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Sympathomimetics and Exercise Enhancement: All in the Mind?

RONALD DEMEERSMAN

Applied Physiology Laboratory, Teachers College, Columbia University

DEBORAH GETTY

Human Performance Laboratory, Virginia Commonwealth University

AND

DAVID C. SCHAEFER[1]

Psychology Service, Keller Army Hospital

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DEMEERSMAN, R , D GETTY AND D C SCHAEFER *Sympathomimetics and exercise enhancement All in the mind?* PHARMACOL BIOCHEM BEHAV **28**(3)361–365, 1987 —During the 1972 Olympic Games, a 16 year old American athlete was compelled to return a gold medal and was disqualified from further participation Rick Demont had used a sympathomimetic drug (ephedrine) prior to competition for treatment of his asthma as prescribed by his physician The present research was carried out to investigate whether the administration of a sympathomimetic drug enhances maximal performance in the normal healthy individual in terms of physiological and psychological processes? Ten subjects participated in a double-blind, cross-over, counterbalanced incremental cycle ergometer test on two different occasions, once after ingesting placebo, once after ingesting ephedrine Repeated measures ANOVA's revealed no significant differences in any of the cardiopulmonary (VE, VO_2, VCO_2, RQ and AT), cardiovascular (HR, BP, O_2 Pulse, RPP) and psychophysiological (RPE) variables between treatments Findings in the current investigation suggest that no advantage is obtained with the use of sympathomimetic drugs to augment one's maximal aerobic capacity

Sympathomimetic Maximal aerobic capacity Perceived exertion

DURING the 1972 Olympic Games in Munich, Germany, a 16 year old American athlete was compelled to return a gold medal during a swimming competition and disqualified from further participation The reason for this action by the International Olympic Committee Medical Commission was a positive test for the presence of a banned drug, ephedrine The swimmer, Rick Demont, had used this sympathomimetic medication prior to competition for treatment of his asthma

The following research was born out of unanswered questions regarding the effects of a sympathomimetic drug on maximal performance. Specifically, does the administration of a sympathomimetic drug enhance maximal performance in the normal healthy individual in terms of physiological and psychological capability? The physiological requirements for a maximum aerobic (oxygen consuming) performance involve a functional coupling of accelerated cardiovascular and pulmonary activity in order to achieve sufficient gas (O_2 and CO_2) transport between the working muscles and the atmosphere to meet increasing metabolic demands These metabolic demands are precisely geared to the rate of work being performed. Consequently, the magnitude of cardiovascular and pulmonary capabilities possess a high predictive value in terms of an athlete's maximum performance capacity Any dysfunction of the cardiopulmonary system puts stress on the other systems impairing the functional capacity of the athletes Could the exogenously introduced drug ephedrine yield a markedly enhanced performance? The answer depends on a careful quantification of the physiological capabilities of the athlete under normal and drug induced conditions. The index of maximal oxygen consumption capacity, VO_2max, is a recognized objective and reproducible measure to achieve this quantifiable data This research compared VO_2max and several other cardiopulmonary and psychophysiologic parameters to elucidate ephedrine induced effects

Vigorous muscular exercise requires increases in blood

[1]Requests for reprints should be addressed to Dr Schaefer, Keller Army Hospital, West Point, NY 10996 The view of the authors do not purport to represent the position of the Army or the Department of Defense

flow to exercising muscles Concomitant increases in plasma catecholamines result in increased heart rate and force of contraction thus producing a greater volume of blood to be pumped into the arteries (stroke volume). In the lungs, catecholamine release causes terminal air passages (bronchioles) to dilate, improving oxygen delivery to the blood Sympathomimetic drugs are synthetic congeners of the naturally occurring catecholamines norepinephrine (noradrenaline) and epinephrine (adrenaline) These hormones have three primary pharmacologic actions, stimulating alpha, beta$_1$, and beta$_2$ receptors [1] The organ response to a sympathomimetic drug depends on the relative selectivity of the drug for the receptor in addition to the type and quantity of the receptor present in the end organ Stimulation of beta receptors elicits vascular smooth muscle contraction, resulting in vasoconstriction. Stimulation of beta receptors also results in the production of intracellular cyclic adenosine monophospate (cAMP) [7] Beta$_1$ receptors are present primarily in cardiac tissue, and their stimulation increases heart rate and force of contraction. Beta$_2$ receptor stimulation relaxes bronchial smooth muscle, resulting in bronchodilation, in addition to dilation of arterioles of skeletal muscle [7] Sympathomimetics have been designed to increase receptor specificity and affinity Furthermore, they delay the drug inactivation, prolonging duration of action and increasing the activity of the administered agent. Included in this class of drugs are synthetic adrenaline, phenylephrine, isoproterenol, albuterol, ephedrine and others [1,7] Concomitant with physiological changes during exercise are psychological, or perceptual, changes of exercise intensity Recent research suggests that people exercising at physiologically equivalent work loads perceive their effort at varying intensities [2] A person perceiving himself exercising, or competing athletically, at a lesser level than another may push himself farther Perceptual effort can be quantitatively rated and compared among individuals during exercise by the scale of rate perceived exertion (RPE) This scale of overall perceived exertion integrates various information, including the many signals elicited from the peripheral working muscles and joints, from the cardiovascular and respiratory systems, and from the central nervous system All of these signals, perceptions, and experiences are integrated by a person into a psychological configuration or "Gestalt" of perceived exertion [3]

METHOD

Ten healthy students, males and females, voluntarily participated in the experiment after the nature of procedures had been fully explained and informed consent was obtained All research was approved by the institution's committee on the conduct of human research

In the current investigation the double-blind cross-over counterbalanced design was used with a one week wash-out period between both protocols Thus, neither the subjects nor the researcher knew which treatment (drug or placebo) condition was being tested. Cardiovascular, cardiopulmonary and psychophysiological variables were compared delineating a rigorous criteria for determining possible differences induced by drug/placebo treatments Subjects were instructed to be at least 4–6 hours post-absorptive and to refrain from smoking, use of stimulants and physical exercise 24 hours before the test. After entering the laboratory the subject's anthropometric measurements were recorded The subject then was asked to perform two consecutive forced vital capacity maneuvers using standard static pul-

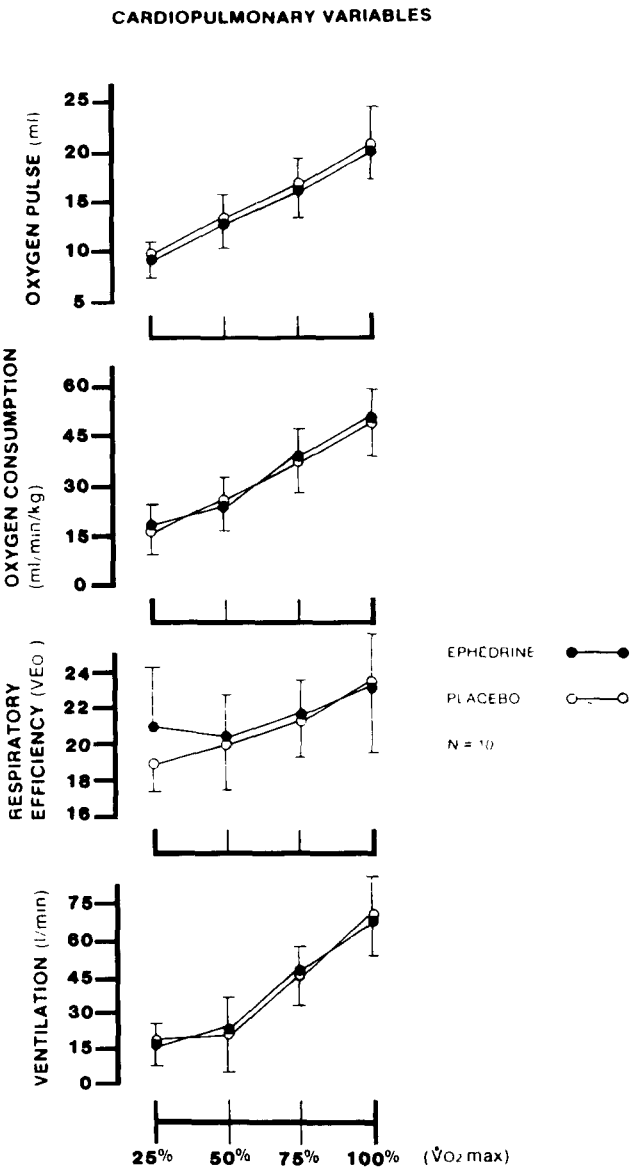

FIG 1 Ventilation volume, respiratory efficiency, oxygen consumption, and oxygen pulse at 25, 50, 75 and 100% of maximum functional capacity after ephedrine and placebo ingestion (mean±S D)

monary function procedures (closed circuit spirometry). All tests were run by an experienced and certified respiratory therapist. Following the pulmonary function test the subject was asked to swallow a pill containing either 40 mg ephedrine or sucrose. The pills were identical in weight and appearance for all conditions The subject remained seated for 30 minutes after which another two static pulmonary function tests were repeated Prior to the experimental trials, subjects were allowed a brief testing protocol training session of 5 minutes to familiarize the subject with the stress testing procedures (cycle ergometry). All of the participants had prior experience as to cycle ergometry and open circuit spirometry procedures The stress testing protocol consisted of riding a cycle ergometer at 50 revolutions per minute (rpm) as dictated by an audiovisual metronome The initial

TABLE 1

THE EFFECTS OF EPHEDRINE AND PLACEBO INGESTION ON RESPIRATORY METABOLISM AT 25, 50, 75, AND 100% OF MAXIMUM OXYGEN CONSUMPTION DURING AN INCREMENTAL CYCLE ERGOMETER TEST

	Heart Rate (beats/min)	Systolic B P (mmHg)	Rate Pressure Product ($HR \times SBP \times 10^{-3}$)	Oxygen Consumption (ml/min/kg)	Ventilation Volume (L/min)	Oxygen Pulse (ml)	
Ephedrine							
$\%VO_2$ max 25	102 ± 11	127 ± 17	12 9 ± 2 8	16 5 ± 3 17	16 5 ± 3 16	9 5 ± 2 20	NS
$\%VO_2$ max 50	130 ± 17	148 ± 21	19 4 ± 4 6	26 9 ± 6 20	26 6 ± 10 8	13 5 ± 3 54	NS
$\%VO_2$ max 75	161 ± 15	162 ± 15	27 4 ± 4 3	39 8 ± 7 69	45 6 ± 10 1	16 4 ± 3 81	NS
$\%VO_2$ max 100	183 ± 8	185 ± 20	33 7 ± 3 5	51 0 ± 9 71	67 4 ± 19 2	21 8 ± 8 52	NS
Placebo							
$\%VO_2$ max 25	104 ± 13	128 ± 14	13 1 ± 2 3	16 4 ± 2 14	16 7 ± 2 30	10 1 ± 1 11	NS
$\%VO_2$ max 50	129 ± 12	146 ± 17	20 6 ± 4 3	27 8 ± 5 48	26 0 ± 11 0	14 0 ± 4 32	NS
$\%VO_2$ max 75	165 ± 9	164 ± 16	27 2 ± 4 3	39 5 ± 6 63	44 2 ± 9 11	16 6 ± 3 48	NS
$\%VO_2$ max 100	180 ± 12	181 ± 23	32 5 ± 4 6	51 3 ± 10 0	68 2 ± 19 4	21 9 ± 9 19	NS

Values are means ± S D
N=10
NS=Not significant

TABLE 2

THE EFFECT OF EPHEDRINE AND PLACEBO INGESTION ON RESPIRATION EFFICIENCY, AND RATINGS OF PERCEIVED EXERTION AT 25, 50, 75 AND 100% of MAXIMUM OXYGEN CONSUMPTION DURING AN INCREMENTAL CYCLE ERGOMETER TEST

	Respiratory Efficiency (VE/VO_2)	Ratings of Perceived Exertion		Vital Capacity	
Ephedrine					
$\%VO_2$ max 25	21 0 ± 2 9	8 ± 1 2	NS		
$\%VO_2$ max 50	20 2 ± 1 4	12 ± 1 2	NS		
$\%VO_2$ max 75	21 7 ± 2 1	15 ± 1 3	NS		
$\%VO_2$ max 100	23 1 ± 1 5	19 ± 1 2	NS	3 74 ± 0 79	NS
Placebo					
$\%VO_2$ max 25	18 6 ± 1 3	8 ± 1 5	NS		
$\%VO_2$ max 50	19 9 ± 1 5	12 ± 1 8	NS		
$\%VO_2$ max 75	21 4 ± 2 4	15 ± 2 0	NS		
$\%VO_2$ max 100	23 6 ± 2 4	19 ± 1 1	NS	3 76 ± 0 78	NS

Values are means ± S D
N=10
NS=Not significant
The effects of ephedrine and placebo ingestion on vital capacity

workload consisted of pedalling at 50 rpm in an unloaded (0 watts) condition Thereafter, the workload (resistance) was increased at each two minute interval by 15 watts for the female subjects and 30 watts for the male subjects until the subject could not maintain the pedalling frequency and dropped below 30 rpm's.

Open-circuit spirometry methods were utilized for collection of metabolic data for all laboratory sessions. Expired ventilatory volume (VE) was continuously measured by a Parkinson-Cowan model CD4 dry gas meter, which was regularly calibrated against a tissot 120 liter spirometer. Calibration involved comparisons of known volumes of air pulled from the tissot spirometer through the meter at predetermined constant flow rates The subjects breathed through a three-way valve into low resistance tubing, to a 5 liter Plexiglas mixing chamber Temperature was monitored immediately prior to the flow rate measurement for gas volume corrections (STPD) Fractional expiration of carbon dioxide (FE_{CO2}) and oxygen (FE_{O2}) was measured from the mixing chamber with a Beckman model LB2 CO_2 analyzer and a Beckman model OM11 O_2 analyzer. The anaerobic threshold was determined according to the non-invasive procedures [8] Gas analyzers were calibrated before and after each test with commercially prepared gas mixtures. The gas concentrations were verified prior to the study by gas chromatography. Throughout all experimental sessions, heart rate response was continuously recorded on a Burdick electrocardiograph model EK/5A. A modified CM5 bipolar lead configuration was used. In addition an experienced cardiopulmonary technician measured the blood pressure (auscultation) at rest, and at every two minutes throughout the exercise protocol Furthermore, subjects were asked to rate their level of perceived exertion once every two minutes. Specifically, subjects were asked to look at a two-foot by one-foot replica of the Borg RPE scale and point at the number corresponding to their choice of effort perception rating at that moment.

RESULTS

Statistical treatment consisted of analysis of variance with repeated measures. Where the omnibus F indicated significance a Duncan multiple range posthoc test was run Comparisons of maximum values between protocols was accomplished by paired t-tests. The level of significance was set at ($p<0.05$) for all statistical analyses.

A consistent plateau of oxygen consumption (VO_2) was seen in all subjects for both protocols A respiratory quotient of greater than 1 2 was also noted for all subjects at levels of peak oxygen consumption. Therefore, it is likely that a true VO_2max was achieved for all protocols Cardiovascular, cardiopulmonary and psychophysiological variables at 25%,

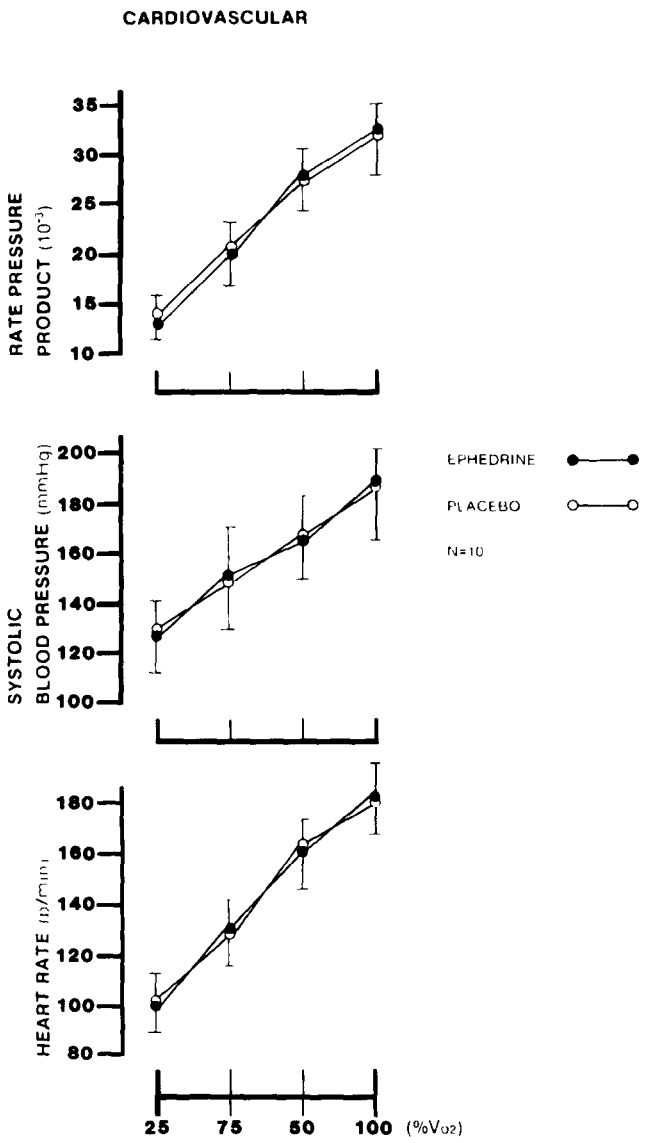

FIG 2 Heart rate, systolic blood pressure, and rate pressure product at 25, 50, 75 and 100% of maximum functional capacity after ephedrine and placebo ingestion (mean±S D)

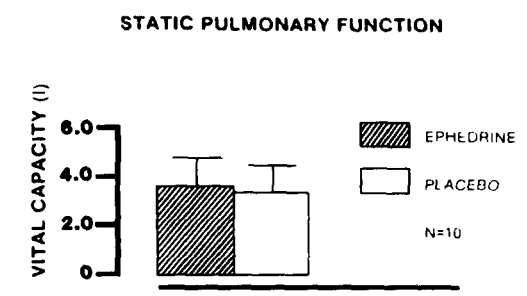

FIG 3 Vital capacity 30 min after ephedrine and placebo ingestion

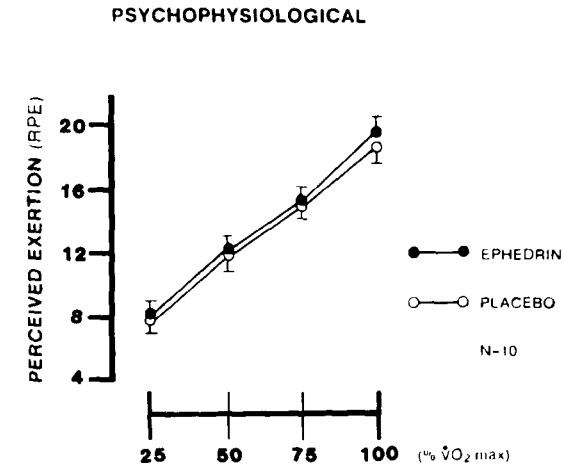

FIG 4 Ratings of perceived exertion at 25, 50, 75 and 100% of maximum functional capacity after ephedrine and placebo ingestion (mean±S D)

50%, 75%, and 100% of the progressive test after ephedrine and placebo are listed in Tables 1 and 2 In addition, the static pulmonary test of vital capacity after 30 minutes post ingestion of ephedrine and placebo is listed in Table 2 No significant differences were noted for the static pulmonary function test between placebo and ephedrine trials (Fig. 1). All values are listed as means and ±SD. The repeated measures analysis of variance did not reveal any statistical significance among any of the variables between the drug treatments *t*-Tests of peak values for both treatments failed to reveal any significant differences. Reanalysis of the data using the analysis of covariance in which the oxygen consumption (a precise measure of metabolic intensity) serves as the covariate also failed to reveal any statistically significant differences

DISCUSSION

The purpose of this research was to ascertain if the administration of a sympathomimetic drug (ephedrine) would enhance maximal performance in normal subjects. The disqualification of Rick Demont during the 1972 Olympic Games by the International Medical Commission after winning the gold medal implied that the sympathomimetic drug ephedrine taken by the asthmatic swimmer not only attenuated his respiratory distress, but also augmented his performance ability. The measurement of maximum oxygen consumption is the primary index and documented evidence of a person's maximal functional aerobic capacity Maximal oxygen consumption equals the product of maximal cardiac output and maximal arteriovenous oxygen difference (A-VO_2). Therefore, if VO_2max is to be increased it must do so by increasing either cardiac output (Q) or the arteriovenous oxygen difference, or a combination of both. However, A-VO_2 can only be measured by invasive techniques. This study used healthy young individuals and no justification for invasive measurements was indicated. In addition, the noninvasive procedures used in this study allow for maximal levels of physical exertion without the use of life-threatening or restrictive measures

Physiologically, Q is the product of heart rate times stroke volume. Findings in the current investigation show that the administration of the sympathomimetic drug ephedrine failed to act as a cardiac stimulant

Heart rate throughout the progressive test at specific metabolic intensities (%VO_2max), and at maximal performance did not differ from placebo (Fig. 2) Our study used oxygen pulse as a non-invasive measure of stroke volume. Since the O_2 pulse at equal intensities is determined almost exclusively by the HR, we can conclude that the HR at these equal power increments can be taken as an expression of the performance capacity of the heart and vascular system [5] In addition, the O_2 pulse increases in a linear proportion to the cardiac volume, this was successfully demonstrated by Galle and Mellerowicz [5]. Consequently, any increase in O_2 pulse is caused by an increase in cardiac volume performance and not a reduction in O_2 peripheral extraction of the blood Our data showed that no significant differences in the O_2 pulse were present (Fig 3)

Therefore, the use of ephedrine did not potentiate the inotropic properties since both the HR and the O_2 pulse remained unaltered for both the ephedrine and the placebo Rate pressure product is considered to be an excellent correlate with myocardial oxygen consumption (MVO_2) [6] An increased O_2 demand in these healthy young individuals would result in an increased cardiac output and ultimately increase VO_2max No evidence was seen from our data which would suggest an enhanced MVO_2 with the use of ephedrine The above parameters of heart rate, oxygen pulse and rate pressure product are all components contributing to the cardiac output Since these parameters failed to increase with ephedrine, it then would come as no surprise that the blood pressure remained unchanged as compared to placebo Cardiovascular and pulmonary systems work as an interactive unit and consequently any change in physiological functioning in one system will ultimately modify the other Therefore, any factor that either reduces the maximum increase in cardiac output or reduces the oxygen carried by the blood at the maximum cardiac output will reduce the maximal oxygen consumption The end result of changes on cardiac output is the amount of oxygen carried to the tissues A decreased delivery of oxygen results in a shift toward anaerobic metabolism. A by-product of anaerobic metabolism is lactic acid. Specific plasma levels of lactic acid coincide with the onset of anaerobiosis or anaerobic threshold. The exercising body attempts to combat this shift which is evidenced by a non-linear deviation of several of the respiratory responses. Plots of ventilation volume, respiratory efficiency, oxygen consumption and oxygen pulse on a minute-by-minute basis failed to reveal any differences between the two treatments The anaerobic threshold occurred at 51.6% and 52 1% of VO_2max for the ephedrine and placebo treatment respectively One might attribute any prolongation in time to exhaustion without a concomitant increase in VO_2max to the ingestion of ephedrine However, all subjects in this experiment had prior ergometry testing experience Since our research did not show differences between drug and placebo trials in time to exhaustion, the ingestion of ephedrine does not appear to delay neuromuscular fatigue and consequently has no performance enhancing effect in this regard

In the current investigation the perception of effort was quantitatively rated by the subject at the end of every workstage. This overall perceived exertion rating integrates signals from the peripheral working muscles, from the cardiovascular and respiratory systems Since the central (heart rate and ventilation volume), and the peripheral signals (lactate accumulation) do not differ between treatments it is of no surprise that the quantitative perceptions of effort remained the same for both treatments (Fig. 4)

These findings support the results of an earlier investigation in our laboratory in which the maximal aerobic capacity was not enhanced in normal subjects after the administration of the sympathomimetic drug salbutamol [4]

The decision to rescind Rick Demont's gold medal implies that the use of ephedrine unfairly enhanced his maximal performance capacity Our data clearly indicate that the use of the sympathomimetic drug ephedrine offers no advantage in enhancing a normal subject's maximal aerobic capacity or psychophysiological functioning

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