

The effects of salmeterol on power output in nonasthmatic athletes

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Background: Salmeterol xinafoate is a new aerosol inhalant that is used in the treatment of asthma. It is currently banned by the International Olympic Committee because of the concern that it may lend an unfair competitive advantage to the user.

Objective: The purpose of this study was to determine whether salmeterol improves short-term anaerobic performance in elite nonasthmatic track cyclists.

Methods: Eleven elite track cyclists volunteered to perform a 30-second all-out cycle ergometer test 3 hours after receiving either 42 µg of salmeterol xinafoate or placebo applied in a double-blind crossover procedure. During the ergometer test, peak power output, total work, time to peak power, and percent fatigue (decline in power output) were measured. Pulmonary measurements were also taken before and at various time points after inhalation and the ergometer test. A methacholine challenge was administered to each subject before participation in the study to ensure that none of the subjects had any reactive airway diseases.

Results: There were no significant differences ($p > 0.05$) between the placebo and salmeterol trials for peak power output, total work performed during the 30-second test, percent fatigue, and time to peak power. No differences between trials were observed for the pulmonary function test variables at any of the time points. Blood lactate concentrations before and after administration of drug or placebo were also not significantly different between trials. Additionally, salmeterol did not affect the maximal heart rate achieved during the test as compared with the placebo.

Conclusion: Short-term salmeterol use within the prescribed dosage was not shown to increase short-term power output in nonasthmatic cyclists. (*J Allergy Clin Immunol* 1997;99:443-9.)

Key words: Salmeterol, performance, track cyclists, Wingate

Salmeterol xinafoate (Serevent) is a new sympathomimetic aerosol inhalant that is used in the treatment of asthma. Like its chemical analog, albuterol, it is a β_2 -adrenergic bronchodilator but is unique structurally in that it possesses a long lipophilic N-substituent side chain that permits binding with greater affinity at the β -adrenoceptor site. This side chain allows repeated contact with the receptor while it remains anchored at the exosite resulting in an extended duration of action

Abbreviations used

FEF _{25-75%} :	Forced expiratory flow between 25% and 75% of FVC
FVC:	Forced vital capacity
PEFR:	Peak expiratory flow rates
PP:	Peak power
TTPP:	Time to peak power
TW:	Total work

that produces bronchodilation for approximately 12 hours.¹ The onset of effective bronchodilation occurs 10 to 20 minutes after administration of a 42 µg dose, and maximum improvement occurs within approximately 180 minutes.² Additionally, salmeterol has the highest β_2 -selectivity of any of the currently available β -agonists, and its bronchodilator effects are approximately 10 times more potent than those of albuterol.^{3,4} In contrast to other β_2 -agonists, such as albuterol and formoterol, the interaction of salmeterol is apparently noncompetitive, and it does not readily dissociate from its membrane-binding sites (half-life >300 minutes vs 2 to 6 minutes for albuterol and formoterol). These binding characteristics thus account for salmeterol's sustained pharmacologic activity.⁴

Salmeterol has been shown to be effective in the treatment of patients with asthma by preventing bronchoconstriction induced by methacholine, histamine, allergens, hyperventilation of cold air, or exercise.⁵⁻⁹ Importantly, salmeterol is more effective than albuterol in reducing the incidence of nocturnal awakenings and daily symptoms and produces greater mean areas under the curve for FEV₁ and greater increases in morning and evening peak expiratory flow rates (PEFRs).^{1,10} As a result, several authors have concluded that for the management of mild-to-moderate asthma, salmeterol, when administered twice daily, is superior to albuterol.^{1,10,11} One disadvantage, however, is that effective bronchodilation and peak improvement in FEV₁ do not occur until approximately 20 and 180 minutes after inhalation, respectively. Salmeterol is, therefore, not recommended for treatment of acute asthmatic symptoms.

Although albuterol is the most commonly prescribed medication for exercise-induced asthma, salmeterol's longer-lasting effects may make its use by athletes with asthma preferable for competitive events or situations that occur over 2 to 6 hours.¹² The concern, however, is that because of its sympathomimetic properties, salmeterol may lend an unfair competitive advantage to the

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TABLE I. Thirty-second Wingate data (mean $\pm$ SEM)

	Placebo	Salmeterol	% Change	95% Confidence interval
Peak power (W)	1050.73 $\pm$ 36.21	1052.27 $\pm$ 40.01	+0.14	(-27.60, 30.69)
Peak power $\cdot$ kg ⁻¹ (W $\cdot$ kg ⁻¹)	14.20 $\pm$ 0.19	13.76 $\pm$ 0.42	+3.10	(-1.48, 0.60)
Total work (J)	23,093 $\pm$ 667.5	23,595 $\pm$ 867.65	+2.13	(-260.53, 1263.44)
Total work $\cdot$ kg ⁻¹ (J $\cdot$ kg ⁻¹)	318.23 $\pm$ 7.27	313.23 $\pm$ 9.50	+1.57	(-3.42, 15.96)
Time to peak power (sec)	4.73 $\pm$ 0.30	4.64 $\pm$ 0.24	-1.90	(-0.56, -0.38)
Fatigue (%)	48.28 $\pm$ 2.63	47.71 $\pm$ 2.62	-1.18	(-3.88, 2.75)
Peak heart rate (beats $\cdot$ min ⁻¹)	182.64 $\pm$ 4.35	183.64 $\pm$ 3.28	+0.54	(-6.30, 8.30)
Resting lactate value (mmol $\cdot$ L ⁻¹)	1.27 $\pm$ 0.10	1.56 $\pm$ 0.13	+18.6	(-0.02, 0.60)
Three-minute post-Wingate lactate value (mmol $\cdot$ L ⁻¹)	13.21 $\pm$ 0.78	12.97 $\pm$ 0.57	-1.82	(-1.55, 1.07)

user. As a result, salmeterol is currently listed as banned by the International Olympic Committee.¹³ To our knowledge, however, there have been no studies that have investigated the potential ergogenic effects of salmeterol in nonasthmatic subjects. Thus the purpose of this study was to examine the effects of salmeterol on anaerobic performance in a group of nonasthmatic well-trained cyclists. Variables determined were peak power (PP), total work (TW), time to peak power (TTPP), percent fatigue (or percent of decline in power output from peak to final value), peak heart rate, lung function, and blood lactate concentrations.

METHODS

Study design

Subjects visited the laboratory on four occasions to perform a 30-second Wingate bicycle ergometer test at a set resistance. The Wingate test consisted of a 30-second, maximal-power output test on a modified Monarch bicycle ergometer (Yamaguchi, Inc., Colorado Springs, Colo.). During the first visit, subjects were instructed as to the protocol of the Wingate test, and a maximal practice trial was performed. Subjects were also instructed in the use of an inhaler and allowed to practice with a placebo (propellants, trichloromonofluoromethane and dichlorodifluoromethane with oleic acid). During the second visit, another practice Wingate test was performed, followed by instruction and practice of the pulmonary function testing procedures. During this visit, all subjects were also administered a methacholine challenge to determine whether they had asthma. If subjects were diagnosed as nonasthmatic, they were allowed to continue with the testing procedures. For the third and fourth visits, either a placebo or salmeterol was administered in a double-blind crossover fashion 4 hours before a Wingate test. There was a 4-hour period between administration of the drug and the Wingate test to allow time for the bronchodilatory effects of salmeterol to peak. Five of the subjects received the salmeterol before the first Wingate test, and six received the placebo. The treatments were then crossed over for the second test day. Test sessions were separated by no less than 1 day and no more than 2 days, and within subjects testing was performed at the same time each day. Subjects were instructed to refrain from hard training 2 days before both tests.

Subjects

Eleven male U.S. Cycling Federation category I ($n = 6$) and category II ($n = 5$) cyclists served as subjects in this investigation. Category I is the highest amateur ranking for cyclists, and

category II is one level below category I. Written consent was obtained from all subjects after they were informed of the possible risks involved in participation in the study. The subjects' mean ($\pm$ SEM) age, height, and body mass were 24.64 $\pm$ 1.11 years, 170.27 $\pm$ 6.45 cm, and 74.39 $\pm$ 2.93 kg, respectively.

Methacholine challenge

The methacholine challenge test was performed as previously described.¹⁴ This was administered to exclude any patients with reactive airway disease. All spirometry tests were performed by using a spirometer (Multi Spiro; Incorporated Equipment, Phoenix, Ariz.) from which FEV₁, forced vital capacity (FVC), and forced expiratory flow between 25% and 75% of FVC (FEF_{25-75%}) were determined. Initially, three trials of a pulmonary lung function test were performed to establish a baseline (FEV₁ values). The pulmonary function tests were then repeated 3 minutes after inhalation of saline solution and subsequent increasing doses of methacholine. The initial methacholine dose was 0.025 mg $\cdot$ ml⁻¹ followed by doses of 0.25, 2.5, and 25.0 mg $\cdot$ ml⁻¹. All doses were administered by inhaling five times for five consecutive breaths by using a nebulizer breath-actuated timing device (Doseminator; Medical Synergetics, San Diego, Calif.). The criterion for administration of the next dose of methacholine was an FEV₁ greater than 80% of the saline FEV₁. If the FEV₁ value was less than 80% of the saline FEV₁, a recovery period of 10 minutes was allowed, and the FEV₁ test was administered again. At this point, if the FEV₁ value was still less than 80% of the saline FEV₁, the test was terminated, and the subject was considered asthmatic and ineligible for continued participation in the study. If the FEV₁ was greater than 80% of the saline FEV₁, the test was continued, and the next dose of methacholine was administered. Only those subjects who maintained an FEV₁ above 80% of the value obtained with saline solution for all the methacholine doses were identified as nonasthmatic subjects and continued to participate in this study.

Salmeterol dose

The recommended dose of 42 μ g was delivered to each subject by two inhalations from an inhaler with each actuation delivering 21 μ g of salmeterol xinafoate. Seventeen-gram canisters, containing 200 inhalations per canister (Severent; Allen and Hanburys, Research Triangle Park, N.C.) or placebo, were used to deliver the inhalant. The inhalations were separated by 1 minute, and subjects were required to hold their breath for 15 seconds after each inhalation. The placebo was administered in the same manner from an identical-looking canister. The placebo and salmeterol canisters were masked, such that nei-

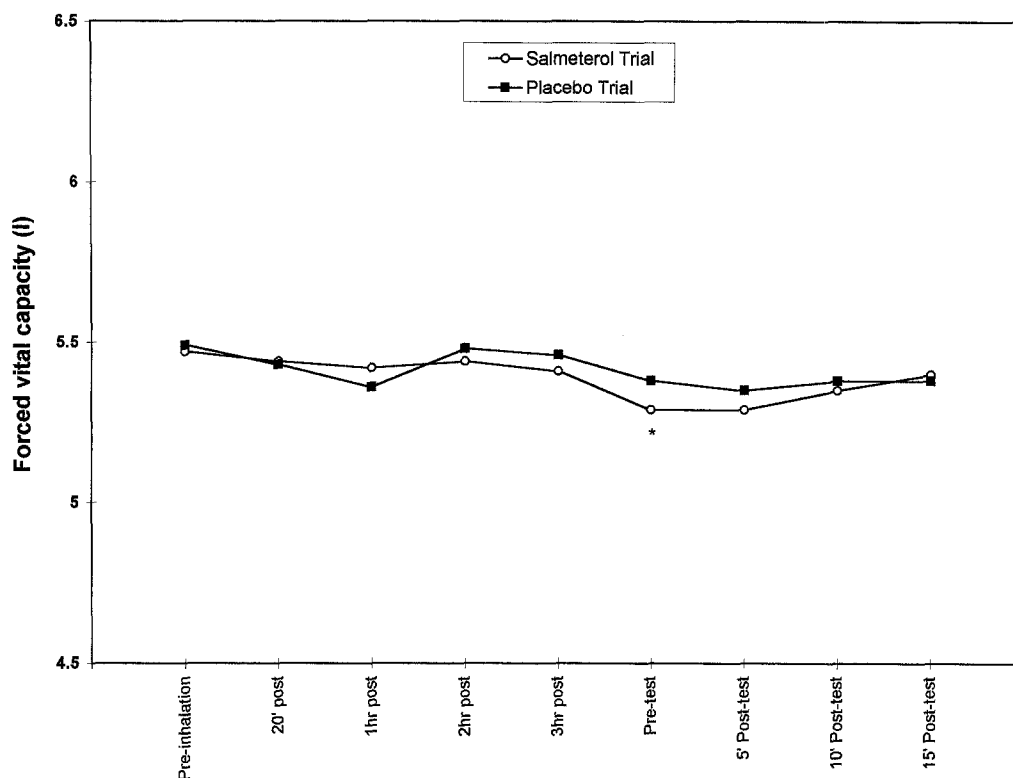


FIG. 1. Changes in FVC (in liters) during testing protocol (mean $\pm$ SEM). *Significant difference between salmeterol and placebo trials.

ther the subjects nor investigators knew which treatment was being administered.

Wingate test protocol

The Wingate test was administered 4 hours after inhalation of either salmeterol or placebo. Subjects were required to stay in the laboratory during this time. Seat height, handlebar height, seat position relative to the bottom bracket, and the distance from the seat to the handlebar were adjusted on the test bicycle to approximate the subjects' own bicycle as closely as possible. The recommended resistance for Wingate testing is 0.08 to 0.09 kg $\cdot$ (kg of body mass)⁻¹. However, higher loads have been shown to elicit maximal power outputs in trained subjects; thus, a resistance of 0.10 kg $\cdot$ (kg of body mass)⁻¹ was used in this study.^{15, 16} The resistance was applied by adding weights to a tray, which in turn applied resistance to a flywheel.

Before the test, subjects performed a warm-up with a resistance of 0.03 kg $\cdot$ (kg of body mass)⁻¹ at 60 pedal revolutions per minute (rpm), which was controlled by using a bicycle cyclometer (Cateye Micro Model CC-6000; Tsuyama Manufacturing Co., Ltd., Osaka, Japan). During the last 5 seconds of the third, fourth, and fifth minutes of the warm-up, subjects performed an all-out sprint. After the completion of the 5-minute warm-up, subjects rested passively for 2 minutes. After the 2-minute rest, subjects attained a pedal rate of 60 rpms by using the same resistance as during the warm-up. When subjects attained 60 rpms, a 5-second countdown was initiated. At the end of the 5 seconds, the remaining weight was added to attain a resistance of 0.10 kg $\cdot$ (kg of body mass)⁻¹. Simultaneously to the increase in resistance, the subjects initiated an all-out maximal effort on the ergometer for 30 seconds. During the test, the number of

flywheel revolutions was determined to the nearest one sixteenth of a revolution by using an SMI Opto-Sensor (Sports Medicine Industries, Inc., St. Cloud, Minn.), which contains a photogate that is tripped by a reflected infrared beam as the flywheel rotates. This was interfaced to a computer; and PP, TTPP, percent fatigue, and TW outputs were calculated by using the computer program SMI Extend v2.01 (Sports Medicine Industries, Inc.). Peak heart rates achieved during the test were determined by using a heart rate monitor (Polar USA Inc., Stamford, Conn.). Subjects were allowed a 3-minute active cooldown with a resistance of 0.5 kg.

Before the Wingate test, baseline whole blood lactate concentrations were determined from a 25 μ l sample obtained by means of a finger prick. The sample was analyzed by using an automated whole blood lactate analyzer (2300 STAT PLUS, YSI Inc., Yellow Springs, Ohio). After the cooldown (at 3 minutes after the test), a similar sample was obtained and analyzed for lactate concentration.

Pulmonary function tests

All pulmonary function tests were performed as previously described with standard pulmonary function equipment (Sensor Medics Corp., Anaheim, Calif.).¹⁷ A flow-volume loop was used to determine FEV₁, FVC, and FEF_{25-75%}. On the day of the test, subjects performed a pulmonary function test before inhalation of the drug or placebo. Pulmonary function tests were then performed 20 minutes, 1, 2, and 3 hours after the inhalation of placebo or salmeterol; 15 minutes before the Wingate test; and 5, 10, and 15 minutes after the Wingate test. Three trials were performed for the initial pulmonary test, and the best effort was used in the determination of all pulmonary

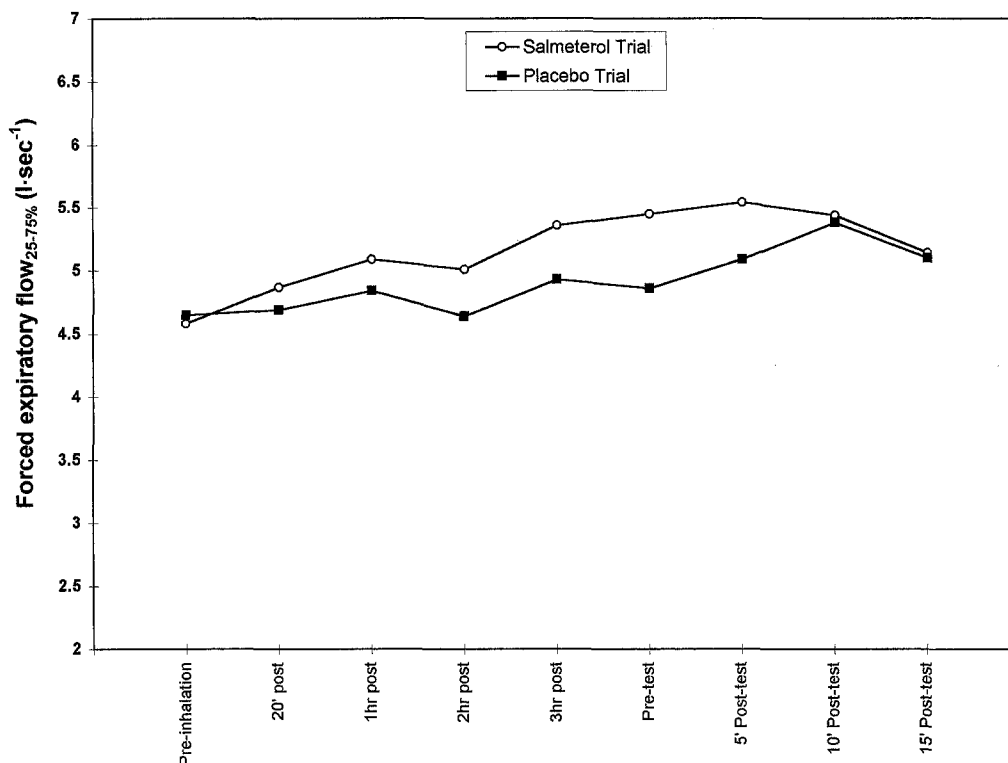


FIG. 2. Changes in FEF_{25-75%} (in liters per second) (mean $\pm$ SEM) during testing protocol.

variables. Only one trial was performed for all subsequent pulmonary function tests.

Statistical analysis

All variables were analyzed by using repeated-measures multivariate analysis of variance techniques (treatment vs workload). One-way bivariate analysis of repeated measures was used when significant main effects were observed. The 0.05 level of significance was used for all analyses.

RESULTS

Methacholine challenge

Mean resting FEV₁ before inhalation of methacholine was 4.9 ± 0.22 (mean $\pm$ SEM). The changes in FEV₁ after inhalation of 0.025, 0.25, 2.5, 10.0, and 25.0 mg $\cdot$ ml⁻¹ methacholine were $+0.53\% \pm 1.02\%$, $+0.27\% \pm 0.98\%$, $-0.43\% \pm 0.83\%$, $-2.48\% \pm 1.46\%$, and $-3.2\% \pm 2.32\%$, respectively. These results show that none of the subjects had obstructive airway disease.

Thirty-second Wingate cycle ergometer test

There were slight but nonsignificant ($p \geq 0.05$) changes in favor of the salmeterol trial for PP, TW, percent fatigue, TTPP, and peak heart rate (Table I). The percent changes for these variables ranged from 0.14% to 3.10%. PP and TW, when expressed relative to body weight, were also not significantly different between trials. In addition, no between-trial differences were observed for the resting and 3-minute post-Wingate blood lactate concentrations (Table I) and peak heart rates. There were also no differences between the

power variables from trial 1 to trial 2, indicating that no learning effect had occurred.

Pulmonary function tests

No significant differences were observed between the placebo and salmeterol trials for FVC, FEV₁, PEFR, or FEF_{25-75%} at any of the time points (Figs. 1-4). FVC for the salmeterol trial was significantly lower before the Wingate test as compared with the value before inhalation (Fig. 1). No significant differences were observed across time for FEV₁ or FEF_{25-75%} for either the placebo or salmeterol trials. FVC for the placebo trial was also not significantly different across time.

DISCUSSION

To our knowledge, no studies have investigated the effect of salmeterol use on either anaerobic performance or endurance. The results of this study demonstrated that short-term salmeterol use has no ergogenic effect on power output in elite nonasthmatic athletes. This was demonstrated by the lack of a statistically significant positive effect of salmeterol use on PP, TW, percent fatigue, and TTPP measured during a 30-second Wingate test as compared with the use of a placebo. There were, however, slight but nonsignificant changes in the power variables ($+0.14\%$ to $+3.1\%$) with salmeterol use. It could be argued that although these changes were not sufficient to produce statistical significance, the changes could be of practical significance in a sport in which even slight improvements in total power output

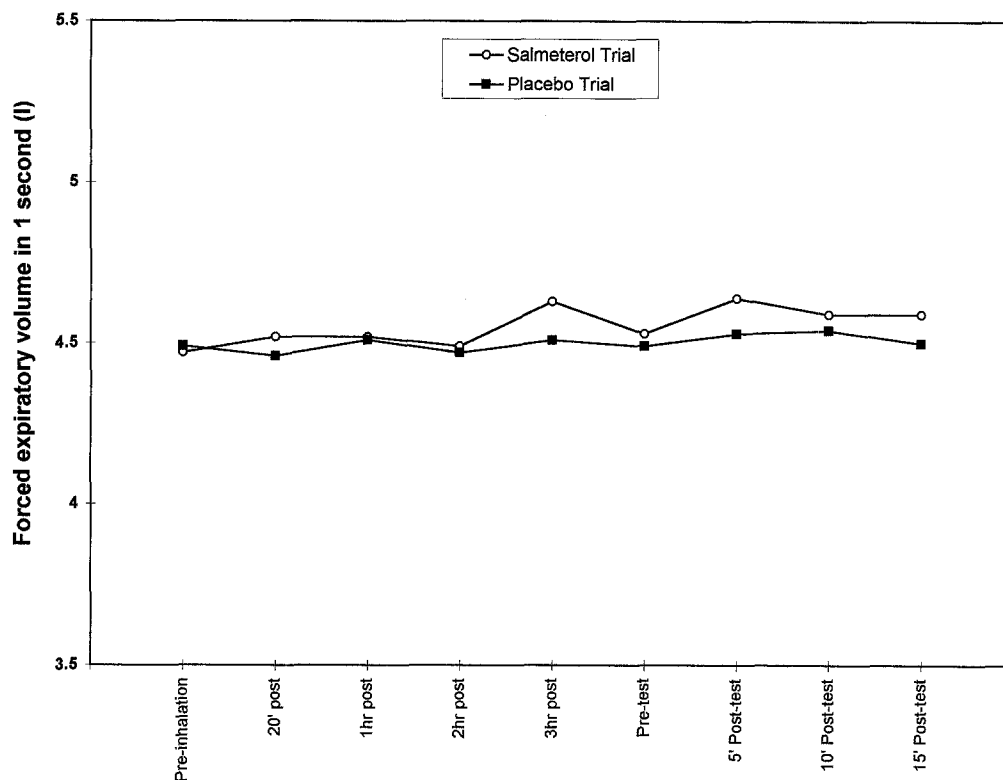


FIG. 3. Changes in FEV₁ (in liters) during testing protocol (mean $\pm$ SEM).

make the difference between winning and losing. Future studies, however, need to consistently show benefit with salmeterol use before such a conclusion can be made. Additionally, any inferences to performance are limited by lack of data regarding the sensitivity of the Wingate test in reflecting differences in track performance that are of practical significance. Thus it is difficult to comment on the potential performance benefits of the slightly higher power outputs achieved during the salmeterol trial.

The use of salmeterol also showed no enhancement of pulmonary function when measured 20 minutes and 1, 2, and 3 hours after inhalation, as well as 5, 10, and 15 minutes after the exercise challenge, as compared with a placebo. Thus short-term use of salmeterol appears to confer no pulmonary benefit to the nonasthmatic athlete.

Previous studies investigating the immediate effects of other β -agonists, such as albuterol, on performance have yielded mixed results.¹⁸⁻²⁰ The majority of evidence appears to indicate the absence of an ergogenic effect for these agents for both endurance and short-term power efforts.²¹⁻²⁴ However, support exists for the enhancement of muscular tension with use of sympathomimetic drugs because of their stimulatory effects on skeletal muscle through β_2 -receptors.²⁵ Stimulation of skeletal β_2 -receptors results in an influx of Ca^{++} into the sarcoplasm, resulting in an increase in the strength and duration of actin and myosin binding.²⁶ Thus theoretic-

ally, there is potential for enhancement of short-term power output with salmeterol, which is highly selective for β_2 -receptors. There is evidence, however, that after long-term training a downregulation of skeletal β_2 -receptor density occurs because of the increased exposure to exercise-induced elevations in blood catecholamine levels.²⁷⁻²⁸ This may explain, in part, the lack of positive effects in this study and the conflicting results of previous studies. For example, when active but untrained subjects were tested for Wingate performance, a significant positive effect for PP and percent fatigue was demonstrated after albuterol inhalation.¹⁹ However, in a subsequent study of elite track cyclists, no changes in Wingate power output measurements were noted after albuterol use.²¹ It was suggested that differences in these results were attributable in part to the lower β_2 -receptor density in the trained athletes, thus mitigating the effects of β_2 -agonists in skeletal muscle.²¹

The lack of an ergogenic effect in this study could also be due to the pharmacokinetics of salmeterol. Salmeterol acts locally in the lungs and is either undetectable or found in very low amounts in plasma. Reportedly, administration of the recommended dose of 42 μg produces low plasma concentrations with peak concentrations of only 150 $\text{pg} \cdot \text{mL}^{-1}$.² There is also no accumulation with repeated doses. Consequently, plasma levels do not predict therapeutic effect. Thus in this study it is plausible that the amount of drug delivered to skeletal muscle after inhalation may have been insufficient to

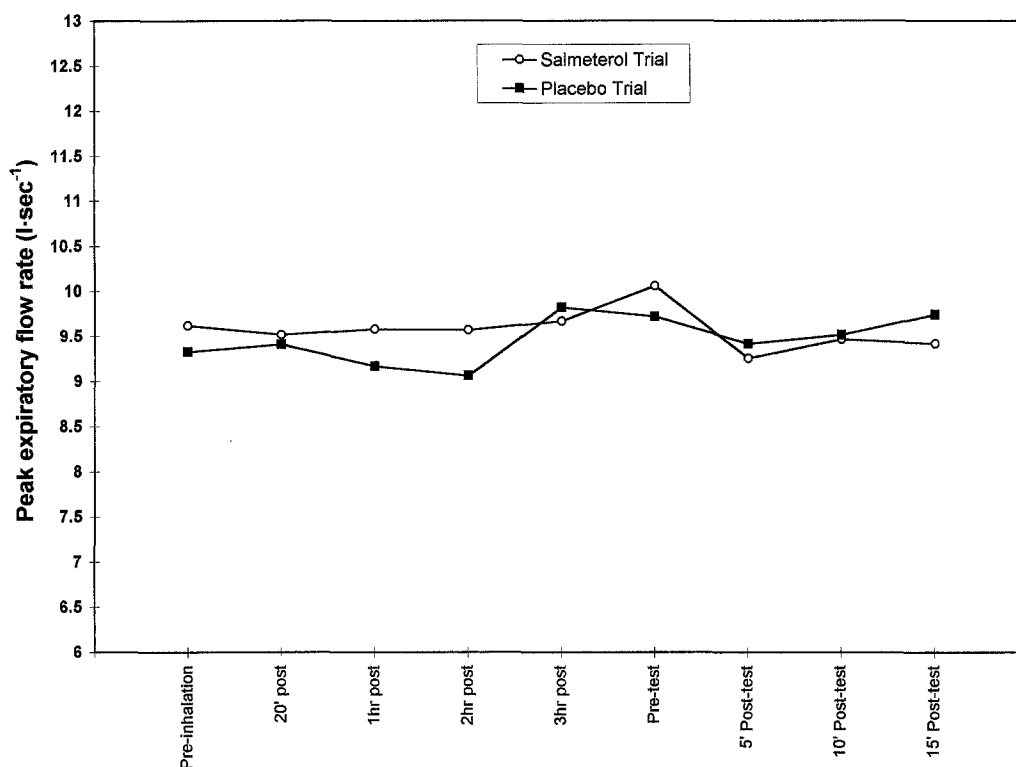


FIG. 4. Changes in PEFR (in liters per second) during testing protocol (mean $\pm$ SEM).

have stimulated β_2 -receptors and was thus ineffective in enhancing short-term power output. Large inhaled doses have been shown to yield proportionally increased blood levels, likely caused by absorption of the swallowed portion of the dose.² Future studies, therefore, need to investigate the effects of higher doses on power performance.

Although short-term exposure to salmeterol was not found to enhance power performance, effects of its long-term use on athletic performance need to be investigated. Long-term exposure to fenoterol, an analog of salmeterol, has been shown to improve muscle force production in animals. For example, 8 weeks of fenoterol administration was shown to increase total protein content of frog sartorius muscle and peak tetanic tension in the same muscle.²⁹ This occurred, however, without the confounding influence of training. Thus long-term exposure to low levels of plasma salmeterol may yield results different from those of this study.

The pulmonary function variables in this study showed no significant differences between the salmeterol and placebo trials. The postinhalation measurements were also not different from the preinhalation values for FEF_{25-75%}, PEFR, or FEV₁. FVC, however, was significantly lower at the time point before the Wingate test for the salmeterol trial as compared with the value before inhalation.

Previous studies with salbuterol or albuterol have shown enhancement of or no change in lung function

after inhalation of the drug.^{19, 21, 23, 24} Lemmer et al.,²¹ who also studied elite track cyclists, reported improvements in FEV₁, FEF, PEFR, and FEF_{25-75%} at various time points after inhalation of albuterol. No previous studies, however, have examined lung function changes in nonasthmatic subjects with salmeterol use. From the results of this study, it appears that salmeterol use does not enhance lung function in healthy subjects.

Blood lactate concentrations after Wingate tests were also not significantly different between the salmeterol and placebo trials. The similarity in blood lactate values after Wingate tests between trials suggests that salmeterol use did not act to delay anaerobic glycolysis, which could have resulted in lower blood lactate values and potentially greater power outputs. The lack of a significant effect on blood lactate concentrations in this study is in agreement with the results of Lemmer et al.²¹ who reported no difference in post-Wingate blood lactates after albuterol use, thus lending support for the neutral effect these β_2 -agonists have on anaerobic power generation.

Maximal heart rates achieved during the Wingate test also did not differ between trials. The heart rates in this study were consistent with those previously reported after albuterol use, when an identical Wingate protocol was used and similar subjects were studied.²¹ Reportedly, resting heart rates tend to increase from 4 to 10 beats/min and 3 to 16 beats/min after inhalation of albuterol and salmeterol, respectively.² Thus both drugs

appear to have similar effects on heart rate; however, the lack of significant difference between either salmeterol or albuterol use and the placebo trials on exercise heart rate indicates that the exercise-induced increase in heart rate superseded any effects the drug may have had on exercise heart rates.

In summary, the results of this study demonstrate that salmeterol has no significant effect on short-term power output in elite nonasthmatic cyclists. In addition, the drug does not affect lung function or maximal exercise heart rates and whole blood lactate concentrations after testing. Future studies need to examine the effects of doses that exceed the recommended amounts, as well as the effects of long-term use on performance.

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