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Effect of nebulised salbutamol on maximal exercise performance in men with mild asthma

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ABSTRACT The effect of 5 mg nebulised salbutamol on the cardiorespiratory responses to a progressive maximal exercise test was investigated in eight asthmatic (mean forced expiratory volume in one second (FEV_1) 3·48 (1·0) litres) and eight non-asthmatic men. Exercise tests were performed on a bicycle ergometer after administration of nebulised salbutamol or matched saline placebo. In the asthmatic subjects salbutamol increased the resting FEV_1 by 11%. The mean (SD) percentage fall in FEV_1 after exercise did not change significantly (salbutamol 9·4 (12·8); placebo 15·0 (8·0)), but because the FEV_1 before exercise was increased the lowest FEV_1 after exercise was also significantly higher after salbutamol than placebo (3·60 (1·13) *v* 2·85 (0·80) litres). Despite the improvement in FEV_1 before exercise there was no significant difference in maximal workload, oxygen uptake, heart rate, or ventilation during exercise after salbutamol compared with placebo in the asthmatic patients. Tidal volume was higher at maximal exercise after salbutamol but there was no change in perception of breathlessness or exertion in the asthmatic subjects. During submaximal progressive exercise the perceived rate of exertion was reduced in the asthmatic patients and oxygen pulse was reduced in both groups owing to a small and non-significant increase in heart rate. The FEV_1 and cardiorespiratory response to the progressive maximal exercise test in the non-asthmatic subjects were otherwise unchanged after salbutamol. The results suggest that 5 mg nebulised salbutamol has little effect on the cardiorespiratory responses to progressive maximal exercise in patients with mild asthma and in non-asthmatic subjects. Salbutamol in this dose may reduce the severity of exercise induced asthma, but no ergogenic effect on maximal exercise performance was shown.

Introduction

Asthmatic patients are encouraged to participate in a wide range of sporting activities. Many have achieved national and international honours,[1 2] while others have obtained physical, social, and psychological benefit.[3] The objective of the clinician is to achieve symptomatically and functionally well controlled asthma with minimal drug side effects. The diverse ambitions and aspirations of individual patients, however, must also be considered—for example, athletes with asthma who wish to compete nationally and internationally require treatment that is effective and allowed by the governing bodies of their sport.

The protective role of the selective β_2 agonist salbutamol in preventing exercise induced asthma in athletes is well documented.[4] The effect of β_2 agonists on other measures of cardiorespiratory performance in exercising asthmatic patients, including ergogenic effects, is less clear. Available evidence suggests that conventional therapeutic doses of salbutamol (200 μg) from a metered dose inhaler do not change maximal exercise capacity in non-asthmatic athletes[5] or the degree of breathlessness experienced by healthy subjects during progressive exercise.[6] It has therefore been suggested, though not confirmed, that salbutamol in this dose will merely prevent or relieve the symptoms of exercise induced asthma in asthmatic athletes. The International Olympic Committee allows athletes with asthma to compete while being treated with "aerosol" salbutamol,[7] which has been interpreted as treatment from a metered dose inhaler (Cowan, personal communication). The permissible dose has not, however, been defined. Asthmatic athletes may require several inhalations of salbutamol from a metered dose inhaler before a competition and may then be vulnerable to accusations of drug abuse. This is defined as the use of a substance "which could

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have the effect of improving artificially the athletes physical and/or mental condition and so augmenting his athletic performance" (International Amateur Athletic Federation, rule 144).

To provide more information on this subject we looked at the effect of a higher dose of nebulised salbutamol (5 mg) on the cardiorespiratory responses to a progressive maximal exercise test in active asthmatic patients and non-asthmatic subjects.

Methods

SUBJECTS

Eight asthmatic and eight non-asthmatic non-smoking men were investigated; their physical characteristics are given in table 1. The participants engaged in regular physical activity but none was highly trained. The asthmatic subjects had a documented increase in the forced expiratory volume in one second (FEV_1) of more than 20%, either spontaneously or as a result of treatment. All patients were receiving regular inhaled salbutamol and prophylactic treatment (five inhaled steroids, three sodium cromoglycate). Treatment had been unchanged for at least four weeks. Subjects gave informed consent to the study, which was approved by the hospital ethical committee.

Before the main study bronchial reactivity to histamine was measured according to the method of Cockcroft *et al*[8] and each subject performed a progressive maximal exercise test to familiarise him with the equipment and protocol.

STUDY DESIGN

The effect of inhaling 5 mg nebulised salbutamol (1 ml 0·5% salbutamol respirator solution, 3 ml 0·9% saline) or matched placebo (4 ml 0·9% saline) on a progressive maximal exercise test was compared in the asthmatic and non-asthmatic subjects. The solutions were administered double blind, the order of treatment being determined by a balanced randomisation code. The exercise tests were performed at the same time of day and about a week apart. In the asthmatic patients inhaled salbutamol and sodium cromoglycate were withdrawn six hours before the tests; inhaled steroids were continued.

MEASUREMENTS

On each study day a series of baseline measurements was taken before the test solution was administered by an air driven nebuliser (Medex Minor II) at a flow rate of 8 l min^{-1}. After a 15 minute rest the baseline measurements were repeated. A progressive maximal exercise test was then performed on an electromagnetically braked cycle ergometer (Rodby Elektronik 820, Sweden) from a starting workload of 50 W, with the workload being increased by 20 W each minute until exhaustion.

Cardiorespiratory measurements were taken for two minutes at rest, both before and 15 minutes after the subject had inhaled from the nebuliser and at five second intervals throughout exercise with a computerised exercise testing system (Magna 88, P K Morgan, Rainham, Kent). Subjects breathed room air through a two way respiratory valve (Hans-Rudolph, Kansas

Table 1 *Physical characteristics and physiological responses to maximal exercise in asthmatic and non-asthmatic subjects with nebulised placebo and salbutamol (mean (SD) values)*

	Asthmatics				*Non-asthmatics*			
	Placebo		*Salbutamol*		*Placebo*		*Salbutamol*	
Age (years)	30·3	(9·9)	—		22·8	(5·5)	—	
Height (m)	1·74	(0·06)	—		1·81	(0·06)	—	
Weight (kg)	73·4	(13·5)	73·5	(13·8)	72·7	(9·4)	72·7	(9·2)
Workload (W)	263	(54)	275	(64)	245	(53)	250	(55)
Time (min)	10·94	(2·73)	11·60	(3·17)	10·09	(2·57)	10·44	(2·62)
$\dot{V}O_2$max (l min^{-1})	3·12	(0·68)	3·20	(0·77)	2·99	(0·72)	3·00	(0·65)
$\dot{V}O_2$max (ml kg^{-1} min^{-1})	43·0	(8·6)	43·6	(7·2)	41·0	(6·4)	41·0	(4·9)
HRmax (beats/min)	186	(18)	190	(17)	194	(9)	195	(7)
$\dot{V}E$max (l min^{-1})	100·7	(22·3)	108·8	(23·4)	105·4	(36·0)	105·2	(32·1)
fmax (b/min)	41·8	(7·9)	41·8	(6·9)	42·4	(18·4)	40·5	(14·2)
VTmax (l)	2·41	(0·30)	2·60	(0·26)*	2·64	(0·59)	2·71	(0·54)
R ($\dot{V}CO_2/\dot{V}O_2$)	1·15	(0·09)	1·14	(0·05)	1·16	(0·05)	1·18	(0·08)
O_2 pulse (ml/beat)	16·8	(3·0)	16·8	(3·3)	15·3	(3·8)	15·4	(3·0)
$\dot{V}E/\dot{V}O_2$	32·6	(5·6)	34·3	(3·8)	35·2	(7·5)	35·4	(7·4)
Sao_2 (%)	94·6	(1·0)	94·8	(1·2)	95·5	(1·4)	95·7	(1·3)
Blood pressure (mm Hg):								
Systolic	194	(27)	202	(30)	195	(33)	204	(24)
Diastolic	89	(35)	89	(24)	79	(20)	89	(21)

*$p < 0·05$: Significant difference between placebo and salbutamol.
$\dot{V}O_2$max—maximal oxygen uptake; HRmax—maximal heart rate; $\dot{V}E$max—maximal expired minute volume; fmax—maximal breathing frequency; VTmax—maximal tidal volume; R—respiratory exchange ratio (carbon dioxide production/oxygen consumption); Sao_2—arterial oxygen saturation.

City). Expired minute ventilation ($\dot{V}E$) and breathing frequency (bf) were measured with a turbine transducer and the fractional concentrations of oxygen (FEO_2%) and carbon dioxide ($FECO_2$%) in expired air with a paramagnetic oxygen analyser (Morgan 252, P K Morgan) and infrared carbon dioxide analyser (Morgan 801D, P K Morgan). Oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were calculated. The respiratory exchange ratio (R: $\dot{V}CO_2/\dot{V}O_2$), ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$), and tidal volume (VT: $\dot{V}E$/bf) were derived. Oxygen saturation was measured simultaneously with an ear oximeter (Hewlett Packard 47201A).

A heart rate monitor (Rigel Research, Sutton, Surrey) was interfaced to the microcomputer and oxygen pulse ($\dot{V}O_2$/heart rate, ml beat^{-1}) calculated. Blood pressure was measured automatically (Infrasonde D4000, Puritan Bennett) at rest (before and after nebulised drug) and every two minutes throughout exercise. Perceived rates of breathlessness and exertion were obtained at the same times with a modified Borg scale from 0 to 10.[9]

FEV_1 was measured with a dry wedge spirometer (Vitalograph) at rest, both before and after salbutamol or placebo and at one, three, five, seven, 10, 15, 20, 25, and 30 minutes after exercise. Measurements were compared with predicted normal values.[10] The percentage change in resting FEV_1 after drug or placebo was calculated. The lowest FEV_1 after exercise was expressed as a percentage change from the FEV_1 at rest after salbutamol or placebo.

ANALYSIS

The cardiorespiratory measurements during the last 30 seconds at each submaximal workload were averaged. To obtain the maximum response to exercise the highest consecutive readings for $\dot{V}O_2$ over 30 seconds were averaged ($\dot{V}O_2$max) and the mean values for the coincident physiological measurements obtained. Statistical analyses compared responses after salbutamol and placebo in the asthmatic and non-asthmatic subjects separately. Measurements made at rest (before and after the nebulised drugs) and FEV_1 after salbutamol and placebo at rest and after exercise were compared by a paired Student's *t* test. The physiological measurements at maximum exercise and during progressive exercise were compared by two way analysis of variance for repeated measures, with treatment and order of treatment as factors. Two tailed analyses were used throughout; data are expressed as means and standard deviations.

Results

LUNG FUNCTION

FEV_1 values and the provocative concentration of histamine needed to produce a 20% fall in FEV_1 (PC_{20}) in the asthmatic subjects are shown in table 2. A low FEV_1 (42% predicted) precluded histamine challenge in one patient (case 3). The mean (SD) FEV_1 before exercise was similar before each treatment (salbutamol 87·4 (20); placebo 86·0 (23) % pred). Baseline FEV_1 increased by 11% after nebulised salbutamol so FEV_1 % pred was significantly higher at the start of exercise after salbutamol than placebo (96·5 (21) *v* 83·4 (23); $p < 0.05$). There was no significant difference in the percentage fall in FEV_1 after exercise after treatment with salbutamol and placebo. The lowest absolute FEV_1 % pred after exercise was higher after salbutamol (salbutamol 87·9 (23), placebo 70·6 (19); $p < 0.05$) and above values at rest before treatment with salbutamol.

FEV_1 at rest before treatment in the non-asthmatic subjects was similar before placebo (4·78 (0·69) litres, 107·1 (9) % pred) and salbutamol (4·78 (0·67) litres, 107·0 (8) % pred) and did not differ significantly after

Table 2 *FEV_1 (litres) at rest before and after nebuliser treatment and in response to exercise in relation to histamine reactivity (PC_{20}) in eight asthmatic subjects*

		Placebo					Salbutamol				
		FEV_1			Lowest FEV_1		FEV_1			Lowest FEV_1	
Case No	PC_{20} (mg/ml)	Before nebuliser	After nebuliser	% Change	after exercise	% Fall	Before nebuliser	After nebuliser	% Change	after exercise	% Fall
1	0·12	3·67	3·37	−8·2	2·75	−18·4	3·64	4·30	18·1	3·10	−27·9
2	0·92	4·50	4·37	−2·9	3·84	−12·1	4·16	4·64	11·5	4·63	−0·2
3	—	1·61	1·56	−3·1	1·32	−15·4	1·87	2·27	21·4	1·57	−30·8
4	0·32	4·92	4·95	0·6	3·54	−28·5	4·90	5·11	4·3	5·12	0·2
5	1·41	3·34	3·36	0·6	2·77	−17·6	3·51	3·90	11·1	3·60	−7·7
6	2·55	2·97	2·90	−2·4	2·74	−5·5	2·88	2·86	−0·7	2·73	−4·5
7	0·85	3·22	2·93	−9·0	2·37	−19·1	3·64	4·45	22·3	4·15	−6·7
8	>16	3·63	3·63	0·0	3·50	−3·6	3·74	3·79	1·3	3·89	+4·6
Mean		3·48	3·38	−3·0	2·85	−15·0	3·54	3·92*	11·2*	3·60*	−8·4
SD		1·00	1·02	3·7	0·80	8·0	0·89	0·94	9·0	1·13	12·8

*$p < 0.05$: significant difference between placebo and salbutamol.

salbutamol or placebo at rest or after exercise. All the non-asthmatic subjects had a histamine PC_{20} greater than 8 mg/ml.

PROGRESSIVE EXERCISE

There were no significant changes in cardiorespiratory measurements at rest after salbutamol or placebo in either group except that at the start of exercise systolic blood pressure was higher after salbutamol (salbutamol 124 (9), placebo 114 (9) mm Hg; $p < 0.001$) and diastolic blood pressure lower (salbutamol 67 (6), placebo 77 (9) mm Hg; $p < 0.05$) for the asthmatic patients.

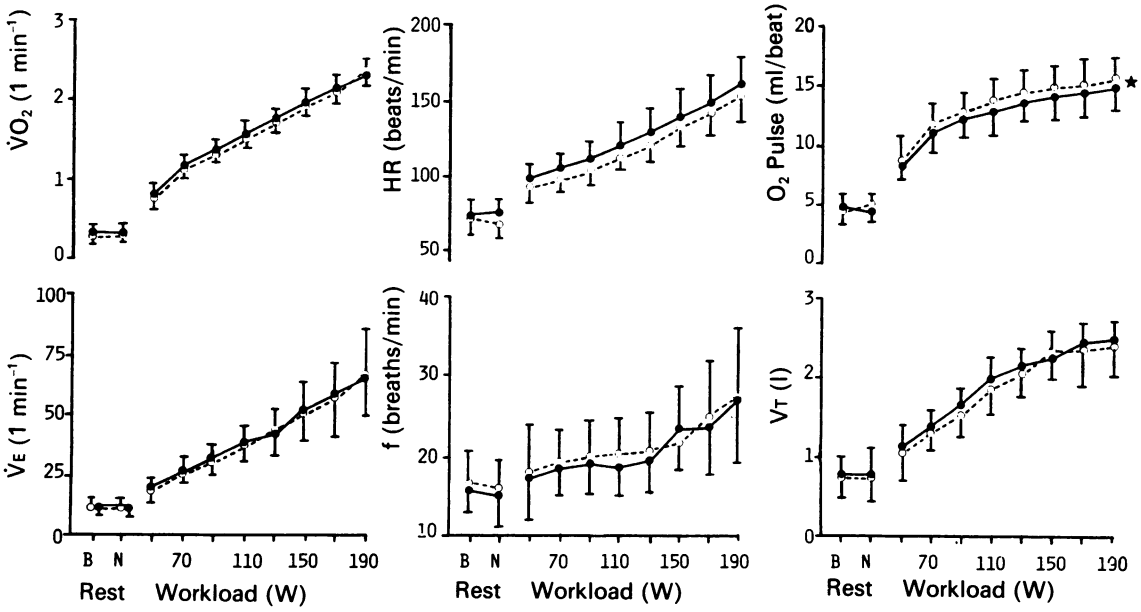
The physiological responses to progressive exercise after salbutamol and placebo were compared from 50 W to 190 W in the asthmatic group and from 50 W to 170 W in the non-asthmatic group. These comparisons were chosen because all subjects completed these workloads in both tests. There were no significant differences in the cardiorespiratory responses of heart rate, $\dot{V}_E$, V_T, bf, and $\dot{V}_{O_2}$ between treatments for the asthmatic (figure) or non-asthmatic subjects and no differences in the ventilatory equivalent for oxygen, $\dot{V}_{CO_2}$, and R, in either group. Salbutamol, however, lowered the oxygen pulse when compared with placebo in both the asthmatic ($F = 7.99$, $p < 0.05$) (figure) and non-asthmatic groups ($F = 8.56$, $p < 0.05$). There were no effects due to order of treatment.

Salbutamol did not change the perception of breathlessness significantly in either group. The perceived rate of exertion during progressive exercise was, however, reduced with salbutamol in the asthmatic subjects ($F = 8.72$, $p < 0.05$) but not in the non-asthmatic subjects. Blood pressure and oxygen saturation did not change significantly in either group.

MAXIMUM EXERCISE

Neither group showed a significant difference in test performance (defined by the maximum workload achieved and the duration of the test) after salbutamol compared with placebo (table 1). Salbutamol caused no significant change in $\dot{V}_{O_2}$max, $\dot{V}_E$max, maximum heart rate, arterial oxygen saturation (%), or blood pressure at maximum exercise; no subject showed oxygen desaturation of more than 4% during any test. V_T in the asthmatic patients increased after salbutamol compared with placebo ($F = 11.43$, $p < 0.02$) and was unchanged in the non-asthmatic group. There were no effects due to order of treatment.

Salbutamol given before exercise did not affect the perception of breathlessness at the end of exercise in the asthmatic (placebo 5·5 (1·9), salbutamol 5·6 (2·8)) or non-asthmatic (placebo 4·0 (2·2), salbutamol 3·9 (2·8)) group. The perceived rate of exertion at the end



*Cardiorespiratory responses (oxygen uptake ($\dot{V}_{O_2}$), heart rate (HR), oxygen pulse, expired minute volume ($\dot{V}_E$), breathing frequency (f), and tidal volume (V_T)) in eight asthmatic subjects at rest (baseline (B) and after nebuliser treatment (N)) and during progressive exercise after salbutamol (●—●) and placebo (○----○). Values are means (SD); *p < 0·05.*

of exercise was also similar for both treatments in the asthmatic (placebo 5·5 (2·4), salbutamol 6·1 (2·5)) and non-asthmatic (placebo 6·5 (2·9), salbutamol 6·9 (2·6)) groups.

Discussion

Our results suggest that 5 mg nebulised salbutamol has little effect on maximum exercise capacity and produces only small changes in the cardiorespiratory response to progressive exercise in both asthmatic and non-asthmatic subjects.

Although β_2 agonists are usually classified as bronchodilators, their clinical value also depends on their prophylactic role, especially in exercise induced asthma.[11] In this group of asthmatic subjects 5 mg nebulised salbutamol (despite its resting bronchodilator action) did not reduce the postexercise percentage fall in FEV_1 significantly. This was perhaps surprising as inhaled salbutamol has been shown to be the most effective agent for reducing exercise induced asthma.[12,13] The ability of salbutamol to protect against such asthma, however, varies between asthmatic patients,[13,14] perhaps because of differences in bronchial reactivity. The bronchodilator properties of salbutamol are not related to its efficacy in blocking exercise induced asthma[12,14] and higher doses of adrenergic agents may be required to prevent such asthma than to maintain bronchodilatation.[11] The bronchodilator effect of salbutamol resulted in bronchodilatation in the asthmatic patients in this study so that the resulting exercise induced deterioration was proportionately less severe.[11] Salbutamol was useful therefore in preserving absolute FEV_1 if not in preventing exercise induced asthma in these subjects.

Although 5 mg nebulised salbutamol increased the FEV_1 at rest and after exercise in the asthmatic group, the maximum exercise performance and the physiological response to maximum exercise was unchanged apart from a small increase in tidal volume. This finding is consistent with Ingemann-Hansen *et al*'s study of five asthmatic patients.[15] In a recent study of work performance Clark and Cochrane recorded a lower $\dot{V}O_2$max and a lower oxygen pulse at maximum exercise in asthmatic subjects after 5 mg nebulised salbutamol compared with untreated controls.[16] The lack of change in $\dot{V}O_2$max and oxygen pulse at maximum exercise with salbutamol in our study supports their hypothesis that the differences between the asthmatic and non-asthmatic groups in their study are unlikely to have been due to differences in treatment and more likely to reflect differences in "fitness." The lack of change in maximum exercise performance in the non-asthmatic subjects after 5 mg nebulised salbutamol is consistent with the findings of a similar study of 200 μg salbutamol in non-asthmatic athletes.[5]

In untrained subjects without disease $\dot{V}O_2$max is usually limited by the capacity for oxygen transport and oxygen utilisation.[17] In patients with severely impaired lung function, however, maximum ventilation may limit $\dot{V}O_2$max; such a limitation is seen with an FEV_1 below 60% predicted in asthmatic children.[18] Nebulised salbutamol has been shown to improve exercise tolerance in patients with chronic airflow obstruction.[19–21] In our study the mean FEV_1 was above 80% predicted, which may explain the lack of change in maximum exercise performance with salbutamol despite an improvement in lung function. Physical training improves the factors that normally limit $\dot{V}O_2$max, so that in highly trained subjects maximum ventilation may become the rate limiting step.[17] Our results may have been different if we had studied patients with more severe airflow obstruction or highly trained asthmatic athletes.

Salbutamol did not change the cardiorespiratory response to progressive exercise, apart from a small but significant reduction in oxygen pulse in both groups, which was attributed to a small but non-significant increase in heart rate. A significant increase in heart rate during exercise after salbutamol in a previous study was blocked by a specific β_2 adrenoceptor antagonist, suggesting that the higher heart rate was mediated by the β_2 adrenoceptor or secondary to peripheral vasodilatation.[22]

Oxygen saturation was not affected adversely by salbutamol during progressive or maximum exercise. This finding is reassuring as ventilation-blood flow balance is known to be influenced by β_2 agonists.[23] Small changes in blood pressure were seen after 5 mg nebulised salbutamol at rest[24] but the blood pressure response during progressive and maximum exercise did not change significantly.

Perceptions of breathlessness and exertion were unchanged at maximum exercise for both groups. This finding was not unexpected because each patient was asked to produce a maximum effort. Neither the asthmatic nor the non-asthmatic subjects, however, showed any change in perception of breathlessness during progressive exercise, supporting previous findings in non-asthmatic subjects[6] but contrasting with other studies in asthmatic subjects, in which breathlessness scores were reduced after salbutamol during exercise.[25] It is interesting that the perceived rate of exertion was reduced in the asthmatic group during progressive exercise after salbutamol; the reasons for this are unclear, but may be related to preliminary findings which suggest that salbutamol has effects on metabolism during exercise.[26]

In conclusion, 5 mg nebulised salbutamol does not influence the maximum exercise performance in patients with mild asthma or in non-asthmatic subjects. It may be expected to minimise or prevent exercise induced asthma only in active but not highly

trained asthmatic subjects with fairly mild airflow obstruction. Although the effect of salbutamol on sports performance and endurance capacity was not measured directly in this study, $\dot{V}O_2$max is known to be highly correlated with running performance.[27]

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