of three workloads (30, 45 and 60% of the maximum workload) was completed without treatment modification, which allowed calculation of the regression equation between workload and oxygen uptake. A "familiarization" endurance test was performed without treatment modification or blood sampling.

Due to the potential influence of diet and previous exercise on endurance capacity, subjects were asked to keep their food intake and activity levels similar for the 3 days before each test.

For each of the three endurance tests, subjects arrived at the laboratory in a fasted state, not having had food or drink (apart from water) for 3 h before each test. An intravenous cannula (Venflon, Viggo, Sweden) 17 G was inserted in a vein at the ante-cubital fossa, and then the subject rested for 10 min. A series of measurements was made at rest, after which the treatment was administered. Thirty minutes after treatment, the resting measurements were repeated, and then exercise commenced. Subjects were instructed to exercise for as long as possible on the cycle ergometer, and they were not reminded of their previous exercise times.

Cardiorespiratory measurements, blood pressure and the perceived ratings of exertion and breathlessness were made at rest (before and after the inhaler), at 15 min intervals during exercise, at the end of exercise, and after 10 min of recovery. At the same times, the respiratory duty cycle was recorded on a strip chart recorder *via* a thermistor inserted into the Hans Rudolph respiratory valve (Hans Rudolph, Kansas, USA), detecting increases in temperature on expiration and decreases in temperature on inspiration. The mean inspiratory time (TI) and mean expiratory time (TE) were divided "by eye" by a single trained observer. This allowed the time for inspiration (TI) and the total breath time ($TTOT$) to be measured for each breath, and the inspiratory flow rate to be calculated (VT/TI).

Venous blood samples (10 ml) were taken without venestasis at rest (pre- and post-inhaler); every 15 min in exercise; at the end of exercise; and after 10 min of recovery. Measurements of haemoglobin, platelets and white cell count by a Coulter S plus (Coultronics, Margency, France), serum potassium and plasma glucose were made by standard methods. In addition, two 20 µl blood samples were deproteinized in 200 µl of 2.5% perchloric acid, and then frozen at -20°C for later analysis for blood lactate, using the methods of MAUGHAN [11] modified from OLSEN [12]. Haematocrit was measured using a microhaematocrit centrifuge. The percentage change in the plasma volume was calculated from the haemoglobin and haematocrit at rest and at the end of exercise [13]. In addition, water was available throughout each test. Body weight was measured before and after each test.

For both the maximum and endurance tests, the FEV_1 was measured with a spirometer (Vitalograph, Bucks, UK) at rest (pre- and post-inhaler) and at 1, 3, 5, 7, 10, 15, 20, 25 and 30 min after exercise. Measurements were compared with predicted normal values [14]. The percentage change in the resting FEV_1 after each treatment was calculated. The lowest FEV_1 after exercise was expressed as a percentage change from rest (post-inhaler) [15].

Table 1. – Forced expiratory volume in one second (FEV_1) at rest, before and after treatment, and after the maximal exercise test

Pat. No.	Age yrs	Placebo						Salmeterol						Salbutamol					
		Pre-exercise FEV_1			Post-exercise FEV_1			Pre-exercise FEV_1			Post-exercise FEV_1			Pre-exercise FEV_1			Post-exercise FEV_1		
		Pre-treat		Post-treat		Lowest		Pre-treat		Post-treat		Lowest		Pre-treat		Post-treat		Lowest	
		l	% pred	*l*	% Change	*l*	% Fall	*l*	% pred	*l*	% Change	*l*	% Fall	*l*	% pred	*l*	% Change	*l*	% Fall
1	43	3.85	118	3.70	-4	3.14	-15	3.75	115	4.01	7	4.04	1	3.60	110	4.02	12	4.11	2
2	49	1.29	36	1.27	-2	0.95	-25	1.34	38	1.67	25	1.42	-15	1.33	37	1.65	24	1.43	-13
3	22	3.85	85	4.25	10	3.73	-12	3.85	85	4.29	11	4.05	-6	3.73	82	4.30	15	4.18	-3
4	43	3.37	95	3.47	3	3.10	-11	3.03	86	3.45	14	3.37	-2	3.23	92	3.31	2	3.10	-6
5	21	3.97	88	4.10	3	3.74	-9	4.01	89	4.30	7	4.33	0	3.77	83	4.62	23	4.29	-7
6	24	4.02	99	4.06	1	4.03	-1	4.00	99	4.47	12	4.23	-5	4.17	103	4.43	6	4.26	-4
7	28	4.38	96	4.39	0	4.27	-4	4.14	91	4.55	10	4.48	-2	4.00	88	4.44	11	4.44	0
8	30	1.13	29	1.05	-7	1.10	-4	1.47	38	1.90	29	1.94	2	1.19	30	1.63	37	1.66	2
Mean	33	3.23	81	3.29	1	2.99	-10	3.20	80	3.58**	14**	3.48***	-3**	3.13	78	3.55*	16**	3.43***	-4
±SD	11	1.28	31	1.35	5	1.30	8	1.16	28	1.16	8	1.17	5	1.19	29	1.24	11	1.24	5

The % fall after exercise is calculated from the resting FEV_1 recorded after treatment. FEV_1: forced expiratory volume in one second; Pat. patient; % pred: percentage of predicted value. Significant difference from placebo; *: p<0.05; **: p<0.02; ***: p<0.01.

Statistics

Statistical analyses compared responses after salmeterol, salbutamol and placebo. The physiological measurements at rest, at maximum exercise, at 15 min and at the end of exercise for the endurance capacity test, and after 10 min of recovery were compared by repeated measures analysis of variance, with treatment as a factor. Where statistical differences were observed, a paired t-test was used to find the pair(s) of treatments where differences existed. Two-tailed analyses were used throughout, and probability value less than 0.05 was considered significant. Data are expressed as means and standard deviations (SD).

Results

Maximum exercise capacity

The FEV_1 values at rest, pre and post treatment, and after the maximal exercise test for each asthmatic patient are shown in table 1. Although the mean % predicted FEV_1 for the study group is within the normal range, the change in FEV_1 varies between 1–25% fall post-exercise during placebo treatment. There was significant bronchodilation at rest both after salmeterol (FEV_1 3.58 (1.16) *l* p<0.02), and salbutamol (FEV_1 3.55 (1.24) *l*; p<0.05), compared with placebo (FEV_1 3.29 (1.35) *l*). The lowest FEV_1 after maximal exercise was significantly higher after salmeterol (3.48(1.17) *l*), and salbutamol (3.43(1.24) *l*) then after placebo (2.99(1.30) *l*); p<0.01. The percentage fall in FEV_1 after exercise was significantly lower after salmeterol (p<0.02) and salbutamol (p<0.05) than after placebo. There were no significant differences between the active treatments.

The effects of salmeterol and salbutamol on the maximal exercise performance, the maximum physiological response to exercise and the perceived ratings of exertion and breathlessness are summarized in tables 2 and 3. Despite the improved FEV_1, there were no significant differences in any of the group means for these parameters for either drug. However, individual data for patients No. 2 and 8 are worthy of note. These patients both had an initial FEV_1 <60% predicted and a >20% improvement in FEV_1 following the active treatment (table 1). Despite this improvement in airflow, $\dot{V}_E max$ and $\dot{V}_{O_2} max$ were unchanged with active medication compared with placebo.

Endurance exercise capacity

For the endurance test, the FEV_1 was higher with salmeterol (3.60(1.19) *l*) and salbutamol (3.59(1.15) *l*) than with placebo (3.19(1.11) *l*) (p<0.01) at rest; and after exercise (3.49(1.21) *l*, 3.48(1.21) *l*, 2.97(1.41) *l*) (p<0.01), respectively. But the % fall in FEV_1 after exercise was not significantly different (F=3.24; p=0.07).

Table 2. – Maximal physiological response to exercise with salmeterol (salm), salbutamol (salb) and placebo

	WLmax W				$\dot{V}O_2$max $l \cdot min^{-1}$				HRmax beats·min^{-1}				$\dot{V}E$max $l \cdot min^{-1}$			
	placebo		salm	salb	placebo		salm	salb	placebo		salm	salb	placebo		salm	salb
Pat No.	% pred				% pred				% pred				% pred MVV			
1	170	112	170	190	1.93	102	2.03	2.04	158	87	162	169	79.0	65	83.6	96.9
2	190	97	210	210	2.34	92	2.42	2.44	146	82	150	152	61.3	101	67.6	69.3
3	250	93	290	290	3.16	80	3.47	3.52	172	88	175	183	81.4	60	89.9	93.6
4	210	115	190	210	2.47	104	2.05	2.43	147	81	146	147	83.6	72	59.3	74.5
5	290	108	290	290	3.28	86	3.25	3.21	221	113	215	214	116.8	89	110.0	107.9
6	130	63	110	130	1.54	57	1.36	1.44	141	73	144	157	44.6	34	39.3	50.4
7	250	93	290	270	3.14	83	3.54	3.36	186	97	191	187	101.2	73	109.7	107.9
8	170	85	190	190	2.01	75	2.02	2.01	178	93	181	181	58.0	105	62.9	62.7
Mean	208	96	218	223	2.48	85	2.52	2.55	169	89	171	174	78.2	75	77.8	82.9
SD	53	17	67	57	0.65	15	0.80	0.74	27	12	25	22	23.6	23	25.0	21.7

WLmax: maximum workload; $\dot{V}O_2$max: maximum oxygen uptake; HR max: maximum heart rate; $\dot{V}E$max: maximum minute ventilation; % pred MVV: percentage of predicted maximum voluntary ventilation; % pred: percentage of predicted normal value; Pat: patient.

Table 3. – Additional physiological responses to maximum exercise and the perceived ratings of exertion and breathlessness at the end of exercise after the pre-exercise administration of placebo, salmeterol and salbutamol

	placebo	salmeterol	salbutamol
Breathing frequency breaths·min^{-1}	31.2 (4.8)	28.9 (3.6)	30.8 (2.8)
Tidal volume l	2.52 (0.73)	2.66 (0.72)	2.71 (0.76)
Respiratory exchange ratio $\dot{V}CO_2/\dot{V}O_2$	1.11 (0.11)	1.10 (0.08)	1.14 (0.10)
Oxygen pulse ml·beat^{-1}	14.7 (2.8)	14.6 (3.6)	14.6 (3.5)
Ventilatory equivalent for oxygen $\dot{V}E/\dot{V}O_2$	31.6 (5.2)	31.1 (4.7)	33.2 (6.4)
Systolic blood pressure mmHg	187 (25)	184 (28)	188 (37)
Diastolic blood pressure mmHg	82 (25)	96 (26)	90 (28)
Perceived exertion Borg rating	8.5 (1.4)	7.4 (2.4)	7.9 (2.3)
Perceived breathlessness Borg rating	6.1 (2.8)	5.5 (2.2)	6.4 (1.5)

Data are presented as mean and SD in parenthesis. $\dot{V}CO_2$: carbon dioxide production; $\dot{V}O_2$: oxygen uptake; $\dot{V}E$: minute ventilation.

Table 4. – Workload, oxygen uptake ($\dot{V}O_2$) and endurance time for the endurance test after placebo, salmeterol and salbutamol

	Workload	$\dot{V}O_2$ 15 min exercise		Endurance time min		
Pat No.	W	$l \cdot min^{-1}$	% max	placebo	salmeterol	salbutamol
1	85	1.31	65.6	40.0	35.0	60.0
2	110	1.64	68.3	75.0	90.0	90.0
3	170	2.29	67.7	22.3	26.2	27.9
4	120	1.72	74.1	90.0	60.0	60.2
5	140	2.25	69.1	60.0	60.1	45.0
6*	65	1.06	72.9	12.6	15.0	30.0
7	142	2.14	63.9	45.0	47.3	60.0
8	90	1.42	70.7	45.1	50.9	55.8
Mean	115	1.73	69.0	48.8	48.1	53.6
SD	35	0.46	3.5	25.7	23.3	19.8

*: see text regarding exercise time.

Table 4 gives the workload, the average oxygen uptake, (after 15 min exercise), and the percent of $\dot{V}O_2$max at 15 min exercise, along with the duration of exercise with each treatment for each subject. The 15 min time-point for endurance capacity analysis was not achieved by subject No. 6, who exercised for 12.6 min after placebo; in all other respects his data sets were comparable and the physiological measurements taken at this time-point were used in the 15 min and in the end of exercise analyses. Endurance times were not different between treatments, despite the higher mean FEV_1.

Mean heart rate (beats·min^{-1}) (fig. 1) was significantly lower after, but not before treatment with salmeterol (70 (9) beats·min^{-1}) compared with salbutamol (78(12) beats·min^{-1}) at rest ($p<0.05$). Similarly, mean heart rate at 15 min exercise and at the end of exercise, was significantly lower after salmeterol than after both salbutamol and placebo, (130 (24), 136 (25) and 136 (22) beats·min^{-1})

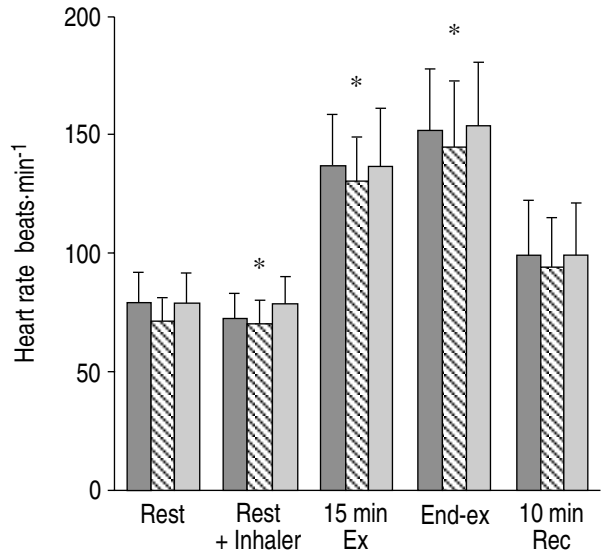

Fig. 1. – Heart rate before, during and after endurance exercise test, following treatment with placebo, salmeterol and salbutamol. Data are presented as mean and SD. Ex: exercise; Rec: recovery. : placebo; : salmeterol; : salbutamol. *: $p<0.05$, significant difference from placebo and salbutamol.

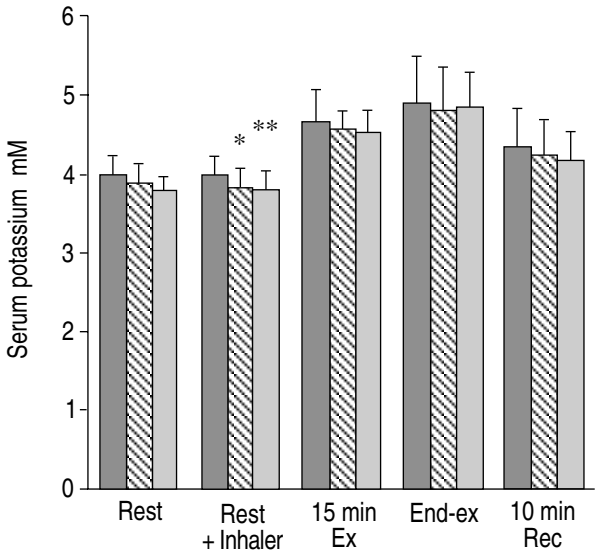

Fig. 3. – Serum potassium before, during and after endurance exercise test following treatment with placebo, salmeterol and salbutamol. Data are presented as mean and SD. Ex: exercise; Rec: recovery. : placebo; : salmeterol; : salbutamol. *: $p<0.05$; **: $p<0.001$, significant difference from placebo.

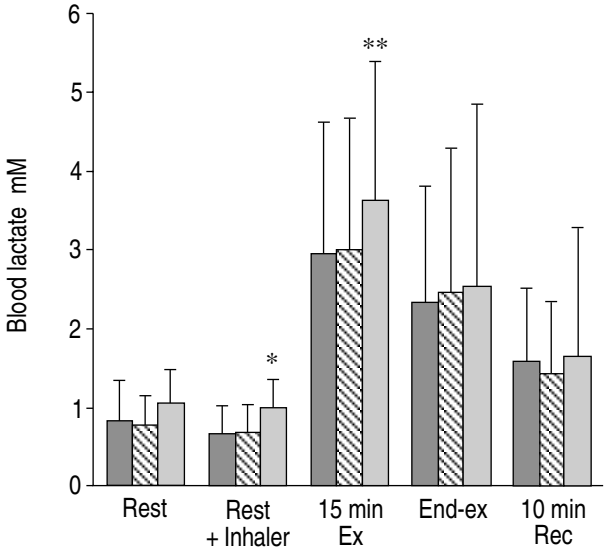

Fig. 2. – Blood lactate before, during and after endurance exercise test, following treatment with placebo, salmeterol and salbutamol. Data are presented as mean and SD. Ex: exercise; Rec: recovery. : placebo; : salmeterol; : salbutamol. *: $p<0.05$; **: $p<0.001$, significant difference from placebo.

and (144 (29), 153 (28) and 151 (26) beats·min^{-1}), respectively ($p<0.05$). Furthermore, the oxygen pulse was significantly higher at the end of exercise with salmeterol (12.5 (2.7) beats·min^{-1}) than with placebo (11.9 (2.8) ml·beat^{-1}; $p<0.001$) and salbutamol (12.0 (2.8) ml·beat^{-1}; $p<0.01$). All other cardiorespiratory measurements, including $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}CO_2/\dot{V}O_2$, $\dot{V}E$, $\dot{V}E/\dot{V}O_2$, fR, VT, systolic and diastolic blood pressure, TI, Ttot, and inspiratory flow rate, were not statistically different between treatments at rest, in exercise or in recovery.

Blood lactate (fig. 2) was significantly higher at rest after treatment with salbutamol, 0.98 (0.37) mM, than with placebo (0.66 (0.38) mM; $p<0.02$) or salmeterol, (0.67 (0.38) mM; $p<0.05$), and higher at 15 min exercise after salbutamol (3.64 (1.83) mM), than with placebo (2.95 (1.69) mM; $p<0.001$). There were no other statistical differences in the blood lactate between treatments. Although, for each time-point there was no statistically significant differences in $\dot{V}CO_2/\dot{V}O_2$ between treatments, there was a trend to lower values at the end of exercise.

Serum potassium (fig. 3) was significantly lower at rest after treatment both with salbutamol ($p<0.001$) and salmeterol ($p<0.05$) compared with placebo, but there were no significant differences with treatment during exercise or in recovery. There were no differences between treatments for blood glucose, haematocrit, haemoglobin, platelet count, or change in plasma volume.

The perceived ratings of breathlessness (Borg rating) were not significantly different between treatments at rest or with exercise; albeit the values at 10 min of recovery were significantly lower with salmeterol (0.8 (0.6)) than with placebo (1.9 (1.2); $p<0.02$) but not different from salbutamol (1.3 (1.0)). The perceived rate of exertion (Borg rating) at 15 min in exercise and at the end of exercise was not different between treatments.

Discussion

Inhaled β_2-agonists are well-established prophylactic agents for exercise-induced asthma. Both salmeterol and salbutamol induced significant bronchodilation and significantly attenuated the falls in FEV_1 after maximal exercise and after endurance exercise. These findings

support those of DHILLON [1] and ANDERSON *et al*. [2], who have both clearly demonstrated the protective effect of salmeterol on exercise-induced asthma and shown that the protection lasts for up to 12 h.

This study, however, is the first to demonstrate that 50 µg salmeterol when given 30 min before the onset of exercise has no effect either on the maximal exercise capacity or the endurance capacity of asthmatic men. Similar findings were demonstrated for 200 µg salbutamol, also given 30 min before exercise.

Although the resting and post-exercise FEV_1 were higher for the asthmatic group after salmeterol and salbutamol, there were no differences in their physiological response and subjective ratings in the maximal exercise test. An improvement in exercise performance, in the presence of enhanced lung function might have been anticipated, but these findings are consistent with the previous studies of the effects of both high and low dose β_2-agonists on the maximum exercise capacity [5, 16, 17], which have shown no significant ergogenic effects.

This study group was recruited on the basis of a declared interest in exercise and physical activity. Fitness is generally defined in terms of the maximal $\dot{V}O_2$, or in terms of the capacity to enjoy moderate endurance activity without discomfort [18]. The term implies optimal use of the oxygen transport mechanisms. The $\dot{V}O_2max$ is not thought to be limited by the rate of ventilation until the FEV_1 is below 60% predicted in asthmatic children [19]. Therefore, in less severe asthma, the $\dot{V}O_2max$ is unlikely to be limited by the ventilation rate, but rather by the capacity for oxygen transport and utilization [20]. However, in patients No. 2 and 8, who did have an initial FEV_1 below 60% predicted and who obtained a good bronchodilator response to both salmeterol and salbutamol, the maximum exercise capacity and endurance capacity on a cycle ergometer were not very different. There was no change in $\dot{V}O_2$ max and only a small increase in endurance time.

The very variable endurance capacity, following placebo in the study group, suggests that exercise tolerance was limited not by ventilation but by general aerobic capacity. It is, perhaps, not surprising that the improvement in spirometry following active treatment was not consistently matched by better endurance times. Patient No. 6 fulfilled the initial recruitment criteria and, although his exercise profile proved unique, he was not excluded once other explanations for his poor performance had been discounted.

With respect to endurance capacity, we have previously shown no effect from 5 mg nebulized salbutamol on endurance capacity in asthmatic men; but in normal subjects the administration of the high dose of salbutamol reduced endurance capacity and this was associated with increased blood lactate levels [7].

Lactate levels, for each treatment, declined towards the end of exercise, indicative of a change from anaerobic to aerobic metabolism and supported by the associated trend in lowered $\dot{V}CO_2/\dot{V}O_2$ values, this reflects a greater reliance on fat as the substrate and, thus, on aerobic metabolism. We have now consistently demonstrated increased blood lactate accumulation after the administration of salbutamol but in this case at a lower dose, 200 µg as compared to 5 mg. Thus, whilst the precise cause of the raised blood lactate is not clear, the findings suggest that it may be related to alterations in carbohydrate and lipid metabolism induced by salbutamol [21], but not salmeterol. This may be explained by differences in β_2-adrenoreceptor selectivity of the two drugs. Previous *in vitro* studies have suggested that salmeterol is a highly selective β_2-agonist, with a significantly higher β_2/β_1 ratio than salbutamol, fenoterol or formoterol [22] which may account for the difference. More recent studies have questioned this hypothesis, suggesting that salmeterol has a partial β_2-agonist activity [23]. Although the precise mechanism may remain controversial, this study in asthmatic men suggests that there are significant *in vivo* differences in the metabolic effects of the two drugs.

The clinical significance of this finding has not been established, but may be of importance in the metabolic status of patients with acute severe asthma, or in unstable asthma where patients inhale or nebulize increasing dosages of salbutamol in the face of deteriorating asthma. Blood lactate is also increased when oxygen delivery does not meet demand, and is, therefore, a potential marker of anaerobic metabolism. In exercise this altered metabolism may simply limit endurance capacity [6], but in situations of critical oxygen delivery, such as in acute severe asthma, this has potentially more serious consequences. It is interesting to note that lactic acidosis is a well-recognized feature of acute severe asthma [24], and the contribution of β_2-agonists to this metabolic disturbance has not been fully elucidated. Given the increasing concerns as to the use and safety of regular inhaled β_2-agonists [25], this phenomenon is worthy of further investigation.

In conclusion, we have demonstrated that 50 µg salmeterol has no demonstrable ergogenic effect, does not alter exercise capacity, and would be suitable for use by asthmatic athletes. No differences were seen in exercise performance after salbutamol as compared to salmeterol. Salbutamol, but not salmeterol, was associated with a significant increase in blood lactate levels and the metabolic implications on endurance performance with this drug should not be neglected.

Acknowledgements: The authors would like to thank T. Lowe and Allen and Hanburys for their support.

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