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Official Research Journal
of the American Society of
Exercise Physiologists
(ASEP)

ISSN 1097-9751

**EFFECTS OF ACUTE ORAL ADMINISTRATION OF
4 MG SALBUTAMOL ON EXERCISE PERFORMANCE
IN NON-ASTHMATIC ELITE ATHLETES**

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ABSTRACT

Andersen KF, Kanstrup I-L. Effects of acute oral administration of 4 mg salbutamol on exercise performance in non-asthmatic elite athletes. *JEPonline* 2009;12(1):36-49. Orally administered salbutamol, a well-known β_2 -adrenergic agonist, has not been investigated in highly trained endurance athletes, even though it is banned by the World Anti-Doping Agency due to a likely ergogenic effect. Seven healthy, elite endurance trained male athletes were included. Following a day of preliminary tests, the athletes received either 4 mg orally administered salbutamol or placebo in a double-blind, randomized, cross-over design. Initially, a maximal oxygen consumption test was performed, followed by a constant-load test until exhaustion on treadmill. Heart rate and SaO_2 were recorded during the performance tests, and respiratory values and venous blood samples were collected immediately after termination. After administration of salbutamol, arterial saturation levels (6.0%, $P = 0.15$) as well as the time to exhaustion (14.9%, Cohen's $d = 0.41$, $> \frac{1}{2}$ the CV of the test) were increased during the constant-load test. There were no statistically significant changes in VO_2 max, other respiratory values, heart rate or plasma lactate concentrations. In conclusion, after administering a single oral therapeutic dose of the β_2 -adrenergic agonist salbutamol to healthy, elite endurance trained male athletes, acute ergogenic effects were demonstrated in terms of a reduced extent of exercise induced arterial hypoxemia (EIAH), as well as an improvement in time to exhaustion during a constant-load test, which indicated a meaningful performance-enhancing effect in a race situation.

Key Words: β_2 -Adrenergic Agonist, Performance, Constant-load, EIAH, Maximal Oxygen Uptake, Placebo Controlled Study.

INTRODUCTION

β_2 -adrenergic agonists are widely used as bronchodilators in the prevention and treatment of exercise-induced asthma, which is a common entity in high-performance athletes (1). Several reports suggest that the use of β_2 -adrenergic agonists among high-level athletes strongly exceeds the incidence of bronchial asthma and exercise-induced asthma in the same group (2,3), even though the opposite recently have been reported (4,5). The influence of inhaled β_2 -adrenergic agonists on exercise performance has been well documented (6-18), with only two papers proposing a positive effect (6,16). But the acute effect of orally administered salbutamol, a well-known β_2 -adrenergic agonist, has not been investigated in highly trained endurance athletes. This in spite of the fact that the World Anti-Doping Agency (WADA) has banned oral administration of salbutamol as well as several other β_2 -adrenergic agonists due to a presumed ergogenic action (19).

It is well-documented that a fall in arterial oxygen saturation may take place in highly trained athletes working with high intensity (20,21). There are many explanations to this exercise-induced arterial hypoxemia (EIAH). Temperature- and acid-induced shifts in O_2 dissociation at any given arterial PO_2 contribute to EIAH, as do both an excessive alveolar-to-arterial PO_2 difference and inadequate compensatory hyperventilation (20,21). The effect on performance level after a drop in arterial oxygen saturation, though, is questioned (21,22). Theoretically, the use of β_2 -adrenergic agonists may result in an improvement in the oxygen transfer from the alveoli to the arterial blood in elite endurance athletes with extreme demands to the oxygen transport system, because it reduces the risk of pulmonary edema by up-regulating the sodium-driven clearance of alveolar fluid (20,23). On the other hand, Stewart et al. (24) demonstrated no enhancement of arterial oxygen saturation during exercise when an acute, inhaled, therapeutic dose of salbutamol was administered to highly trained non-asthmatic athletes with EIAH.

It is unlikely that the bronchodilatory effect of salbutamol and other β_2 -agonists is ergogenic, because in healthy, non-asthmatic subjects bronchoconstriction is not a performance limiting factor. Therefore, β_2 -adrenergic agonists probably have to reach the systemic circulation in order to display its assumed ergogenic action. Comparing with orally administered therapeutic doses, clinically relevant doses in the form of aerosols result in much lower systemic plasma concentrations (25). In order to optimize chances of an effect on the acute aerobic performance, we studied performance in healthy elite athletes after oral, instead of aerosol administration of 4 mg (a normal therapeutic dose) salbutamol. Collomp et al. (26) and Van Baak et al. (27) found an enhancement in time to exhaustion during sub-maximal exercise after a single administration of 6 mg and 4 mg salbutamol, respectively. Their subjects, though, were moderately trained.

The adaptation of the human body to exercise is strongly associated with β -adrenergic stimulation. Increased muscle contractility, transport capacity as well as increased availability of substrates for energy metabolism are all, more or less, mediated by stimulation of β -adrenergic receptors. Several studies have demonstrated increased plasma lactate concentrations after systemic administration of β_2 -adrenergic agonists during exercise, which together with changes in the respiratory exchange ratio (RER), could be seen as indirect measures of carbohydrate oxidation and glycolytic flux (26-28). Through these mechanisms, a possible meaningful effect in a competitive situation could be demonstrated after administration of salbutamol.

Thus, we investigated a possible effect in highly endurance-trained athletes, and based on the existing literature, the hypothesis was an enhanced time to exhaustion among the implemented study subjects after administration of a single oral dose (4 mg) of the β_2 -adrenergic agonist salbutamol.

METHODS

Subjects

Seven male athletes, all highly endurance-trained (runners and cross-country skiers), participated in the study, age 25 (18 – 30) years (median (range)), weight 72.9 (65.0 – 82.5) kg, maximal oxygen uptake ($\dot{V}O_2\text{max}$) of 72.5 (68.1 – 76.9) $\text{ml} \times \text{kg}^{-1} \times \text{min}^{-1}$. The participants had no history of asthma, exercise-induced asthma, chronic bronchitis or other respiratory diseases. Neither were they on any kind of medication. This was based on the answers to a brief questionnaire. Subjects were asked not to change their habitual sports activities during the study. Due to the high physical demands, we did not manage to include more subjects. The protocol was approved by the Ethics Committee of Copenhagen County, and all subjects gave written informed consent before participating in the study.

Procedures

Subjects reported to the laboratory on three occasions within two weeks. On the first day the athlete's physical performance level ($\dot{V}O_2\text{max}$, lactate threshold and respiratory values) was determined, using a treadmill with increasing workload. On the two experimental test days the athletes received either a single oral dose of 4 mg salbutamol or placebo in a double-blind, randomized, cross-over design. Following a maximal oxygen uptake test (Astrand protocol) (29), the participants performed an endurance test (both tests on treadmill) with constant load above the lactate threshold, and the time to exhaustion was measured. The load was set to be ~ 1.5 km/h faster than the individual running speed obtained at the subject's lactate threshold; this to ensure exhaustion inside a period of reasonable time.

Screening procedure

Initially, body weight was measured in the morning before the experiments started. Upon arrival a venous catheter was inserted into an antecubital vein for blood sampling, and resting measurements were performed after a minimum of 30 min of rest with the athlete in a sitting position. Before warm-up and after the $\dot{V}O_2\text{max}$ test, each subject performed a pulmonary function test, with measurements of dynamic pulmonary volumes. A pulmonary function Testing System 1070 (Medical Graphics Corp., MN, USA) was applied. Volume calibration was performed by means of a 3-liter syringe. After familiarization, the athlete got 3 trials in a standing position. The data with the highest $\text{FEV}_{1.0}$, and where the result was $\geq 90\%$ of the expected, was recorded.

During the maximal oxygen uptake test, gas exchange was recorded continuously with recording intervals of 15 s with a Medical Graphics CPX/d system (St. Paul, MN, USA). Before use, the system was calibrated with calibration gases with known concentrations of O_2 and CO_2 , which previously had been analyzed by the micro-Scholander technique. Volume calibration was performed by means of a 3-liter syringe. The subjects had to meet at least three standard indicators for achieving $\dot{V}O_2\text{max}$: respiratory exchange ratio ≥ 1.15 , volitional fatigue, heart rate $\geq 90\%$ of age predicted maximum, and a plateau in $\dot{V}O_2$ with increasing work load. Once the criteria were met, oxygen uptake was calculated as the mean of the two highest consecutive values. Exercise was performed on a Runrace treadmill (Technogym, Italy) with the equipped pulse monitor (Cardiotester) measuring continuously. All athletes met the criteria set for both pulmonary function as well as the $\dot{V}O_2\text{max}$ test, thus, no subjects were removed from the study.

Oxygen saturation was measured at rest and continuously during exercise by a pulse oximeter (Oxi, Radiometer, Copenhagen, Denmark) with the sensor attached to the second finger. The validity and reliability of the mentioned pulse oximeter during different conditions (exercise, normoxia and hypoxia) are well documented (30-32).

During the tests venous plasma was sampled for lactate concentrations. Lactate concentrations were measured in an ABL 625 blood gas and electrolyte system (Radiometer, Copenhagen, Denmark).

Experimental procedure

As specified earlier, each subject went through three days of testing. On the first day the athlete's physical performance ($\dot{V}O_2$ max, lactate threshold and respiratory values) was determined. Constant-load and maximal oxygen uptake tests were conducted the consecutive days, which were under the two experimental conditions, salbutamol and placebo. All tests were performed between 1.5 and 4 hours after administration of the medication.

Approximately 90 minutes before the testing sessions, the participants took either 4 mg orally administered salbutamol or placebo (no active medication). In treatment of asthma, a single oral dose of 4 mg salbutamol is in the normal therapeutic range, but considerably higher than the therapeutic dose of salbutamol given by inhalation products (0.2 – 0.4 mg). Orally administered salbutamol shows an initial onset at approximately 30 min, and full effect after 1.5-2 hours. With a bioavailability of 40-50%, maximal plasma levels are achieved within a time-window from 1 to 4 hours. $T_{1/2}$ has been reported to be 2.7-5.5 hours (25,33-36). To our best knowledge, exercise does not influence the metabolism of salbutamol. The medication was randomly coded, and therefore blinded for both the subjects and the investigators. The subjects' weights were recorded in the morning before the test session each day. A venous catheter was inserted in an antecubital vein, and after collecting a venous blood sample and performing a spirometric test in resting conditions, the subjects were allowed a 10 min warm-up, followed by a maximal oxygen uptake test on a treadmill according to the Astrand protocol (29). $\dot{V}O_2$ and other respiratory parameters were continuously registered. Spirometric values were registered 1, 2, 5 and 10 min after termination of the $\dot{V}O_2$ max test, and blood samples were collected immediately and 3 min after the maximum. Heart rate values and arterial saturation levels were collected every 15 s during the maximal oxygen uptake test.

After resting one hour, the athletes were allowed another 10 min warm-up before performing an endurance test with constant intensity on a treadmill, where time to exhaustion was measured. The level of intensity was set on the basis of the individual result at the lactate threshold test on the first occasion. The latter was determined by an incremental test on a treadmill with the traditional 4 mmol/L measure, which has been reported to be one of the most reliable measures of lactate anaerobic threshold (37). For each individual, to make the trial conditions as comparable as possible, the tests were performed approximately the same time of the day. The subjects were asked to do the same preparation before the tests, and the treadmill instrument board (including the time counter) was blinded for the athletes. Venous blood samples were collected before, during and after performance. Heart rate values and saturation levels were recorded each minute during the constant-load test. We chose not to register respiratory values during the endurance test due to a possible influence on the outcome of the time to exhaustion.

Statistical Analyses

All statistics were calculated with use of a one-way ANOVA. The statistical significance level was set to $P < 0.05$. When appropriate, Cohen's d was used for determination of effect sizes. SPSS 16.0 (SPSS inc., Chicago, USA) was used for all statistical calculations.

RESULTS

Results are shown in Tables 1, 2 and 3. None of the subjects experienced side-effects of any kind. When using a one-way ANOVA, none of the pulmonary function variables turned out to be significant after administration of salbutamol or placebo (table 1). On the other hand, the results before ($P =$

Table 1 – Pulmonary Function Data			
<i>PEF (L/s)</i>	<i>Salbutamol (Mean ± SD)</i>	<i>Placebo (Mean ± SD)</i>	<i>P</i>
Rest	12.91 ± 1.7	12.08 ± 1.9	0.40
1 min after VO_{2max}	12.63 ± 1.6	13.04 ± 1.6	0.64
2 min after VO_{2max}	13.36 ± 1.6	13.08 ± 1.7	0.76
5 min after VO_{2max}	12.58 ± 1.9	12.61 ± 1.7	0.98
10 min after VO_{2max}	12.88 ± 1.5	11.74 ± 1.7	0.20
<i>FEV_{1.0} (L)</i>			
Rest	4.97 ± 0.4	4.99 ± 0.3	0.92
1 min after VO_{2max}	4.93 ± 0.5	4.97 ± 0.5	0.90
2 min after VO_{2max}	4.93 ± 0.5	4.88 ± 0.5	0.85
5 min after VO_{2max}	4.95 ± 0.4	4.88 ± 0.5	0.76
10 min after VO_{2max}	4.93 ± 0.4	4.90 ± 0.4	0.90
<i>FVC (L)</i>			
Rest	5.66 ± 0.7	5.64 ± 0.6	0.95
1 min after VO_{2max}	5.26 ± 0.7	5.31 ± 0.8	0.90
2 min after VO_{2max}	5.29 ± 0.8	5.25 ± 0.9	0.93
5 min after VO_{2max}	5.45 ± 0.7	5.34 ± 0.9	0.80
10 min after VO_{2max}	5.56 ± 0.8	5.46 ± 0.8	0.83

PEF, peak expiratory flow; FEV_{1.0}, forced expired volume in 1 s; FVC, forced vital capacity.

0.40), and especially 10 min after ($P = 0.20$) the maximal consumption test indicated a trend towards increment of PEF after administration of salbutamol. When looking on effect sizes, Cohen's d was 0.49 (~ 33% non-overlap) and 0.76 (~ 46% non-overlap), respectively, which should be seen as a moderately large to large effect size.

Table 2 – Exercise Data Summary			
<i>Maximal oxygen uptake test</i>	<i>Salbutamol (Mean ± SD)</i>	<i>Placebo (Mean ± SD)</i>	<i>P</i>
VO_{2max} (ml/kg/min)	72.2 ± 3.2	72.5 ± 3.2	0.90
V_E (L/min)	173.8 ± 15.6	179.7 ± 16.3	0.50
RER	1.15 ± 0.03	1.14 ± 0.02	0.76
SaO ₂ (%)	89.7 ± 3.7	90.9 ± 2.7	0.53
Work-time (s)	367 ± 46	371 ± 37	0.84
Heart rate (bpm)	185 ± 13	185 ± 12	0.93
<i>Constant-load test</i>			
SaO ₂ (%)	93.3 ± 2.0	88.0 ± 8.9	0.15
Time to exhaustion (s)	966 ± 530	841 ± 305	0.60
Heart rate (bpm)	180 ± 11	181 ± 12	0.93

VO_{2max} , maximal oxygen consumption; V_E , minute ventilation; RER, respiratory exchange ratio; SaO₂; arterial oxygen saturation level.

Regarding the maximal oxygen uptake test (Table 2), there were no statistically significant changes between salbutamol and placebo, neither in VO_{2max} ($P = 0.90$), nor in V_E ($P = 0.50$) and work-time (P

= 0.84). RER ($P = 0.76$), as well as HR ($P = 0.93$) and SaO_2 ($P = 0.53$) at the time of the subjects' maximal oxygen consumption were also unchanged (Fig. 1).

Table 3 – Lactate Concentrations

Lactate (mmol/L)	Salbutamol (Mean \pm SD)	Placebo (Mean \pm SD)	P
$\text{VO}_{2\text{max}}$	12.1 \pm 1.9	12.9 \pm 2.5	0.55
$\text{VO}_{2\text{max}}$ + 3 min	11.6 \pm 1.8	12.4 \pm 2.3	0.48
After rest	2.5 \pm 0.7	2.5 \pm 0.6	0.87
Exhaustion	8.2 \pm 1.9	8.6 \pm 2.4	0.75
Exhaustion + 10 min	4.6 \pm 1.3	4.6 \pm 1.3	0.95

At the constant-load test on treadmill (table 2), we observed an average increase in time to exhaustion of 14.9% after administration of salbutamol; from 841 s to 966 s. The individual results, though, were rather diverged, and consequently, the difference between the two groups turned out to be insignificant ($P = 0.60$). Though, Cohen's d was 0.41, and according to Cohen's revised criteria for effect sizes, this should be considered as a moderately large effect size. When comparing with placebo, we registered an increase of 6.0% in arterial saturation levels at the time of exhaustion (from 88 to 93.3%; $P = 0.15$); this in contrast to the no significant differences in SaO_2 between the two testing conditions at the start of the test ($P = 0.94$). There were no differences in HR throughout the test ($P = 0.93$ at time of exhaustion). The increases in time to exhaustion as well as in SaO_2 after administering salbutamol will be discussed later (Fig. 2 and 3).

Finally, venous blood samples of lactate showed no statistically significant differences between the two testing conditions (Table 3).

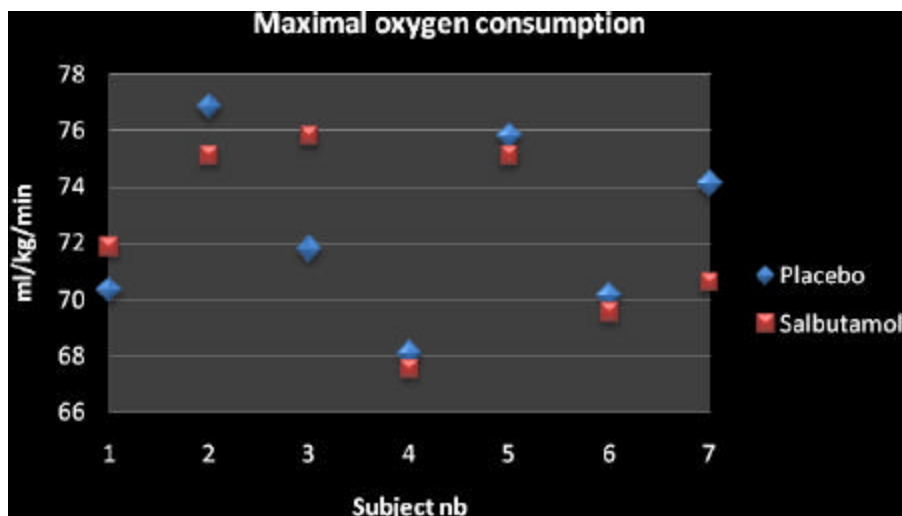


Figure 1. Scatterplot of the individual maximal oxygen consumption after administration of salbutamol and placebo in elite endurance athletes (n = 7).

administered therapeutic dose of salbutamol. Both Collomp et al. (26,38) and Van Baak et al. (27) have previously shown an improvement both in time to exhaustion and (supra)maximal workload in healthy male athletes after orally administered salbutamol, but the subjects were not highly endurance trained.

DISCUSSION

It is well documented that inhaled β_2 -adrenergic agonists, despite the dosage or the medication involved, do not have any performance enhancing effects in healthy subjects (7-15,17,18). Thus, only two studies have demonstrated a statistically significant effect of a single inhaled therapeutic dose of salbutamol (6,16). By our knowledge, this is the first study to report the acute effects on performance in elite male endurance athletes without asthma after a single, orally

Theoretically, it is unlikely that the bronchodilatory action of salbutamol and other β_2 -agonists has an ergogenic effect in healthy non-athletes, because bronchoconstriction is not a performance limiting factor. What should be remembered, though, is that several studies have demonstrated that elite endurance athletes have a huge demand to the pulmonary diffusing capacity, as the pulmonary transit time is reduced to $\frac{1}{3}$ s or less (20,21,39). Additionally, through up-regulation of the sodium-driven clearance of alveolar fluid, and consequently a reduced risk of pulmonary oedema, the use of β_2 -adrenergic agonists may result in an improvement in the oxygen transfer from the alveoli to the arterial blood in elite endurance athletes with extreme demands to the oxygen transport system.

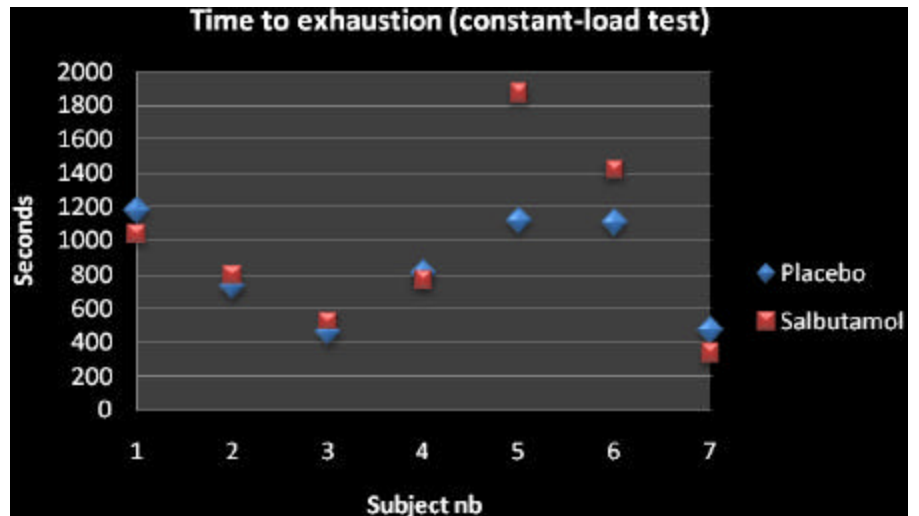


Figure 2. Scatterplot of the individual time to exhaustion during a constant-load test after administration of salbutamol and placebo in elite endurance athletes (n = 7).

Exercise induces potential problems related to the accuracy of pulse oximetry (motion artefacts, perfusion state, pH and temperature), and devices using finger probes have a tendency to underestimate SaO_2 (40). But even though the pulse oximeter used in this study was not evaluated against directly measured arterial blood samples during exercise in the same group of athletes, it did offer several advantages in a clinical setting, constantly offering a conservative estimate of SaO_2 .

Additionally, the validity and reliability of the pulse oximeter during different conditions (exercise, normoxia and hypoxia) are well documented (30-32).

There were no significant changes in terms of VO_2max under the two experimental conditions. Thus, this is a confirmation of the observations from previous studies (6-15,17,18). Additionally, in agreement with Dempsey's and Wagner's (20) suggestions, we found a moderate EIAH in both

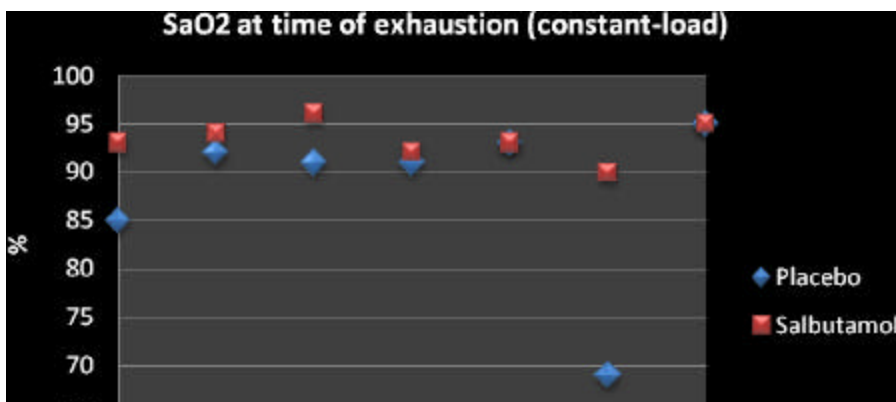


Figure 3. Scatterplot of the individual arterial oxygen saturation levels at the time of exhaustion during a constant-load test after administration of salbutamol and placebo (n = 7).

groups (SaO_2 between 88 – 93%) during the maximal oxygen consumption test. The detrimental effects of EIAH on the VO_2max are widely discussed. Koskolou and McKenzie (22) have suggested that SaO_2 has to be $< 87\%$ before it results in a poorer maximal oxygen uptake. Then again, Harms et al. (21) demonstrated that even a slight EIAH have a significant detrimental effect on VO_2max .

Stewart et al. (24) demonstrated no enhancement of arterial oxygen saturation during a maximal aerobic performance test when an acute, inhaled therapeutic dose of salbutamol was administered to highly trained non-asthmatic athletes with EIAH. When focusing on SaO_2 at the time of VO_2max , our findings correspond with this, even though salbutamol in this study was administered orally (table 2). In contrast, after administration of salbutamol, arterial oxygen saturation levels were increased at the time of exhaustion during the constant-load test; from 88.0% in the placebo group to 93.3%. According to the previous mentioned suggestions by Dempsey and Wagner, this should be regarded as a shift from moderate to mild (SaO_2 between 93 – 95%) EIAH (20). Even though this finding was not significant ($P = 0.15$), we propose it should be regarded as a trend. When the arterial saturation levels are integrated with the pulmonary function results, our data suggest that the mechanism for EIAH is at least partly airway calibre. Though, the influence of a possible increased clearance of alveolar fluid, thereby reducing the risk for pulmonary oedema and consequently a decrement of a possible diffusion limitation and higher arterial saturation levels, should not be disregarded (20).

The increment of 14.9% in time to exhaustion after administration of salbutamol was not significant ($P = 0.60$), and the individual response after administration of salbutamol compared to placebo was rather diverged (from -29.0% to +67.0%). Consequently, a higher number of subjects would be desirable, but this turned out to be difficult due to the high demands before a subject could be included in the protocol. On the other hand, Cohen's d was 0.41, and according to Cohen's revised criteria for effect sizes, this should be considered as a moderately large effect size, with an approximate non-overlap of 28% in the two distributions (41). Additionally, the results should be seen in the light of the test chosen for this study. Anyone using a constant-power test to monitor for small changes in performance will see much larger changes in time to exhaustion, but against a background of much more noise. When the change or noise in time to exhaustion is converted back into the change or noise in mean power, constant-load tests are actually more reliable than other tests (37), probably due to the fact that the subjects do not have to pace themselves in these tests. Coefficients of variability for constant-load tests-retests in athletes with a durability from 1 – 60 min have been reported to be approximately 10-30% (42-44), and when considering the report by Hopkins and co-workers in terms of assessment of performance (45), where they propose, that anything that can change the performance $\frac{1}{2}$ the coefficient of the variability of a test, is likely to change finishing position in a race, the increment of 14.9% in this study is likely to be meaningful in a competitive situation, and it should not be seen as meaningless.

Due to the fact that coefficients of variability in physical performance tests are lower in athletes than in non-athletes (37), our results do support the conclusion of Collomp et al. (26), which after oral administration of salbutamol demonstrated an increment in time to exhaustion of approximately 19% in moderately trained, healthy men when cycling at 80-85% of VO_2max . Thus, an increased time to exhaustion of 14.9% in elite endurance trained athletes should probably be regarded more meaningful in a race than the 19% in just moderately trained subject. The present study also corresponds with the results of Van Baak et al. (27), which suggested that in moderately trained, healthy men oral administration of 4 mg salbutamol leads to an improvement in the time to exhaustion (~ 29%) if side-effects are not experienced. Summarized, these three studies propose an ergogenic effect of orally administered salbutamol, and should be considered as a counterweight to studies, which have demonstrated no significant changes in a 20 km cycling time trial after inhalation of salbutamol, regardless of dose administered (17,46).

When focusing on heart rate, we did not observe any statistically significant changes between placebo and salbutamol during all stages of exercise. This corresponds with previous studies, which after oral administration as well as inhalation of salbutamol have demonstrated no significant

difference in cardiovascular variables between salbutamol and placebo, both in asthmatics and non-asthmatics (9,12,13,17,27,47,48).

We did not find any statistically significant changes in plasma concentrations of lactate. This does not correspond with other studies, who have found increased lactate plasma concentrations after systemic administration of salbutamol during exercise (26-28). Furthermore, we did not see any changes in the respiratory exchange ratio (RER), which together with the plasma concentration of lactate, are indirect measures of carbohydrate oxidation and glycolytic flux. Therefore, the present study can not support the suggestion of a possible performance enhancement in a race situation through an increased β_2 -adrenergic receptor-mediated glycolytic flux in skeletal muscle.

CONCLUSIONS

In conclusion, after administering a single oral therapeutic dose (4 mg) of the β_2 -adrenergic agonist salbutamol to healthy, elite endurance trained male athletes, acute ergogenic effects were shown in terms of a reduced extent of EIAH as well as an increment in time to exhaustion during a constant-load test, which indicated a meaningful performance-enhancing effect in a race situation.

ACKNOWLEDGEMENTS

We are grateful to L. Bülow and K.-L. Rygaard for aid during the test sessions.

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REFERENCES

1. Carlsen KH, Anderson SD, Bjermer L, Bonini S, Brusasco V, Canonica W, Cummiskey J, Delgado L, Del G, Sr., Drobnic F, Haahtela T, Larsson K, Palange P, Popov T, Van CP. Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. *Allergy* 2008 April;63(4):387-403.
2. Weiler JM, Layton T, Hunt M. Asthma in United States Olympic athletes who participated in the 1996 Summer Games. *J Allergy Clin Immunol* 1998 November;102(5):722-6.
3. Weiler JM, Ryan EJ, III. Asthma in United States olympic athletes who participated in the 1998 olympic winter games. *J Allergy Clin Immunol* 2000 August;106(2):267-71.
4. Alaranta A, Alaranta H, Palmu P, Alha P, Pietila K, Heliövaara M, Helenius I. Asthma medication in Finnish olympic athletes: no signs of inhaled beta2-agonist overuse. *Med Sci Sports Exerc* 2004 June;36(6):919-24.
5. Lund T, Pedersen L, Larsson B, Backer V. Prevalence of asthma-like symptoms, asthma and its treatment in elite athletes. *Scand J Med Sci Sports* 2008 February 17.

6. Bedi JF, Gong H, Jr., Horvath SM. Enhancement of exercise performance with inhaled albuterol. **Can J Sport Sci** 1988 June;13(2):144-8.
7. Carlsen KH, Ingjer F, Kirkegaard H, Thyness B. The effect of inhaled salbutamol and salmeterol on lung function and endurance performance in healthy well-trained athletes. **Scand J Med Sci Sports** 1997 June;7(3):160-5.
8. Fleck SJ, Lucia A, Storms WW, Wallach JM, Vint PF, Zimmerman SD. Effects of acute inhalation of albuterol on submaximal and maximal VO₂ and blood lactate. **Int J Sports Med** 1993 July;14(5):239-43.
9. Freeman W, Packe GE, Cayton RM. Effect of nebulised salbutamol on maximal exercise performance in men with mild asthma. **Thorax** 1989 November;44(11):942-7.
10. Heir T, Stemshaug H. Salbutamol and high-intensity treadmill running in nonasthmatic highly conditioned athletes. **Scand J Med Sci Sports** 1995 August;5(4):231-6.
11. Larsson K, Gavhed D, Larsson L, Holmer I, Jorfelt L, Ohlsen P. Influence of a beta2-agonist on physical performance at low temperature in elite athletes. **Med Sci Sports Exerc** 1997 December;29(12):1631-6.
12. McKenzie DC, Rhodes EC, Stirling DR, Wiley JP, Dunwoody DW, Filsinger IB, Jang F, Stevens A. Salbutamol and treadmill performance in non-atopic athletes. **Med Sci Sports Exerc** 1983;15(6):520-2.
13. Meeuwisse WH, McKenzie DC, Hopkins SR, Road JD. The effect of salbutamol on performance in elite nonasthmatic athletes. **Med Sci Sports Exerc** 1992 October;24(10):1161-6.
14. Morton AR, Joyce K, Papalia SM, Carroll NG, Fitch KD. Is salmeterol ergogenic? **Clin J Sport Med** 1996 October;6(4):220-5.
15. Sandsund M, Sue-Chu M, Helgerud J, Reinertsen RE, Bjermer L. Effect of cold exposure (-15 degrees C) and salbutamol treatment on physical performance in elite nonasthmatic cross-country skiers. **Eur J Appl Physiol Occup Physiol** 1998 March;77(4):297-304.
16. Signorile JF, Kaplan TA, Applegate B, Perry AC. Effects of acute inhalation of the bronchodilator, albuterol, on power output. **Med Sci Sports Exerc** 1992 June;24(6):638-42.
17. Sporer BC, Sheel AW, McKenzie DC. Dose response of inhaled salbutamol on exercise performance and urine concentrations. **Med Sci Sports Exerc** 2008 January;40(1):149-57.
18. Stewart IB, Labreche JM, McKenzie DC. Acute formoterol administration has no ergogenic effect in nonasthmatic athletes. **Med Sci Sports Exerc** 2002 February;34(2):213-7.
19. World Anti-Doping Agency. **The World Anti-Doping Code - The 2008 Prohibited List (International Standard)**. http://www.olympic.org/uk/utilities/reports/level2_uk.asp?HEAD2=1&HEAD1=1 8 A.D. May 22;
20. Dempsey JA, Wagner PD. Exercise-induced arterial hypoxemia. **J Appl Physiol** 1999 December;87(6):1997-2006.

21. Harms CA, McClaran SR, Nickele GA, Pegelow DF, Nelson WB, Dempsey JA. Effect of exercise-induced arterial O₂ desaturation on VO₂max in women. **Med Sci Sports Exerc** 2000 June;32(6):1101-8.
22. Koskolou MD, McKenzie DC. Arterial hypoxemia and performance during intense exercise. **Eur J Appl Physiol Occup Physiol** 1994;68(1):80-6.
23. Sartori C, Allemann Y, Duplain H, Lepori M, Egli M, Lipp E, Hutter D, Turini P, Hugli O, Cook S, Nicod P, Scherrer U. Salmeterol for the prevention of high-altitude pulmonary edema. **N Engl J Med** 2002 May 23;346(21):1631-6.
24. Stewart IB, Labreche JM, McKenzie DC. Effect of a long- and short-acting beta₂-agonist on exercise-induced arterial hypoxemia. **Med Sci Sports Exerc** 2003 April;35(4):603-7.
25. Walker SR, Evans ME, Richards AJ, Paterson JW. The clinical pharmacology of oral and inhaled salbutamol. **Clin Pharmacol Ther** 1972 November;13(6):861-7.
26. Collomp K, Candau R, Collomp R, Carra J, Lasne F, Prefaut C, De CJ. Effects of acute ingestion of salbutamol during submaximal exercise. **Int J Sports Med** 2000 October;21(7):480-4.
27. Van Baak MA, Mayer LH, Kempinski RE, Hartgens F. Effect of salbutamol on muscle strength and endurance performance in nonasthmatic men. **Med Sci Sports Exerc** 2000 July;32(7):1300-6.
28. Hallen J, Saltin B, Sejersted OM. K⁺ balance during exercise and role of beta-adrenergic stimulation. **Am J Physiol** 1996 June;270(6 Pt 2):R1347-R1354.
29. Aastrand PO, Rodahl K. **Textbook of Work Physiology**. New York: McGraw-Hill; 1987.
30. Barthelemy JC, Geysant A, Riffat J, Antoniadis A, Berruyer J, Lacour JR. Accuracy of pulse oximetry during moderate exercise: a comparative study. **Scand J Clin Lab Invest** 1990 September;50(5):533-9.
31. Hannhart B, Haberer JP, Saunier C, Laxenaire MC. Accuracy and precision of fourteen pulse oximeters. **Eur Respir J** 1991 January;4(1):115-9.
32. Shitikov II, Flerov EV, Arsen'ev SB. [A comparative study of five pulse oximeters]. **Med Tekh** 1993 January;(1):21-4.
33. Evans ME, Walker SR, Brittain RT, Paterson JW. The metabolism of salbutamol in man. **Xenobiotica** 1973 February;3(2):113-20.
34. Jonkman JH, Freie HM, van der Boon WJ, Grasmeijer G. Single dose absorption profiles and bioavailability of two different salbutamol tablets. **Arzneimittelforschung** 1986 July;36(7):1133-5.
35. Morgan DJ, Paull JD, Richmond BH, Wilson-Evered E, Ziccone SP. Pharmacokinetics of intravenous and oral salbutamol and its sulphate conjugate. **Br J Clin Pharmacol** 1986 November;22(5):587-93.

36. Powell ML, Weisberger M, Gural R, Chung M, Patrick JE, Radwanski E, Symchowicz SS. Comparative bioavailability and pharmacokinetics of three formulations of albuterol. **J Pharm Sci** 1985 February;74(2):217-9.
37. Hopkins WG, Schabert EJ, Hawley JA. Reliability of power in physical performance tests. **Sports Med** 2001;31(3):211-34.
38. Collomp K, Le PB, Portier H, Lecoq AM, Jaffre C, Beaupied H, Richard O, Benhamou L, Courteix D, De CJ. Effects of acute salbutamol intake during a Wingate test. **Int J Sports Med** 2005 September;26(7):513-7.
39. Miyachi M, Tabata I. Relationship between arterial oxygen desaturation and ventilation during maximal exercise. **J Appl Physiol** 1992 December;73(6):2588-91.
40. Yamaya Y, Bogaard HJ, Wagner PD, Niizeki K, Hopkins SR. Validity of pulse oximetry during maximal exercise in normoxia, hypoxia, and hyperoxia. **J Appl Physiol** 2002 January;92(1):162-8.
41. Cohen J. **Statistical power analysis for the behavioral sciences**. 2nd ed. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
42. Jeukendrup A, Saris WH, Brouns F, Kester AD. A new validated endurance performance test. **Med Sci Sports Exerc** 1996 February;28(2):266-70.
43. Jeukendrup AE, Currell K. Should time trial performance be predicted from three serial time-to-exhaustion tests? **Med Sci Sports Exerc** 2005 October;37(10):1820.
44. McLellan TM, Cheung SS, Jacobs I. Variability of time to exhaustion during submaximal exercise. **Can J Appl Physiol** 1995 March;20(1):39-51.
45. Hopkins WG, Hawley JA, Burke LM. Design and analysis of research on sport performance enhancement. **Med Sci Sports Exerc** 1999 March;31(3):472-85.
46. Norris SR, Petersen SR, Jones RL. The effect of salbutamol on performance in endurance cyclists. **Eur J Appl Physiol Occup Physiol** 1996;73(3-4):364-8.
47. Lenna TM, McKenzie DC. The asthmatic athlete: metabolic and ventilatory responses to exercise with and without pre-exercise medication. **Int J Sports Med** 1997 February;18(2):142-8.
48. Violante B, Pellegrino R, Vinay C, Selleri R, Ghinamo G. Failure of aminophylline and salbutamol to improve respiratory muscle function and exercise tolerance in healthy humans. **Respiration** 1989;55(4):227-36.