THE EFFECT OF SALBUTAMOL ON PERFORMANCE IN ELITE NON-ASTHMATIC ATHLETES

by

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ABSTRACT

The effect of salbutamol on performance was studied in 7 male non-asthmatic elite (VO_{2max} ≥ 60 ml/kg/min) athletes. The subjects entered the study just prior to their competitive season. Salbutamol (2 puffs=200 μg) or placebo was administered by metered-dose inhaler, through a spacer device, 20 minutes prior to testing in a double-blind, randomized cross-over design. Pulmonary functions including maximum flow volume curves were performed on the first two visits, at 5 intervals (pre-medication, 20 minutes post-medication, and 5, 10, and 20 minutes post-exercise). The first two sessions combined these pulmonary function measures with an exercise bout consisting of a continuously ramped cycle ergometer ride to exhaustion to determine maximal oxygen uptake (VO_{2max}), peak power, and maximal heart rate. Pulse oximetry was used to measure the oxygen saturation of hemoglobin. The next sessions involved performing a 45 minute ride at 70% of VO_{2max}, followed by a timed sprint to exhaustion. Lastly, a Wingate anaerobic test was used to measure total work and peak power.

There was a non-significant decrease in VO_{2max} from a mean of 63.5 ml/kg/min (± 3.2) for the placebo (P) trial, to a mean of 62.6 (± 3.3) with salbutamol (S). No difference was found in peak power (P= 438 Watts ±26.3, S= 438 ±27.9) or maximum heart rate (P=191 beats/min ±5.4, S=191 ±6.0). The performance related variables of endurance sprint time (P=104 seconds ±22.8, S= 97 ±31.4), and Wingate peak power (P= 10.12 Watts/kg ±0.57, S= 9.97 ±0.60) showed a non-significant decrease, while the total work performed on the Wingate test (P= 19.30 kJ ±2.09, S= 19.61 ±1.54) displayed a non-significant increase. The data failed to show significance

despite using statistical analysis with a level of significance of $p<0.20$ to maximize the power of the tests.

There was a statistically significant ($p<0.05$) increase in post medication (pre-exercise) forced expiratory volume (FEV_1) of 4.5% with salbutamol. This baseline increase persisted post-exercise, but there was no interaction effect of salbutamol and placebo over time. This represents an expected effect in non-asthmatic individuals, and although statistical significance was achieved, the magnitude of difference is not considered to be clinically significant.

It was concluded that a therapeutic dose of aerosol salbutamol does not have an ergogenic effect in elite non-asthmatic athletes and it is therefore recommended that inhaled salbutamol continue to be permitted in international competition for individuals with exercise induced asthma.

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List of Symbols

ß	beta
AMP	adenosine monophosphate
ATP	adenosine triphosphate
cAMP	cyclic adenosine monophosphate
FEF_{25-75}	mid-maximal expiratory flow
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
IOC	International Olympic Commission
VO_{2max}	maximal oxygen consumption

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The completion of a work such as this represents not only the investigation of a research question, but also an exploration of self. It is through this process that a scientist is born, and also that an individual grows. For this, I would like to gratefully acknowledge my advisors Drs. Doug Clement, Jack Taunton, and Jeremy Road for their help and guidance. Special appreciation goes to my committee chairman, Dr. Don McKenzie both for his continued support and thoughts in helping this study out of its embryonic stages. I am indebted to the subjects for volunteering their time, and for the assistance of Dr. Sue Hopkins. Thanks also go to Dr. Bob Schutz for his help in the statistical analysis, and Dr. Gord Matheson for his encouragement and advice. I also wish to thank Sport Canada for their financial support in this worthwhile endeavor.

I dedicate this work to my wife Mary Beth for her affection, encouragement and good humor in helping me through while nurturing our unborn child.

INTRODUCTION

Exercise induced asthma (EIA) is a clinical entity that affects approximately 10% of athletes [87]. Standard treatment and prophylaxis involves the use of inhaled salbutamol, which is widely accepted as the treatment of choice in EIA [5, 24, 30, 49, 79]. It is sanctioned by the International Olympic Committee for use in competition when accompanied by a medical letter [83]. This medication exerts its effect by selective action on the Beta-2 (β_2) receptors in bronchial and vascular smooth muscle, in addition to other sites in the heart, uterus, and muscle. Its effectiveness in treating EIA is well established and is one of its principle therapeutic indications [69]. The mechanism by which this occurs is via a direct effect on the airways to prevent bronchoconstriction and mediator release. Additionally, it is thought that the medication-induced bronchodilation could compensate for constriction during exercise [79].

Because of its widespread use, concerns have been raised as to the potential performance enhancing properties of salbutamol [8]. There are data that indicates that salbutamol does not give an unfair advantage to asthmatics; the only change found was a reduction in the degree of post-exercise bronchoconstriction [28, 40, 75]. Several authors have studied the effect of salbutamol on performance in non- asthmatic athletes, with conflicting results. McKenzie (1983) found no difference in VO_{2max}, or pulmonary function in trained runners [61]. However, Bedi (1988) found an increase in post-medication pulmonary function, in addition to an improvement in sprint time following an endurance ride [8].

The issue of performance enhancement has two implications. First, salbutamol has been shown to be a safe, very effective and easy to

administer medication [61]. Banning its use unnecessarily would likely preclude some asthmatics from participation in competitive sport, as alternative drugs are not as effective.

Secondly, if it was found to have a performance enhancing effect, it would be at risk of becoming an abused medication.

The purpose of this study is to more firmly establish the effect of salbutamol on performance through the determination of a variety of pulmonary and performance indices in a homogeneous group of elite athletes.

METHODS

DESIGN

This study was conducted with a double-blind, randomized crossover design. The subjects were tested in random order under both experimental conditions. These included placebo or salbutamol (2 puffs = 200 μg), 20 minutes prior to exercise. The experiment received approval from the University of British Columbia Committee on Human Experimentation.

SUBJECTS

The subjects included 7 volunteer elite male athletes ($V0_{2max}$ >/ 60 ml/kg/min) from a convenience sample of cyclists residing locally, who were competitive at a category 3 (provincial) level or higher. All subjects were entering their competitive season at the time of investigation. They were required to undergo screening with a medical history and physical examination to exclude those subjects with a history of asthma or atopy. Exclusion criteria included any suggestion of cough or wheezing post-exercise, in association with respiratory tract infections, or on exposure to other airway irritants. Any allergies or use of medication was noted.

The pulmonary function data was analyzed post-hoc to ensure the subjects did not have asthma or exercise-induced asthma. Those with a significant post-exercise fall in FEV_1 under the placebo condition were excluded. Prior to entering the study, informed consent was obtained.

EXPERIMENTAL PROCEDURES

Three different performance related measures were obtained on separate laboratory visits, under both the placebo and salbutamol

conditions, for a total of 6 sessions. The subjects were requested to not perform an exhaustive training session or race 24 hours prior to the laboratory visits.

For each testing session, the subjects took 2 puffs from a coded metered-dose inhaler containing either placebo or salbutamol (1 puff=100 μg). The inhalers were individually (randomly) coded, and labelled as 'A' or 'B', thereby blinding both the subject and the investigator as to their contents. Since the subjects were not accustomed to using inhalers, a Vent-a-haler® spacer devise was used to ensure proper delivery of the compound, and to avoid the learning effect common with the use of inhalers.

This procedure was repeated approximately 1 week later using inhaler 'A' for the first trial, and inhaler 'B' for the second.

i) Maximal Oxygen Uptake and Pulmonary Function Tests:

Upon arrival, each subject had their height and weight recorded, after which their pulmonary functions were measured. This consisted of a flow-volume loop using a Medical Graphics Metabolic cart with 1070 Pulmonary Function Software. Calibration was performed prior to each session. With this and subsequent measures, three trials were performed in a standing position, and the data from the trial with the highest forced expiratory volume in 1 second (FEV_1) was recorded as the measure for that point in time. The trial was considered valid if the value was close to (>90%) the predicted value.

The subject then took 2 inhalations as described above. After 20 minutes, the pulmonary functions were repeated. Immediately thereafter, a maximal oxygen uptake test was performed on a Mijnhardt electronically-

braked cycle ergometer. It was continuously ramped at 30 watts per minute until exhaustion prevented the subject from continuing. Oxygen (VO_2) uptake, carbon dioxide (VCO_2), and ventilation (VE) were measured on a breath-by-breath basis using the Medical Graphics cart with the 2001 exercise system. The heart rate was recorded using a Physio-Control Lifepac 6 ECG monitor, linked to the metabolic cart. These data were subsequently calculated by the system software and reported as 15 second averages.

Lastly, a Puritan Bennett Datex pulse oximeter was attached to the ear lobe permitting measurement of the oxygen saturation of hemoglobin. As the design of this device is based on a plethysmographic wave recording, the pulse and signal quality could also be noted and compared to the ECG monitor. Values were noted and recorded at 1, 5, 10, 12, and 15 minutes and at exhaustion. Maximal oxygen uptake (VO_{2max}) was calculated as the four highest consecutive 15 second values.

Pulmonary function was repeated at 5, 10 and 20 minutes of recovery, again taking the best of three trials at each time. Of the values obtained on collecting flow-volume loops, the forced expiratory volume in 1 second (FEV_1) was the pulmonary parameter that was specifically analyzed.

ii) Endurance Sprint Test:

Approximately 1 week after the VO_{2max} tests, the subjects completed a 45 minute endurance ride followed by a maximal sprint to volitional exhaustion. The 45 min. ride was performed on the same cycle ergometer at approximately 70% of VO_{2max}, calculated as an average of trials A and B.

Metabolic measurements were taken initially and at 10 minute intervals throughout the ride to measure VO_2. The work load was adjusted to ensure the subject was exercising at 70% of maximum.

At the 45 minute mark, the work load was set to the highest power output attained during either of the VO_{2max} rides (100% VO_{2max}), and the subject sprinted until voluntary exhaustion. Endurance sprint time in seconds was calculated starting when the new work load had reached the full level (typically after 20 seconds), and stopping when the pedal cadence fell below 60 revolutions per minute despite encouragement.

iii) Wingate Anaerobic Test

The third performance related test consisted of a 30 second maximal sprint. It was conducted using a Monarch cycle ergometer linked to an IBM-XT computer loaded with Labtech Notebook data acquisition software. The workload was calculated as follows:

Workload (Kp) = weight (kg) X 0.075

This value was rounded up to the next 0.5 Kp level. As the subject increased the revolutions, the load was abruptly added and time started. The total work (Joules) and 5 second average of peak power (Watts/kg) were calculated from the raw data with the software program.

STATISTICAL ANALYSIS

The dependent variables of VO_{2max}, endurance sprint time, peak power, maximum heart rate, Wingate total work and Wingate peak power were analyzed with a t-test for dependent means over the placebo and salbutamol trials. The level of significance (alpha) was set a-priori at $p<0.20$ to maximize the power of the tests, and thus increase the ability to detect a small difference in outcome.

Since it was decided a-priori that there was an expected increase in FEV_1 with administration of salbutamol, the FEV_1 data were treated with 2 statistical procedures. First, a t-test for dependent means was applied to the pre and post-medication values to examine this expected effect. Acknowledging that there was a medication main effect, an analysis of variance (ANOVA) with repeated measures was conducted on the post-medication and post-exercise values to examine any interaction of the experimental condition over time.

The oxygen saturation of hemoglobin was analyzed with a 2X6 ANOVA for repeated measures with trend analysis.

All analysis was performed on an Apple Macintosh SE/30 computer using DataDesk Professional statistical software (Odesta Corp.), with the exception of the ANOVA which was done using BMDP:2V software on the U.B.C. mainframe computer.

RESULTS

The demographic data on the subjects are presented in Table 1. No subject was on any medication, and none had a history of atopy.

TABLE I : Summary of Physical Characteristics

Parameter	Subject							Mean	Std. Dev
	1	2	3	4	5	6	7		
Age (years)	23	23	24	27	19	25	24	24	2.4
Height (cm)	183	182	189	178	185	185	187	184	3.6
Weight (kg)	72	72	71	72	68	72	87	73	6.1
VO_{2max}(ml/kg/min)	61	69	64	60	63	62	62	63	3.0

Cardiopulmonary physical examination was entirely normal in all subjects.

No significant difference in V02 max, endurance sprint time,peak power, max. heart rate, Wingate total work or peak power was found with salbutamol when compared to placebo. The means and standard deviations are shown in Table 2, and the results are presented in graphical format in Figures 1 to 6.

Table II : Summary of Data

Dependent Variable	Condition	SUBJECTS							MEAN	Std. Dev.	P
		1	2	3	4	5	6	7			
V02 max (ml/kg/min)	Placebo	60.8	68.7	64.9	59.1	62.6	63.0	65.4	63.5	3.17	
	Salbutamol	61.1	69.3	63.5	61.4	62.8	61.5	58.8	62.6	3.29	NS
Peak Power (Watts)	Placebo	452	451	444	405	415	417	479	438	26.3	
	Salbutamol	435	475	441	402	414	424	473	438	27.9	NS
Max Heart Rate (beats/min)	Placebo	183	199	193	189	189	197	190	191	5.4	
	Salbutamol	183	200	194	192	188	193	184	191	6.0	NS
Endurance Sprint Time (seconds)	Placebo	119	83	97	113	144	90	81	104	22.8	
	Salbutamol	100	99	78	41	138	124	97	97	31.4	NS
Wingate Total Work (kJoules)	Placebo	19.08	19.00	19.87	17.25	17.67	18.65	23.58	19.30	2.086	
	Salbutamol	18.82	19.61	19.61	18.56	19.09	18.65	22.97	19.61	1.537	NS
Wingate Peak Power (Watts/kg)	Placebo	10.10	10.69	10.58	9.19	9.55	10.14	10.59	10.12	0.570	
	Salbutamol	9.92	10.82	9.63	9.13	10.60	9.56	10.14	9.97	0.597	NS

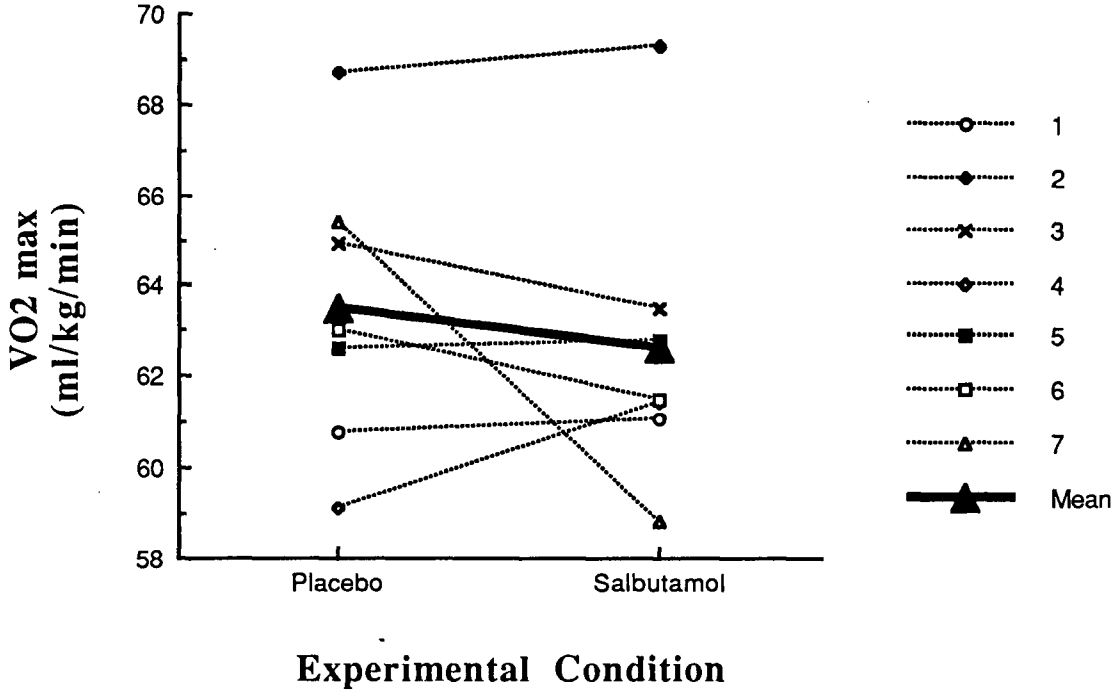

Figure 1 **Maximal oxygen uptake** under experimental and placebo conditions - individual and mean values plotted (p=0.45)

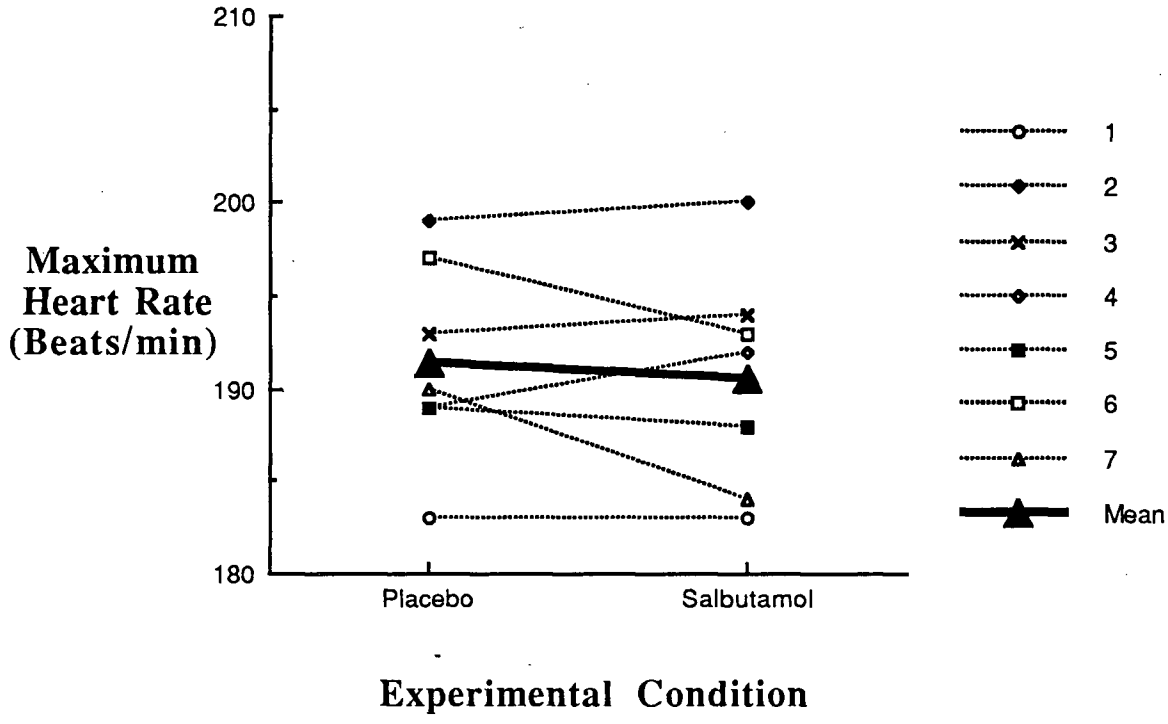

Figure 2 **Maximum heart rate** during VO_{2max} ride - under experimental and placebo conditions - individual and mean values plotted (p=0.50)

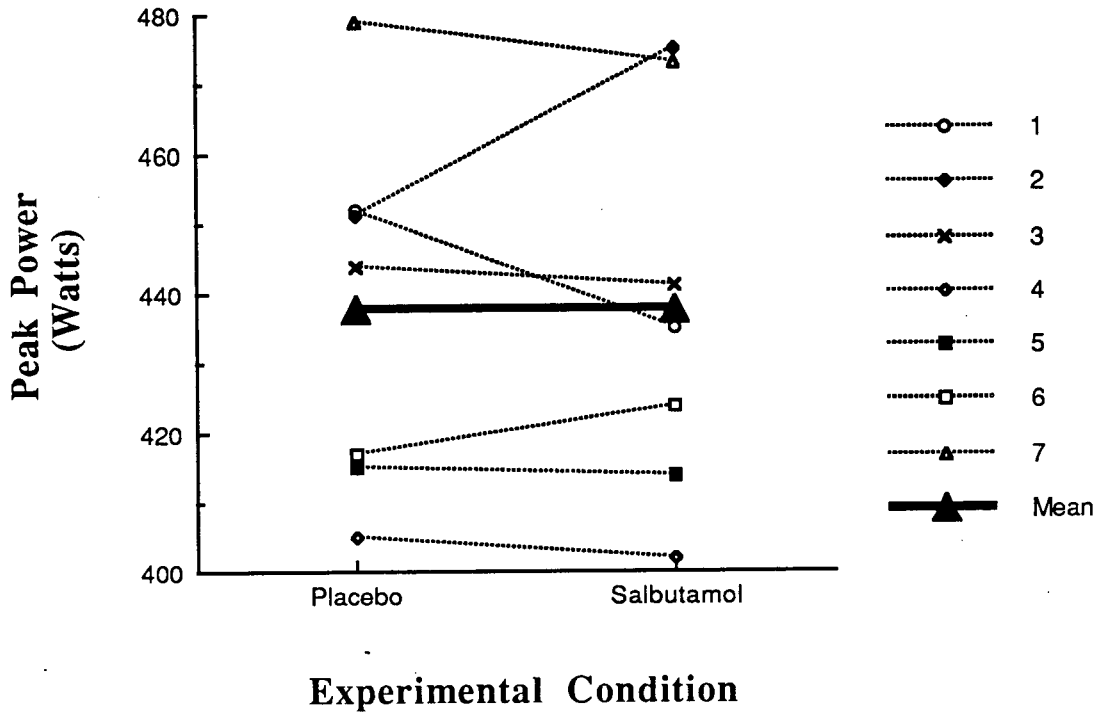

Figure 3 Peak power during VO_{2max} ride - under experimental and placebo conditions - individual and mean values plotted (p=0.98)

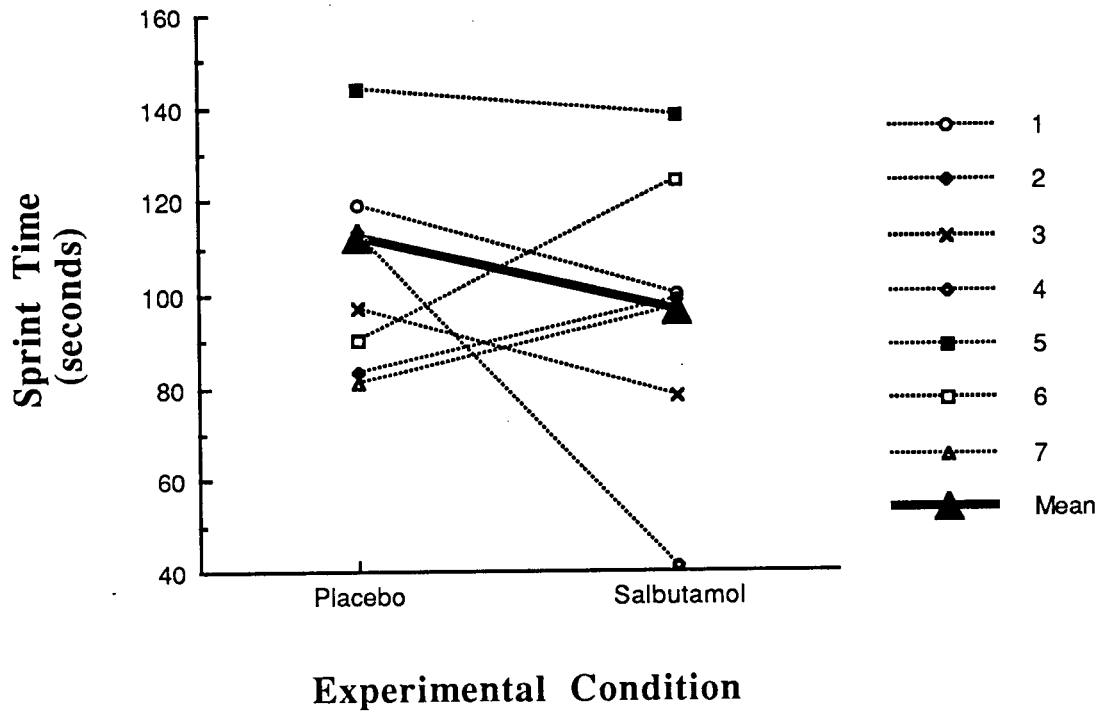

Figure 4 Endurance sprint time - under experimental and placebo conditions - individual and mean values plotted (p=0.61)

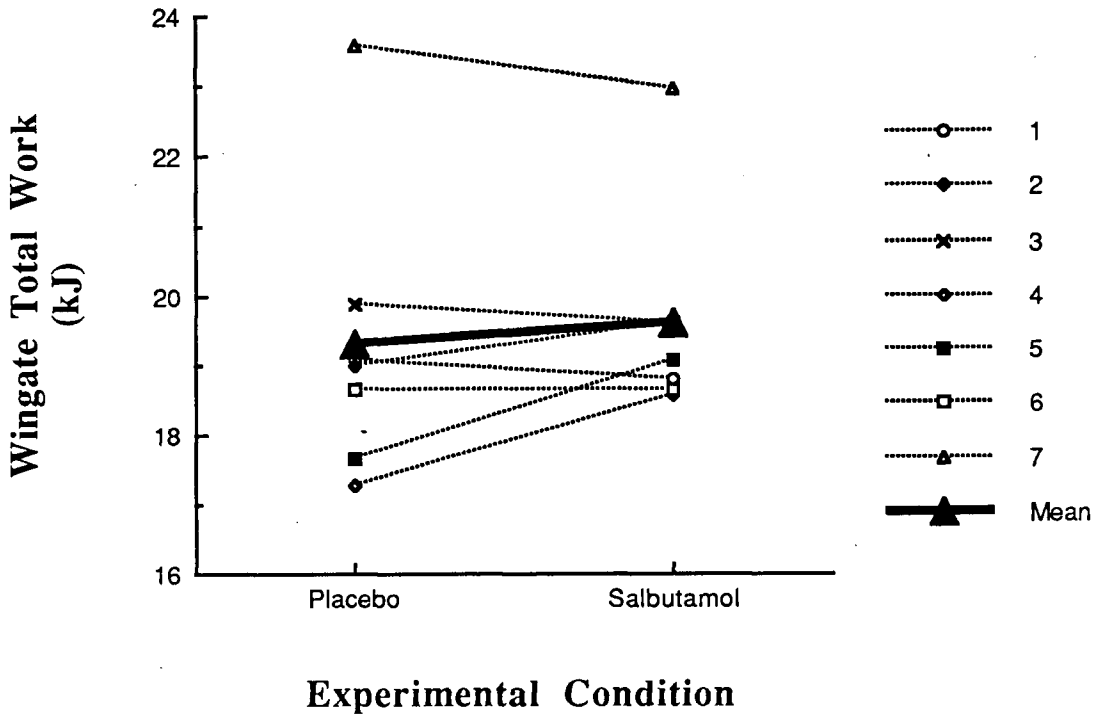

Figure 5 Wingate total work (kJoules) under experimental and placebo conditions- individual and mean values plotted (p=0.34)

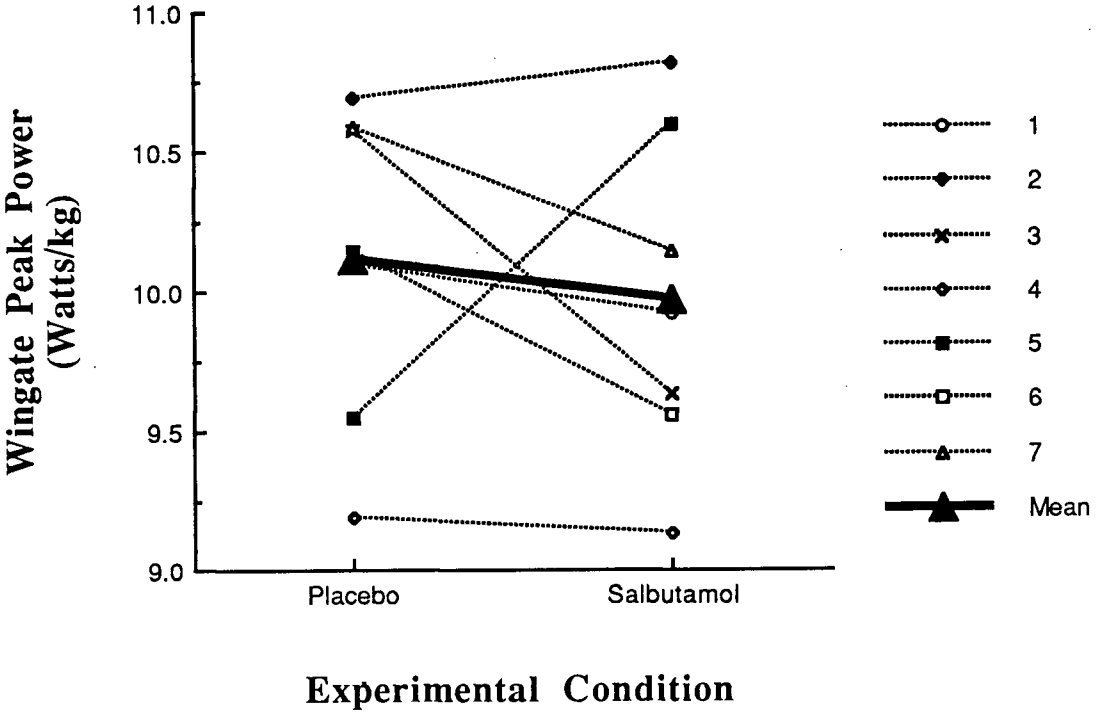

Figure 6 **Wingate peak power** - under experimental and placebo conditions - individual and mean values plotted (p=0.56)

There was a statistically significant increase in post medication FEV_1 under the salbutamol condition, at a $p<0.05$ level ($p=0.002$). The amount of mean change (pre-post medication) in FEV_1 with salbutamol was 4.5%.

Table III : FEV-1 Data

Condition	Time	FEV-1 (L/sec)							MEAN	Std. Dev.
		1	2	3	4	5	6	7		
Placebo	pre -med	4.40	5.16	5.18	5.02	5.53	4.55	4.76	4.94	0.40
Placebo	post -med	4.43	5.12	5.19	5.07	5.47	4.63	4.73	4.94	0.36
Placebo	5 min	4.67		5.37	5.32	5.15	4.80	4.94	5.04	0.28
Placebo	10 min	4.62	5.10	5.30	5.43	5.45	4.69	5.02	5.09	0.34
Placebo	20 min	4.67	5.00	5.23	5.24	5.46	4.63	4.79	5.00	0.32
Salbutamol	pre -med	4.36	4.98	5.00	5.14	5.44	4.26	4.81	4.85	0.42
Salbutamol	post -med	4.88	5.18	5.18	5.13	5.54	4.57	5.07	5.07	0.30
Salbutamol	5 min		5.36	5.18	5.32	5.49	4.67	4.96	5.16	0.30
Salbutamol	10 min	4.97	5.30	5.21	5.42	5.55	4.60	5.11	5.17	0.31
Salbutamol	20 min	4.90	5.33	5.14	5.26	5.56	4.58	5.15	5.13	0.32

Analysis of variance of the pre and post-exercise FEV_1 data showed a significant time main effect , with a mean increase peaking 10 minutes post-exercise (see Figure 7). Observation of the above table shows that 2 data points are missing at the 5 min. post-exercise point. Since all subjects had their highest FEV_1 at 10 min post-exercise, a factitious value was calculated for the missing data points as an average of the post-med and 10 min. values. This was done only for the purposes of running the ANOVA, to avoid the elimination of these two subjects from analysis.

As previously acknowledged, there was a medication main effect with the pre-post medication t-test. However, in analyzing the interaction of medication and time over the last 4 data points, no significant difference

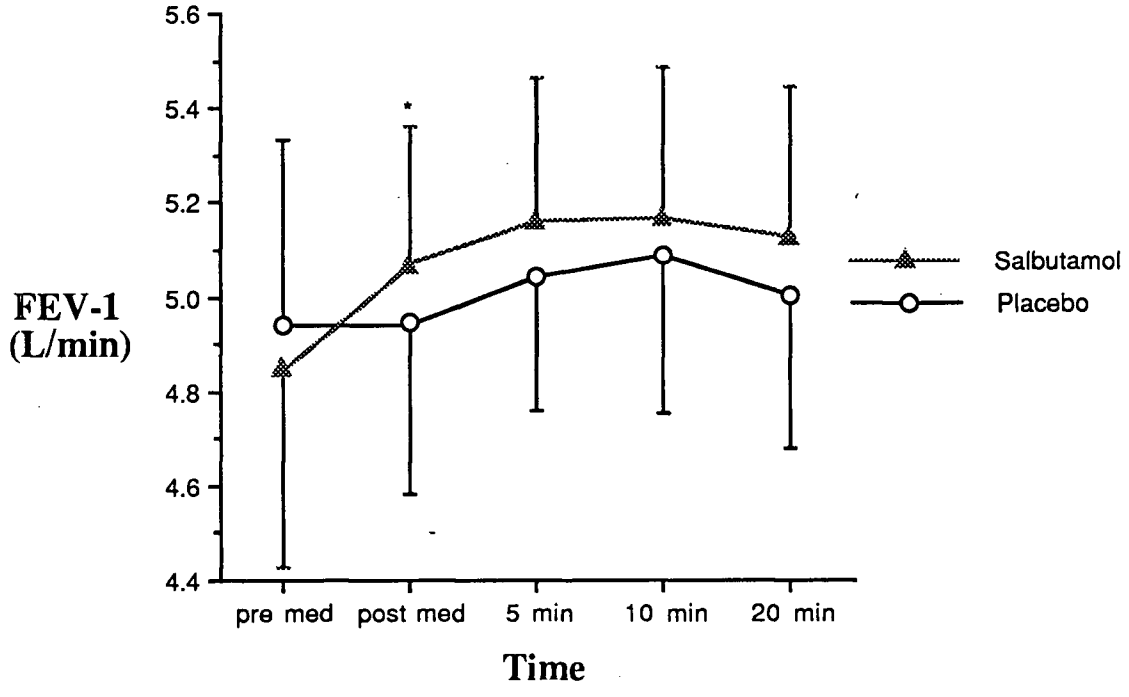

Figure 7 FEV_1- with error bars of ±1 S.D. Mean values are plotted under experimental and placebo conditions (* significant at $p \leq 0.05$ ($p=0.013$) for pre-med - post-med t-test).

was found, meaning that once salbutamol had changed the pre-exercise baseline, there was no effect of the medication on the pattern of change over time.

In examining the oximetry readings of oxygen saturation, it was found that the signal was lost at fatigue. Since the oximetry pulse was measured with a plethysmographic wave that was displayed on a cathode ray tube, we were able observe signal degradation at exercise, which correlated exactly (by definition) with a difference in the pulse rate compared to that seen on direct ECG monitoring. Indeed, this occurred with all but one subject, who showed no desaturation at fatigue. All other subjects displayed a saturation reading of ≥95% until partial or complete loss of signal, suggesting that no desaturation occurred.

DISCUSSION

The findings of this study demonstrate that 200 μg of salbutamol delivered by metered dose inhaler 20 minutes before exercise does not have an effect on the performance-related variables: VO_{2max}, maximum heart rate, or peak power during a maximal exercise test. The specific performance measures of sprint time (following an endurance ride), or total work and peak power (during a Wingate anaerobic test) did not differ significantly under the experimental condition.

The change in pulmonary flow, as measured by the forced expiratory volume in 1 second (FEV_1) after administration of salbutamol is an expected effect, as salbutamol is known to cause bronchodilation. In fact, the dose required to produce this effect is lower in non-asthmatics as compared to asthmatics [6]. The test itself has a significant degree of variability, with a coefficient of variation in the neighborhood of 3 percent. This is evident in our results, with a difference in the pre-medication FEV_1 means of 2%. Since no intervention had yet been applied, the difference is effectively the coefficient of variation for this experiment. The magnitude of mean change in FEV_1 after salbutamol was 4.5%. Although this was statistically significant when compared to placebo, it does not represent a clinically significant change. Usually a difference of ≥10% is needed to be considered clinically significant [30]. Similar changes have been reported in other studies [31].

The inability to measure the oxygen saturation of hemoglobin by means of a pulse oximeter was due to a loss of a reliable pulse signal. Since the pulse reading was based on a plethysmographic signal, we observed that the pulse rate at or near exhaustion dropped with respect to that reported on the ECG monitor, thereby invalidating any saturation reading. On

observing the status of the subject at the point of signal degradation, it was apparent that the skin had become mottled. This was suggestive of cutaneous vasoconstriction which presumably occurred in light of the increased metabolic demands of maximal exercise. This effect has not been observed in less elite athletes [82]. However, signal failure is acknowledged as being the most significant limitation of oximetry, and has been noted in hypothermic patients where perfusion is reduced [63].

These results support the findings of McKenzie et al. (1983) who found no change in VO_{2max}, anaerobic threshold, ventilation, or heart rate in highly trained non-asthmatic runners [61]. Their protocol differed slightly in that after baseline testing the subjects took 2 puffs, 4 times daily of inhaled salbutamol for a week preceding the follow-up, with the last dose 30 minutes prior to exercise testing.

The findings concur, in part, with the work of Bedi et al. (1988) in that a post medication rise in FEV_1 was observed with salbutamol. In their study, the same medication protocol as this study was used, and a mean rise in FEV_1 of 3.0% was observed with salbutamol [8].

In contrast to Bedi et al. (1988), no increase was observed in sprint time after an endurance ride at 70% of VO_{2max}. In fact, a non-significant decrease in sprint time was found. This may be due to the fact that the present study used a homogeneous group af elite athletes who, by selection, were of similar ability and experience. Those used in Bedi's study were of varying athletic ability and background, and the performance of 2 outliers accounted for the main effect in the difference of the means. One subject in the present study showed a disproportional decrease, but removal of this 'outlier' would not have changed our results. Given that there was a wide standard deviation in the results, and that the test-retest correlation was low

(r=.21) in this study, the endurance sprint test is not a very good measure of performance. In Bedi's work the standard deviation was wider, so the correlation would likely have been even lower.

On reviewing the literature, there appears to be several mechanisms through which salbutamol could hypothetically have an effect on performance.

In addition to the respiratory system, effects of salbutamol have been noted due to ß2-adrenergic receptor stimulation in the heart and skeletal muscle. Systemic effects including glycogenolysis [71], hypokalemia [72], lipolysis [77] and increased levels of serum insulin [71] have also been found.

The effect of salbutamol on muscle has been studied, and it has been shown to increase contractility and fast-twitch fibre response [91]. There have also been conflicting reports in the animal literature regarding the ability of salbutamol to increase muscle mass [70, 89]. However, in performance studies on non-asthmatics, no difference was found in muscle strength or respiratory muscle function with either oral or intravenous salbutamol [42, 86].

The cardiovascular effects include a lowering of systemic vascular resistance causing a fall in systolic blood pressure, plus a positive inotropic and chronotropic effect centrally [12, 38, 65]. A direct vasodilatory effect on coronary vessels has also been demonstrated [19, 33, 77].

Most research to date has focused on the use of parenteral and oral forms, or higher doses of the inhaled medication, and therefore the ability to extrapolate the results to studies using therapeutic inhaled doses may be somewhat in question. However, they do suggest a mechanism by which subtle changes could effect performance.

Several studies assessing these mechanisms with inhaled salbutamol observed a ceiling effect in the bronchodilatory response in both normal and asthmatic individuals [28, 53]. In contrast, Lipworth and McDevitt (1989), did find a change in heart rate and blood pressure that became manifest at a dose of >1.0 mg. and did not exhibit a ceiling in the dose-response curve [53].

These various changes could in theory have some effect on performance. However, in commenting on the cardiovascular changes with intravenous salbutamol, Imai et al. (1975) felt that the ability to produce changes in vitro, or in isolation would be of minimal significance under normal physiologic conditions since they would be completely masked by the response to increased oxygen demand [39].

An additional hypothesis would be that there may be little effect in exercise due to the fact that changes in vascular resistance, blood flow, contractility, etc. would already be maximized. The results of this study would lend support to this theory in that no difference was found in maximal heart rate. Also, no difference was found in other exercise studies, regardless of whether parenteral, oral or inhaled salbutamol was used [28, 40, 42, 61, 75, 86]. Thus, the same may be expected of other parameters.

In summary, no performance enhancing effect was observed with a therapeutic dose of aerosolized salbutamol when administered to elite male non-asthmatic cyclists. Currently, salbutamol is permitted in the aerosol form by the Medical Commission of the IOC, providing notification is given prior to competition [83]. Fitch (1986) made a strong point for not only allowing salbutamol, but even removing it from the list of notifiable medications, and our results would add strength to that position [24].

Based on the results of this study, it is recommend that inhaled salbutamol, in therapeutic doses, continue to be permitted for use in athletic competition, as no ergogenic effect could be expected from its use.

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APPENDIX A - Review of Literature

EXERCISE INDUCED ASTHMA

i)Introduction

Asthma is a disease of reversible airway obstruction (bronchospasm) that affects 5-10 % of the population [75]. Exercise-induced asthma (EIA) is airway reactivity precipitated by exercise, and has been outlined in numerous comprehensive reviews in the past [3, 11, 21, 60, 80]. In fact, EIA was described as early as 1697 by Willis who noted a clear association between exercise and asthma [3]. It is part of the spectrum of asthma and may occur as a manifestation of a long term asthmatic condition, or as a clinical entity on its own. The presence of EIA does not preclude participation in elite athletics, with Voy (1986) reporting a 10% incidence among the US athletes who participated in the 1984 Los Angeles Olympic Games [87].

The clinical spectrum of disease in EIA is well recognized [78]. Typically, athletes experience chest tightness with coughing and decreased ventilatory capacity. Pulmonary obstruction reaches its peak 5-10 minutes post exercise and spontaneously resolves after 20-120 minutes [75, 87]. Studies on asthmatic children have shown a post-exercise fall in FEV1 in the order of 15% [46].

ii) Pathogenesis:

There have been many mechanisms proposed as to the etiology of EIA, and considerable debate still exists about the relative importance of each. McFadden (1979) described the heat-flux hypothesis, based on the

theory that airway cooling and dehydration was the primary mechanism responsible for the bronchoconstriction [60]. In earlier work, Strauss et al. (1978) had demonstrated that EIA was completely abolished when 100% humidified air was given to subjects during exercise [84]. Additional studies have found similar results [4, 21, 47].

Other factors have been proposed including lactic acidosis, stimulation of pharyngeal receptor or carotid bodies, the release of stored chemical mediators, hypocapnea, and an imbalance of alpha and beta-sympathomimetic discharge [3, 60].

Regardless of the initial trigger, there seems to be little disagreement on the mechanism of the reaction itself. After the inciting event, bronchial smooth muscle contraction occurs, with a varying degree of hyperemia, mucosal edema and histamine release from mast cell degranulation. De Marzo (1989) found that the bronchial smooth muscle molecular structure differed in asthmatics, which might be the basis for the difference in normal versus reactive airways [16].

iii) Diagnosis

In a survey of Olympic athletes, Voy (1986) found that 90% of athletes with EIA were detected through the use of a questionnaire that selected those that regularly used a bronchodilator, who had a history of asthma, or who had a positive history of chest tightness, wheezing or cough related to or following strenuous exercise. Resting pulmonary function studies were not found to be helpful in detecting athletes with EIA, but post-exercise measurement of FEV_1 showed a predictable fall [87]. Jones (1963) felt that this post-exercise decrease in flow is so specific that a lack of it should lead one to reconsider the diagnosis [44].

However, Bundgaard (1986) felt that exercise is not the best test to diagnose EIA, as inhalation challenge tests are more specific [11]. The difficulty with this statement is that several studies have noted that inhalation challenge produces unreliable results [10, 13, 45]. An additional problem arises in determining valid measurements for trained athletes, as there is evidence that different prediction equations should be used [66].

iv) Treatment

EIA may be treated in a variety of ways. Firstly, it may be reduced or abolished by the use of a proper warm-up [84]. McLuckie (1986) demonstrated that the use of a 15 min continuous warm-up significantly reduced post-exercise bronchoconstriction in asthmatics [62]. Edmunds (1983) reported that this was due to a refractory period of 30-90 minutes that followed an initial episode of bronchconstriction [20]. If the initial exercise produces a more severe bronchoconstriction, the subsequent inhibition tends to be more complete [21].

The avoidance of other triggers to EIA such as cold, dry air, and hyperventilation can also play a role in its management. Katz (1986) suggested exercising in a warm, humid environment, using nasal breathing, and avoiding hyperventilation by breathing slower and deeper, in addition to doing a proper warm-up [47]. Exercise itself can be therapeutic in those with asthma or EIA [27].

Once these factors are maximized, the mainstay of treatment is pharmacotherapy.

PHARMACOTHERAPY

Recently, Fitch (1986) published an excellent review of the medications used in EIA, and discussed their potential effect on performance [24]. There are 5 main classes of medications including the methyl xanthines, corticosteroids, sodium cromoglycate, belladonna alkaloids, and sympathomimetics. Currently, the International Olympic Commission (IOC) has sanctioned the use of all these medications in international competition, with the exception of certain sympathomimetics [83].

i) Methyl Xanthines

One of the most well known compounds in this category is caffeine, which is permitted in competitive sports, up to a urine level of 12 micrograms per milliliter [83]. It has been shown to have a bronchodilatory effect in asthmatic children and adolescents [7]. However, it has not been used as a bronchodilator therapeutically.

Theophylline is a medication that has been in use for many years, with improved efficacy since the introduction of sustained-release compounds, and a recognition of the need to monitor serum concentrations [24]. It has been shown to be effective in the treatment of EIA [23]. However, there are known toxicity problems, necessitating the close observation with periodical serum monitoring. Although the effect of theophylline on performance has not been studied directly, there appears to be some evidence to justify further investigation [24].

ii) Corticosteroids

The role of systemic and topical glucocorticoids in the management of acute and chronic asthma is well established, and has been used for many years [48, 88]. However, its effectiveness in EIA is doubtful, and no ergogenic effect could be expected from topical or local use [24]. Their use therefore, would likely be confined to the long-term management of an asthmatic individual.

iii) Sodium Cromoglycate

In a recent review, Patalano (1989) noted that cromoglycate is effective in preventing bronchoconstriction induced by a variety of stimuli, including allergen-induced bronchial hyper-responsiveness [68]. Initially its mechanism of action was attributed to a stabilizing effect on the degranulation of mast cells, but it now appears it may have an effect on other systems involved in the inflammatory process [68]. It is effective in preventing or inhibiting bronchospasm in 70% of patients with EIA [30]. However, it will not reverse EIA, and does not have a place in the treatment of acute asthma [24]. There is no literature to suggest that sodium cromoglycate has an effect on performance.

iv) Belladonna Alkaloids

Parasympathomimetic compounds such as the atropine derivative ipratropium bromide play a role in the treatment of asthma. However, Fitch (1986) summarized the results of several studies which showed conflicting evidence as to the effectiveness of ipratropium bromide in the treatment of EIA. At best, it approaches the efficacy of sodium cromoglycate, and cannot compare with ß2 agonists in preventing or

treating EIA [24, 43]. As with sodium cromoglycate the only potential performance enhancing properties would be the protection from exercise-induced bronchospasm [24].

v) Sympathomimetics

There is little disagreement that selective (ß2) sympathomimetics are the drug of choice in the prevention and treatment of EIA. What follows below is a review of the literature on selective sympathomimetics, their mechanism of action, related metabolic and physiologic effects, and potential effects on performance.

a) Basic Physiology of the Autonomic Nervous System:

The autonomic nervous system is comprised of two relatively antagonistic components; the sympathetic and parasympathetic systems. While the latter is usually active in a relaxation state, the former has been labelled the 'stress hormones', or 'stress system' [35].

The sympathetic nervous system can be divided by the effect of its receptors into alpha (a) and beta (ß) adrenoreceptors. Alpha-receptors, physiologically stimulated by the endogenous catecholamines norepinephrine (noradrenaline) and epinephrine (adrenalin), produce a number of responses including vasoconstriction, iris dilation, intestinal relaxation, intestinal and bladder sphincter contraction, and pilomotor contraction [35]. The beta-receptor functions are described below.

b) Non-Selective Sympathomimetic Amines

The first compounds used in treatment of EIA were non-selective sympathomimetics that caused side effects related to stimulation of the

cardiovascular system due to their stimulation of both alpha and beta receptors [61]. Due to this effect, they have been banned in Olympic competition. Other excitatory effects such as heightened alertness and restlessness from central nervous stimulation have led some athletes to abuse these medications in the past, based on the assumption that they could augment performance [24]. The death of K. Jensen, a Danish cyclist, in 1960 Olympic Games as a result of sympathomimetic abuse was the inciting event in instituting what we now know as the modern practice of doping control.

The therapeutic compounds in this class include epinephrine and ephedrine. Epinephrine is an effective bronchodilator but its use in asthma is normally confined to the treatment of acute respiratory distress [67]. Other uses include treatment of anaphylaxis and cardiac arrest. It has been demonstrated to be effective in preventing exercise-induced asthma, but because of the need for parenteral administration, it has not been used in the treatment of EIA [24]. It is available in a mist for inhalation, but is not considered the drug of choice in EIA. In addition, because of the potential performance enhancement, and arrhythmogenic capacity, it is classified as a banned substance by the medical Commission of the IOC.

Ephedrine is a non-selective derivative the has similar action to epinephrine, but lasts 10 times longer. Thus, like epinephrine, it has been shown to be effective in preventing EIA, but is banned in competition because of its mood elevating and cardiac stimulating properties [24]. It is predominantly used as a decongestant, and since it is present in many over the counter preparations, it is at risk of being inadvertently used by competitive athletes.

c) Selective ß-Sympathomimetics

Isoproterenol is a selective ß-agonist with very little alpha-receptor effects [24]. Sly (1984) noted that it has been used as a bronchodilator in the past, but it has been replaced by more selective agents in treating asthma, and its use today is confined to clinical medicine for its potent cardiac stimulating properties [24, 38, 79]. Its side effects include muscle cramps which could have a negative effect on performance in the athlete [67]. However, it has been banned in competition because of its ability to stimulate the myocardium [24].

d) Selective ß2-Adrenoreceptor Agonists

In 1967, Lands et al. first described the differentiation of beta receptors into $ß_1$ and $ß_2$. While studying the effect of various sympathomimetic amines, they noted that certain compounds caused lipolysis and cardiac stimulation ($ß_1$), while others had a bronchodilator/vasodepressor action ($ß_2$). Physiologically, $ß_1$ receptors are non-selectively stimulated by epinephrine, causing lipolysis and increased myocardial contractility and conduction, while also stimulating $ß_2$ receptors [35, 67]. Other than bronchodilation and vasodilation, $ß_2$ effects include calorigenesis, glycogenolysis, and bladder, intestinal and uterine relaxation [35].

With the discovery of this differentiation, compounds were developed to take advantage of the selective bronchodilatory effect of $ß_2$-receptor stimulation. Leifer and Wittig (1975) reported that, using epinephrine as a prototype, the structure was altered through enlargement of the moiety attached to the nitrogen end of the catecholamine [51]. They

noted that if a more bulky nitrogen-attached moiety was on the catechol or resorcinol base, the resulting compound would have more β_2 specific activity; the so-called "keyhole theory".

Simply put, the keyhole theory states that the smaller the key, the less selective the drug would be, and the larger the key (moiety) the more (β_2) selective it would be [51].

In 1961 the first compound, metaproterenol, was developed as a resorcinol derivative of isoproterenol [41]. Schoeffel et al., (1981) found it effective in preventing EIA [76]. It is classed as a doping agent by the IOC, despite evidence that evidence that oral and inhaled preparations were shown to have no effect on the cardiovascular system [24]. However, all of the β_2 selective compounds are considered to have some β_1-effects [67].

The next preparation to be developed was terbutaline, a N-tertiary butyl homologue of metaproterenol which was shown to have 25% of its cardiac effects while being twice as potent a bronchodilator [24]. Next, salbutamol was developed as a saligen analogue of metaproterenol [41]. Other compounds including fenoterol and rimiterol followed shortly afterward [24].

Fitch (1986) classified these newer compounds in the same category since they all have similar pharmacologic properties, and are all highly effective in their clinical response. They do differ in their time of onset and duration of action, with salbutamol having the quickest onset of action [67], and fenoterol having the longest duration of action [24].

Fenoterol is not permitted by the IOC, but salbutamol, terbutaline and rimiterol are sanctioned for use in the aerosol form [83]. In a recent study by Crane et al. (1989), inhaled fenoterol was compared to salbutamol and isoproterenol, and it was found that fenoterol had a greater

chronotropic, electrocardiographic and hypokalemic effects than the latter two medications. However, the inotropic effect of fenoterol was much greater, and similar to that of isoproterenol [15].

Since salbutamol is one of the most widely used preparation, and the inhaled form is considered by many to be the drug of choice in EIA [5, 24, 30, 49, 79], the remainder of this review will be limited to the discussion of salbutamol.

SALBUTAMOL

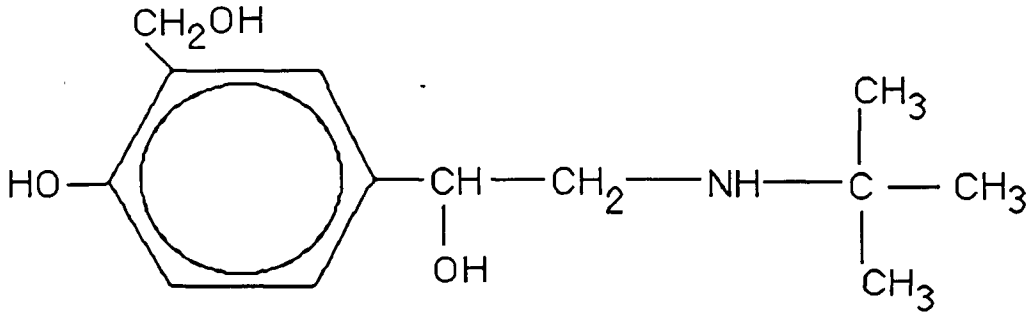
i) Efficacy

Many studies have been done to compare salbutamol to the other medications used in treating EIA. In a study on 15 children, Godfrey and Konig (1976) found salbutamol to be superior to theophylline, sodium cromoglycate, atropine and placebo in reducing the post-exercise fall in peak expiratory flow. In fact, in most cases the fall in peak flow (as a percentage of resting values) was 45% under the placebo condition, but less than 10% with salbutamol, which is within normal limits. They were able to demonstrate complete protection in 87% of children and partial protection in 13% after pre-medication with salbutamol [30]. The superiority of salbutamol over ipratropium has also been established in adult asthmatics [43]. This differs slightly from the results of Boulet et al. (1989) who found salbutamol, ipratropium bromide and sodium cromoglycate to be equally efficacious in the prevention of EIA when they studied subjects with stable asthma [9]. Also, Sly (1975) found inhaled salbutamol to be more effective than isoproterenol in preventing EIA [81].

In adults with mild extrinsic asthma, Sturani et al. (1983) found that salbutamol and fenoterol were able to inhibit bronchconstriction, but the degree of inhibition was greater with fenoterol [85]. In addition, Flint et al. (1983) found a combination of fenoterol and ipratropium bromide to be superior to salbutamol in treating asthma [25]. However, as outlined above, salbutamol remains the drug of choice in EIA and, in contrast to fenoterol, is permitted in international competition.

Several studies have concluded that the inhaled preparations are more effective in treating and preventing EIA [26, 29], and are less prone to the development of tolerance than oral salbutamol [5, 49]. In addition, Lipworth et al. (1989) studied the effects of sublingual salbutamol and found it to be similar to the oral drug, while being less efficacious than the metered dose inhaler in treating asthma [52].

ii) Structure:



The Molecular Structure of Salbutamol

Salbutamol differs from compounds such as fenoterol in that it is a saligen derivative [69]. The ß2-specificity is believed to be conferred upon

salbutamol by the terbutyl group attached to the terminal nitrogen, which is similar to terbutaline. The unique characteristic of salbutamol is the combination of this with a methanol group in the 3 position on the ring. This helps salbutamol escape degradation by catechol o-methyl transferase, thereby increasing its duration of action [51].

iii) Salbutamol Preparations and Associated Side-Effects:

Salbutamol is available in inhaled, oral, sublingual, and parenteral (intravenous or intramuscular) preparations. There are wide differences in the actions and side-effects that differ with the mode of administration. Godfrey (1981) reviewed some of the earlier work which showed that the inhaled preparations are virtually free from cardiovascular side effects when compared to oral administration [29]. He also reported that an intravenous dose required to produce the same amount of bronchodilation as an inhaled dose was associated with a much higher incidence of side effects. Leifer (1975) believed that this was due to a loss of some of the ß2 selectivity upon parenteral administration [51].

The inhaled forms include metered dose aerosols and powder inhalers. A nebulized preparation is also used, but tends to be used for administering significantly higher doses. Small differences exist in the response to inhaled preparations that appear to be dose related. For example, the nebulized form tends to be administered in a higher dose, and would therefore be prone to the development of more side effects.

On reviewing the side effects from the inhaled preparations, Leifer (1975) reported that the incidence of headache is 1%, dizziness 1%, and tremor 3%. Systemic side effects have been shown to occur with high

dose inhaled salbutamol, but long term treatment produces a decrease in these effects without decreasing the bronchodilatory response [54].

iv) Pharmacokinetics

Inhalation of salbutamol has an onset of action within 15 minutes, produces peak bronchodilation in 30 -60 minutes, and increases pulmonary function for approximately 4 hours [51, 67].

The amount of drug delivered to the lung by metered dose-inhaler is surprisingly low. Dolvich (1981) reported pulmonary values less than 10% of the metered dose, with most of the drug handled orally and swallowed [18].

v) Pharmacodynamic Properties

Salbutamol is a selective ß2-agonist with a powerful bronchodilatory effect. It accomplishes this by reducing bronchomotor tone [69].

On a cellular level, it is generally regarded that stimulation of ß2 receptors causes the production of cyclic adenosine monophosphate (cAMP) through conversion of ATP by adenyl cyclase. The cAMP then stimulates a chain of intracellular events which produce the physiologic effect [69].

The actions of salbutamol can be best understood by reviewing the various systems affected by $ß_2$-adrenoreceptor stimulation.

a) Cardiovascular Effects

There is a well-recognized cardiovascular response to Salbutamol. In the past, the chronotropic and inotropic effect of ß2-agonists were believed to be a direct response to the peripheral vasodilation. For

example, in examining the effect of salbutamol infusion in patients with chronic obstructive pulmonary disease, Mols et al. (1988) concluded that salbutamol improved left ventricular performance by decreasing ventricular afterload (vasodilation) and by having a positive inotropic effect [65]. They also found a significant chronotropic effect. Canepa-Anson et al. (1982) noted that in patients in heart failure, salbutamol increased cardiac output and lowered systemic vascular resistance [12].

Animal studies have also shown a positive inotropic and chronotropic response in a combination of in vivo and in vitro studies in the dog and guinea pig [38]. These responses were much less than that found with isoproterenol.

However, Grassi et al. (1989) reported that when salbutamol was continuously infused for 1 hour in normal subjects there was an initial rise in heart rate, but no inotropic effect or change in systolic blood pressure was noted [32].

This response could be explained by the findings of Hall et al. (1989) who studied the effect of direct infusion of salbutamol into the right coronary artery in men with chronic stable angina [36]. The direct infusion produced sinus tachycardia, while injection into the aorta itself produced no change in heart rate. By using propranolol to produce a β_2-blockade, the chronotropic response was markedly reduced, showing that the chronotropic response was, in fact, due to β_2-stimulation. When discussing their results in light of the findings of other studies, the authors did not feel that this stimulation would necessarily play a role in exercise tachycardia in normal individuals [36].

When the metabolic cost of these changes were assessed in the dog, it was found that the increased oxygen requirement of salbutamol-induced

tachycardia was supplied by an increase in coronary blood flow [77]. However, in other work using a rabbit model, Grover et al. (1986) found a salbutamol-induced increase in the percentage of perfused cardiac microvessels that was relatively independent of coronary flow [33].

In an attempt to study the function of salbutamol on ß2-adrenoreceptors in the coronary vessels, Domenech and MacLellan (1980) devised a model in the dog whereby they could study flow independent of circulatory changes, thereby controlling for coronary changes resulting from differences in cardiac oxygen demand [19]. It was found that salbutamol produced a redistribution in coronary flow, with a larger vasodilation in the subendocardial vessels This was independent of coronary resistance, or the metabolic/mechanical influences of heart contraction. Thus, there appears to be sufficient evidence to conclude that there are ß2-adrenoreceptors in coronary vessels that increase flow when stimulated by salbutamol [19, 33, 77].

However, to put these data in perspective, Imai et al. (1975) in earlier work had noted that the increases would be of minor importance under physiologic conditions since they would be completely masked by the vasodilation occurring as a result of increased myocardial oxygen demand [39]. Based on this one might assume that the changes in demand with exercise in the human would likewise mask any coronary vasodilatory effect.

It should be emphasized that all the above studies were done using intravenous preparations. With inhaled salbutamol, a dose of > 1.0 mg is needed to produce a change in heart rate, or blood pressure [53]. At higher doses, this increase did not exhibit a ceiling in the dose-response curve. The weakness of this study is that the hemodynamics were not

studied with the same invasive measurements as the above work, so a less precise assessment was made.

In 1989 review, Price and Clissold noted that usual therapeutic doses of inhaled salbutamol do not significantly affect the cardiovascular system [69].

b) Pulmonary effects

The control of bronchomotor tone was studied by Jindal and Kaur (1989) by administering ipratropium and salbutamol to 12 male stable asthmatics. Although both compounds produced bronchodilation, it was more pronounced with salbutamol, leading the authors to conclude that the dominant autonomic control of bronchial tone is through adrenoreceptors in asthmatics [43].

Sly (1984) hypothesized that the protective effect of salbutamol in EIA could be due to a direct effect on bronchial muscle to prevent constriction, or to inhibit mediator release [79]. He also felt that salbutamol might override the post-exercise bronchoconstriction by enhancing bronchodilation during exercise, or that the medication-induced bronchodilation pre-exercise could compensate for asthma during exercise.

Regardless of the mechanism , salbutamol is well established as an effective bronchodilator both in asthmatics and non-asthmatics. In fact, a lower dose is required to produce bronchodilation in normal subjects as compared to individuals with reactive airways disease [6].

In studying the response to increasing doses of inhaled salbutamol, Lipworth and McDevitt (1989) found that the bronchodilator dose-response curve reached a plateau, meaning that an increase in dose did not produce an increase on bronchodilation [53].

c) Uterine Effects

There is some evidence that salbutamol causes relaxation of the uterus. One pair of investigators found that salbutamol decreased uterine tonicity and provided pain relief in women with severe primary dysmennorhea [50]

However, another group found that little benefit was observed when long-term oral therapy was used in an attempt to abolish preterm labour [34].

d) Endocrine Effects

It appears that progesterone secretion is under the control of ß-adrenoreceptors and is increased by salbutamol [90]. It was found that neonates had a significantly higher level of growth hormone, when the effect of maternal salbutamol use was studied. Presumably this increase was in response to either fluctuating fetal blood glucose, or direct stimulation of the fetal pituitary by episodic betamimetic administration [17].

e) Metabolic Effects

There is good evidence to show that salbutamol causes an increase in blood glucose through glycogenolysis and gluconeogenesis. In addition, insulin levels are known to increase [71], likely by a direct stimulatory action on the pancreatic beta cells [69].

The lipolytic response to salbutamol has been well documented [77], and no differences have been found between rats and humans [37]. The typical response involves an increase in serum non-esterified fatty acids. In

addition, salbutamol oral administration in rats has been associated with an increase in the mass of the intrascapular brown fat pads [70].

A decrease in serum potassium following salbutamol administration has been well documented, with a similar response using intravenous and nebulized preparations [72]. This hypothesized mechanism for this response is an influx into skeletal muscle cells by ß-adrenoreceptor stimulation of membrane-bound sodium-potassium ATPase [71].

f) Muscular Effects

Several studies have been conducted on animals to assess the ability of salbutamol to increase muscle mass, particularly in meat-producing animals. Reeds et al. (1988) found no change in muscle mass when salbutamol was administered orally to young rats [70]. However, Warriss et al. (1990) gave oral salbutamol to pigs from weaning to slaughter and found that the carcasses were less fat, and examination of the longissimus muscles showed them to be larger [89]. The muscle tissue itself had higher final pH values, and slightly reduced heme pigments after slaughter. It was also found that salbutamol had no effect on growth rate.

Salbutamol has been shown to increase skeletal muscle contractility and specifically, the elicited responses of fast-twitch fibres. Whittaker and Cardwell (1981) reported that these changes in muscle contractility may be due to salbutamol-induced increases in muscle fiber membrane potential [91].

Some adverse effects on muscle have been observed. In a recent case report, Lisi (1989) noted one patient who experienced muscle spasms and an elevation of creatine kinase following moderate oral doses of

salbutamol. Aside from one similar case , no other muscular effects have been discovered [55].

There is no evidence in the literature of any muscular effects with inhaled salbutamol.

vi) Other ß2 agonists

In addition to the above work on Salbutamol, a few other related studies are worth mention. Specifically, much work has been conducted on animals to study the effect of ß2-agonists on muscle mass.

One compound in particular, clenbuterol, has been shown to increase the lean muscle mass and protein synthesis in animals [14, 22, 56, 58, 59, 70, 74]. This effect reversed on the withdrawal of clenbuterol [57]. In fact, several studies were able to show an increase in type II (but not type I) myofiber diameter, which was blocked with adrenoreceptor antagonists [1, 64, 92]. The reverse was true when denervated muscles were studied, in that clenbuterol improved the contractile properties of slow-twitch fibers while having little effect on fast-twitch fibers [1].

Due to these effects, the Food Production and Inspection Branch of Agriculture Canada has not approved it for use in food producing animals, and has instituted an extensive testing program for the residues of clenbuterol. It remains approved for treating chronic obstructive pulmonary disease in horses [2]

Because of the difference in response of salbutamol and clenbuterol (among others), Reeds et al. (1988) questioned if this response is actually mediated through ß2-adrenoreceptors, or some as yet undetermined mechanism [70]. Few studies have been done with salbutamol examining these same processes. However, the existence of such a dramatic effect

may lead one to speculate as to the possibility of a similar response to other ß2-adrenoreceptor agonists.

vii) Effect of Salbutamol on Performance

One study has been conducted in the past to assess the effect of salbutamol on oxygen uptake at a cellular level, using an animal model [73]. The model consisted of examining the jejeunal epithelia and liver in chickens after the feeding of oral salbutamol. The authors found that salbutamol increased oxygen uptake, but did not alter sodium-potassium ATPase activity. No studies to date have directly examined the cellular effect of inhaled preparations on tissue oxygen uptake.

a) Asthmatics

Schmidt et al. (1988) conducted a study to determine if there was any effect of inhaled ß2-agonists on performance in 8 known asthmatics [75]. They found no significant change in total working time, maximal lactate concentration, heart rate or rating of perceived exertion when compared to placebo in a double blind fashion. Expiratory flow was measured during each minute of exercise and during recovery. They found that the post-exercise decrease in peak expiratory flow was reduced following pre-treatment with salbutamol. This is the expected therapeutic response in asthmatics.

Earlier work by Ingemann-Hansen et al. (1980) showed no difference between inhaled salbutamol and saline control values in 5 males with exercise-induced asthma [40]. An exception being a higher mean blood pressure and heart rate for a given level of oxygen uptake during exercise with significantly different regression lines. However, there was no

difference in maximal heart rate or maximal oxygen uptake measured either running or bicycling. It should be noted that no pulmonary flow parameters were measured.

Both of these authors felt that athletes should continue to be allowed to use salbutamol in competition as no ergogenic effect was observed [40, 75].

Most recently, Freeman et al. (1989) studied the effect of administering a higher dose by giving 5 mg. of nebulized of salbutamol to 8 asthmatic, and 8 non-asthmatic men [28]. They noted an increase of 11% in resting FEV_1 in asthmatics that persisted throughout recovery, although some fall in FEV_1 post-exercise did occur. In addition, the asthmatics were found to have a higher tidal volume at maximal exercise. There was no difference with salbutamol in the cardiorespiratory response to exercise in either group. Again, salbutamol was found to reduce the severity of exercise-induced asthma, and produce no ergogenic effect in either asthmatics or non-asthmatics. The only weakness of this well conducted study was that the subjects were not elite (mean VO_{2max} was ~42 ml/kg/min), and no direct measures of performance were made. This would limit the generalizability of the results to elite athletes.

b) Non-Asthmatics

In addition to the above study comparing asthmatics to normal subjects, several investigations have focussed on non-asthmatics alone. Specific to pulmonary effects and muscle, Javaheri et al. (1988) examined the changes in diaphragmatic fatigue in 5 healthy male subjects given either placebo or 4 mg of salbutamol orally, 3 times daily [42]. They concluded

that salbutamol had no effect on the strength of fatigued or fresh diaphragm muscle, or on the endurance time of the diaphragm during inspiratory resistance loading. Lastly, there was no effect on recovery of diaphragm function [42].

In related work, Violante et al. (1989) examined the effect of intravenous infusion of salbutamol on respiratory muscle function and exercise tolerance in 7 healthy sedentary males [86]. They received this medication at therapeutic levels in a double blind, randomized cross-over design with both placebo and aminophylline. The authors reported no difference in exercise tolerance, VO_{2max}, anaerobic threshold, or respiratory muscle strength. The only effect found with salbutamol was a higher heart rate and respiratory exchange ratio at certain work loads with salbutamol [86]. However, there was no difference in (peak) heart rate at maximal exercise.

To date, two authors have studied the potential performance enhancing properties of salbutamol in athletes, with conflicting results. McKenzie et. al. (1983) studied 19 highly-trained male and female runners after baseline pulmonary measurements to ensure they were non-asthmatic [61]. Each athlete completed one maximal treadmill run to voluntary exhaustion and then took either placebo or a therapeutic dose of inhaled salbutamol for a one week period in a double-blind fashion. Following the treatment, the same measures were repeated. There was no significant change in pulmonary function, VO_{2max}, anaerobic threshold, ventilation, or heart rate.

In contrast, Bedi and co-workers (1988) studied 15 non-asthmatic subjects of varying athletic ability. Baseline measurements and a histamine

challenge test were conducted to ensure the subjects had non-reactive airways [8]. They were then given either placebo or salbutamol (180 μg) in a double-blind manner. Two puffs were administered, 30 minutes prior to performing a 60 minute ride on a cycle ergometer, followed by a timed sprint to exhaustion. A second trial was performed more than one week later in a cross-over design. Although the author found no significant change in VO_{2max}, ventilation, or oxygen uptake, they did note a significant increase in forced respiratory flow parameters following salbutamol. Also, the subjects had an significantly increased sprint time after taking salbutamol.

The weakness of McKenzie's study was that no direct measurements of performance were made, although they stated that VO_{2max} and anaerobic threshold have been shown to correlate with successful athletic performance.

The subjects in McKenzie's study were a fairly homogeneous group of elite runners. In contrast, those in Bedi's work were of variable athletic ability. Bedi (1988) acknowledges this, and stated that if the dramatic difference in sprint time of two of the subjects (one of whom was a non-competitive cyclist) were discounted as outliers, the difference in sprint time was non-significant.

Thus, the evidence for a performance enhancing effect in athletes is rather tenuous. However, Bedi (1988) suggested that, on the basis of his results ß-adrenergic bronchodilators should be banned in competition. He acknowledged that such a ruling would effectively eliminate asthmatics from competition, and that further research should be conducted on elite athletes.

APPENDIX B - Raw Data

VO_{2max} and Endurance Ride Measurements

Dependent Variable	Condition	SUBJECTS						
		1	2	3	4	5	6	7
V02 max (ml/kg/min)	Placebo	60.8	68.7	64.9	59.1	62.6	63.0	65.4
	Salbutamol	61.1	69.3	63.5	61.4	62.8	61.5	58.8
Peak Power (Watts)	Placebo	452	451	444	405	415	417	479
	Salbutamol	435	475	441	402	414	424	473
Max Heart Rate (beats/min)	Placebo	183	199	193	189	189	197	190
	Salbutamol	183	200	194	192	188	193	184
Endurance Sprint (seconds)	Placebo	119	83	97	113	144	90	81
	Salbutamol	100	99	78	41	138	124	97

APPENDIX C - Wingate Data

Subject # 1

		5 sec.Interval						
	Condition	1	2	3	4	5	6	Tot.
Power (Watts/kg)	Placebo	10.10	9.86	9.13	8.65	7.69	7.21	
	Salbutamol	9.92	9.68	9.20	8.47	7.75	7.26	
Work (kJoules)	Placebo	3.66	3.57	3.31	3.14	2.79	2.61	19.08
	Salbutamol	3.57	3.49	3.31	3.05	2.79	2.61	18.82

Subject # 2

		5 sec.Interval						
	Condition	1	2	3	4	5	6	Tot.
Power (Watts/kg)	Placebo	10.69	9.48	8.99	8.51	7.78	7.53	
	Salbutamol	10.82	9.86	9.14	8.66	8.18	7.46	
Work (kJoules)	Placebo	3.83	3.40	3.22	3.05	2.79	2.70	19.00
	Salbutamol	3.92	3.57	3.31	3.14	2.96	2.70	19.61

Subject # 3

	Condition	5 sec.Interval 1	2	3	4	5	6	Tot.
Power (Watts/kg)	Placebo	9.60	10.58	9.85	9.35	8.86	7.88	
	Salbutamol	9.39	9.63	9.63	8.91	8.67	7.94	
Work (kJoules)	Placebo	3.40	3.75	3.49	3.31	3.14	2.79	19.87
	Salbutamol	3.40	3.49	3.49	3.22	3.14	2.88	19.61

Subject # 4

	Condition	5 sec.Interval 1	2	3	4	5	6	Tot.
Power (Watts/kg)	Placebo	8.70	9.19	8.70	7.73	7.25	6.28	
	Salbutamol	8.89	9.13	8.89	8.65	7.93	7.69	
Work (kJoules)	Placebo	3.14	3.31	3.14	2.79	2.61	2.27	17.25
	Salbutamol	3.22	3.31	3.22	3.14	2.88	2.79	18.56

Subject # 5

	Condition	5 sec.Interval 1	2	3	4	5	6	Tot.
Power (Watts/kg)	Placebo	9.33	9.55	8.42	8.19	7.73	7.51	
	Salbutamol	10.60	10.37	9.66	9.19	8.95	8.01	
Work (kJoules)	Placebo	3.25	3.33	2.93	2.85	2.69	2.61	17.67
	Salbutamol	3.57	3.49	3.25	3.09	3.01	2.69	19.09

Subject # 6

	Condition	5 sec.Interval 1	2	3	4	5	6	Tot.
Power (Watts/kg)	Placebo	10.14	9.42	8.45	7.97	8.21	7.49	
	Salbutamol	9.56	9.07	8.82	8.58	8.33	8.09	
Work (kJoules)	Placebo	3.66	3.40	3.05	2.88	2.96	2.70	18.65
	Salbutamol	3.40	3.22	3.14	3.05	2.96	2.88	18.65

Subject # 7

	Condition	5 sec.Interval 1	2	3	4	5	6	Tot.
Power (Watts/kg)	Placebo	10.59	9.89	9.42	8.71	7.77	7.53	
	Salbutamol	9.67	10.14	9.20	8.26	8.02	7.31	
Work (kJoules)	Placebo	4.63	4.33	4.12	3.81	3.40	3.30	23.58
	Salbutamol	4.22	4.42	4.02	3.60	3.50	3.19	22.97

APPENDIX D - Pulmonary Function Data

Subject # 1

Parameter	Condition	Pre-exercise		Post-exercise		
		pre-med	post-med	5 min	10 min	20 min
FEV_1	Placebo	4.40	4.43	4.67	4.62	4.67
	Salbutamol	4.36	4.88		4.97	4.90
FEF_{25-75}	Placebo	3.48	3.50	3.23	3.63	3.66
	Salbutamol	2.78	4.44		4.20	4.17
FVC	Placebo	5.91	6.05	6.46	6.29	6.32
	Salbutamol	6.50	6.07		6.43	6.32

Subject # 2

Parameter	Condition	Pre-exercise		Post-exercise		
		pre-med	post-med	5 min	10 min	20 min
FEV_1	Placebo	5.16	5.12		5.10	5.00
	Salbutamol	4.98	5.18	5.36	5.30	5.33
FEF_{25-75}	Placebo	3.84	3.76		3.92	3.67
	Salbutamol	3.70	4.01	4.43	4.24	4.15
FVC	Placebo	7.29	7.28		7.07	7.10
	Salbutamol	7.07	7.10	7.13	7.17	7.31

Subject # 3

Parameter	Condition	Pre-exercise		Post-exercise		
		pre-med	post-med	5 min	10 min	20 min
FEV_1	Placebo	5.18	5.19	5.37	5.30	5.23
	Salbutamol	5.00	5.18	5.18	5.21	5.14
FEF_{25-75}	Placebo	5.14	5.44	5.65	5.36	5.37
	Salbutamol	5.07	5.20	5.19	5.01	5.19
FVC	Placebo	6.10	5.95	5.88	5.98	6.00
	Salbutamol	5.93	6.08	6.11	6.24	6.11

Subject # 4

Parameter	Condition	Pre-exercise		Post-exercise		
		pre-med	post-med	5 min	10 min	20 min
FEV_1	Placebo	5.02	5.07	5.32	5.43	5.24
	Salbutamol	5.14	5.13	5.32	5.42	5.26
FEF_{25-75}	Placebo	3.89	3.64	4.07	4.19	3.95
	Salbutamol	3.54	3.56	3.74	3.89	3.76
FVC	Placebo	6.85	6.94	7.24	7.35	7.26
	Salbutamol	7.44	7.50	7.61	7.58	7.49

Subject # 5

Parameter	Condition	Pre-exercise		Post-exercise		
		pre-med	post-med	5 min	10 min	20 min
FEV_1	Placebo	5.53	5.47	5.15	5.45	5.46
	Salbutamol	5.44	4.29	5.49	5.55	5.56
FEF_{25-75}	Placebo	6.44	6.27	7.67	7.32	6.93
	Salbutamol	6.33	6.93	7.84	7.45	7.54
FVC	Placebo	6.09	6.04	5.47	5.82	5.80
	Salbutamol	5.97	5.99	5.63	5.74	5.83

Subject # 6

Parameter	Condition	Pre-exercise		Post-exercise		
		pre-med	post-med	5 min	10 min	20 min
FEV_1	Placebo	4.55	4.63	4.80	4.69	4.63
	Salbutamol	4.26	4.57	4.67	4.60	4.58
FEF_{25-75}	Placebo	4.24	4.30	4.70	4.54	4.44
	Salbutamol	3.75	4.71	4.96	4.80	4.56
FVC	Placebo	5.55	5.63	5.69	5.70	5.59
	Salbutamol	5.28	5.48	5.34	5.35	5.49

Subject # 7

Parameter	Condition	Pre-exercise		Post-exercise		
		pre-med	post-med	5 min	10 min	20 min
FEV_1	Placebo	4.76	4.73	4.94	5.02	4.79
	Salbutamol	4.81	5.07	4.96	5.11	5.15
FEF_{25-75}	Placebo	3.26	3.14	3.35	3.61	3.05
	Salbutamol	3.22	3.47	3.18	3.53	3.65
FVC	Placebo	6.95	7.05	7.07	7.08	7.24
	Salbutamol	7.12	7.28	7.29	7.27	7.23