INFORMATION TO USERS

This reproduction was made from a copy of a document sent to us for microfilming. While the most advanced technology has been used to photograph and reproduce this document, the quality of the reproduction is heavily dependent upon the quality of the material submitted.

The following explanation of techniques is provided to help clarify markings or notations which may appear on this reproduction.

1. The sign or "target" for pages apparently lacking from the document photographed is "Missing Page(s)". If it was possible to obtain the missing page(s) or section, they are spliced into the film along with adjacent pages. This may have necessitated cutting through an image and duplicating adjacent pages to assure complete continuity.

2. When an image on the film is obliterated with a round black mark, it is an indication of either blurred copy because of movement during exposure, duplicate copy, or copyrighted materials that should not have been filmed. For blurred pages, a good image of the page can be found in the adjacent frame. If copyrighted materials were deleted, a target note will appear listing the pages in the adjacent frame.

3. When a map, drawing or chart, etc., is part of the material being photographed, a definite method of "sectioning" the material has been followed. It is customary to begin filming at the upper left hand corner of a large sheet and to continue from left to right in equal sections with small overlaps. If necessary, sectioning is continued again—beginning below the first row and continuing on until complete.

4. For illustrations that cannot be satisfactorily reproduced by xerographic means, photographic prints can be purchased at additional cost and inserted into your xerographic copy. These prints are available upon request from the Dissertations Customer Services Department.

5. Some pages in any document may have indistinct print. In all cases the best available copy has been filmed.

University Microfilms International
300 N. Zeeb Road
Ann Arbor, MI 48106

ANDERSON, RICHARD LLOYD

THE EFFECTS OF CARDIOSELECTIVE AND NON-SELECTIVE BETA ADRENERGIC BLOCKADE ON THE PERFORMANCE OF HIGHLY TRAINED RUNNERS

THE UNIVERSITY OF ARIZONA M.S. 1984

PLEASE NOTE:

In all cases this material has been filmed in the best possible way from the available copy. Problems encountered with this document have been identified here with a check mark __✓__.

1. Glossy photographs or pages _____
2. Colored illustrations, paper or print _____
3. Photographs with dark background _____
4. Illustrations are poor copy _____
5. Pages with black marks, not original copy _____
6. Print shows through as there is text on both sides of page _____
7. Indistinct, broken or small print on several pages ✓
8. Print exceeds margin requirements _____
9. Tightly bound copy with print lost in spine _____
10. Computer printout pages with indistinct print _____
11. Page(s) _____ lacking when material received, and not available from school or author.
12. Page(s) _____ seem to be missing in numbering only as text follows.
13. Two pages numbered _____. Text follows.
14. Curling and wrinkled pages _____
15. Other _____

THE EFFECTS OF CARDIOSELECTIVE AND NON-SELECTIVE BETA ADRENERGIC BLOCKADE ON THE PERFORMANCE OF HIGHLY TRAINED RUNNERS

by

Richard Lloyd Anderson

A Thesis Submitted to the Faculty of the

COMMITTEE ON ANIMAL PHYSIOLOGY (GRADUATE)

In Partial Fulfillment of the Requirements
For the Degree of

MASTER OF SCIENCE

In the Graduate College

THE UNIVERSITY OF ARIZONA

1 9 8 4

STATEMENT BY AUTHOR

This thesis has been submitted in partial fulfillment of requirements for an advanced degree at the University of Arizona and is deposited in the University Library to be made available to borrowers under rules of the Library.

Brief quotations from this thesis are allowable without special permission, provided that accurate acknowledgement of source is made. Requests for permission for extended quotation from or reproduction of this manuscript in whole or in part may be granted by the head of the major department or the Dean of the Graduate College when in his or her judgment the proposed use of the material is in the interests of scholarship. In all other instances, however, permission must be obtained from the author.

SIGNED: Richard L. Anderson

APPROVAL BY THESIS DIRECTOR

This thesis has been approved on the date shown below:

Jack H. Wilmore
Professor of Animal Physiology

20 August 1984
Date

ACKNOWLEDGEMENTS

To the countless number of individuals who played a role in the creation, execution, and completion of this project, only three words can truly express my undying gratitude. "Beautiful Job, Folks!"

Love,

"Buck"

"Buck"

TABLE OF CONTENTS

TABLE OF CONTENTS (cont.)

LIST OF TABLES

LIST OF TABLES (cont.)

LIST OF FIGURES

LIST OF FIGURES (cont.)

ABSTRACT

Twenty-five highly trained runners ($\dot{V}O_2$ max 64.7 ± 4.3 $ml \cdot kg^{-1} \cdot min^{-1}$) were administered clinically equivalent doses of non-selective (propranolol) and cardioselective (atenolol) beta blocking agents as well as a placebo. On the eighth day of medication, the subjects performed a horizontal treadmill test during which both submaximal (240 $m \cdot min^{-1}$ • 6 min) and maximal data were obtained. A 10-km track race was conducted on the tenth day of each treatment. A double-blind, crossover experimental design was used. Beta blockade decreased submaximal heart rate with propranolol causing the largest decrease. Propranolol decreased submaximal $\dot{V}O_2$, and increased submaximal RER. Both medications raised RPE. Beta blockade caused a decrease in HR max, $\dot{V}O_2$ max, $\dot{V}E$ max, RER max, and treadmill time. Propranolol caused a greater decrease than atenolol in each case. The 10-km race times were significantly slower during beta blockade. Propranolol race times were slower than atenolol race times.

CHAPTER I

INTRODUCTION

Even though beta adrenergic blockade and aerobic exercise are both widely prescribed for cardiovascular diseases, their interactive effects are not well understood. In fact, many of the acute treatment effects of either of these therapeutic modalities tend to contradict the other. In general, beta adrenergic blockade (BAB) acts on the heart as a stress "reducer", while exercise exerts its effect as a stress "inducer".

BAB is used extensively in patients with essential hypertension and cardiac arrythmias, as well as in patients who have had myocardial infarctions. Beta blocking agents generally exert their influence through specific beta (B) receptors, i.e., the B-1 receptors located predominantly in the myocardium. However, some beta blocking agents also affect the B-2 receptors which are located in skeletal muscle, organs, blood vessels and airways. The blockade of these B-2 receptors may produce undesirable side effects when the sole purpose of medication is for the treatment of cardiovascular disease.

BAB is achieved by pharmacological agents which occupy the beta receptors, thus blocking the normal action of epinephrine and norepinephrine which are released with sympathetic stimulation.

These drugs compete with the catecholamines for these beta receptors, but they do not activate the occupied sites. Thus, the general "fight or flight" responses normally resulting from adrenergic receptor activation is attenuated. Moreover, BAB tends to reduce the systemic arterial pressure, thus reducing circulatory afterload during sympathetic stimulation. This is advantageous since it delays the onset of angina reflecting a reduction in myocardial ischemia.

Conversely, chronic exercise is a stressor to the cardiovascular system. It is effective in inducing alterations in the circulatory system, increasing its capacity during maximal exercise and enabling it to become more efficient. One mechanism by which this occurs is through an increased period of diastolic filling which results in an increased ventricular preload. Also, increased muscle blood flow results in a decreased afterload. Furthermore, improvement in maximal oxygen uptake results from endurance exercise training and is associated with decreases in heart rate and systolic blood pressure, i.e., double product, as well as decreases in general sympathetic activity at the same absolute workload.

Acute exercise increases sympathetic outflow and epinephrine release resulting in an increase in heart rate, stroke volume, and myocardial contractility. BAB, in essence, confounds this normal sequence of events during exercise. With the inhibition of B-1 activation, exercise performance has been found to be impaired in some studies, but unaffected in others.

In untrained individuals, Epstein et al. (1) found that BAB decreased maximal oxygen uptake as well as treadmill time to the endpoint of exhaustion. Reybrouck et al. (2), however, found that in both untrained normal subjects as well as in cardiac patients, maximal oxygen uptake and treadmill time were maintained. They hypothesized that although BAB did markedly decrease maximal heart rate, oxygen uptake was maintained by increases in stroke volume and in peripheral oxygen extraction by the working muscles.

Highly trained endurance athletes, however, have theoretically maximized both their stroke volume and their peripheral oxygen extraction capabilities. Consequently, they have less effective compensatory mechanisms by which they may override the effects of acute BAB (3). Therefore, the impairment of performance with BAB should be much greater in endurance trained subjects.

The effects of BAB on distance running performance have not been well documented. It is presently unknown as to which of the physiological mechanisms associated with successful distance running performance are most affected by BAB. Costill et al. (4) have described three parameters which determine endurance running performance. These parameters include maximal oxygen uptake ($\dot{V}O_2$ max), metabolic/mechanical efficiency expressed as the oxygen uptake for a standard running velocity, and the running velocity at lactate threshold.

Early work by Costill et al. (4) indicated that $\dot{V}O_2$ max was the factor most closely correlated to distance running performance.

Later work by Farrell et al. (5) showed that among a homogenous group of trained runners, velocity at lactate threshold appeared to be most closely correlated with performance. Finally, Costill et al. (6) and Connelly et al. (7) found that running performance correlated highly with metabolic/mechanical efficiency as well as velocity at lactate threshold.

Considering each of these parameters, the effects of BAB on endurance exercise performance can be more closely analyzed. In addition, possible differences between cardioselective (atenolol) and non-selective (propranolol) beta blocking agents can be ascertained.

At present, cardioselectivity is an important issue. Kendall and Smith (8) claim that cardioselectivity does not influence the effect of BAB on the heart rate or blood pressure during exercise. If cardioselectivity does not influence central circulatory factors, then variability in exercise performance between the two classes of beta blocking agents would be due primarily to peripheral effects, i.e., B-2 receptor mediated effects.

Kaiser et al. (9), and Kaijser (10), showed a greater decrease in exercise tolerance in a group of endurance trained subjects using propranolol (non-selective) as compared to atenolol (cardioselective). Karlsson (11), in a study on endurance trained subjects, showed that times run over a given distance were faster when the subjects were medicated with atenolol as opposed to

propranolol. The decrease in performance time also correlated positively with the subject's percentage of slow twitch fibers.

Other researchers have attempted to describe the peripheral mechanistic effects of BAB with and without regard to cardioselectivity. Lundborg et al. (12) found changes in the liberation and uptake of both free fatty acids and glycogen in subjects under BAB. Others (13,14,15) have found variability in the uptake of fuel sources such as glucose, as well as the blood lactate response.

Statement of the Problem

Results of studies investigating the response to submaximal and maximal exercise while under the influence of BAB have been quite variable. This is due, in part, to the class of medication used, the dosages administered, as well as the subject's level of conditioning.

Thus, the purpose of this study was to investigate the effects of cardioselective (atenolol) and non-selective (propranolol) beta blocking agents on both the submaximal and maximal endurance performance of highly trained distance runners. Submaximal performance was evaluated by the physiological responses to a constant velocity, steady-state run at 240 $m \cdot min^{-1}$ on a horizontal treadmill. Maximal performance was evaluated by the maximal physiological responses to a progressive speed incremented treadmill run, maximal treadmill time, and the time to complete a competitive 10-km track race.

CHAPTER 2

A REVIEW OF LITERATURE

Adrenergic Blocking Agents

Various forms of acute stress including exercise and fear stimulate the sympathetic nervous system causing the release of catecholamines. This release, in turn, prepares the body to respond to this stress. These responses include cardiovascular and metabolic adaptations which improve the blood supply to skeletal muscle and increase oxygen uptake as well as increasing mobilization of carbohydrates and free fatty acids in anticipation of a need to raise the level of energy consumption. BAB generally attenuates these actions.

Beta blocking agents exert their effect by occupying the receptor sites for catecholamines. These receptor sites were originally described by Dale (16) in 1906. Later, Ahlquist (17), after looking at the effects of various sympathetic agents identified two distinct receptors; alpha (A) and beta (B). Both of these receptors interacted with catecholamines; however, they provided different responses.

Finally, in 1967, Lands et al. (18) demonstrated two varieties of B-receptors based on their varying responses to epinephrine and norepinephrine. According to Lands et al. (18), B-1

receptors are found predominately in the heart while B-2 receptors are located in the peripheral arteries, organs, and airways. They further stated that alpha receptors tend to be the antagonists of the B-2 receptors. Later, Lewis et al., (19) showed that dilation of the coronary vessels is entirely mediated by B-1 receptors in isolated coronary preparations.

The general mechanism by which beta blocking agents work is through competitive binding with catecholamines for beta receptor sites. In a study on young normal males, Irving et al. (20) found that beta blocking agents significantly increase the adrenergic response to exercise as evidenced by increased plasma catecholamine levels. Furthermore, Robertson (21), in a review article, concluded that common clinical doses of beta blocking agents were ineffective in reducing blood pressure in patients with hypertension which was associated with excessive secretion of catecholamines. These studies demonstrate the competitive nature of beta blocking agents and catecholamines for adrenergic receptor sites.

BAB is most important because of its effectiveness in reducing the oxygen demand of the myocardium. Effective BAB has been shown to lower blood pressure, reduce the contractility of the myocardium and decrease heart rate. This, in turn, reduces the work of the heart, as evidenced by a reduction in rate-pressure product, and thus its oxygen demand. As a result, BAB decreases the chance of the heart becoming ischemic at the same rate of work by reducing the heart rate and blood pressure responses (8,19).

Studies have been conducted to evaluate the effectiveness of BAB in the management of cardiovascular diseases. Since the mid-1970's, many large epidemiological studies have been conducted in this area. These studies have generally shown that among survivors of myocardial infarction, chronic treatment with beta blocking agents is more effective in reducing mortality than similar treatment with a placebo (22,23). In fact, Shan (24) of Duke University Medical Center states, "the development and introduction of B-blockers ranks as the most important therapeutic advance in the treatment of cardiovascular disease to date. Not only have these drugs proved effective in treatment of angina, arrythmias and hypertension, several have recently been shown effective in secondary prevention of death following myocardial infarction, (pg. 97)."

Physiological Characteristics of Cardioselective vs. Non-Selective Beta Blocking Agents

Cardioselective beta blocking agents are relatively specific in their actions to the B-1 receptor sites. Non-selective beta blocking agents are active at both the B-1 and B-2 receptor sites. Since most beta blockers are prescribed because of their B-1 effects, e.g., reduction in blood pressure and heart rate, the B-2 effects elicited by non-cardioselective agents, e.g., constriction of peripheral vessels and bronchi, may be undesirable in the management of patients with cardiovascular disease.

Frishman et al. (25) in a study on patients with severe but stable angina reported that although moderate doses of propanolol

improved exercise performance in this group, higher doses caused decreased work capacity. They hypothesized that this decreased capacity at higher doses may have been the result of the non-selective nature of propranolol, i.e., its influence on the B-2 receptors. According to Kendall (26), cardioselective drugs do not influence heart rate or blood pressure during exercise any differently than non-selective drugs. Moreover, cardioselective agents are less likely to interfere with airway function during exercise than are non-selective agents.

Recent work by Tesch et al. (27) has shown that non-selective beta blocking agents do indeed effect various peripheral factors during exercise. By having 14 physically active men perform sustained isometric exercise during placebo, propranolol-induced blockade, and control conditions, they were able to factor out central circulation as a possible limiting factor. Endurance time was significantly decreased during the propranolol treatment as compared to control and placebo conditions. These results indicate that muscular performance is impaired by the peripheral effects of propranolol irrespective of accompanying changes in central circulation.

Cardioselective and non-selective beta blocking agents also demonstrate differences in metabolic pathway, clearance rate, and half life. In general, nonselective drugs are considered to be lipophilic. They are completely absorbed by the gut, and are eliminated by bio-transformation in the liver. These lipophilic

agents tend to have short half-lives of 3-4 hours. Thus, two to four doses per day are needed to maintain adequate blood levels of the drug (8,28). Conversely, cardioselective drugs are generally hydrophilic. Although they are not as well absorbed by the gut, they are excreted unchanged via the kidney. As a result, these agents have a half life as long as 6-13 hours, and may be effective when administered as a single daily dose (8,29).

Effectiveness of Exercise Therapy for Cardiac Rehabilitation

While BAB has been shown to be effective in the treatment of cardiovascular disease through decreasing the myocardial oxygen demands, chronic aerobic exercise has been shown to be an effective therapy in a different manner. Nevertheless, many of the resulting adaptations are similar to those of BAB. Exercise training is effective in improving cardiovascular function both at rest and during exercise through peripheral vascular alterations (30), as well as through central circulatory adaptations, including changes in heart rate and stroke volume (30,31). Moreover, these changes cause lowered oxidative demand on the heart at a given rate of work. Due to an increase in diastolic filling time, left ventricular preload is increased, thus allowing for an increased stroke volume. Increased muscle blood flow decreases the ventricular afterload, also enhancing increases in stroke volume. Furthermore, the increased muscle blood flow reduces peripheral vascular resistance which, in turn, reduces blood pressure. With cardiac output

remaining constant for the same rate of work, heart rate is reduced as stroke volume is increased. The decreases in both heart rate and blood pressure reduce the double product, an index of myocardial oxygen demand. With a smaller absolute myocardial oxygen demand for each level of exercise intensity, the onset of myocardial ischemia is delayed to higher rates of work (32,33). The response of patients with cardiovascular disease to training is similar to those of normal subjects, but generally not as marked (33).

Several prospective randomized studies have been conducted over the last decade to determine the benefits of exercise training in the treatment of subjects who have survived myocardial infarction. Although none have shown significant differences in mortality between exercise and control groups, virtually all these studies reveal a positive trend favoring the physical training group (34).

While May et al. (34) have shown that exercise may be beneficial in the treatment of coronary artery disease on an epidemiological level, Hagberg et al. (35) have described both the cardiovascular and the peripheral adaptations which occur during conditioning of cardiac patients. Previous to this study, it was believed that cardiac patients improve exercise tolerance primarily through changes in peripheral adaptations. Hagberg et al. (35) in their study of 11 cardiac patients, found that central cardiac adaptations were responsible for much of the improvement in maximal oxygen uptake associated with training. While some of the improvement was attributed to alterations in peripheral factors,

measures of myocardial contractility, such as stroke volume and stroke work as well as blood pressure responses, all improved substantially after 12 months of training. Thus, the heart became a more efficient pump, and its oxygen demands were reduced.

While beta blocking agents and exercise are both widely prescribed for rehabilitation of cardiovascular diseased patients, their combined usage has been considered contraindicated by many clinicians. The effects of beta receptor blockade have often been compared to those of training in that both cause a reduced heart rate and systolic blood pressure at maximal and at standardized submaximal levels of work. However, these reductions are accomplished by different mechanisms. While training reduces heart rate and systolic blood pressure, in part, by a reduced sympathetic stimulation of the heart and blood vessels at any given $\dot{V}O_2$, BAB actually attenuates the heart's response to sympathetic stimulation. However, BAB does cause a compensatory increase in alpha-receptor controlled peripheral vasoconstriction (33).

Effects of Beta Blocking Agents on Exercise in Patients with Cardiovascular Disease

After the establishment of both BAB and exercise as viable therapies in the control of hypertension and coronary artery disease, investigators began to study their mutual effect in both acute and chronic situations. Initially, beta blocking agents were used in cardiovascular diseased patients because they tended to reduce myocardial oxygen requirements, i.e., depress the double

product, thereby delaying the onset of angina during acute bouts of exercise (8). However, early investigators theorized that possibly this therapeutically induced limitation of cardiac function might prohibit a training effect from occurring in patients taking beta blocking agents (36). Considerable controversy exists today concerning this issue. Because beta blockers have acute benefits in delaying onset of angina, and also have been shown to decrease morbidity and mortality of cardiovascular diseased patients, they will be used in the rehabilitation of these patients regardless of whether exercise training is included as adjunct therapy. If a trained state cannot be obtained while exercising under the influence of BAB then, quite possibly, exercise will no longer be included in the treatment regimen for cardiovascular diseased patients.

Response of Patients Under BAB During Acute Exercise

Early work by Dwyer et al. (36) showed that propranolol was effective in treating patients with angina pectoris because it allowed patients to do physical work while requiring less myocardial oxygen delivery compared to the unblocked state. This, in turn, delayed the onset of ischemia and the occurrence of angina.

Later, Frishman et al. (25), using angina patients, found that during control tests, the patients' cessation of exercise was mainly attributed to angina. After taking moderate doses of propranolol, the onset of anginal pain was delayed, e.g., angina

occurred at a higher rate of work. They also found with higher doses of propranolol angina was no longer a limiting factor. Instead, work time was decreased, and fatigue became the limiting factor causing patients to stop exercising. This fatigue was associated with the higher doses of medication, not the higher levels of work.

According to Powles (37), the effectiveness of BAB during acute exercise is due to the decreased peripheral vascular resistance which results in a lowering of blood pressure. Furthermore, decreases in heart rate at each workload including maximal rates, lowers the double product, thus delaying the onset of angina. Thus, higher workloads may be tolerated before myocardial ischemia and accompanying angina begin to occur.

In order to determine the effects of BAB on $\dot{V}O_2$ max, Reybrouck et al. (2) used 31 hypertensive patients and did maximal effort tests on cycle ergometers. The patients were given both a placebo and up to 600 mg/day of atenolol. They found that although maximal cardiac output was decreased, compensatory mechanisms allowed both $\dot{V}O_2$ max and maximal physical working capacity to be maintained at control levels. It was postulated that the cardioselectivity of atenolol allowed factors such as stroke volume and arterial-venous oxygen difference to compensate for the noted decrease in heart rate. It was felt that the peripheral B-2 interactions which occur normally during BAB with atenolol helped maintain maximal work capacity.

In a similar study, Franciosa et al. (38) found that hypertensive patients using propranolol were unable to match the maximal work time of other patients using oxprenolol (a non-selective beta blocking agent with alpha agonist activity) during exercise on a cycle ergometer. Although both medications were equally effective in diminishing heart rate and systolic blood pressure during exercise, only propranolol reduced cardiac output and $\dot{V}O_2$ max.

Bruce et al. (39) observed both increases and decreases in $\dot{V}O_2$ max among cardiovascular diseased patients during propranolol treatment, with the direction of the response dependent on the type of disease and the degree of existing myocardial damage. Heart rate reduction with BAB was similar in all patients. However, only those with less than 15% ventricular impairment had decreases in $\dot{V}O_2$ max. Conversely, patients with more than 15% ventricular impairment showed increases in $\dot{V}O_2$ max.

Response of Patients to Exercise Training While Under BAB

Dwyer et al. (36) in 1968 and Malborg et al. (40) in 1974 hypothesized that it might not be possible to achieve a trained state while under BAB. However, there appears to be evidence to the contrary.

Studies by Pratt et al. (41) and Obina et al. (42) showed that patients with documented coronary artery disease, who were chronically administered doses of propranolol, could achieve a substantial training effect through endurance exercise. Pratt et

al. (41) administered either varying amounts of propranolol or no beta blocking agent to 35 coronary patients. The patients underwent a maximal treadmill test using the Bruce protocol before embarking on a 12-week training program of aerobic exercise. Following the training program, the treadmill test was repeated. Both groups showed improvements in treadmill time and estimated $\dot{V}O_2$ max. Moreover, there was no difference in the improvements noted between the two groups. In a study using a similar design, Obina et al. (42), also found that propranolol did not impair the training effects of exercise among coronary patients when compared to another group of patients exercising while taking placebos.

More recent studies have also demonstrated that a training effect can be obtained by patients using beta blocking agents. Studies by Smith et al. (43), and Roberts et al. (44) measured $\dot{V}O_2$ directly in patients that trained while taking beta blockers. They both reported improvements in treadmill time and in $\dot{V}O_2$ max after training. Smith et al. (43) hypothesized that BAB does not attenuate the salutory effects of exercise training. Roberts et al. (44), however, found in their study that although patients did improve $\dot{V}O_2$ max and treadmill time while taking propranolol, the magnitude of improvement was inversely related to the prescribed doses.

Beta Adrenergic Blockade During Acute Exercise of Normal Subjects

In order to discover the interactive physiological responses to BAB and exercise, many investigators have used a normal, non-diseased subject sample. Most studies have used sedentary normal subjects while a few have used more highly trained participants.

Initial work in this area began in the early 1960's. Epstein et al. (1) investigated several aspects of BAB and exercise including: 1) the acute responses to exercise with and without BAB on the same day, 2) the effects of BAB on submaximal and maximal exercise performance, and 3) the effects of BAB on peripheral oxygen extraction during steady-state exercise. Subjects were tested on a motor driven treadmill and BAB was obtained by intravenous administration of propranolol. Propranolol caused a 40% decrease in time on treadmill compared to either control or placebo conditions. When propranolol was administered during a steady-state run, cardiac output, mean arterial pressure, and left ventricular minute work all declined and a new circulatory steady-state was established; however, submaximal $\dot{V}O_2$ was unchanged throughout the entire exercise. This latter finding was attributed to a compensatory increase in peripheral oxygen extraction. During maximal exercise propranolol caused reductions in heart rate, cardiac output, mean arterial pressure and left ventricular minute work, as compared to the control tests. Although $\dot{V}O_2$ max also decreased when compared to the controls, the magnitude of this decrease was much smaller

than the concomittant decreases seen in the cirulatory function. From these results, Epstein et al. postulated that the reduced $\dot{V}O_2$ at maximal effort was due to the inability of the increased peripheral oxygen extraction to fully compensate for the decreased cardiac output. Moreover, they reasoned that the lowered cardiac output was due to a marked drop in maximal heart rate as opposed to changes in stroke volume.

Furberg (3) studied the effect of BAB with propranolol on three different groups of subjects differentiated by their physical working capacities. He found that maximal work capacity actually improved during BAB in the group with the lowest physical working capacity which was comprised of patients with cardiovascular disease. In normal sedentary subjects, maximal work capacity remained relatively unchanged during BAB, while maximal work capacity actually decreased with BAB in the highly trained group. Weighing the evidence presented by Epstein et al. (1), Furberg proposed that trained athletes have maximized their peripheral oxygen extraction capability during heavy work, which may limit their ability to compensate for the BAB-induced decrease in maximal cardiac output.

Maksud et al. (45) found lowered heart rates and decreased minute ventilations during submaximal and maximal exercise in healthy young men taking propranolol. Contrary to the findings of Epstein et al. (1), Maksud et al. (45) found no changes in $\dot{V}O_2$ max, or exercise endurance times as compared to control tests. They

theorized that the difference between their study and those of preceding investigators may have been due to the doses administered in each study. The doses used in the Maksud et al. (45) study were approximately one-quarter the dose applied by Epstein et. al. (1).

Ekblom et al. (46), in a study of healthy subjects performing submaximal and maximal cycle ergometer exercise, found that intravenously administered propranolol decreased heart rate, cardiac output and maximal work time. While these results supported the results obtained by Epstein (1), they (46) did not find significant changes in $\dot{V}O_2$ max between the propranolol and control treatments.

Pearson et al. (47) showed not only decreases in work time and $\dot{V}O_2$ max in normal healthy males, but also a 3.5% reduction in submaximal $\dot{V}O_2$ over the entire work range during BAB with propranolol. This was accompanied by an increase in the respiratory exchange ratio of 0.06 units for every increment in workload. During submaximal work, propranolol also decreased steady-state cardiac output. This was attributed to a 22% decrease in heart rate. Stroke volume actually increased thus preventing an even larger drop in cardiac output. Reybrouck et al. (2) reported similar changes in stroke volume using hypertensive patients during BAB with atenolol. They also found lowered $\dot{V}O_2$ up to, but not including, the higher rates of work.

More recently, Wilmore et al. (48) conducted a similar study using the non-selective drug sotalol. While maximal heart rate was

reduced during BAB, treadmill time to exhaustion was unchanged, and $\dot{V}O_2$ max was only slightly decreased. Contrary to the findings of Reybrouck et al. (2) and Pearson et al. (47), no change was seen in $\dot{V}O_2$ or respiratory exchange ratio during submaximal exercise. It was theorized from this data, as well as previous work, that many of the varied results may have been due to drug-specific as well as dose-specific responses.

Trainability of Subjects While Under Beta Adrenergic Blockade

Much of the recent interest in the area of BAB research has focused on the trainability of subjects while under the influence of BAB. An early study by Maksud et al. (49) on normal subjects was conducted to demonstrate the effects of a single acute dose of propranolol and a placebo on various physiological parameters both before and after physical conditioning. Following training, administration of propranolol resulted in lower heart rates both at rest and during submaximal exercise as compared to pre-training propranolol values. Maximal heart rates and blood pressure responses did not change as a result of conditioning. The $\dot{V}E$ during exercise was lower during the tests conducted with propranolol as compared to a placebo both before and after the conditioning program. $\dot{V}O_2$ max improved after training under both conditions; however submaximal $\dot{V}O_2$ at each rate of work was unchanged by training or medication. The percentage decrease in exercise time stayed constant when comparing propranolol to placebo conditions

both before and after training. However training improved endurance time in both situations. Maksud et al. (49) postulated that the effects of training in normal subjects are not diminished by the acute administration of propranolol as compared to the pre-trained state.

Recently BAB studies have been conducted on normals to determine if it is possible to achieve the trained state while under BAB. Sable et al. (50) found that subjects taking propranolol during five weeks of training showed no training effect when their pre- and post-training treadmill tests were compared in the unblocked state. On the other hand, a comparable group taking a placebo during the training regime showed all of the classical signs of a training effect, including improvements in $\dot{V}O_2$ max, $\dot{V}E$ max and exercise duration. In the beta blocked group only $\dot{V}E$ max increased in a similar fashion to the placebo group after training. Moreover, this increase was evident only when the subjects had discontinued medication for a period of one week. The pre-training beta-blocked treadmill test did not affect $\dot{V}E$ max as compared to the pre-training control test. Thus, it follows that changes in $\dot{V}E$ brought about by training were masked by BAB and were not evident until the subjects discontinued medication. Still no changes were seen in $\dot{V}O_2$ max or work time in the propranolol group between their pre- and post-training unblocked control tests. Sable et al. postulated that the inability to demonstrate change in $\dot{V}E$ max in the

BAB group post-training was due to B-2 affects of propranolol on bronchiolar smooth muscle.

Ewy et al. (51), in a study design similar to the study of Sable et al. (50), using Sotalol and a 13 week training period, found no training effect in the beta-blocked group from pre- to post-training while subjects were still under the influence of BAB. However, one week following the discontinuation of medication, the subjects who had been on beta blocking agents demonstrated significant improvement in $\dot{V}E$ max similar to that seen by Sable et al. (49). In addition, increases were noted in both $\dot{V}O_2$ max and treadmill time. These adaptations were seen only when comparing the initial pre-training unblocked control test to the final post-training unblocked control test. Ewy et al. (51) similarly postulated that these findings were caused by a masking effect of the drug on central and peripheral changes elicited by training. They felt that the main factor causing this masking phenomenon was the decrease in heart rate induced by BAB. Effectively, the inability to reach normal maximal heart rate during BAB did not allow the training-induced changes in stroke volume to improve cardiac output. This inhibition of an increased cardiac output coupled with B-2 specific responses attenuated improvements in $\dot{V}O_2$ max. With removal of BAB, restoration of normal maximal heart rate, along with the training-induced increase in stroke volume caused significant improvement in cardiac output. Thus, $\dot{V}O_2$ max and performance time were suddenly improved.

More recently, Svedenhag et al. (52), have shown that a central and peripheral training effect can be obtained in healthy subjects taking propranolol while training for 12 weeks on a cycle ergometer. They claim, however, that these effects are not optimal, and suggest that the sympathoadrenal system plays some role in normal adaptation to training.

Beta Adrenergic Blockade During Acute Exercise in Trained Subjects

Little work has been done to describe the effects of BAB on trained subjects. There are, however, indications that the trained athlete's response to exercise during BAB may vary from responses seen in cardiovascular diseased patients or normal subjects (3).

Studies by Kaiser et al. (9), and Kaijser (10), showed that exercise tolerance and performance time were diminished in groups of highly trained distance runners consequent to BAB. The former study was double blinded and consisted of three treatment periods using either 50 mg of atenolol per day, 80 mg of propranolol per day, or a placebo. Treadmill tests were performed under each condition with incremental increases in workload every four minutes until subjects reached exhaustion. The results indicated that at lower submaximal workloads, the decreases in heart rate were the same when under the influence of both drugs. However, at workloads requiring more than 57% of $\dot{V}O_2$ max, a greater decrease in heart rate was seen with propranolol than atenolol. Both drugs depressed systolic blood pressure to the same level below that of the placebo, both at rest and during levels of exercise up to 77% of $\dot{V}O_2$ max. Contrary to

previous findings in normal sedendary subjects (47), $\dot{V}O_2$ at submaximal workloads was the same during all three treatments. Nevertheless, $\dot{V}O_2$ max, and performance time, were decreased by both drugs as compared to the placebo. These decreases were greater with propranolol than atenolol.

Another investigation, by Kaijser (10), on trained subjects was conducted to determine the dose dependent effects between cardioselective and non-selective BAB on distance running performance. Varying amounts of either atenolol or propranolol were given acutely to subjects in a double blind crossover design. Subjects were then allowed to follow their own running routes. Although a significant decrease in performance time was caused by the lowest dose of propranolol (40 mg), neither of the two lowest doses of atenolol (25 and 50 mg) impaired running performance. Nevertheless, higher dosages of atenolol did produce slower running times, although these times were significantly faster than those times run during corresponding doses of propranolol. Furthermore, peak perceived exertion plotted against peak impairment of running capacity showed that doses of propranolol caused greater fatigue, both subjectively and objectively, than similar doses of atenolol.

Kaijser (10) postulated that the consistent decrease in performance by all doses of propranolol is due to local B-2 blockade in the exercising muscle which would not be present with atenolol. However, during high doses of atenolol a partial B-2 blockade is

possible, thus causing an impairment in exercise performance similar to what is seen during BAB by propranolol.

Recent work done by Karlsson (11), attempted to clarify the results obtained in the two previous studies concerning the effects of atenolol and propranolol on running performance. Using highly trained subjects, as well as doses of propranolol and atenolol that were determined to be equivalent in terms of their antihypertensive effects, the subjects performed graded maximal treadmill and cycle ergometer tests. During submaximal exercise, there was no difference in heart rate and systolic blood pressure between either beta blocking agents. Using a vastus lateralis muscle biopsy, Karlsson found a positive correlation between diminished heart rate response during BAB and % slow twitch muscle fibers. Greater reductions in heart rate were discovered in subjects having a greater % of slow twitch muscle fibers. Moreover, during running, performance time was decreased more by propranolol than by atenolol among those subjects rich in slow twitch fibers. This may be due to the increased capillary density present in slow twitch muscle.

In a study on maximal work capacity during both acute and chronic BAB, von Baak et al. (53) found that low doses of metoprolol (non-selective) reduced cardiac output, but did not reduce $\dot{V}O_2$ max, or maximal work time in active, normal subjects. However, at higher doses, reductions in $\dot{V}O_2$ max and maximal work time occurred along with a diminished cardiac output.

Tesch et al. (54) found a decrease in maximal and submaximal $\dot{V}O_2$ in 13 subjects under BAB performing cycling exercise. Although the subjects were ingesting propranolol two hours before exercise, no changes in ventilation were seen at any level of exercise as compared to control values. RPE values also varied with control values when subjects were under BAB, with higher "local" RPE values being the major difference.

Physiological Parameters Associated with Success in Distance Running Performance

In trained runners who have maximized their physiological capabilities, there appear to be several discriminating factors which determine successful performance, and which allow the accurate prediction of distance running performance. Initially, Costill et al. (4) showed that the prime consideration for successful distance running performance was an individual's $\dot{V}O_2$ max. Later work (5,6), however, showed that while virtually all elite distance runners have high $\dot{V}O_2$ max values, there are large variations in other physiological parameters which are associated with distance running performance. Farrell et al. (5) demonstrated that running velocity at the onset of plasma lactate accumulation (OPLA) correlated quite highly with running performance in a group of well-trained runners who had similar $\dot{V}O_2$ max values. Furthermore, both Costill et al. (6) and Connelly and Krahenbuhl (7) showed a high correlation between submaximal running efficiency and performance when efficiency was defined as the $\dot{V}O_2$ for a given velocity

expressed both relative to body weight and as a percentage of $\dot{V}O_2$ max. This study also used a group of exceptional runners who had similar $\dot{V}O_2$ max values. They postulated that additional variation in performance not accounted for by the differences in running efficiency are due to inter-individual differences in running speed at OPLA, or possibly other factors including peak muscle lactate, blood lactate tolerance, and differences in muscle fiber type.

It is obvious that although a high $\dot{V}O_2$ max is a prerequisite for distance running success, other factors such as running efficiency and speed at OPLA are more important among a homogenous group of highly trained runners with similar performance times.

Beta Blockade and its Effects on Physiological Mechanisms Involving Performance Parameters

There are many mechanisms by which BAB could influence exercise performance. Many of these mechanisms have been described throughout this review; however, many others affected by training and BAB have not been discussed. Although the central effects of BAB on cardiac output and $\dot{V}O_2$ max have been studied thoroughly, some of the more subtle peripheral effects and their impact on running performance parameters are not clearly understood. BAB effects on ventilation may be responsible for impairment of $\dot{V}O_2$ both maximally and submaximally (50). Moreover, BAB has been alleged to affect substrate metabolism of glucose, glycogen and free fatty acids during exercise, as well as to alter blood lactate

response to submaximal and maximal exercise (12,13,14,15). Many of the findings in these areas are equivocal, and many of the conclusions drawn by the investigators concerning these findings are speculative. Because of the uncertainties, and since these issues deviate from the central theme of this paper, they will be addressed no further.

CHAPTER 3

METHODS

Twenty five highly trained endurance runners, with a mean age of 28.6 ± 5 years, were recruited from the Tucson, Arizona running community. Their physical characteristics are described in Table 1. Their general training included 50 to 100 miles of running per week, and they had an average of 5 years of competitive road racing experience at a variety of distances. Previous 10-km personal records ranged from 30.75 minutes to 38.50 minutes. All subjects reported in good condition for the testing which took place throughout the months of March and April, 1984.

A meeting was held to brief the subjects on the design of the study as well as to explain the effects of both types of BAB. Subjects filled out a brief personal and family history form and were asked to read and sign the consent form which had been approved by the University of Arizona Human Subjects Committee (see Appendix 1). Before initiating testing, each subject underwent a physical examination by a cardiologist to establish final clearance into the study.

Control data were obtained by having all subjects complete two maximal effort treadmill tests and two 10-km races during the initial three weeks of the study. Throughout the study, the

TABLE 1: Subject Characteristics

Subject	Age (yr)	Ht. (cm)	Wt. (kg)	Fat (%)	Lean Wt. (kg)	Fat Wt. (kg)
1. R.A.	25	187.5	85.2	12.9	74.2	11.0
2. K.C.	27	179.6	66.4	11.4	58.9	7.5
3. S.D.	27	182.8	73.3	10.4	65.7	7.6
4. G.D.	33	178.8	68.5	8.1	62.9	5.6
5. J.E.	39	177.0	64.9	12.7	56.6	8.3
6. B.F.	24	179.3	67.6	3.4	65.3	2.3
7. D.G.	24	175.5	58.2	6.5	54.4	3.8
8. R.G.	34	165.2	57.7	11.9	50.8	6.9
9. M.G.	21	176.4	69.2	6.9	64.4	4.8
10. R.H.	28	169.4	60.9	10.6	54.5	6.4
11. J.H.	34	173.9	64.2	11.3	57.0	7.2
12. T.H.	29	173.2	60.0	9.3	54.4	5.6
13. T.J.	23	191.9	70.5	8.0	64.8	5.7
14. M.J.	25	195.0	80.0	11.7	70.6	9.4
15. M.L.	26	175.0	68.7	7.5	63.6	5.1
16. K.L.	25	191.2	79.9	10.9	71.2	8.7
17. M.Ma.	24	187.4	72.1	8.2	66.2	5.9
18. M.My.	25	179.2	70.1	6.2	65.7	4.4
19. L.P.	35	174.5	73.8	12.1	64.9	8.9
20. T.R.	36	173.0	56.0	10.8	49.9	6.1
21. H.S.	36	173.2	61.3	8.2	56.2	5.1
22. D.S.	34	181.5	73.1	13.1	63.5	9.6
23. R.T.	32	185.2	75.8	10.6	67.7	8.1
24. C.T.	24	185.2	74.9	10.0	67.4	7.5
25. R.W.	26	177.0	62.7	9.2	56.9	5.8
$\bar{x}$	28.6	179.1	68.6	9.7	61.9	6.7
S.D.	5.1	7.3	7.5	2.4	6.5	2.0

treadmill tests were administered by appointment on Thursdays. Each subject maintained the same appointment time throughout the course of the study. On the Saturday morning following the treadmill test, the subjects participated in 10-km track races. All testing and races were conducted every other week throughout the control and treatment portions of the study.

Following the two control tests, the subjects began three separate 10 day treatment periods during which they performed the treadmill tests and 10-km track races, maintaining the same Thursday-Saturday pattern of every other week. The three experimental treatments included: (1) 80 mg of propranolol BID; (2) 100 mg of atenalol daily in the am with a pm placebo; and (3) a placebo given BID. The medication was taken between 7:00 and 9:00 am and pm maintaining a twelve hour interval between doses. This pattern was followed during each 10-day medication period with the exception of the treadmill test and race days. This pattern of dosage was chosen in order to provide equivalent blockade between both types of BAB. According to Kendall and Smith (7), the potency of propranolol and atenolol at these doses is equal. BID doses of propranolol were administered due to the relatively short plasma half-life of propranolol (3-4 hrs) as compared to atenolol (6-7 hrs) (7). Furthermore, studies by Ambrosioni et al. (55) indicate that a daily dose of atenolol was a more effective hypertensive agent than equivalent BID doses of propranolol in mildly hypertensive patients. Magnani et al. (56) showed that the circulatory effects of 100 mg

of atenolol were still present during exercise up to 20 hours past the ingestion of medication.

The difference between the absolute amounts of medication administered are due to the variation in bio-availability of the two drugs. The bio-availability in % of dose for atenolol is approximately 50-60% while for propranolol is approximately 25-35% (8). Also, Schwartz (57) found that there was no difference in exercise heart rate between 100 mg and 200 mg of atenolol at either 2 or 24 hours post-ingestion. In general, the doses given were similar to conventional clinical doses.

The subjects had a four day interval between the second control session and the beginnning of the first treatment period. A four day washout period followed each treatment period before the next treatment period began. This washout period was chosen to allow time for the complete bio-transformation of propranolol or for the plasma clearance of atenolol. Due to its longer half life, atenolol takes longer than propranolol to be eliminated (8). Studies by Petrie et al. (58) have shown that in hypertensive patients, baseline blood pressure and heart rate values will return to pre-medication levels approximately 72 hours following the final dose.

On the treadmill test days, the subjects who had morning treadmill tests took their medication 2.5 hours before their test. The subjects who had pm tests took their am medication eight hours pre-test and their pm medication 2.5 hours before treadmill

testing. This was done to allow the particular medications to reach peak blood levels. Studies by Folgering and van Bussel (59), as well as Petrie et al. (58) indicated that peak blood levels of beta blocking agents occur no earlier than 1.5 hrs following ingestion. The subjects medicated 2.5 hours before starting time on all race days for the same reason.

During all three treatment periods, the treadmill test and 10-km races were run on the eighth and tenth days of medication respectively. Thus, medication was given for a total of 9 and 1/2 days. No further medication was taken following the 10-km race as this began the washout period preceding the next medication period. The 10-day medication period was used to simulate a chronic physiological blockade which would be found in cardiovascular diseased patients who would be taking beta blockers by prescription.

The medications were distributed randomly in a double-blind manner following a latin square statistical design. This was done to minimize the possible changes in performance due to the variability in the subject's training throughout the study. Also, this type of design minimized the various, uncontrollable environmental effects on the 10-km race performance during the course of the two month project. Moreover, this design avoided either subject or experimentor bias. A code known only by the packagers of the drugs was broken at the completion of the study.

Treadmill testing was conducted in the University of Arizona's Exercise and Sport Sciences Laboratory. The subjects were

instructed as to the protocol being used and were allowed to familiarize themselves to treadmill running.

The test itself included a two minute warmup at 220 $m \cdot min^{-1}$ at a grade of 0%. During the remainder of the test, the grade was maintained at 0%, while the velocity of the treadmill was incrementally increased. The horizontal protocol described by Sucec (60) was modified for this study. Although protocols which include grade changes usually show an approximately 5% higher $\dot{V}O_2$ max than do horizontal protocols (61), a horizontal test was used to effectively simulate the 10-km track racing used in this project.

After the two minute warmup, treadmill speed was increased to 240 $m \cdot min^{-1}$. This speed was maintained for six minutes to measure steady state $\dot{V}O_2$, $\dot{V}E$, HR and the subject's rating of perceived exertion (RPE). This speed was chosen to avoid OPLA for all subjects involved in the study. Many studies have used 266.6 $m \cdot min^{-1}$ (10 mph) as the criterion speed for measuring running economy, however these studies usually included top collegiate, national, and international caliber runners. It was felt that 10 mph would be too fast for some of the subjects in the present study, particularly during the BAB portion of this study. There was a possibility that the slower subjects would not be able to reach steady state $\dot{V}O_2$ levels at higher speeds.

Recent investigations by both Whipp et al. (62) and Linnarsson et al. (63) indicate that at levels well below OPLA, the kinetics of $\dot{V}O_2$, as a first order function, reach steady within

two minutes. At levels just below OPLA, oxygen kinetics necessitate approximately four minutes to reach steady state values. Thus, six minutes was used to ensure that steady state $\dot{V}O_2$ could be attained. Furthermore, Conley and Krahenbuhl (7) showed that running economy appeared to be a linear function in which the % variation between individuals remained similar at all running speeds below OPLA.

After the steady state period was completed, the treadmill velocity was increased 20 $m \cdot min^{-1}$ each minute until the subjects reached exhaustion. Maximal treadmill time and speed at exhaustion were recorded. The treadmill test was designed to last no longer than 16 minutes to avoid the effects of cardiovascular drift on heart rate responses. Room temperature varied between 24° and 27°C during treadmill tests over the course of the study.

The tests were run on a manually controlled, motor driven Quinton treadmill (Model 24-72). The treadmill was calibrated before each day's testing to make sure that the belt speed was consistent throughout the study. During the test, expired air was collected through a Hans-Rudolph non-rebreathing valve connected to a mixing chamber and volume transducer contained within the Beckman Metabolic Measurement Cart (BMMC). The O_2 and CO_2 fractions were sensed by Beckman OM-11 and LB-2 analyzers (64). Before each testing day began, ventilation values were calibrated by introducing given volumes into the system. O_2 and CO_2 analyzers were

calibrated before and after each test using a standard gas mixture previously calibrated by the micro-Scholander technique.

Other physiological measurements obtained by the BMMC during treadmill testing included $\dot{V}O_2$ in $L \cdot min^{-1}$, $\dot{V}O_2$ in $ml.kg^{-1}.min^{-1}$, respiratory exchange ratio (RER), $\dot{V}CO_2$ in $L \cdot min^{-1}$, $\dot{V}E$ (BTPS), $\dot{V}E$ (ATPS), FeO_2, $FeCO_2$. All measurements were taken every minute through minute 9. Beginning with minute 10, measurements were taken every 30 seconds until completion of the test. Electrocardiograms (ECG) were recorded via a 12-lead electrode placement during the initial control run, and by CM-5 lead configuration throughout the rest of the study. Heart rates were calculated from the ECG which was run for the last five seconds of each minute.

$\dot{V}O_2$ max criteria included the following (65): (1) leveling of $\dot{V}O_2$ despite increases in workload; (2) RER values greater than 1.15; (3) subject's sense of maximal exertion according to Borg's scale of Perceived Exertion (66) which was measured each minute. Running economy was measured by taking the mean $\dot{V}O_2$ $ml.kg^{-1}.min^{-1}$ of the final three minutes of exercise at 240 $m \cdot min^{-1}$ (7). All other submaximal data were obtained in this particular manner.

Two days following each treadmill test, the subjects reported to the University of Arizona track for the 10-km races. The subjects were separated into two groups according to their previous best 10-km times.

The track was a surveyed 400-m tartan track. Adequate warmup was allowed before the start of the race. The subjects received intermittent lap times, and were encouraged to use proper pacing techniques during the race. Subjects ran the races at maximal effort and were encouraged to keep training, dietary, and sleep habits similar during the course of the study. Technicians were at track side to count laps and to provide assistance at a water and spray station in order to keep subjects hydrated and cool. The subjects were stopped immediately following the run, and a 15-sec pulse count was taken by a technician to determine the immediate post-race heart rate. This heart rate was assumed to be the maximal race heart rate achieved by the subjects. Estimated race $\dot{V}O_2$ values were determined by calculating the particular treatment race speed in $m \cdot min^{-1}$. This race speed was then introduced into a regression equation which determined $\dot{V}O_2$ at various treadmill velocities corresponding to the particular condition.

Temperature and relative humidity values for each race day are found in Table 2. Race starting times were varied as conditions became warmer during the spring. Moving starting times to earlier in the morning helped maintain conditions constant throughout the study.

Following the study, all subjects turned in a training log which indicated their daily mileage and hours spent running. Furthermore, after the study, all subjects filled out a subjective evaluation of the three treatment periods concerning their

TABLE 2: Race Atmospheric Conditions

	Race 1	Race 2	Race 3	Race 4	Race 5
			Treatments		
Group 1					
Temp. °C	63	69	66	74	61
Relative Humidity %	52	52	41	44	57
			Treatments		
Group 2					
Temp. °C	69	72	78	82	52
Relative Humidity %	50	45	32	28	60

differences and similarities. The subjects were then asked to rank each period from most to least difficult in terms of their ability to train. All subjects were measured for height in centimeters, and received a body composition assessment using the hydrostatic weighing technique as described by Behnke and Wilmore (67), with residual lung volume measured using the nitrogen dilution technique (68).

Standard statistical practices were employed. These included repeated measures analysis of variance and Scheffé's post-hoc test. In all cases, the level of significance was set at the 0.05 level.

CHAPTER 4

RESULTS

With the exception of the $\dot{V}O_2$ for the submaximal, steady-state run at 240 $m \cdot min^{-1}$, the values obtained during the control tests were similar to placebo values for all parameters. Also, these control values reflected the same relationships with the propranolol and atenolol trials as seen with the placebo. This finding indicates the absence of a "placebo effect". Therefore, the placebo values were used as baseline physiological values for comparison with the two drug conditions.

Resting values, as seen in Table 3, indicate that both propranolol and atenolol depressed heart rate below normal resting levels. Systolic blood pressure was also decreased by both beta blocking agents as compared to placebo values, while diastolic values remained unchanged.

Values obtained during the submaximal, steady-state run at 240 $m \cdot min^{-1}$ are found in Table 4. Submaximal heart rates under both atenolol and propranolol conditions were lower than under the placebo condition. In addition, the submaximal heart rate during the propranolol trial was significantly lower than that obtained during the atenolol trial. Submaximal heart rate under placebo conditions represented 83.7% of the placebo maximal heart rate,

TABLE 3: Resting Values

		Treatment[a] C-1	C-2	PLAC	PROP	ATEN
Heart Rate b·min-1	$\bar{x}$	66.4	64.3	62.4	46.6[b]	49.7[b]
	±S.D.	12.0	9.9	8.9	6.3	8.7
Systolic BP mmHg	$\bar{x}$	129.1	131.5	131.0	121.4[b]	121.6[b]
	±S.D.	12.3	12.9	12.0	10.4	7.6
Diastolic BP mmHg	$\bar{x}$	77.2	80.5	80.8	77.3	76.7
	±S.D.	8.6	8.3	9.2	8.9	5.7
Weight kg	$\bar{x}$	69.0	69.0	69.1	69.3	69.1
	±S.D.	6.8	6.9	7.4	7.1	7.1

[a]Treatment: C-1, C-2 = first and second control tests, respectively; PLAC = placebo; PROP = propranolol; ATEN = atenolol.

[b]Significantly different from placebo values, $p<0.05$.

[c]Significantly different from propranolol, $p<0.05$.

NOTE: There were no significant differences between C-1, C-2 and PLAC. Furthermore, C-1 and C-2 demonstrated identical relationships with PROP and ATEN as did PLAC.

TABLE 4: Submaximal Treadmill Values (240 $m \cdot min^{-1}$ for 6 min)

		Treatment[a] C-1	C-2	PLAC	PROP	ATEN
Heart Rate b·min-1	$\bar{x}$	158.5	155.4	154.3	116.0[b]	123.8[b,c]
	±S.D.	8.7	8.5	10.0	6.7	11.58
$\dot{V}O_2$ $ml \cdot kg^{-1} \cdot min^{-1}$	$\bar{x}$	49.2	48.9	47.6	45.9[b]	46.9
	±S.D.	3.4	3.6	3.2	3.4	4.1
$\dot{V}E$ $L \cdot min^{-1}$	$\bar{x}$	93.6	93.5	92.0	94.4	91.8
	±S.D.	11.4	9.7	10.5	15.0	10.7
RER	$\bar{x}$	0.94	0.94	0.94	0.98[b]	0.95
	±S.D.	0.04	0.03	0.04	0.04	0.04
RPE	$\bar{x}$	12.6	12.1	11.8	14.1[b]	13.0[b]
	±S.D.	1.7	1.5	1.5	2.0	1.7
$\dot{V}E/\dot{V}O_2$	$\bar{x}$	27.6	27.8	28.0	29.6	28.5
	±S.D.	2.9	2.7	2.9	3.9	3.5
O2 Pulse $\dot{V}O_2$(ml)/HR	$\bar{x}$	21	22	21	27[b]	26[b]
	±S.D.	2	2	2	2	3
FeO_2	$\bar{x}$	16.15	16.19	16.21	16.41	16.26
	±S.D.	0.49	0.41	0.37	0.55	0.44
$FeCO_2$	$\bar{x}$	4.55	4.51	4.52	4.24	4.51
	±S.D.	0.48	0.39	0.39	0.60	0.42

[a,b,c]Refer to footnotes in Table 3.

NOTE: There were no significant differences between C-1, C-2 and PLAC, with the one exception of $\dot{V}O_2$ for C-1.

while propranolol and atenolol submaximal heart rates were 86.5% and 80.0% of their respective maximal heart rates. Individual and group values can be found in Appendix 3.

The submaximal $\dot{V}O_2$ decreased over the two control tests, and placebo values obtained throughout the study indicated a further decrease in submaximal $\dot{V}O_2$. The difference between the first control and the placebo trial was statistically significant. Furthermore, the submaximal $\dot{V}O_2$ for the propranolol trial was significantly lower than the placebo trial. Submaximal $\dot{V}O_2$ values for the placebo, propranolol, and atenolol trials represented 74.3%, 82%, and 76.6% of their respective $\dot{V}O_2$ max values. Individual and group data appear in Appendix 3.

No changes in ventilation were seen between trials, and submaximal $\dot{V}E$ under placebo, propranolol, and atenolol conditions accounted for 56.6%, 67.6%, and 58.6% of their $\dot{V}E$ max (see Appendix 3). Respiratory exchange ratio (RER) values during submaximal exercise were not different across trials, except for the propranolol trial which was significantly higher than the others. Ratings of perceived exertion (RPE) were significantly higher during BAB when compared to placebo, but propranolol and atenolol RPE values did not differ statistically from one another. Oxygen pulse (O_2 pulse) was higher for both atenolol and propranolol trials than for the placebo; however there was no difference between the two drugs.

Maximal treadmill values are found in Table 5. HR max was lower in both propranolol and atenolol trials as compared to placebo with atenolol decreasing HR max to a lesser extent ($p<0.05$). Figure 1 shows the effect of the three treatments on HR at various levels of work. The HR max with propranolol is 27.2% lower than the placebo value, while the HR max with atenolol is 16.4% lower than the placebo value. These differences were consistent with the differences seen in the race heart rates, as well as the submaximal and resting rates, although in some cases statistical significance was not reached (Figure 1). $\dot{V}O_2$ max, expressed in both $L \cdot min^{-1}$, or $ml \cdot kg^{-1} \cdot min^{-1}$, was significantly lower in both propranolol and atenolol trials compared to the placebo trials. Also, $\dot{V}O_2$ max with propranolol was significantly lower than with atenolol. The effects of the three treatments on $\dot{V}O_2$ at both maximal and submaximal levels is illustrated in Figure 2.

Maximal treadmill time was highest under the placebo condition as compared to the two BAB conditions. Figure 3 shows the relationships between the three conditions for maximal treadmill time. $\dot{V}E$ max values were not significantly different between placebo and atenolol trials, but $\dot{V}E$ max for both of these trials were significantly higher than for the propranolol trial. Figure 4 describes the effects of the three conditions on $\dot{V}E$ at both maximal and submaximal work rates. Maximal RER was similar across all trials except with propranolol. In contrast to the submaximal RER values where the propranolol trial was higher, the maximal RER with

TABLE 5: Maximal Treadmill Values

		Treatment[a] C-1	C-2	PLAC	PROP	ATEN
Heart Rate b•min-1	$\bar{x}$	185.3	182.7	184.0	133.7[b]	153.9[b,c]
	±S.D.	4.6	4.7	6.0	9.5	11.1
$\dot{V}O2$ $L \cdot min^{-1}$	$\bar{x}$	4.46	4.44	4.41	3.88[b]	4.20[b,c]
	±S.D.	0.50	0.50	0.50	0.60	0.40
$\dot{V}O_2$ $ml \cdot kg^{-1} \cdot min^{-1}$	$\bar{x}$	64.7	64.6	63.8	56.1[b]	61.6[b,c]
	±S.D.	4.3	4.6	4.2	5.0	5.6
$\dot{V}E$ $L \cdot min^{-1}$	$\bar{x}$	166.0	166.8	163.5	141.1[b]	157.5[c]
	±S.D.	17.7	14.4	17.5	18.4	14.6
Treadmill time min	$\bar{x}$	13.1	13.2	13.4	11.5[b]	12.7[b,c]
	±S.D.	0.9	1.0	1.0	1.5	1.0
RER	$\bar{x}$	1.18	1.17	1.20	1.14[b]	1.18
	±S.D.	0.07	0.06	0.08	0.07	0.06
$\dot{V}E/\dot{V}O_2$	$\bar{x}$	37.4	37.7	37.2	36.7	37.7
	±S.D.	3.7	3.2	3.7	4.2	3.1
02 Pulse $\dot{V}O_2$(ml)/HR	$\bar{x}$	24	24	24	29[b]	27[b,c]
	±S.D.	3	3	3	4	4
FeO_2	$\bar{x}$	17.20	17.24	17.07	17.11	17.20
	±S.D.	0.40	0.32	0.43	0.42	0.32
$FeCO_2$	$\bar{x}$	4.23	4.19	4.36	4.24	4.22
	±S.D.	0.42	0.42	0.43	0.49	0.41

[a,b,c]Refer to footnotes in Table 3.

NOTE: There were no significant differences between C-1, C-2 and PLAC. Furthermore, C-1 and C-2 demonstrated identical relationships with PROP and ATEN as did PLAC.

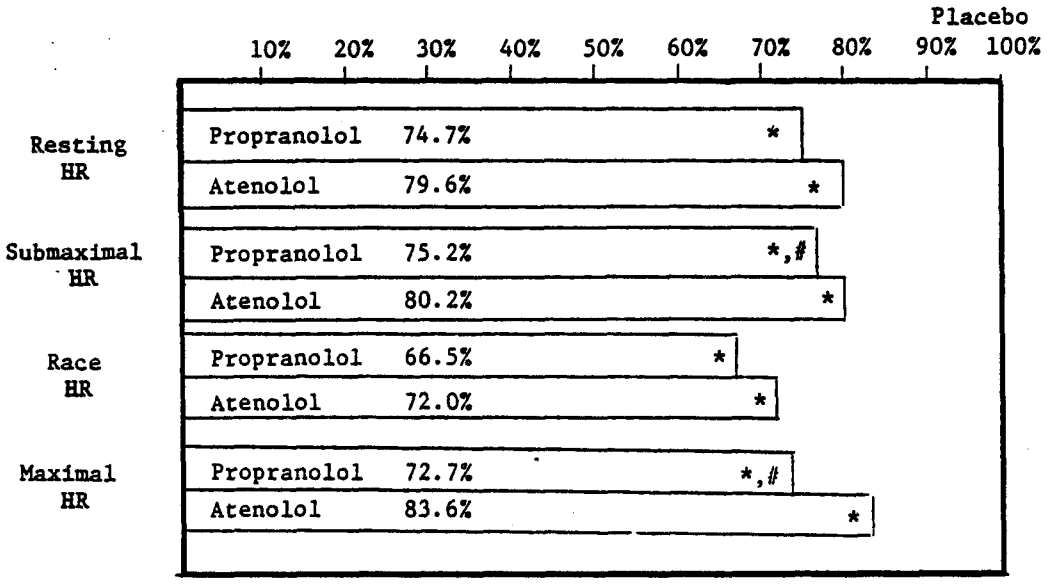

Figure 1a: Percent of placebo heart rate seen during BAB at various levels of exercise

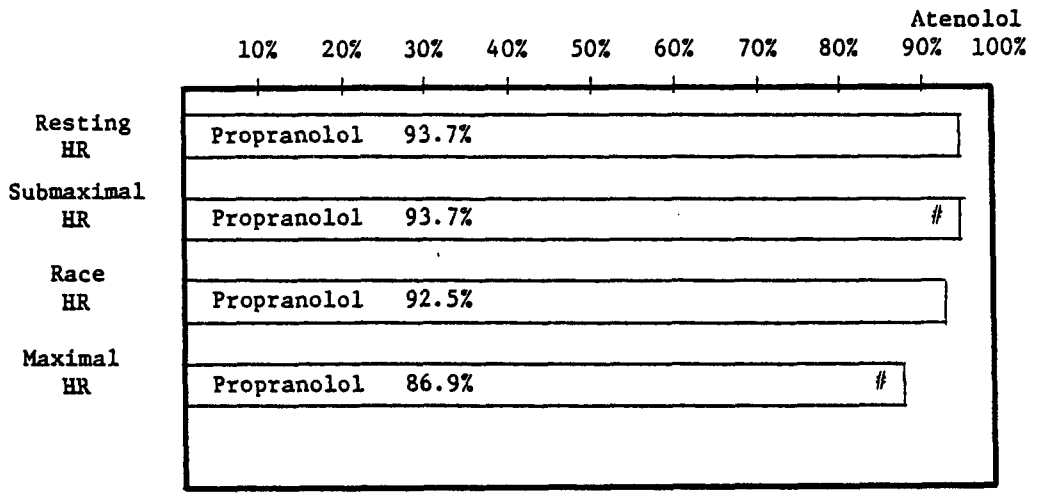

Figure 1b: Percent of atenolol heart rate seen during propranolol BAB at various levels of exercise.

*Significantly different from placebo ($p < 0.05$)

#Significantly different from atenolol ($p < 0.05$)

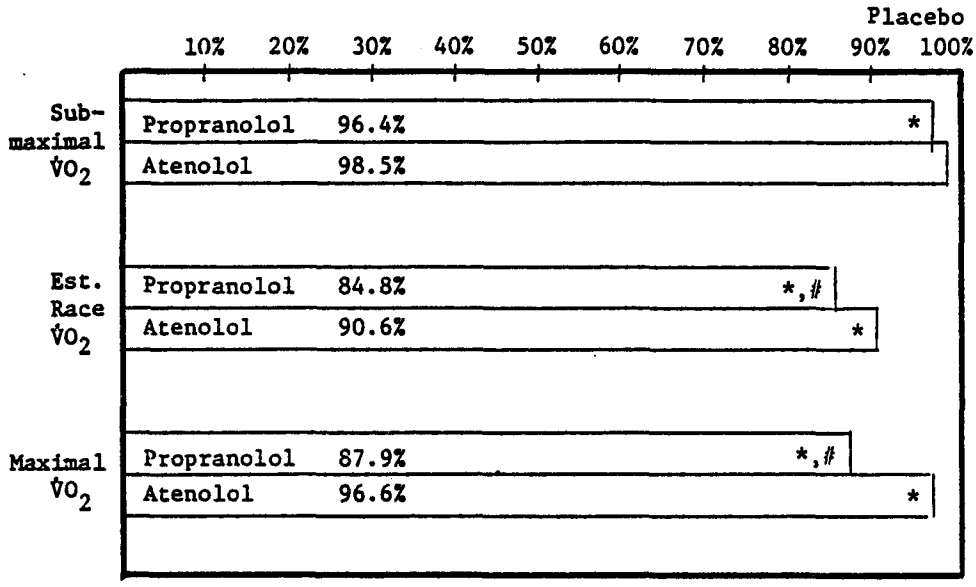

Figure 2a: Percent of placebo $\dot{V}O_2$ seen during BAB at various levels of exercise

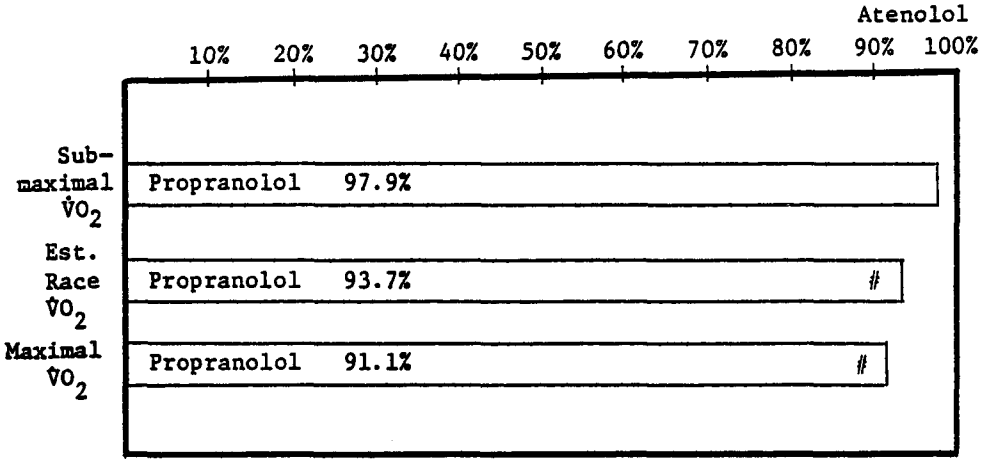

Figure 2b: Percent of atenolol $\dot{V}O_2$ seen during propranolol BAB at various levels of exercise.

*Significantly different from placebo ($p < 0.05$)

#Significantly different from atenolol ($p < 0.05$)

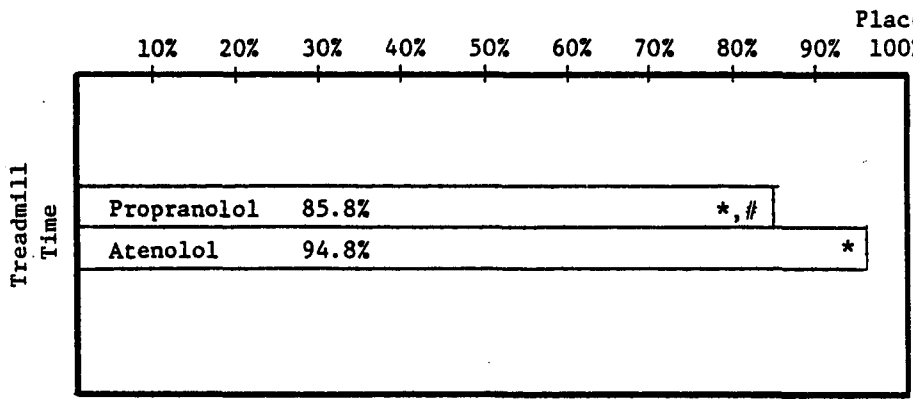

Figure 3a: Percent of placebo treadmill time attained during BAB tests.

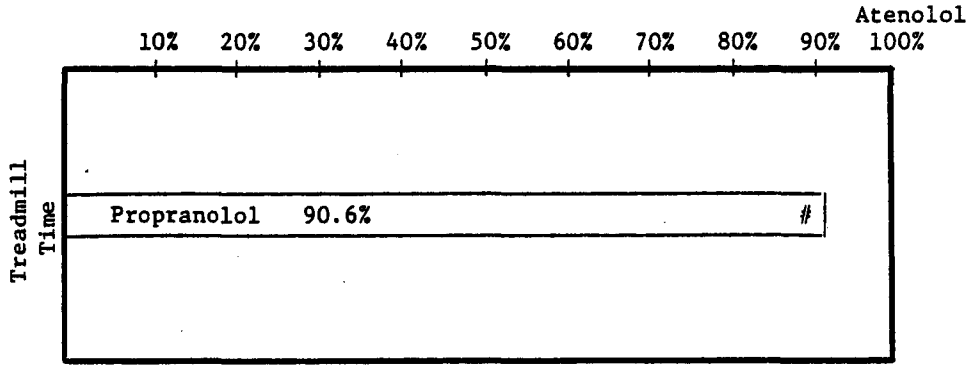

Figure 3b: Percent of atenolol treadmill time attained during the propranolol test.

*Significantly different from placebo ($p < 0.05$)

#Significantly different from atenolol ($p < 0.05$)

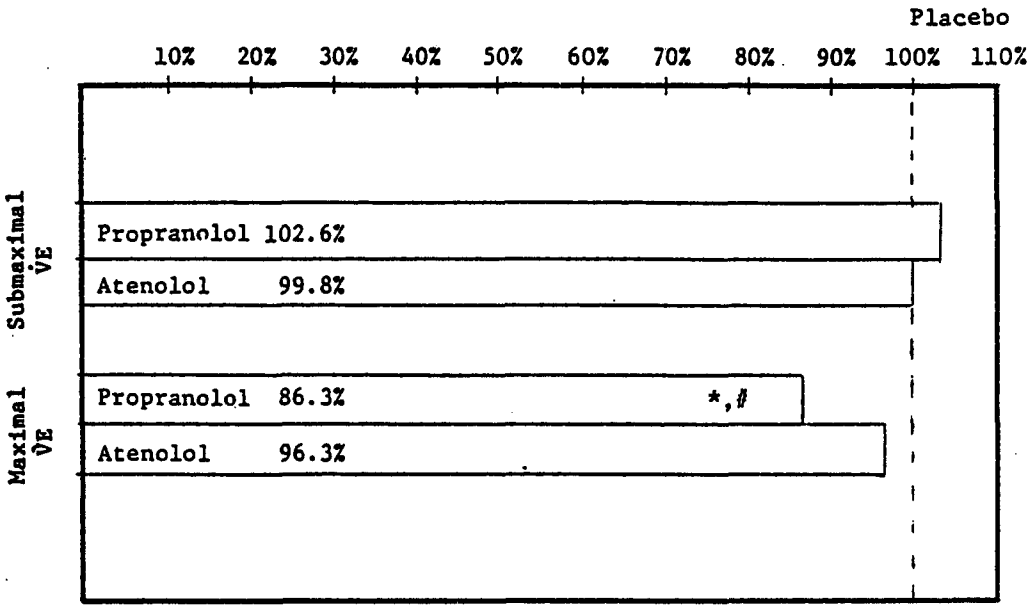

Figure 4a: Percent of placebo $\dot{V}E$ seen during BAB at various levels of exercise.

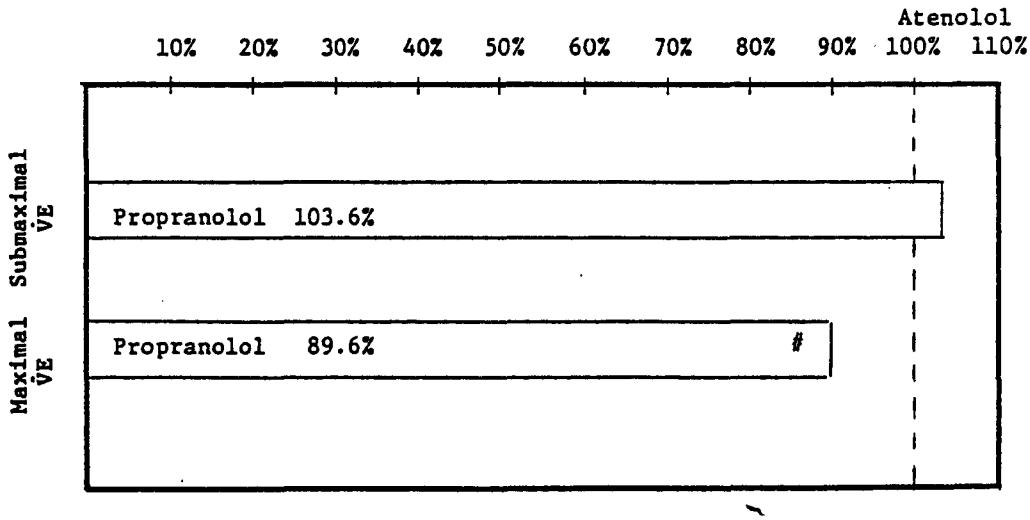

Figure 4b: Percent of atenolol $\dot{V}E$ used during propranolol BAB at various levels of exercise.

*Significantly different from placebo ($p < 0.05$)

#Significantly different from atenolol ($p < 0.05$)

propranolol was lower than with the other treatments. As a result of significant decreases in HR max, which were of greater magnitude than the decreases in $\dot{V}O_2$ max, maximal O_2 pulse was higher during BAB than during placebo. Furthermore, maximal O_2 pulse with propranolol pulse was significantly higher than with atenolol. Conversely, no changes were seen in the ventilatory equivalent for oxygen across trials, although propranolol did have the lowest absolute value.

The 10-km race results, as seen in Table 6, show that the placebo race time was significantly faster than either propranolol or atenolol conditions, with atenolol resulting in faster times across the two beta blocker trials (see Figure 5). Both propranolol and atenolol race heart rates were lower than those under the placebo condition, but in contrast to the treadmill steady-state submaximal heart rates, the two BAB conditions were not significantly different from each other (see Figure 1). When compared to the HR max for that specific condition, the placebo race heart rate constituted 97.3% of its maximal heart rate, while propranolol and atenolol race heart rates were 89.2% and 84.1% of their respective maximal heart rates. Estimated race $\dot{V}O_2$ expressed in $ml \cdot kg^{-1} min^{-1}$, and relative to $\dot{V}O_2$ max values (% of $\dot{V}O_2$ max) are found in Table 6. Estimated $\dot{V}O_2$ values during the race were significantly lower during BAB as compared to the placebo, with propranolol being significantly lower than atenolol. Expressed as a percentage

TABLE 6: 10-km Race Values

		Treatment[a]				
		C-1	C-2	PLAC	PROP	ATEN
Race time	$\bar{x}$	35.7	35.9	35.8	41.0[b]	39.2[b,c]
min	±S.D.	1.8	1.7	1.9	2.7	2.8
Heart Rate	$\bar{x}$	172.8	173.4	179.0	119.1[b]	128.8[b]
b·min-1	±S.D.	6.9	7.3	8.4	12.2	21.4
Est. $\dot{V}O_2$	$\bar{x}$	56.3	55.1	54.1	45.9[b]	49.0[b,c]
$ml \cdot kg^{-1} \cdot min^{-1}$	±S.D.	3.7	4.0	4.5	4.6	5.1
Est. $\dot{V}O_2$	$\bar{x}$	87.1	85.5	84.7	82.0	80.5[b]
% of $\dot{V}O_2$ max	±S.D.	4.8	4.1	3.1	7.7	6.3

[a,b,c]Refer to footnotes in Table 3.

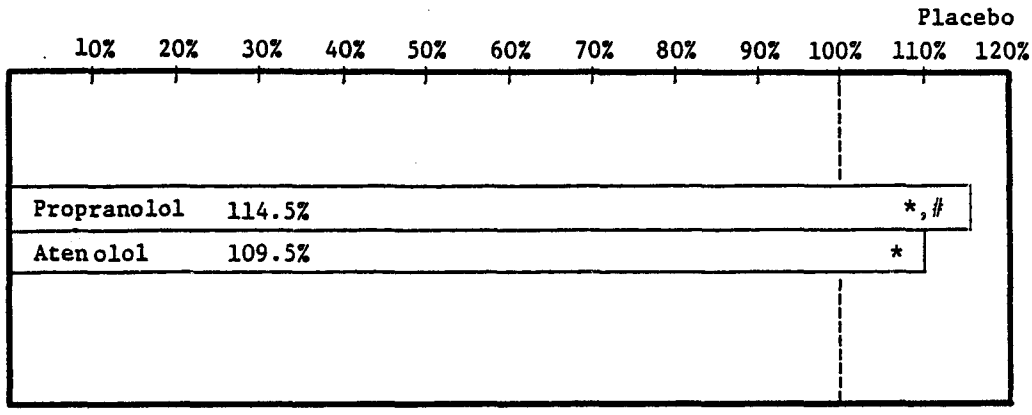

Figure 5a: Percent of placebo race time achieved during the BAB runs.

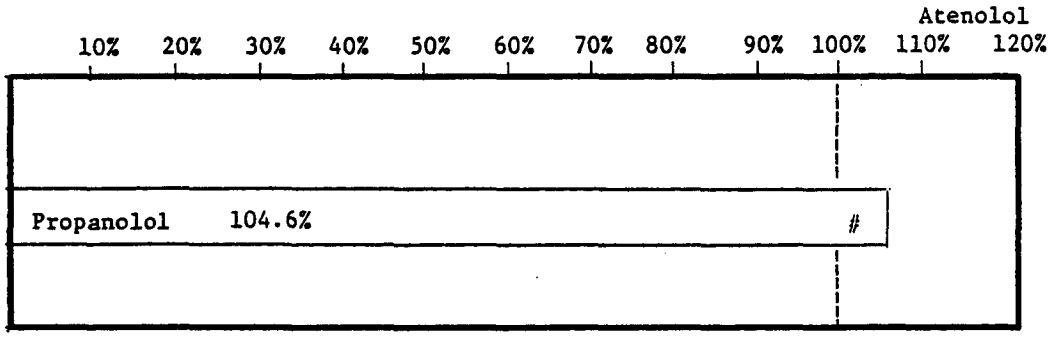

Figure 5b: Percent of atenolol race time achieved during the propranolol run.

*Significantly different from placebo ($p < 0.05$)

#Significantly different from atenolol ($p < 0.05$)

of $\dot{V}O_2$ max, however, only the placebo and atenolol trials were different with the atenolol value being lower.

When matching a written response questionnaire with the actual treatment period after breaking the code, the subjects indicated that lethargy was the biggest problem in both their training and activities of daily living while under BAB. Some subjects complained of dizziness, excessive sweating, cold chills, and hyperventilation during training runs which were associated with periods during BAB. Twenty-three of 25 subjects complained that their symptoms were most severe and their training most difficult during the propranolol treatment. The other two subjects indicated that training was most difficult during the atenolol treatment period. All 25 subjects found their training to be unaffected by the placebo.

The effects of both cardioselective and non-selective BAB on relationships between various physiological variables during exercise can be found in Figures included in Appendix 4. Figure 6 shows the relationship between the percent of the placebo $\dot{V}O_2$ max vs. the percent of the placebo HR max for each of the beta blocking agents. Figure 7 shows the relationship between the percent of the placebo $\dot{V}O_2$ max vs. the percent of the placebo $\dot{V}E$ max for the two beta blocking agents. Figure 8 reveals the relationship between the percent of the placebo $\dot{V}O_2$ max vs. the percent of the placebo treadmill time. Figure 9 shows the percent of the placebo HR max vs. the percent of placebo treadmill time for the two BAB

treatments. Figure 10 describes the relationship between percent of the placebo HR max vs. the percent of the placebo treadmill time for both BAB conditions.

CHAPTER 5

DISCUSSION

The BAB-induced responses that have been reported during acute exercise tend to be dependent upon the subject population being studied (1,2,3,9,10,11,25,27,36,38,39,45,46,47,53,54,59). Studies indicate that patients with severe cardiovascular disease show actual improvement in exercise capacity, $\dot{V}O_2$ max, and circulatory function while under BAB (3,25,36,39,40). Studies involving normal and slightly hypertensive subjects have been somewhat equivocal. While several studies have failed to show change in exercise capacity, $\dot{V}O_2$ max, or circulatory function (2,3,45), others have shown significant decreases in exercise tolerance and/or $\dot{V}O_2$ max during BAB (1,38,39,46,47,48,59). Moreover, the results of the present study, as well as those of others, have shown that highly trained subjects have very marked decreases in exercise capacity and $\dot{V}O_2$ max during BAB (3,9,10,11,27,53,54).

The results of the present study show that both atenolol and propranolol were equally effective in reducing heart rate and systolic blood pressure below placebo levels at rest. Diastolic blood pressure values, however, remained unchanged. This suggests that beta blocking agents are effective in blunting the effects of

anticipatory stress seen in subjects about to engage in intense exercise. Maksud et al. (49), however, found no difference in resting blood pressure and heart rate values between propranolol and placebo conditions in subjects who had been previously trained. The subjects involved in their study received only one acute dose of medication given 45 minutes before engaging in exercise, as opposed to the seven day dosing schedule used in the present study. Also, the dosage administered by Maksud et al. (49) constituted approximately one fourth of the daily dose of propranolol administered in the present study. Their resting results are not comparable to the present study because of the small doses of propranolol that were administered. Also, the short ingestion period of 45 minutes did not allow time for peak blood levels of medication to induce maximal BAB effects at rest, before exercise testing began (58,59).

Marked reductions were seen in submaximal heart rate following treatment with both beta blocking agents in comparison to placebo conditions. The magnitude of the reductions in submaximal heart rate with propranolol and atenolol were in agreement with Kaiser et al. (9) who compared the same two drugs. In their study, heart rate values while on the two drugs were nearly identical up to approximately 57% of $\dot{V}O_2$ max, at which point they began to diverge. This difference between the two drugs became greater, i.e., the propranolol values were lower compared to atenolol values, as exercise intensity increased. In the present study, mean steady-state submaximal $\dot{V}O_2$ values were 74% of their respective

$\dot{V}O_2$ max or greater across all trials, and as Kaiser et al. (9) reported submaximal heart rate was significantly lower with propranolol than atenolol. Using the same drug dosage and dosing schedule on another group of 11 highly trained runners, our laboratory found identical submaximal heart rates (107 b·min^{-1}) with atenolol and propranolol. HR max with propranolol, however, was 6.8 b·min^{-1} lower than HR max with atenolol. The present study used an absolute submaximal work rate of 240 m·min^{-1} while in the other unpublished study, the submaximal work rate was set at 60% of each subject's control $\dot{V}O_2$ max. If the subjects in the present study would have run at a constant relative workload, i.e., 60% of control max, instead of an absolute workload in which the individual relative workloads ranged from 64.9% to 86.8% of control $\dot{V}O_2$ max, it is quite possible that propranolol and atenolol submaximal heart rates would have been similar. This is an important point, as the present submaximal heart rate data would suggest that the subjects were not equally blocked. This data does indicate that propranolol is more effective than atenolol in reducing heart rate at higher relative workloads.

The submaximal $\dot{V}O_2$ under the first control condition was higher than under any of the other trials. However, this is possibly explained by a learning effect which allowed the subjects to refine their treadmill running skills, allowing them to be more relaxed, and thus more efficient, in subsequent trials. This was not considered to be an issue during the treatment periods due to

the randomization of trial sequences. Submaximal $\dot{V}O_2$ was significantly decreased by propranolol, but not by atenolol, when compared to the placebo condition. This 3.5% drop in submaximal $\dot{V}O_2$ with propranolol confirmed the earlier results of Pearson et al. (47) and Tesch et al. (54). Reybrouck et al. (2) found slight but non-significant decreases in submaximal $\dot{V}O_2$ among hypertensive subjects taking atenolol. The mean submaximal $\dot{V}O_2$ value with atenolol in the present study was lower compared to placebo conditions, but the difference between these conditions was not statistically significant. Other investigators have shown no change in submaximal $\dot{V}O_2$ in hypertensive, normal, or trained subjects during BAB compared to control/placebo conditions (9,39,45,46,48, 49).

Various investigators have shown that an individual's relative $\dot{V}O_2$ cost at an absolute submaximal workload remains constant across a number of trials; therefore our BAB submaximal $\dot{V}O_2$ data is somewhat surprising. There are two major components that will largely determine the oxygen cost for a given absolute workload, i.e., the mechanical efficiency of performing the task and a metabolic component which may or may not be related to the task being performed. Tesch et al. (54) postulated that changes in submaximal $\dot{V}O_2$ during BAB are due to an improved metabolic efficiency as opposed to specific biomechanical changes. Possibly, this improved submaximal metabolic efficiency during BAB is due to increased carbohydrate utilization by the working muscles. This

increase could be the result of a limited release and uptake of free fatty acids caused by peripheral BAB activity (12,15,48). There is an approximately 10% higher energy yield per liter of oxygen used when carbohydrate is combusted as opposed to fat (65). This difference in energy yield with increased carbohydrate utilization could account for the lower relative oxygen costs at this submaximal, absolute workload. The elevated submaximal RER values found in the present study, and by others (47,54) who found both increased RER and decreased $\dot{V}O_2$ during BAB at submaximal levels, provide evidence for this hypothesis.

The decreases in submaximal $\dot{V}O_2$ during BAB are very small when compared to the decrease in submaximal heart rate. The compensatory mechanisms by which $\dot{V}O_2$ is either fully or partially maintained, even after large decreases in heart rate, include increases in stroke volume and in arterial-mixed venous O_2 difference (a-$\bar{v}$ O_2 diff) (2,38,39,46). Furberg (3) noted that highly trained individuals were unable to elicit these compensatory mechanisms to the same extent as untrained or diseased subjects. He found that sedentary normal individuals as well as those with cardiovascular disease were able to maintain their $\dot{V}O_2$ values during BAB regardless of exercise intensity. From the present study, and others (9,54), it appears that compensatory mechanisms do occur in highly trained individuals at submaximal levels of exercise. Unpublished data from this laboratory show that highly trained individuals under BAB maintain cardiac output compared to

placebo values when exercising at a relative workload of 60% of $\dot{V}O_2$ max. The increased O_2 pulse values for both BAB trials in the present study suggest that either or both increased stroke volume and a-$\bar{v}$ O_2 diff were at least partially able to compensate for the reduced heart rate.

Whereas submaximal heart rate was markedly affected by both drugs, and submaximal $\dot{V}O_2$ only slightly, submaximal $\dot{V}E$ was unaffected by BAB. For the placebo group, this submaximal steady-state run represented 83.7% of maximal heart rate and 74.3% of the $\dot{V}O_2$ max, but it represented only 56.6% of the $\dot{V}E$ max. Possibly, this relatively low ventilatory requirement does not elicit a large sympathetic response resulting in the dilation of airways as is seen with higher rates of work. Probably, the limitations of BAB on $\dot{V}E$ do not occur until above OPLA when ventilation rises exponentially (63).

The higher submaximal RER value with propranolol was probably due to increased carbohydrate utilization during the exercise, as discussed previously. This could be due to both inhibition of lipolysis by propranolol BAB (12,13,14,15) as well as the fact that this submaximal workload required 82.0% of the $\dot{V}O_2$ max. At this particular workload, it is quite possible that some subjects were above OPLA during propranolol BAB and, as a result, generated non-metabolic CO_2. In turn, this non-metabolic CO_2 elevated the RER values to a much higher level than the RER values which would have been seen by inhibition of lipolysis alone. In

contrast, the placebo and atenolol submaximal $\dot{V}O_2$ levels represented only 74.3% and 76.6% of their respective $\dot{V}O_2$ max values. The lower relative workload, the lack of excessive non-metabolic CO_2 production, and an absence of B-2 inhibition of lipolysis (2,9,10,11) are all possible reasons why RER was not elevated with atenolol.

While submaximal RPE was significantly lower for the placebo compared to the two drug trials, there was not a significant difference between the two drug trials. This was unexpected, as the subject's comments obtained by questionnaire indicated that propranolol was much more difficult to tolerate both at rest and during exercise. It must be pointed out that while statistical significance was barely obtained between the placebo and atenolol ($p<0.04$) trials, the mean difference between the atenolol and propranolol trials fell just short of attaining significance ($p<0.06$). Others have also indicated that RPE is higher at all absolute work levels during BAB (47), and that with propranolol, the rises in RPE are due more to "local" than "central" effects. In the present study, submaximal RPE showed a tendency to relate more closely to relative rather than absolute physiological values; i.e., $\dot{V}O_2$, HR, $\dot{V}E$. This confirms earlier findings by Ekblom et al. (46) and Wilmore et al. (48) who concluded that RPE did not track absolute heart rate during BAB. Previously, absolute heart rate was considered one of the primary cues for RPE (66).

Maximal heart rate was decreased more by propranolol than by atenolol. At rest, as well as at both levels of exercise, heart rates under propranolol were approximately 70-75% of the corresponding placebo values, while with atenolol, heart rates were approximately 80-85% of their placebo values. Kaiser et al. (9) also found atenolol to be less effective than propranolol in reducing HR max while using doses corresponding to one-half of the doses used in the present study. Conversely, Karlsson (11) found that atenolol induced greater reductions in HR max than corresponding doses of propranolol among subjects with high percentages of slow twitch muscle fibers. Although previous studies would support the design of the present study in that clinically equivalent doses of both drugs were used (8,9,10,11,55,56), it appears that atenolol was not as effective in blocking heart rate at the higher levels of exercise.

The decrease in $\dot{V}O_2$ max with BAB is consistent with the findings of a number of investigators who have used either trained or normal subjects (1,9,10,11,38,39,47,48). However, other studies using normal or diseased subjects showed no change in $\dot{V}O_2$ max during BAB indicating either or both complete central and peripheral compensation for the depressed maximal heart rates (2,3,46,49).

The diminished $\dot{V}O_2$ max seen during BAB in the highly trained subjects used in the present study supports Furberg's (3) hypothesis that highly trained individuals cannot fully compensate for the reduced maximal heart rate to maintain $\dot{V}O_2$ max as do

normal or diseased individuals. Still, the decreases in HR max with both BAB agents were far greater than the decreases in $\dot{V}O_2$ max, indicating that these athletes were able to partially compensate for their lowered heart rates. The higher O_2 pulse values with BAB observed during maximal exercise support this idea. The O_2 pulse values while on propranolol, however, were higher than those values while on atenolol. This was not expected due to the non-selective nature of propranolol. It was assumed that the inhibition of peripheral B-2 mechanisms, especially by propranolol, would limit peripheral oxygen extraction during BAB (10). It is possible, however, that peripheral oxygen extraction during propranolol BAB was only minimally increased and that O_2 pulse increases were due to a more substantial increase in stroke volume. This could have resulted from the increased end-diastolic filling time associated with the significantly lower heart rate, increasing the end diastolic volume, and thus myocardial contractility via the Starling phenomenon. Regardless of what compensatory mechanisms were active during BAB, the subjects were unable to maintain the unblocked $\dot{V}O_2$ max level.

A 27.3% decrease in maximal heart rate with propranolol resulted in a 12.1% decreas in $\dot{V}O_2$ max, while a 16.4% decrease in maximal heart rate with atenolol resulted in a 3.4% decrease in $\dot{V}O_2$ max. It is unknown whether the difference between the two BAB drugs with respect to decreased $\dot{V}O_2$ max values was the result of the lower maximal heart rate with propranolol as compared to

atenolol, or a diminished B-2 mediated oxygen extraction capability while on propranolol. Although O_2 pulse values indicate that stroke volume was probably higher on propranolol than atenolol, the decrease in HR max with propranolol was just too great for compensatory mechanisms to overcome.

Decreased $\dot{V}E$ max values seen during BAB with propranolol were probably due to the inhibition of the B-2 mediated dilation of the bronchioles. Other studies have shown decreased $\dot{V}E$ max during BAB with propranolol using different subject populations (47,49, 50,51).

Maximal RER values were lower on propranolol which is in contrast to what was observed for submaximal RER values. Several studies (47,48,54) have reported increased maximal RER values during BAB. Other studies (9,11), however, have found diminished post-exercise blood lactate values with propranolol as opposed to placebo or atenolol conditions. This indicates that either the subjects in the present study experienced a diminished glycolytic ability at the higher levels of exercise with propranolol, or that they were unable to tolerate high lactate levels. Possibly, the lethargy reported by the subjects while on propranolol made it difficult for them to tolerate the higher levels of exercise, thus resulting in reduced maximal RER values. These results support the findings of Tesch et al. (54) who found that trained subjects experienced severe local fatigue during maximal exercise with propranolol, but not during similar exercise with a placebo.

It is possible that the problem of lethargy encountered both at rest and during exercise with propranolol BAB could be due to neurological effects caused by the drug. Since propranolol is lipid-soluable, it easily passes through the blood-brain barrier and into the central nervous system (8). Atenolol, however, is not lipid-soluable and is therefore unable to cross into the central nervous system (8). This is possibly why the subjects reported so few complaints about this drug.

Various investigators (1,38,39,46,47) using normal or diseased subjects have found decreased endurance capability during BAB. Others (2,48,49) using the same subject populations have found that BAB does not effect exercise capacity. Endurance times from both the maximal treadmill test and 10-km races suggest that trained subjects tolerate atenolol better than propranolol, although both caused significant reductions in performance. This finding has been noted perviously (9,10,11). In the present study this phenomenon was most evident in the treadmill run where all but two of 25 subjects endured longer on atenolol than propranolol. In the 10-km race where pacing, race tactics and environmental conditions played roles, 17 of 25 ran faster times while on atenolol. Of the eight who ran faster on propranolol, there was a negligible difference between the two BAB times. The most obvious reasons for poorer treadmill and 10-km times while on propranolol include the greater reduction in $\dot{V}O_2$ max, HR max, subjective complaints, and possibly lowered $\dot{V}E$ max. One other factor which must be considered, but was

not investigated in this study is lactate threshold (OPLA). Along with $\dot{V}O_2$ max, and running economy, it is considered a major factor in determining distance running performance (4,5,6,7).

Various investigators have suggested that BAB causes changes in either or both muscle and blood lactate levels, as well as lactate clearance and tolerance (9,11,12,13,14,15), all of which affect lactate threshold. Although it is probable that OPLA occurs at a lower absolute work level during BAB as compared to placebo conditions, it is unknown whether BAB causes OPLA to occur at a lower relative workload.

By using equivalent clinical doses of propranolol and atenolol, it is clear from the present study as well as those of others (9,10,11), that performance is affected more by propranolol than by atenolol, but both attenuate endurance performance. It is evident, however, that dosage plays a major role in determining the response of trained runners during BAB influenced exercise (10,53). This also is the case among other subject populations (1,25,45). It is possible that this dosage-phenomenon is responsible for some of the equivocal results that have been noted in previous studies. Specifically, although individuals performed better on atenolol than on propranolol in the current study, atenolol appeared to be less effective than propranolol in reducing the heart rate at the higher workloads. Further research in this area must equate doses to elicit similar heart rate reductions at various levels of exercise. This, in turn, will allow more objective evaluation of the differences between cardioselective and non-selective BAB.

CHAPTER 6

SUMMARY

This study determined the effects of beta adrenergic blockade (BAB) on the endurance running performance of highly trained distance runners. In addition, differences between cardioselective BAB (atenolol) and non-selective BAB (propranolol) were investigated. Twenty-five highly trained runners ($\dot{V}O_2$ max 64.7 ± 4.3 $ml \cdot kg^{-1} \cdot min^{-1}$) were tested on a horizontal treadmill protocol, during which both steady-state submaximal and maximal data were obtained. Also, the subjects participated in a series of 10-km track races. The subjects performed two control treadmill tests, and two control 10-km track races before beginning the three 10-day treatment periods. The treatments consisted of: a) 80 mg propranolol BID; b) 100 mg atenolol in the am with a pm placebo; and c) a placebo BID. A four day washout period occurred between each treatment. Furthermore, the treatments were administered according to a randomized, double-blind, crossover, latin square experimental design to minimize the effects of changes in race day atmospheric conditions. All data were analyzed using a repeated measures analysis of variance followed by Scheffé's post-hoc test for mean differences. The level of significance was set at $p<0.05$.

Resting heart rate was depressed by both beta blocking agents as was systolic blood pressure. Diastolic blood pressure was unchanged by BAB. This demonstrated the ability of BAB to limit the sympathetic-induced physiological responses normally associated with the anticipatory stress observed prior to maximal treadmill tests.

Submaximal heart rate was decreased by both beta blocking agents, but more so by propranolol than atenolol. Propranolol decreased submaximal $\dot{V}O_2$, while at the same time increasing submaximal RER values. This particular relationship between submaximal $\dot{V}O_2$ and RER would indicate a possible shift of substrate utilization from free fatty acids to carbohydrate during propranolol BAB. RPE was higher during the BAB trials than the placebo trial. Propranolol increased RPE more than atenolol; however, this difference did not reach statistical significance. Submaximal O_2 pulse was higher during BAB than during the placebo trial.

Results obtained during maximal exercise revealed that HR max, $\dot{V}O_2$ max and treadmill times were diminished by BAB, but more so by propranolol than by atenolol. $\dot{V}E$ max and RER max were attenuated by propranolol but not atenolol. Maximal O_2 pulse values obtained during the BAB trials were higher than placebo values, with the propranolol O_2 pulse value being the highest.

The 10-km race results demonstrated that BAB adversely effects racing performance in trained runners. Furthermore, non-selective BAB attenuates racing performance to a greater extent than is seen with cardioselective BAB. Race heart rates were also

significantly decreased by BAB. Estimated race $\dot{V}O_2$ values were decreased by BAB with the propranolol value being the lowest. However, expressed as a percentage of $\dot{V}O_2$ max, only placebo and atenolol race $\dot{V}O_2$ values differed.

Although highly trained runners are unable to fully compensate to maximal exercise during BAB, i.e., maintain $\dot{V}O_2$ max, increases in O_2 pulse during BAB suggest a partial compensatory effect does occur. This elevated O_2 pulse during BAB could be due to either or both increased stroke volume and increased a-$\bar{v}$ O_2 diff. It appears that trained subjects are able to fully compensate for BAB-induced decreases in heart rate at moderate submaximal work rates. Furthermore, these results demonstrate that trained runners performed better during cardioselective (atenolol) BAB than during non-selective (propranolol) BAB. It is unknown whether the more marked negative effects on exercise capacity, and $\dot{V}O_2$ max during propranolol BAB, as compared to atenolol BAB, were due to propranolol's greater negative influence on the exercise heart rate or its inhibition of B-2 mediated sympathetic responses.

APPENDIX 1

MISCELLANEOUS FORMS AND EVALUATIONS

Revised January 20, 1984

SUBJECT'S CONSENT FORM

University of Arizona

Effect of Beta Blockage During Exercise of Several Fitness Levels

I understand that I am being asked to voluntarily participate in a study titled, Effect of Beta Blockage During Exercise on Subjects of Several Fitness Levels. The purpose of the study is to compare the effect of two different beta blocking drugs (atenolol and propranolol) on two different groups of subjects. One group of subjects will be a control group (untrained) and the other will be trained runners. Beta blocking drugs slow the heart rate during exercise and generally "block" the affects of the substance "adrenalin," which is released under stresses like exercise.

Your participation in the study will include five maximal treadmill tests to exhaustion. These tests involve running, with the speed and grade of the treadmill increasing gradually until you are too fatigued to continue. The first two tests will be control tests to familiarize you with normal laboratory procedures. The next three tests will occur following seven days of ingesting each of three coded capsules: a placebo, propranolol, or atenolol. During the treadmill test, you will be wearing electrodes to record your heart rate and breathing through a mouthpiece so your expired air can be measured. Your heart rate, oxygen consumption, and cardiac output (volume of blood pumped by the heart per minute) will be measured during these runs. There will be at least one week rest between each of the four tests. Before every test, 10 ml of blood (less than one tablespoon) will be drawn from your arm so that the amount of drug in your body can be measured. Also, you will be weighed underwater to determine your percentage of body fat. This involves submerging you ten times after you have blown out all your air, and having the volume of air trapped in your lungs measured by breathing in a spirometer for 5-10 seconds. Trained subjects will also compete in a 10,000 meter run two days following each maximal treadmill test.

Most importantly, I understand that there are several risks involved with this study. Maximal treadmill tests result in shortness of breath, fatigue, and muscle soreness, and occasionally nausea. Blood draws can cause small bruises and the needle may hurt when it punctures the skin. Beta blocking drugs can cause stomach upset and may cause you to feel sluggish during the time you are on the medication.

Conditions of Participation

As a participant in this study, I will gain an understanding of my medical and physiological profile. I am also aware that these findings may have significant implications for the future prescription of exercise in patients with coronary heart disease and the use of drugs in such patients.

I understand that all information concerning my performance of the various tests associated with this study will be kept confidential, and all data will be filed according to subject identification code system. I realize that all procedures will be under the supervision of a physician and an exercise physiologist.

I also understand that this consent form will be filed in an area designated by the Human Subjects Committee, with access restricted to the principle investigators or authorized representatives of their particular departments.

I am also aware that in the event of injury resulting from any of the above stated procedures, I will receive no compensation for wages, lost time, medical expenses, or hospitalization.

I understand that my involvement in this study will not cost me any money, and that I will receive $200 for completing all aspects of the study for untrained subjects and $400 for trained subjects who complete all tests and all 10,000 meter races.

I have read the above "Subject's Consent Form." The nature, demands, risk, and benefits of the project have been explained to me. I understand that I may ask questions, that I am free to withdraw from the project at any time without ill will, and that the investigators can be contacted at McKale Center 228 (621-2420) during normal business hours, or at 297-9890 at other times.

_____ _____
Subject's Signature Date

_____ _____
Witness' Signature Date

I have carefully explained to the subject the nature of the above project. I hereby certify that, to the best of my knowledge, the subject signing this consent form understands clearly the nature, demands, benefits, and risks involved in participating in this study. A medical problem, or language or educational barrier has not precluded a clear understanding of his/her involvement in this project.

A copy of this consent form is available to subjects on request.

_____ _____
Investigator's Signature Date

_____ _____
Witness' Signature Date

d:25

THE UNIVERSITY OF ARIZONA
HEALTH SCIENCES CENTER
TUCSON, ARIZONA 85724

HUMAN SUBJECTS COMMITTEE
1609 N. WARREN (BUILDING 220), ROOM 112

TELEPHONE: (602) 626-6721 or 626-7575

23 January 1984

Jack H. Wilmore, Ph.D.
Department of Physical Education
Exercise and Sport Sciences Laboratory
McKale Memorial Center
MAIN CAMPUS

Dear Dr. Wilmore:

We are in receipt of your 19 January 1984 memorandum and the accompanying revised consent form for your project, "Effect of Beta Blockage during Exercise on Subjects of Several Fitness Levels". The changes reflected in this revision are minor and pose no further risk to the participating subjects. Therefore, approval for these changes is granted effective 23 January 1984.

The changes approved are:

1. Addition of a 10,000 meter competitive race two days following each maximal treadmill test for the "highly fit" group.

2. Increase in subject remuneration to $400 for those subjects who will participate in the races described above.

Approval is granted with the understanding that no further additions or changes will be made in either the procedures followed or in the consent form(s) to be used (copies of which we have on file) without the knowledge and approval of the Human Subjects Committee and the College or Departmental Review Committee. Any physical or psychological harm to any subject must also be reported to each committee.

A university policy requires that all signed subject consent forms be kept in a permanent file in an area designated for that purpose by the Department Head or comparable authority. This will assure their accessibility in the event that university officials require the information and the principal investigator is unavailable for some reason.

Sincerely yours,

Milan Novak

Milan Novak, M.D., Ph.D.
Chairman
Human Subjects Committee

MN/jm

cc: Patricia C. Fairchild, Ph.D.
Departmental Review Committee

THE UNIVERSITY OF ARIZONA
TUCSON, ARIZONA 85721

DEPARTMENT OF PHYSICAL EDUCATION
EXERCISE & SPORT SCIENCES LABORATORY
McKALE MEMORIAL CENTER

Name_____Age_____ Sex_____

1) SMOKER: YES_____ NO_____
   (If yes, packs per day _____)
   (If quit, years ago _____)

2) HISTORY OF LUNG PROBLEMS
   (asthma, emphysema, COPD) YES_____ NO_____

3) HISTORY OF HYPERTENSION YES_____ NO_____
   First diagnosed _____
   Controlled with: (Diet, medication)

4) HISTORY OF CHEST PAIN YES_____ NO_____

5) HISTORY OF CORONARY ARTERY DISEASE
   (angina, myocardial infarction, sudden death, or coronary artery bypass surgery) YES_____ NO_____
   In family:(mother, father, grandparents, brothers or sisters) YES_____ NO_____
   Under age 55 YES_____ NO_____

6) DIABETES IN PATIENT OR FAMILY
   (as described above--under age 50) YES_____ NO_____

7) CHOLESTEROL LEVEL Unknown_____ >250_____ <250_____

8) MEDICATIONS:_____
   _____

   _____

EXERCISE TOLERANCE TEST REPORT - A F P

(2 + 3) is a (4) -year-old (5) M F referred for evaluation of activity tolerance for the University of Arizona Adult Fitness Program.

Presenting symptoms: (6)

Significant past history and/or risk factors: (7)

Present medications: (8)

Cardiovascular examination: (9)

Baseline EKG: (10)

The patient exercised on the treadmill according to the modified Bruce-Sheffield protocol. (11) He She completed Stages (12) for a total of (13) minutes. The peak heart rate attained was (14) beats per minute, which is (15) % of the maximum predicted heart rate for a person of this age and fitness level.

The exercise was terminated because of (16)

The blood pressure response was (17)

ST-T changes: (18)

Arrhythmias: (19)

FINAL INTERPRETATION

1. POSITIVE NEGATIVE NONDIAGNOSTIC (20) exercise test
2. ST-T CHANGES: (21)
3. ARRHYTHMIAS: (22)
4. BLOOD PRESSURE RESPONSE: (23)
5. CARDIAC SYMPTOMS ON EXERCISE: (24)

_____ (1)_____

Testing Physician Date of test

BETA BLOCKER STUDY

Subjective Drug Reaction Survey

Over the past six weeks you have taken three different medications. While we have considerable physiological data on your responses to each of these medications, we would also like to have your subjective evaluation of all three medications. Please provide us with as much information as possible relative to your reactions to each medication.

Period I

Period II

Period III

Additional Comments:

Name_____

Date_____

APPENDIX 2

TREADMILL SPEED CONVERSION TABLE AND TIME CONVERSION TABLE

Table 7a. Treadmill Speed Conversion Table

meters · min^{-1}	200	210	220	230	240	250	260	270	280	290
miles · hr^{-1}	7.50	7.88	8.25	8.63	9.00	9.38	9.75	10.13	10.50	10.88
min · mile^{-1}	8.00	7.61	7.24	6.95	6.67	6.40	6.15	5.92	4.71	5.51
meters · min^{-1}	300	310	320	330	340	350	360	370	380	390
miles · hr^{-1}	11.25	11.63	12.00	12.34	12.75	13.13	13.50	13.88	14.25	14.63
min · mile^{-1}	5.33	5.16	5.00	4.86	4.71	4.57	4.44	4.32	4.21	4.10
meters · min^{-1}	400	410	420	430	440	450	460	470	480	490
miles · hr^{-1}	15.00	15.38	15.75	16.16	16.50	16.88	17.25	17.63	18.00	18.38
min · mile^{-1}	4.00	3.90	3.81	3.72	3.64	3.55	3.48	3.40	3.33	3.26

Table 7b. Time Conversion Factor

sec	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
% · min	.00	.02	.03	.05	.07	.08	.10	.12	.13	.15	.17	.18	.20	.22	.23
sec	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
% · min	.25	.27	.28	.30	.32	.33	.35	.37	.38	.40	.42	.43	.54	.47	.48
sec	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
% · min	.50	.52	.53	.55	.57	.58	.60	.62	.63	.65	.67	.68	.70	.72	.73
sec	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59
% · min	.75	.77	.78	.80	.82	.83	.85	.87	.88	.90	.92	.93	.95	.97	.98

APPENDIX 3

INDIVIDUAL AND GROUP DATA FOR SELECTED VARIABLES

Table 8. Resting Heart Rate Beats · min^{-1}

Subject	Control-1	Control-2	Placebo	Propranolol	Atenolol
1. R.A.	55	57	64	45	52
2. K.C.	60	60	60	43	41
3. S.D.	58	61	57	47	40
4. G.D.	64	62	66	53	46
5. J.E.	63	48	62	39	47
6. B.F.	56	64	54	58	50
7. D.G.	73	66	84	49	47
8. R.G.	90	91	76	52	54
9. M.G.	48	48	52	37	38
10. R.H.	47	49	56	44	41
11. J.H.	58	57	56	43	42
12. T.H.	88	61	73	40	45
13. T.J.	84	67	57	52	51
14. M.J.	69	67	57	62	55
15. M.L.	65	64	63	48	40
16. K.L.	90	72	78	49	58
17. M.Ma.	75	75	64	47	69
18. M.My.	72	75	67	47	52
19. L.P.	56	82	74	46	57
20. T.R.	63	73	63	49	67
21. H.S.	67	58	52	37	41
22. D.S.	57	53	56	51	40
23. R.T.	78	68	65	44	52
24. C.T.	54	56	55	42	54
25. R.W.	60	64	50	51	63
$\bar{X}$	66.4	64.3	62.4	46.6	59.7
S.D.	12.0	9.9	8.9	6.3	8.7

Table 9. Resting Blood Pressure mm Hg

Subject	Control-1	Control 2	Placebo	Propranolol	Atenolol
1. R.A.	162/97	152/66	160/100	136/62	132/74
2. K.C.	128/62	136/74	134/72	108/84	118/82
3. S.D.	134/78	136/78	134/82	132/82	118/78
4. G.D.	126/78	136/82	122/80	124/76	124/76
5. J.E.	128/78	136/80	124/82	116/82	126/76
6. B.F.	120/72	120/74	138/82	108/78	122/82
7. D.G.	130.74	158/92	132/92	128/82	120/78
8. R.G.	130.90	128/90	126/84	122/82	110/66
9. M.G.	118/76	118/74	126/82	114/76	112/82
10. R.H.	108/80	124/76	112/66	110/62	124/72
11. J.H.	128/78	122/70	120/78	118/72	108/66
12. T.H.	136/94	152/90	150/90	132/98	128/90
13. T.J.	124/79	118/84	124/77	146/76	114/74
14. M.J.	128/89	125/90	126/82	116/78	118/79
15. M.L.	146/68	142/96	140/90	138/92	135/82
16. K.L.	130/84	134/76	138/74	128/82	127/76
17. M.Ma.	142/70	134/84	140/76	112/64	118/74
18. M.My.	136/77	112/88	128/72	114/70	116/82
19. L.P.	126/80	148/92	152/86	132/88	138/84
20. T.R.	140.72	138/84	140/72	124/74	116/74
21. H.S.	118/76	130/78	122/68	120/76	124/80
22. D.S.	128/70	124/70	109/74	116/72	120/70
23. R.T.	136/76	132/72	128/70	122/84	132/72
24. C.T.	98/68	204/70	120/90	108/64	116/70
25. R.W.	128/64	128/82	130/100	112/77	122/78
$\bar{X}$	129.1/77.2	131.5/80.5	131.0/80.9	121.4/77.3	121.6/76.7
S.D.	12.3/8.6	12.9/8.3	12.0/9.2	10.4/8.9	7.6/5.7

Table 10. Submaximal Heart Rate Beats · min^{-1} (240 m · min^{-1} for 6 min)

Subject	Control-1	Control-2	Placebo	Propranolol	Atenolol
1. R.A.	138	138	141	106	097
2. K.C.	160	151	152	115	108
3. S.D.	157	157	153	119	127
4. G.D.	163	160	155	129	130
5. J.E.	155	156	154	111	112
6. B.F.	165	166	167	116	124
7. D.G.	156	154	155	119	118
8. R.G.	173	165	171	119	126
9. M.G.	169	160	152	114	133
10. R.H.	161	148	151	113	122
11. J.H.	147	151	145	102	109
12. T.H.	165	167	164	128	141
13. T.J.	160	156	145	113	115
14. M.J.	143	134	139	116	132
15. M.L.	162	159	152	108	117
16. K.L.	175	168	176	122	145
17. M.Ma.	163	160	161	114	131
18. M.My.	153	153	148	112	116
19. L.P.	162	160	160	125	142
20. T.R.	163	159	163	118	127
21. H.S.	149	142	147	120	115
22. D.S.	158	160	159	120	136
23. R.T.	149	150	144	104	124
24. C.T.	150	160	165	118	120
25. R.W.	158	151	149	119	128
$\bar{X}$	158.5	155.4	154.3	116.0	123.8
S.D.	8.7	8.5	10.0	6.7	11.5

Table 11. Submaximal HR Expressed as % of HR Max

Subject	Control-1 (%)	Control-2 (%)	Placebo (%)	Propranolol (%)	Atenolol (%)
1. R.A.	75.8	75.8	76.2	79.1	71.9
2. K.C.	87.9	83.9	83.1	76.7	78.8
3. S.D.	87.2	89.2	85.0	82.6	81.4
4. G.D.	89.6	88.9	87.1	92.8	84.4
5. J.E.	86.1	87.2	85.6	100.0	82.4
6. B.F.	90.7	91.2	87.0	86.6	78.9
7. D.G.	82.1	82.8	84.2	81.5	77.6
8. R.G.	90.1	85.9	83.6	84.4	81.3
9. N.G.	91.4	86.5	84.4	87.7	78.2
10. R.H.	85.6	80.4	81.6	89.0	78.7
11. J.H.	80.8	83.9	80.6	81.6	75.2
12. T.H.	86.8	90.8	85.4	97.0	90.4
13. T.J.	86.0	83.0	79.7	86.9	78.8
14. M.J.	77.7	73.6	76.4	77.9	87.9
15. M.L.	86.2	86.4	80.0	83.7	77.0
16. K.L.	89.3	87.5	90.3	86.5	83.3
17. M.Ma.	85.8	87.9	87.5	86.4	79.4
18. M.My.	81.4	83.2	80.4	84.8	76.3
19. L.P.	86.6	88.9	87.9	85.6	84.5
20. T.R.	88.6	88.3	88.6	97.5	81.4
21. H.S.	84.7	83.5	79.7	86.7	76.2
22. D.S.	86.3	87.9	89.3	89.6	85.0
23. R.T.	82.8	82.4	80.9	83.2	76.5
24. C.T.	84.0	84.2	86.8	88.1	78.9
25. R.W.	84.0	83.0	81.4	87.5	75.3
$\bar{X}$	85.5	85.0	83.7	86.5	80.0
S.D.	3.8	4.2	3.9	5.7	43.

Table 12. Submaximal $\dot{V}O_2$ ml · kg^{-1} · min^{-1} (240 m · min^{-1} for 6 min)

Subject		Control-1	Control-2	Placebo	Propranolol	Atenolol
1.	R.A.	47.4	45.3	46.4	42.5	43.9
2.	K.L.	47.6	49.0	46.7	43.6	45.2
3.	S.D.	51.4	50.7	50.5	49.1	51.2
4.	G.D.	55.6	51.1	49.6	53.2	50.5
5.	J.E.	48.3	47.7	45.3	46.6	44.4
6.	B.F.	46.5	48.6	46.1	43.2	45.7
7.	D.G.	46.4	47.0	45.3	42.6	45.7
8.	R.G.	49.4	47.0	46.3	47.9	45.8
9.	M.G.	49.3	47.6	46.9	45.9	48.5
10.	R.H.	51.9	48.2	48.3	46.9	48.1
11.	J.H.	49.8	50.4	45.6	42.3	44.2
12.	T.H.	50.4	52.6	51.2	47.9	50.7
13.	T.J.	52.3	49.8	47.9	45.8	46.9
14.	M.J.	40.5	41.8	41.2	40.6	38.5
15.	M.L.	51.1	49.4	48.2	48.9	50.8
16.	K.L.	47.9	49.0	46.5	44.4	46.7
17.	M.Ma.	48.3	46.0	45.1	42.4	44.8
18.	M.My.	47.3	44.0	42.5	41.8	49.3
19.	L.P.	54.4	54.5	48.9	49.9	52.5
20.	T.R.	55.8	58.5	55.8	50/4	55.6
21.	H.S.	49.2	49.8	49.6	44.9	47.5
22.	D.S.	48.1	53.1	54.3	51.3	52.5
23.	R.T.	48.0	47.6	48.9	43.2	44.3
24.	C.T.	44.0	43.3	45.7	43.4	41.1
25.	R.W.	48.3	49.7	46.5	49.5	47.6
	$\bar{X}$	49.2	48.9	47.6	45.9	46.9
	S.D.	3.4	3.6	3.2	3.4	4.1

Table 13. Submaximal $\dot{V}O_2$ Expressed as % of $\dot{V}O_2$ Max

Subject	Control-1 (%)	Control-2 (%)	Placebo (%)	Propranolol (%)	Atenolol (%)
1. R.A.	63.7	64.9	68.3	66.5	71.0
2. K.C.	72.8	73.6	71.3	74.4	71.1
3. S.D.	78.2	75.9	75.3	82.0	79.1
4. G.D.	90.3	85.7	82.1	91.4	90.2
5. J.E.	81.2	83.2	79.3	98.1	89.7
6. B.F.	77.9	78.4	73.2	82.8	75.7
7. D.G.	69.8	71.8	70.2	76.3	71.4
8. R.G.	73.6	69.5	72.0	74.6	69.4
9. M.G.	82.2	82.5	78.2	80.8	75.8
10. R.H.	76.5	69.5	75.0	82.1	74.8
11. J.H.	78.5	77.1	70.2	78.2	73.3
12. T.H.	79.2	79.0	71.8	83.3	81.7
13. T.J.	79.7	77.1	74.5	86.9	80.9
14. M.J.	61.5	64.9	63.5	68.1	69.5
15. M.L.	76.5	74.0	69.5	75.8	73.2
16. K.L.	85.2	83.1	80.5	86.5	84.6
17. M.Ma.	72.6	72.8	73.9	85.0	73.7
18. M.My	79.0	73.8	75.1	82.3	72.9
19. L.P.	88.2	86.8	78.9	92.2	86.5
20. T.R.	78.3	77.5	75.8	96.0	75.6
21. H.S.	69.7	71.2	73.3	79.9	70.0
22. D.S.	72.2	78.0	79.0	82.2	80.4
23. R.T.	72.1	71.8	72.8	70.6	76.0
24. C.T.	73.0	76.9	78.0	89.5	73.5
25. R.W.	76.9	76.3	76.4	84.6	74.0
$\bar{X}$	76.4	75.8	74.3	82.0	76.6
S.D.	6.6	5.7	4.3	8.0	6.1

Table 14. Submaximal Ventilation L · min^{-1} (240 m · min^{-1} for 6 min)

Subject	Control-1	Control-2	Placebo	Propranolol	Atenolol
1. R.A.	90.9	91.8	102.9	97.0	96.4
2. K.C.	90.5	103.4	96.6	79.8	91.4
3. S.D.	100.5	110.1	107.1	105.3	104.5
4. G.D.	116.3	102.5	103.6	107.4	98.0
5. J.E.	95.2	91.1	92.7	112.6	102.8
6. B.F.	96.0	95.6	93.5	89.0	91.3
7. D.G.	75.4	82.5	78.0	73.7	76.1
8. R.G.	81.5	86.3	80.0	84.7	75.8
9. M.G.	88.8	81.7	79.6	78.5	78.2
10. R.H.	85.9	82.8	80.4	89.3	84.4
11. J.H.	94.2	97.2	84.7	86.1	89.4
12. T.H.	108.7	90.9	92.3	98.3	96.3
13. T.J.	102.9	101.6	98.1	105.8	101.3
14. M.J.	88.0	87.0	87.2	85.6	83.6
15. M.L.	86.6	86.1	77.9	82.8	85.3
16. K.L.	77.7	87.8	95.2	89.6	90.8
17. M.Ma.	93.5	92.9	87.7	87.3	89.6
18. M.My.	93.7	90.3	84.4	86.9	82.9
19. L.P.	127.0	124.2	116.9	125.0	121.0
20. T.R.	89.7	93.3	92.4	137.4	95.3
21. H.S.	87.9	85.7	89.0	84.9	83.5
22. D.S.	95.2	96.0	103.5	98.4	100.5
23. R.T.	97.6	95.4	95.5	82.1	90.5
24. C.T.	94.3	98.1	103.2	105.3	105.4
25. R.W.	81.0	84.3	78.2	88.0	80.4
$\bar{X}$	93.6	93.5	92.0	94.4	91.8
S.D.	11.4	9.7	10.5	15.0	10.7

Table 15. Submaximal $\dot{V}E$ Expressed as % of $\dot{V}E$ Max

Subject	Control-1 (%)	Control-2 (%)	Placebo (%)	Propranolol (%)	Atenolol (%)
1. R.A.	43.8	48.5	59.8	49.7	50.4
2. K.C.	50.3	54.5	51.4	52.5	52.4
3. S.D.	55.4	57.5	55.3	63.9	60.9
4. G.D.	80.7	70.1	63.4	72.1	69.5
5. J.E.	60.5	62.3	57.7	97.0	73.9
6. B.F.	60.9	56.7	53.9	62.2	54.2
7. D.G.	56.2	59.1	60.1	65.3	61.5
8. R.G.	50.5	53.3	51.1	55.4	50.2
9. M.G.	59.5	60.1	58.8	64.4	52.3
10. R.H.	52.6	49.8	52.2	70.8	54.5
11. J.H.	64.6	56.6	52.4	64.6	59.5
12. T.H.	67.9	54.4	69.2	89.5	66.2
13. T.J.	62.9	56.6	57.2	71.1	64.6
14. M.J.	50.7	53.0	51.5	56.5	54.7
15. M.L.	53.2	50.8	48.7	61.0	57.3
16. K.L.	61.0	57.6	59.4	63.4	59.5
17. M.Ma.	54.4	54.8	52.6	72.0	56.1
18. M.My.	56.1	53.6	55.5	61.9	53.5
19. L.P.	73.7	76.7	78.4	80.4	76.1
20. T.R.	48.7	54.1	55.5	90.5	55.7
21. H.S.	47.2	48.6	50.9	58.6	51.3
22. D.S.	50.2	53.0	62.3	64.0	54.4
23. R.T.	57.4	58.2	60.5	59.9	61.1
24. C.T.	56.3	57.5	57.5	79.5	66.0
25. R.W.	47.1	50.9	49.9	64.7	48.3
$\bar{X}$	56.9	56.3	56.6	67.6	58.6
S.D.	8.6	6.3	6.0	11.9	7.4

Table 16. Maximal Heart Rate Beats · min^{-1}

Subject	Control-1	Control-2	Placebo	Propranolol	Atenolol
1. R.A.	182	182	185	134	135
2. K.C.	182	180	183	150	137
3. S.D.	180	176	180	144	156
4. G.D.	182	180	178	139	154
5. J.E.	180	179	180	111	136
6. B.F.	182	182	192	134	157
7. D.G.	190	186	184	146	152
8. R.G.	192	192	198	141	155
9. M.G.	185	185	180	130	170
10. R.H.	188	184	185	127	155
11. J.R.	182	180	180	125	145
12. T.H.	190	184	192	132	156
13. T.J.	186	188	182	130	146
14. M.J.	184	182	182	149	132
15. M.L.	188	184	190	130	152
16. K.L.	196	192	195	141	174
17. M.Ma.	190	182	184	132	165
18. M.My.	188	184	184	132	152
19. L.P.	187	184	182	146	168
20. T.R.	184	180	184	121	156
21. H.S.	176	170	172	120	151
22. D.S.	183	182	178	134	160
23. R.T.	180	182	178	125	162
24. C.T.	188	190	190	134	152
25. R.W.	188	182	183	136	170
$\bar{X}$	185.3	182.7	184.0	133.7	153.9
S.D.	4.6	4.7	6.0	9.5	11.1

Table 17. $\dot{V}O_2$ Max $ml \cdot kg^{-1} \cdot min^{-1}$

Subject	Control-1	Control-2	Placebo	Propranolol	Atenolol
1. R.A.	74.4	69.8	67.9	63.9	61.8
2. K.C.	65.6	66.6	65.5	58.6	63.6
3. S.D.	65.7	66.8	67.1	59.9	64.7
4. G.D.	61.6	59.6	60.4	58.2	56.0
5. J.E.	59.5	57.3	57.1	47.5	49.5
6. B.F.	59.7	62.0	63.0	52.2	60.4
7. D.G.	66.5	67.7	65.7	56.6	64.0
8. R.G.	67.1	67.6	64.3	64.2	65.9
9. M.G.	60.0	57.7	60.0	56.8	64.0
10. R.H.	67.8	69.4	64.4	57.1	64.3
11. J.H.	63.4	65.4	65.0	54.1	60.3
12. T.H.	62.9	63.8	63.5	50.8	54.1
13. T.J.	65.6	64.6	64.3	52.7	58.0
14. M.J.	65.9	64.4	64.5	59.6	55.4
15. M.L.	68.6	66.8	69.4	64.5	69.4
16. K.L.	56.2	59.0	57.8	51.3	55.2
17. M.Ma.	66.5	63.2	61.0	49.9	60.8
18. M.My.	59.9	59.6	56.6	50.8	53.9
19. L.P.	61.7	62.8	62.0	54.1	60.7
20. T.R.	71.3	75.5	73.6	52.5	73.5
21. H.S.	70.6	69.5	67.7	56.2	67.9
22. D.S.	66.6	68.1	68.7	62.4	65.3
23. R.T.	66.6	66.3	67.2	61.2	58.3
24. C.T.	60.3	56.3	58.6	48.5	55.9
25. R.W.	62.8	56.1	60.9	58.5	64.3
$\bar{X}$	64.7	64.6	63.8	56.1	61.1
S.D.	4.3	4.6	4.2	5.0	5.6

Table 18. $\dot{V}O_2$ Max $L \cdot min^{-1}$

Subject	Control-1	Control-2	Placebo	Propranolol	Atenolol
1. R.A.	6.05	5.75	5.78	5.39	5.14
2. K.C.	4.25	4.38	4.36	3.85	4.17
3. S.D.	4.83	5.00	4.97	4.46	4.82
4. G.D.	4.20	4.02	4.58	4.00	3.81
5. J.E.	3.95	3.83	3.77	3.18	3.31
6. B.F.	4.29	4.23	4.28	3.53	4.08
7. D.G.	3.87	4.00	3.91	3.35	3.73
8. R.G.	3.93	4.00	3.70	3.73	3.81
9. N.G.	4.12	3.97	4.06	3.70	4.36
10. R.H.	4.05	4.10	3.86	3.47	3.96
11. J.H.	4.16	4.26	4.19	3.54	3.94
12. T.H.	3.89	4.02	3.96	3.25	3.43
13. T.J.	4.69	4.69	4.61	3.80	4.18
14. M.J.	5.27	5.15	5.16	4.83	4.49
15. M.L.	4.94	4.81	4.84	4.48	4.89
16. K.L.	4.39	4.63	4.57	4.09	4.39
17. M.Ma.	4.74	4.58	4.38	3.63	4.17
18. M.My.	4.21	4.23	3.84	3.53	3.77
19. L.P.	4.53	4.50	4.61	4.00	4.50
20. T.R.	4.11	4.32	4.19	3.08	4.20
21. H.S.	4.45	4.31	4.17	3.54	4.21
22. D.S.	4.90	5.01	5.05	4.63	4.77
23. R.T.	5.00	4.99	5.10	4.64	4.42
24. C.T.	4.61	4.21	4.47	3.53	4.22
25. R.W.	4.11	4.11	3.95	3.67	4.17
$\bar{X}$	4.46	4.44	4.41	3.88	4.20
S.D.	0.50	0.50	0.50	0.60	0.40

Table 19. Maximal Ventilation $L \cdot min^{-1}$

Subject	Control-1	Control-2	Placebo	Propranolol	Atenolol
1. R.A.	207.40	189.37	206.50	195.26	191.12
2. K.C.	279.40	189.70	187.90	152.10	174.40
3. S.D.	181.38	191.50	193.60	164.60	171.55
4. G.D.	144.10	146.20	163.40	148.90	141.10
5. J.E.	157.28	146.34	160.60	116.10	139.09
6. B.F.	157.60	168.64	123.50	143.00	168.60
7. D.G.	134.16	139.67	129.72	112.80	123.70
8. R.G.	161.50	162.00	156.60	152.80	151.00
9. N.G.	149.12	136.01	135.45	121.80	149.60
10. R.H.	163.32	166.10	154.10	126.20	154.90
11. J.H.	145.79	171.64	161.60	133.24	149.35
12. T.H.	160.00	167.10	133.47	109.80	145.50
13. T.J.	163.50	179.60	171.60	148.90	156.70
14. M.J.	173.62	164.20	169.30	151.40	152.80
15. M.L.	162.78	169.50	160.10	135.80	148.80
16. K.L.	127.30	152.54	160.30	141.40	152.49
17. M.Ma.	171.97	169.60	166.70	121.20	159.70
18. M.My.	166.90	168.33	152.20	140.40	155.00
19. L.P.	172.27	162.00	159.10	155.50	159.00
20. T.R.	184.20	172.48	166.47	151.83	171.14
21. H.S.	186.30	176.50	174.90	144.80	162.80
22. D.S.	189.60	181.10	166.00	153.70	184.90
23. R.T.	170.00	163.90	157.80	137.10	148.00
24. C.T.	167.50	170.50	179.50	132.38	159.70
25. R.W.	172.00	165.70	156.60	136.00	166.50
$\bar{X}$	166.00	166.80	163.50	141.60	157.50
S.D.	17.70	14.40	17.50	18.40	14.60

Table 20. Maximal Treadmill Time min

Subject	Control-1	Control-2	Placebo	Propranolol	Atenolol
1. R.A.	15.00	14.57	13.77	14.05	14.05
2. K.C.	13.55	14.02	14.07	13.00	13.03
3. S.D.	12.53	12.50	13.03	11.13	12.00
4. G.D.	11.00	12.00	11.47	10.02	11.02
5. J.E.	12.03	12.00	12.47	07.25	10.50
6. B.F.	13.00	13.13	14.05	12.03	13.02
7. D.G.	13.00	12.08	13.28	12.03	12.98
8. R.G.	13.00	13.66	14.00	12.50	13.18
9. M.G.	12.00	12.50	12.32	11.48	12.33
10. R.H.	13.33	14.03	13.47	11.47	12.90
11. J.H.	13.17	13.53	13.93	11.70	12.50
12. T.H.	12.07	11.01	12.30	9.12	10.57
13. T.J.	12.50	13.17	13.25	11.35	12.23
14. M.J.	14.50	15.03	15.00	13.20	13.05
15. M.L.	14.17	14.00	15.00	12.58	13.65
16. K.L.	12.00	12.08	12.00	12.28	12.30
17. M.Ma.	14.00	14.25	14.67	12.00	13.60
18. M.My.	13.50	14.00	14.55	13.25	13.65
19. L.P.	12.00	11.50	11.60	11.50	11.93
20. T.R.	13.15	13.00	13.17	9.03	12.52
21. H.S.	13.67	13.65	13.93	11.53	13.77
22. D.S.	14.05	13.50	13.25	11.03	13.05
23. R.T.	14.00	14.05	13.15	12.25	13.22
24. C.T.	12.98	13.12	13.25	10.45	12.25
25. R.W.	13.17	13.00	13.12	10.74	13.68
$\bar{X}$	13.10	13.20	13.40	11.50	12.70
S.D.	0.90	1.00	1.00	1.49	1.00

Table 21. Race Times min

Subject	Control-1	Control-2	Placebo	Propranolol	Atenolol
1. R.A.	32.25	33.85	34.63	37.30	37.45
2. K.C.	34.57	34.52	34.23	38.03	37.07
3. S.D.	36.58	37.30	37.08	41.92	40.72
4. G.D.	38.53	38.52	38.02	40.88	41.23
5. J.E.	38.65	38.78	38.72	48.38	44.95
6. B.F.	36.77	36.30	36.30	41.77	38.15
7. D.G.	34.85	36.58	35.23	41.33	37.78
8. R.G.	34.92	34.96	34.30	37.07	36.18
9. M.G.	36.79	36.70	35.70	40.28	40.77
10. R.H.	34.23	34.15	35.78	37.77	41.90
11. J.H.	33.85	34.70	33.28	42.90	36.48
12. T.H.	33.87	34.43	35.65	39.35	40.92
13. T.J.	37.48	36.53	38.02	41.95	37.88
14. M.J.	34.27	33.97	34.30	40.13	43.97
15. M.L.	34.87	33.70	33.18	38.40	36.55
16. K.L.	36.88	37.32	39.72	40.73	38.53
17. M.Ma.	33.77	33.63	34.07	39.92	35.60
18. M.My.	35.58	35.75	35.73	38.88	39.52
19. L.P.	38.90	39.87	40.10	41.95	40.73
20. T.R.	36.08	35.07	35.17	47.43	43.70
21. H.S.	34.98	35.38	34.18	41.00	36.77
22. D.S.	33.38	37.18	34.92	44.02	35.93
23. R.T.	34.70	35.17	34.37	39.60	38.37
24. C.T.	37.20	37.13	36.53	41.10	43.48
25. R.W.	35.43	36.80	36.17	41.80	36.10
$\bar{X}$	35.70	35.90	35.80	41.00	39.20
S.D.	1.80	1.70	1.90	2.70	2.80

Table 22. Control-1 Race $\dot{V}O_2$ Estimates

Subject	Race Speed $m \cdot min^{-1}$	Est. $\dot{V}O_2$ $ml \cdot kg^{-1} \cdot min^{-1}$	% $\dot{V}O_2$ max
1. R.A.	310.1	61.6	82.3
2. K.C.	289.3	56.3	85.8
3. S.D.	273.4	57.2	87.1
4. G.D.	259.5	58.6	95.1
5. J.E.	258.7	51.3	86.3
6. B.F.	272.0	51.4	82.3
7. D.G.	286.9	55.0	82.3
8. R.G.	286.4	58.2	86.7
9. M.G.	271.8	53.7	89.4
10. R.H.	292.1	60.1	88.7
11. J.H.	295.4	56.7	94.9
12. T.H.	295.2	62.5	99.3
13. T.J.	266.8	56.7	86.4
14. M.J.	291.8	50.2	76.2
15. M.L.	286.8	59.5	86.8
16. K.L.	271.1	51.0	90.8
17. M.Ma.	296.1	57.9	87.0
18. M.My.	281.1	52.0	86.8
19. L.P.	257.1	56.7	92.0
20. T.R.	277.2	62.5	87.7
21. H.S.	285.9	58.3	82.6
22. D.S.	299.6	48.4	87.7
23. R.T.	288.2	56.5	85.0
24. C.T.	268.8	49.4	81.9
25. R.W.	282.2	54.8	87.3
$\bar{X}$	281.7	56.3	87.1
S.D.	13.7	3.7	4.8

Table 23. Control-2 Race $\dot{V}O_2$ Estimates

Subject	Race Speed $m \cdot min^{-1}$	Est. $\dot{V}O_2$ $ml \cdot kg^{-1} \cdot min^{-1}$	% $\dot{V}O_2$ max
1. R.A.	295.4	56.0	80.2
2. K.C.	289.7	56.6	85.0
3. S.D.	268.1	56.0	83.9
4. G.D.	259.6	53.6	89.9
5. J.E.	257.9	49.6	86.6
6. B.F.	275.5	53.8	86.7
7. D.G.	273.4	52.0	76.9
8. R.G.	286.0	54.4	80.5
9. M.G.	272.5	51.3	89.0
10. R.H.	292.8	59.0	85.0
11. J.H.	288.2	56.7	86.7
12. T.H.	290.4	61.6	96.5
13. T.J.	273.7	54.7	84.7
14. M.J.	294.4	51.9	80.5
15. M.L.	296.7	57.6	85.0
16. K.L.	268.0	52.6	89.1
17. M.Ma.	297.4	54.8	86.7
18. M.My.	279.7	50.3	84.5
19. L.P.	250.8	56.1	90.5
20. T.R.	285.1	67.7	89.7
21. H.S.	282.6	57.4	82.6
22. D.S.	269.0	57.5	84.4
23. R.T.	284.3	54.0	81.5
24. L.T.	269.3	47.9	85.1
25. R.W.	271.7	55.4	85.1
$\bar{X}$	278.9	55.1	85.5
S.D.	13.0	4.0	4.1

Table 24. Placebo Race $\dot{V}O_2$ Estimates

Subject	Race Speed $m \cdot min^{-1}$	Est. $\dot{V}O_2$ $ml \cdot kg^{-1} \cdot min^{-1}$	% $\dot{V}O_2$ max
1. R.A.	288.8	56.3	83.0
2. K.C.	292.1	54.8	86.6
3. S.D.	269.7	56.0	83.5
4. G.D.	263.0	53.2	88.0
5. J.E.	258.3	47.2	82.7
6. B.F.	275.5	50.9	80.8
7. D.G.	283.8	53.5	81.4
8. R.G.	291.5	54.9	85.3
9. M.G.	280.1	53.0	88.4
10. R.H.	279.5	54.0	83.8
11. J.H.	300.5	56.9	87.4
12. T.H.	280.5	57.1	89.9
13. T.J.	263.0	51.4	79.9
14. N.J.	291.5	51.0	79.1
15. M.L.	301.4	59.5	85.5
16. K.L.	251.8	47.3	81.9
17. M.Ma.	293.5	51.7	84.8
18. M.My.	279.9	47.6	84.1
19. L.P.	249.4	50.3	81.0
20. T.R.	284.3	64.9	88.2
21. H.S.	292.6	58.4	86.6
22. D.S.	286.4	62.0	90.3
23. R.T.	291.0	58.7	87.3
24. C.T.	273.7	50.7	86.5
25. R.W.	276.5	52.0	85.4
$\bar{X}$	279.9	54.1	84.7
S.D.	14.2	4.5	3.1

Table 25. Propranolol Race $\dot{V}O_2$ Estimates

Subject	Race Speed $m \cdot min^{-1}$	Est. $\dot{V}O_2$ $ml \cdot kg^{-1} \cdot min^{-1}$	% $\dot{V}O_2$ max
1. R.A.	268.1	48.2	75.4
2. K.C.	263.0	47.0	80.2
3. S.D.	238.5	49.8	83.1
4. G.D.	244.6	52.6	90.4
5. J.E.	206.7	31.2	65.6
6. B.F.	239.4	42.1	80.6
7. D.G.	242.0	42.7	75.4
8. R.G.	269.8	52.8	82.3
9. M.G.	248.3	46.5	81.8
10. R.H.	264.8	49.4	86.5
11. J.H.	233.1	41.1	75.9
12. T.H.	254.1	50.1	98.7
13. T.J.	238.4	43.8	83.0
14. N.J.	249.2	42.0	70.4
15. M.L.	260.4	51.2	79.3
16. K.L.	245.5	43.7	85.2
17. M.Ma.	250.5	43.4	87.0
18. M.My.	257.2	43.7	86.0
19. L.P.	238.4	47.7	88.2
20. T.R.	210.8	49.1	93.6
21. H.S.	243.9	45.2	80.4
22. D.S.	227.1	46.9	75.1
23. R.T.	252.5	43.3	70.7
24. C.T.	243.3	44.8	92.4
25. R.W.	239.2	48.2	82.4
$\bar{X}$	245.2	45.9	82.0
S.D.	15.5	4.6	7.7

Table 26. Atenolol Race $\dot{V}O_2$ Estimates

Subject	Race Speed $m \cdot min^{-1}$	Est. $\dot{V}O_2$ $ml \cdot kg^{-1} \cdot min^{-1}$	% $\dot{V}O_2$ max
1. R.A.	267.0	48.4	78.4
2. K.C.	269.8	51.0	80.2
3. S.D.	245.6	53.0	81.9
4. G.D.	242.5	49.5	88.5
5. J.E.	227.5	41.7	84.3
6. B.F.	262.1	47.9	79.3
7. D.G.	264.7	50.2	78.4
8. R.G.	276.4	52.7	80.0
9. M.G.	245.3	47.8	77.8
10. R.H.	238.6	46.8	72.7
11. J.H.	274.1	49.4	81.9
12. T.H.	244.4	49.6	91.7
13. T.J.	264.0	50.4	86.9
14. N.J.	228.5	35.9	64.7
15. M.L.	273.6	56.6	81.6
16. K.L.	259.5	47.8	86.6
17. M.Ma.	280.9	51.6	85.8
18. M.My.	253.0	39.9	74.0
19. L.P.	245.5	53.1	87.4
20. T.R.	228.8	51.9	70.5
21. H.S.	272.0	52.7	77.6
22. D.S.	278.3	57.2	87.6
23. R.T.	260.6	46.9	80.5
24. C.T.	230.0	40.7	72.9
25. R.W.	277.0	52.6	81.9
$\bar{X}$	256.4	49.0	80.5
S.D.	17.5	5.1	6.3

Table 27. Race Heart Rate Beats • min^{-1}

Subject	Control-1	Control-2	Placebo	Propranolol	Atenolol
1. R.A.	174	176	176	112	112
2. K.C.	172	172	184	128	120
3. S.D.	172	180	184	120	132
4. G.D.	172	184	180	134	116
5. J.E.	168	172	172	100	100
6. B.F.	178	184	188	124	136
7. D.G.	176	168	190	116	132
8. R.G.	176	168	184	140	136
9. M.G.	172	168	176	108	116
10. R.Y.	172	176	158	104	104
11. J.H.	180	172	188	108	128
12. T.H.	192	172	180	128	96
13. T.J.	170	168	176	120	136
14. M.J.	168	176	172	104	112
15. M.L.	180	172	184	128	132
16. K.L.	176	184	192	140	160
17. M.Ma.	156	184	180	128	170
18. M.My.	176	172	184	132	124
19. L.P.	172	172	180	132	132
20. T.R.	172	168	190	100	116
21. H.S.	168	172	162	108	120
22. D.S.	160	152	172	120	172
23. R.T.	178	184	176	112	114
24. C.T.	168	168	172	124	128
25. R.W.	168	172	176	108	176
$\bar{X}$	172.8	173.4	179.0	119.1	128.8
S.D.	6.9	7.3	8.4	12.2	21.4

Table 28. Race Heart Rate Expressed as % of HR Max

Subject	Control-1 (%)	Control-2 (%)	Placebo (%)	Propranolol (%)	Atenolol (%)
1. R.A.	95.6	96.7	95.1	83.6	83.0
2. K.C.	94.5	95.6	100.5	85.3	87.6
3. S.D.	95.5	102.2	102.2	83.3	84.6
4. G.D.	94.5	102.2	101.1	96.4	75.3
5. J.E.	93.3	96.1	95.6	90.1	73.5
6. B.F.	97.8	101.1	97.9	92.5	86.6
7. D.G.	92.6	90.3	103.3	79.5	86.8
8. R.G.	91.7	87.5	93.0	99.3	87.7
9. M.G.	93.0	90.1	97.8	83.1	68.2
10. R.H.	91.5	95.7	85.4	81.9	67.1
11. J.H.	98.9	95.6	104.4	86.4	88.3
12. T.H.	101.1	93.5	93.8	97.0	61.5
13. T.J.	91.4	89.4	96.7	92.3	93.2
14. M.J.	91.3	96.7	94.5	69.8	84.8
15. M.L.	95.7	93.5	96.8	98.5	86.8
16. K.L.	89.8	95.8	98.5	99.3	92.0
17. M.Ma.	82.1	101.1	97.8	97.0	103.0
18. M.My.	93.6	93.5	100.0	100.0	93.9
19. L.P.	92.0	95.6	98.9	90.4	78.6
20. T.R.	95.7	93.3	103.3	82.6	74.4
21. H.S.	95.5	101.1	94.2	90.0	79.5
22. D.S.	87.4	83.5	96.6	89.6	107.5
23. R.T.	98.9	101.1	98.9	89.6	70.4
24. C.T.	89.4	88.4	90.5	92.5	84.2
25. R.W.	89.4	94.5	96.2	79.4	103.5
$\bar{X}$	93.3	95.0	97.3	89.2	84.1
S.D.	4.0	4.9	4.2	7.7	11.5

APPENDIX 4

BAB-INDUCED RELATIONSHIPS BETWEEN SELECTED PHYSIOLOGICAL VARIABLES

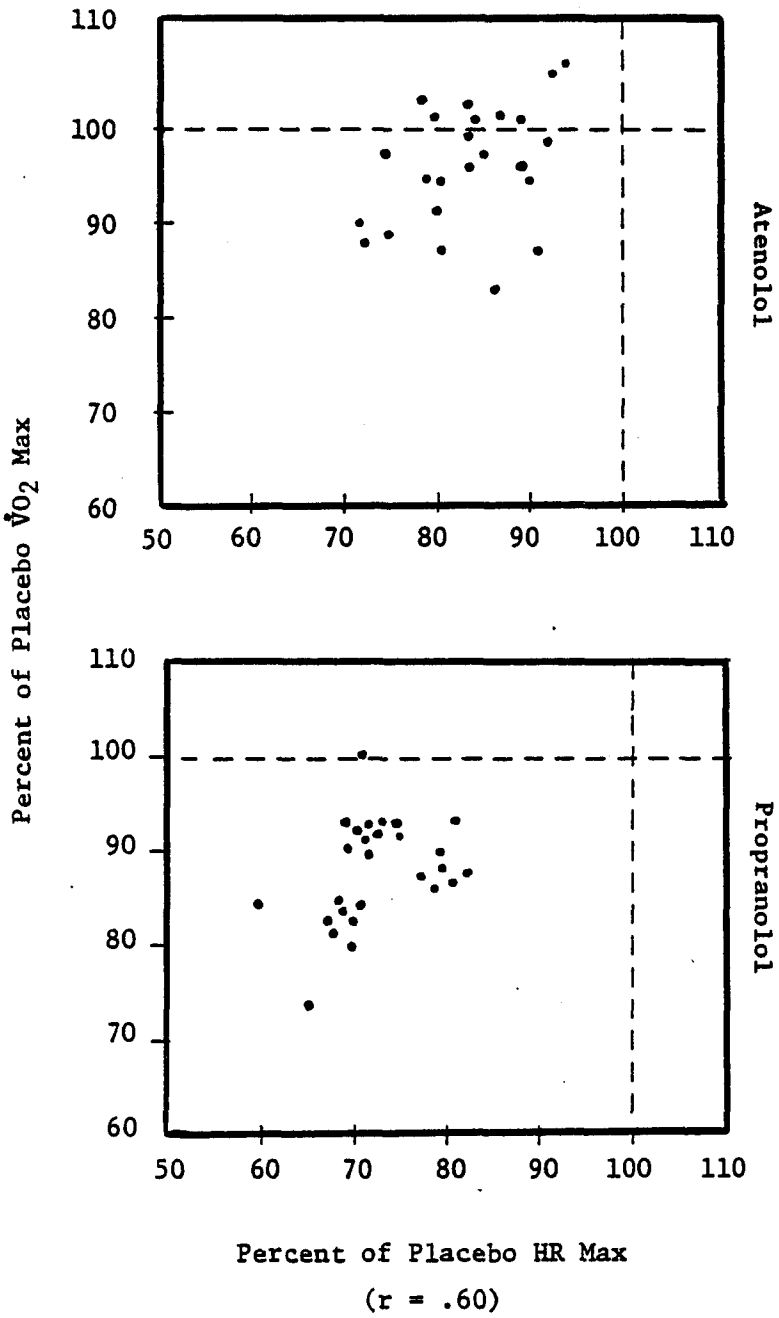

Figure 6. The relationship between BAB $\dot{V}O_2$ Max and BAB HR Max expressed as a percentage of the corresponding placebo values.

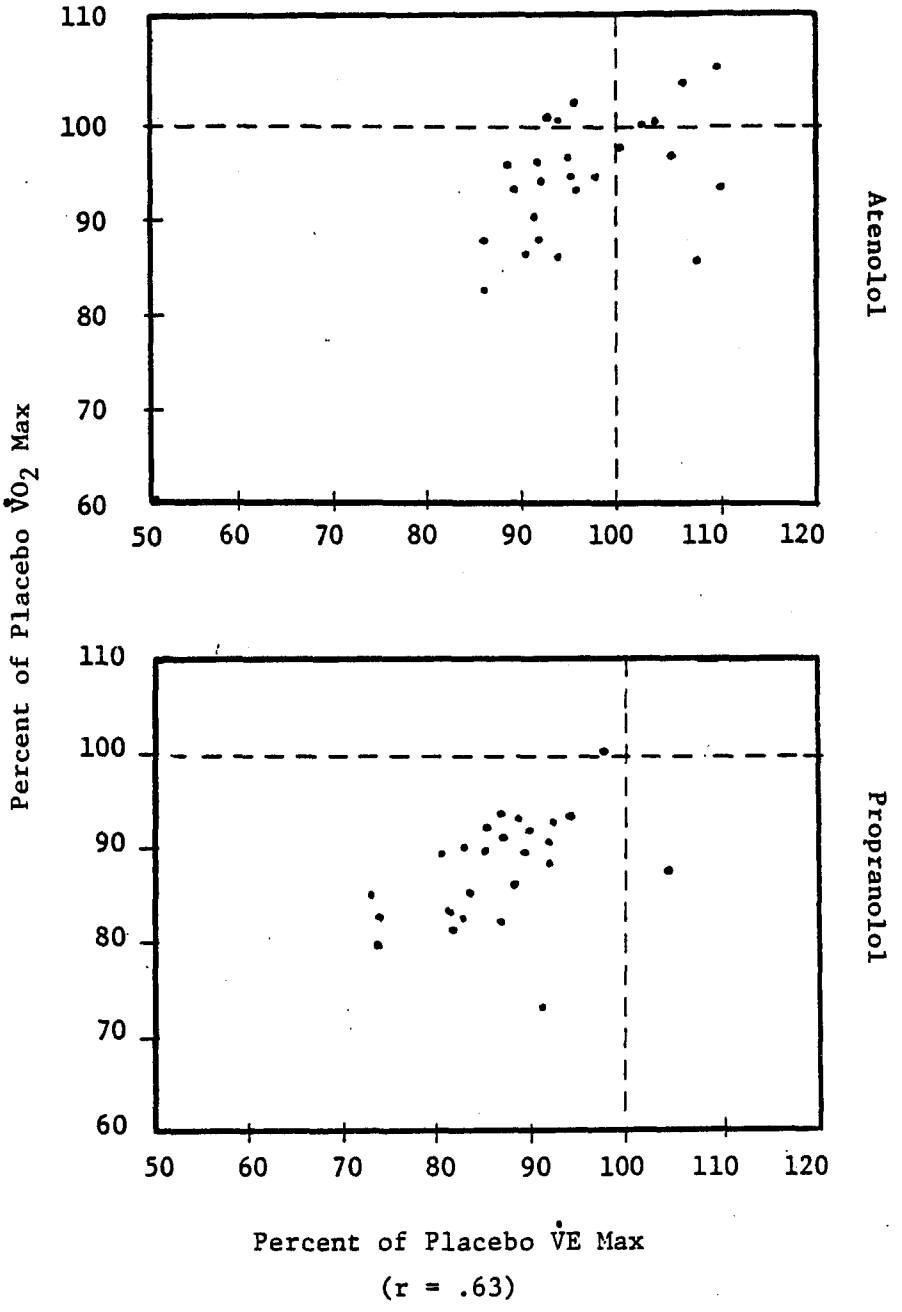

Figure 7. The relationship between BAB $\dot{V}O_2$ Max and BAB $\dot{V}E$ Max expressed as a percentage of the corresponding placebo values.

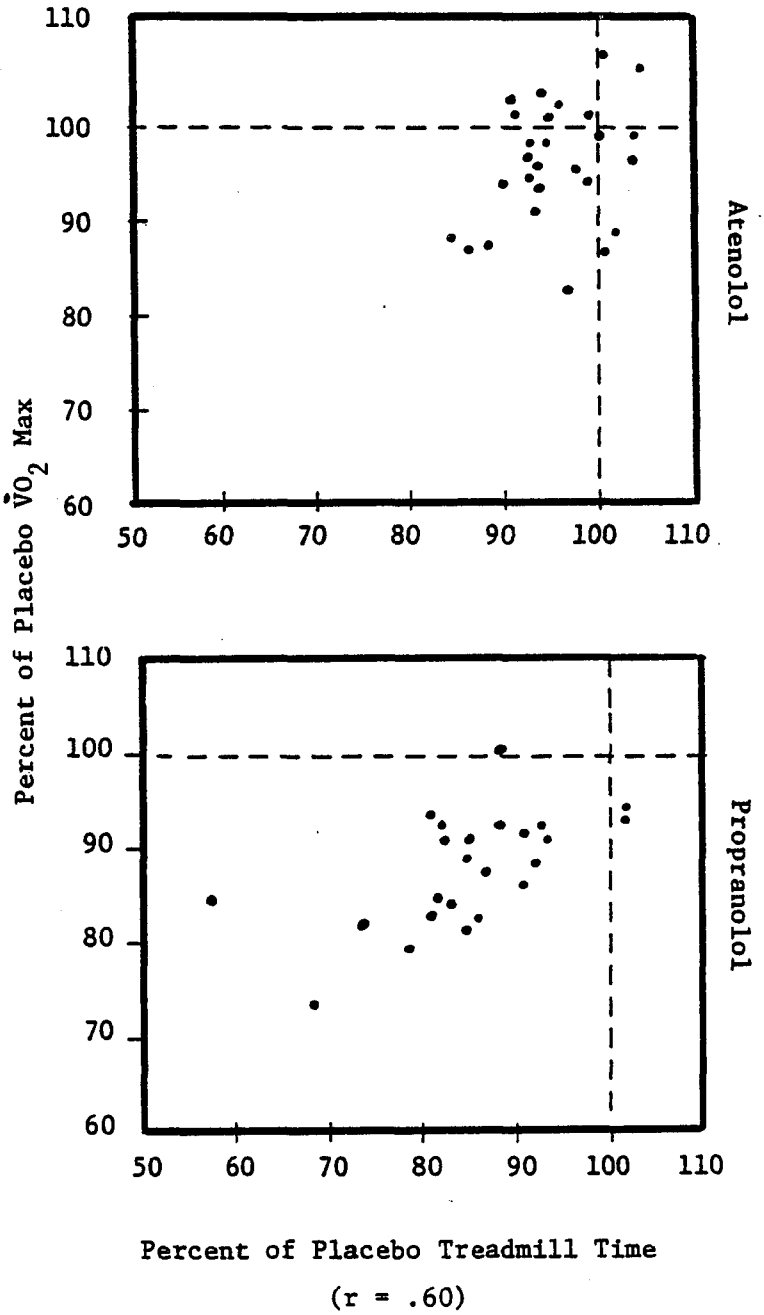

Figure 8. The relationship between BAB $\dot{V}O_2$ Max and BAB treadmill time expressed as a percentage of the corresponding placebo value.

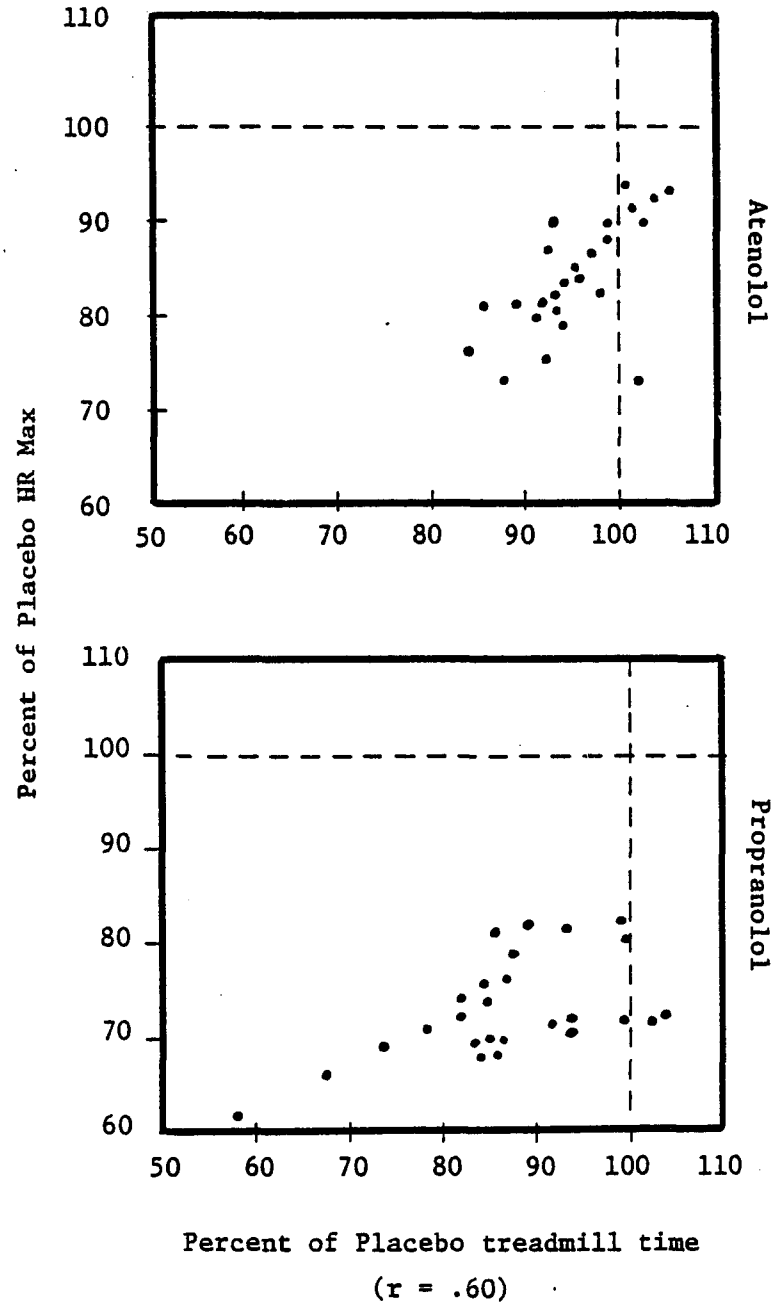

Figure 9. The relationship between BAB HR Max and BAB treadmill time expressed as a percentage of the corresponding placebo values.

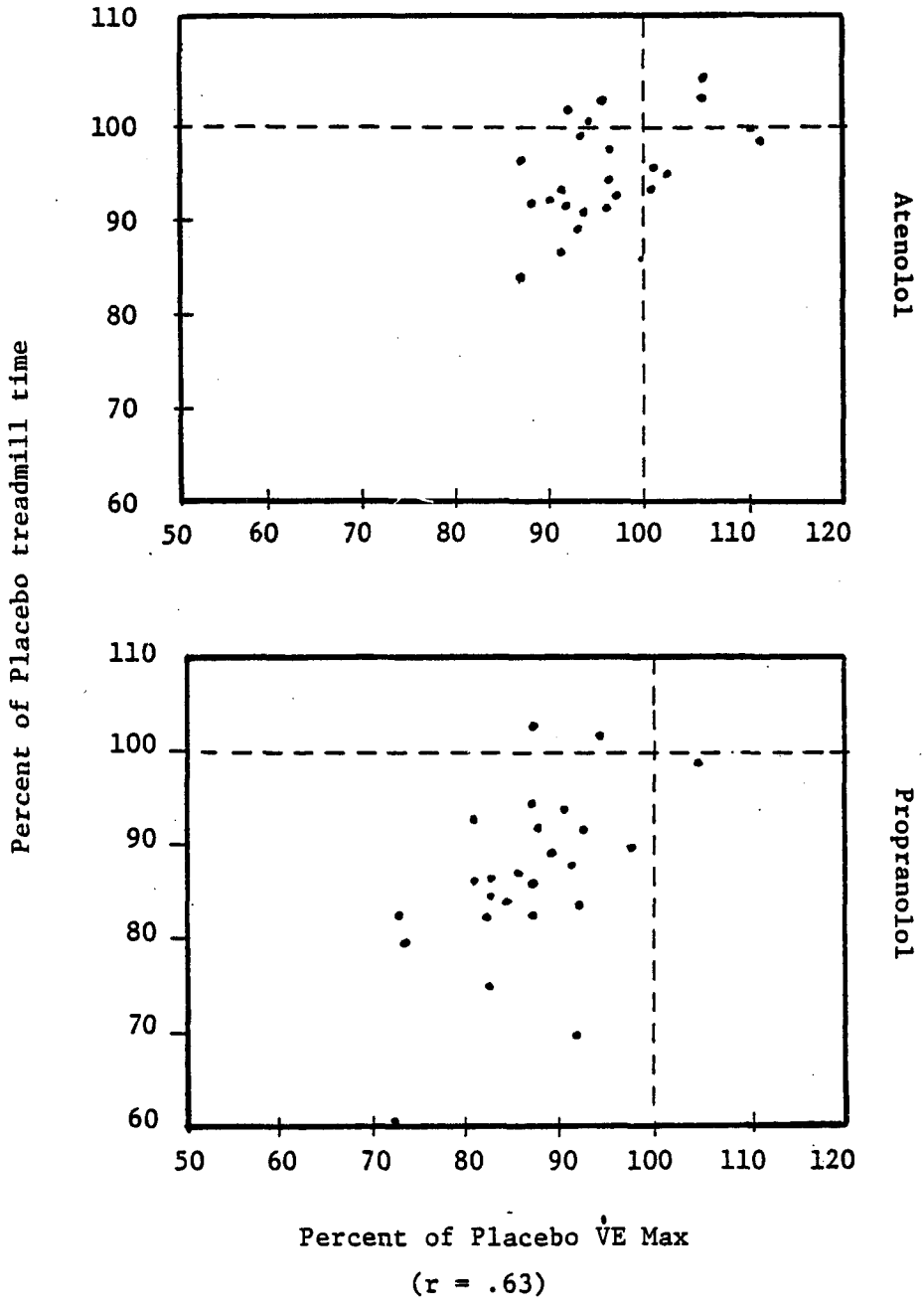

Figure 10. The relationship between BAB treadmill time and BAB $\dot{V}E$ Max expressed as a percentage of the corresponding placebo values.

REFERENCES

1. Epstein, S.E., Robinson, B.F., Kahler, R.L., and Braunwald, E. "Effects of Beta Adrenergic Blockade on the Cardiac Response to Maximal and Submaximal Exercise in Man", J. Clin. Invest., (1965), 44: 1745.

2. Reybrouck, T., Armery, A., and Billiet, L. "Hemodynamic Response to Graded Exercise After Chronic Beta-Adrenergic Blockade", J. Appl. Physiol., (1977), 42: 133.

3. Furberg, C. "Adrenergic Beta Blockade and Physical Working Capacity", Acta Med. Scand., (1967), 182: 119.

4. Costill, D.L. "The Relationship Between Selected Physiological Variables and Distance Running Performance", J. Sports Med., (1967), 7: 61.

5. Farrell, P.A., Wilmore, J.H., Coyle, E.F., Billing, J.E., and Costill, D.L. "Plasma Lactate Accumulation and Distance Running Performance", Med. and Sci. in Sports, (1979), 11: 338.

6. Costill, D.L., Thomason, H., and Roberts, E. "Fractional Utilization of the Aerobic Capacity During Distance Running", Med. and Sci. in Sports, (1973), 5: 248.

7. Conley, D.L. and Krahenbuhl, G.S. "Running Economy and Distance Running Performance of Highly Trained Athletes", Med. and Sci. in Sports, (1980), 12: 357.

8. Kendall, M.J. and Smith, S.R. "Adrenergic Blocking Agents", J. Clin. and Hosp. Pharm., (1983), 8: 155.

9. Kaiser, P., Tesch, P., Turner, S., Karlsson, J., and Kaijser, L. "Oxygen Consumption and Lactate Metabolism During Exercise Following B-Adrenoceptor Blockade", Drugs, (1983), 25 (Sup. 2): 260.

10. Kaijser, L. "Beta Blockers and Running", Amer. Heart J., (1980), 100: 943.

11. Karlsson, J. "Muscle Fibre Composition, Short Term B_1 and B_2 and B_1 Blockade and Endurance Performance in Healthy Young Men", Drugs, (1983), 25 (Sup. 2): 241.

12. Lundborg, P., Astrom, H., Bengtsson, C., Fellenius, E., Von Schenk, H., Svensson, L., and Smith, U. "Effect of B-Adrenoceptor Blockade on Exercise Performance and Metabolism", Clin. Sci., (1981), 61: 299.

13. Lyngsoe, J., Lauridsen, U.B., and Christensen, N.J. "Effects of Atenolol and Propranolol on Glucose Metabolism and Hormonal Responses During Insulin-induced Hypoglycemia in Normal Man", Drugs, (1983), 25 (Sup. 2): 237.

14. Koch, G., Franz, I., and Lohmann, F. "Effects of Short Term and Long Term Treatment with Cardioselective and Non-cardioselective Beta Receptor Blockade on Carbohydrate and Lipid Metabolism and on Plasma Catecholamines at Rest and During Exercise", Clin. Sci., (1981), 65 (Sup. 7): 433.

15. Snow, D.H., Summers, R.J., and Guy, P.S. "The Actions of B-Adrenoreceptor Blocking Agents Propranolol and Metoprolol in the Maximally Exercised Horse", Res. in Vet. Sci., (1979), 27: 22.

16. Dale, H.H. "On Some Physiological Actions of Ergot", J. Physiol., (1906), 34 : 163.

17. Alquist, R.P. "A Study of the Adrenotropic Receptors", Amer. J. Physiol., (1948), 153: 586.

18. Lands, A.M., Arnold, A., McAuliff, J.P., Lunduena, F.P., and Brown, T.G. "Differentiation of Receptor Systems Activated by Sympathomimetic Amines", Nat., (1967), 214: 597.

19. Lewis, M.J., Griffith, T.M., and Henderson, A.H. "B-Blockade and Coronary Arteries", Drugs, (1983), 25 (Sup. 2): 247.

20. Irving, M.H., Britton, B.J., Wood, W.G., Padgham, C., and Carruthers, M. "Effects of B Adrenergic Blockade on Plasma Catecholamines in Exercise", Nat., (1974), 248: 531.

21. Robertson, J.I.S. "B-Blockade and Treatment of Hypertension", Drugs, (1983), 25 (Sup. 2): 5.

22. Furberg, C.D. "B-Blocker Heart Attack Trial", Drugs, (1983), 25 (Sup. 2): 314.

23. Norwegian Multi-Center Study Group. "Timolol-Induced Reduction in Mortality and Re-Infarction in Patients Surviving Acute Myocardial Infarction", N. Engl. J. Med., (1981), 304: 801.

24. Shand, D.G. "State of the Art: Comparative Pharmacology of the B-Adrenoceptor Blocking Drugs", Drugs, (1983), 25 (Sup. 2): 92.

25. Frishman, W., Smithen, C., Befler, B., Kligfield, P., and Killip, T. "Noninvasive Assessment of Clinical Response to Oral Propranolol Therapy", Amer. J. Cardiol., (1975), 35: 635.

26. Kendall, M.J. "Beta Blockade and Respiratory Function", Cardiovas. Rev. and Rep., (1981), 2: 572.

27. Tesch, P.A., Kaijser, L., and Kaiser, P. "Isometric Muscle Endurance During Acute Beta Blockade", Abs. Med. and Sci. in Sports, (1983), 15: 3.

28. Routledge, P.A. and Shand, D.G. "Clinical Pharmacokinetics of Propranolol", Clin. Pharmaco., (1979), 4: 73.

29. Shwartz, J.B., Jackson, G., Kates, R.E., and Harrison, D.C. "Long Term Benefit of Cardioselective Beta Blockade with Once Daily Atenolol Therapy in Angina Pectoris", Amer. Heart J., (1981), 101: 380.

30. Clausen, J.P., Klausen, K., and Rasmussen, B. "Central and Peripheral Circulatory Changes After Training the Arms and Legs", Amer. J. Physiol., (1973), 225: 675.

31. Ekblom, B. Hermansen, L. "Cardiac Outputs in Athletes", J. Appl. Physiol., (1968), 25: 619.

32. Saltin B., Blomquist, G., and Mitchell, J.H. "Response to Exercise After Bed Rest and After Training", Circ., (1968), 38 (Sup. 7): 1.

33. Clausen, J.P. "Circulatory Adjustments to Dynamic Exercise and Effect of Physical Training in Normal Subjects and in Patients with Coronary Artery Disease", Prog. in Cardiovas. Dis., (1976) 18: 459.

34. May, G.S., Eberlein, K.A., Furberg, C.D., Passamani, E.R., and DeMets, D.L. "Secondary Prevedntion After Myocardial Infarction: A Review of Long-Term Trials", Prog. in Cardiovas. Dis., (1982), 24: 331.

35. Hagberg, J.M., Ehsani, A.A., and Holloszy, J.O. "Effect of Prolonged and Intense Exercise Training on Patients with Coronary Artery Disease", Circ., (1983), 67: 1194.

36. Dwyer, E.M., Wiener, L., and Cox, J.W. "Effects of Beta Adrenergic Blockade on Left Ventricular Hemodynamics and the Electro- cardiogram During Exercise Induced Angina Pectoris", Circ., (1968), 38: 250.

37. Powles, A.C.P. "The Effect of Drugs on Cardiovascular Response to Exercise", Med. Sci.in Sports, (1981), 13: 252.

38. Franciosa, J.A., Johnson, S.M., and Tobian, L.J. "Exercise Performance in Mildly Hypertensive Patients", Chest, (1980), 78: 291.

39. Bruce, R.A., Hossack, K.F., Kusumi, F., and Clark, L.J. "Acute Effects of Oral Propranolol on Hemodynamic Responses to Upright Exercise", Amer. J. Cardiol., (1979), 44: 132.

40. Malborg, R., Isaacson, S. and Kallivroussis, G. "The Effects of Beta Blockade and/or Physical Training in Patients with Angina Pectoris", Curr. Ther. Res., (1974), 16: 171.

41. Pratt, C.M., Welton, D.E., Squires, W.G., Kirby, T.E., Hartung, G.H., and Miller, R.R. "Demonstration of Training Effect During Chronic B-Adrenergic Blockade in Patients with Coronary Artery Disease", Circ., (1981), 64: 1125.

42. Obina, R., Wilson, R., Goebel, M., and Campbell, D. "Effect of a Conditioning Program on Patients Taking Propranolol for Angina Pectoris", Cardiol., (1979), 64: 365.

43. Smith, J.L., Dressendorfer, R., Cameron, J., Borysyk, L., Gordon, S., and Timmis, G.C. "Failure of Beta-Blockade to Attenuate Desired Training Benefits During Early Outpatient Cardiac Rehabilitation", Abs. Med. Sci. in Sports, (1983), 15: 132.

44. Roberts, M., Sullivan, M., and Froelicher, V. "The Effect of Chronic Beta Adrenergic Blockade on Changes in Maximal Oxygen Uptake in Coronary Artery Disease Patients", Abs. Med. Sci. in Sports, (1983), 15: 133.

45. Maksud, M.G., Tristani, F.E., Coutts, K.D., Barboriak, J.J., and Hamilton, L.H. "Effects of Propranolol on Several Physiological Responses During Orthostatic and Exercise Stress in Healthy Male Subjects", Can. J. of Physio. and Pharmaco., (1971), 49: 867.

46. Ekblom, B., Goldbarg, A.N., Kilbom, A., and Astrand, P.O. "Effects of Atropine and Propranolol on Oxygen Transport System During Exercise in Man", Scand. J. Clin. Lab. Invest., (1972), 30: 35.

47. Pearson, S.B., Banks, D.C., and Patrick, J.M. "The Effect of B-Adrenoceptor Blockade on Factors Affecting Exercise Tolerance in Normal Man", Br. J. of Pharmaco., (1979), 8: 143.

48. Wilmore, J.H., Ewy, G.A., Morton, A.R., Stanforth, P.R., Constable, S.H., Buono, M.J., Conrad, K.A., Miller, H., and Gatewood, C.F. "The Effect of Beta Adrenergic Blockade on Submaximal and Maximal Exercise Performance", J. Cardiac Rehab., (1983), 3: 30.

49. Maksud, M.G., Coutts, K.D., Tristani, F.E., Dorchak, J.R., Barboriak, J.J., and Hamilton, L.H. "The Effects of Physical Conditioning and Propranolol on Physical Work Capacity", Med. Sci. in Sports, (1972), 4: 225.

50. Sable, D.L., Brammell, H.L., Sheehan, M.W., Nies, A.S., Gerber, J.G., and Horwitz, L.D. "Attenuation of Exercise Conditioning by Beta Adrenergic Blockade", Circ., (1982), 65: 679.

51. Ewy, G.A., Wilmore, J.H., Morton, A.R., Stanforth, P.R., Constable, S.H., Buono, M.J., Conrad, K.A., Miller, H., and Galewood, C.F. "The Effect of Beta Adrenergic Blockade on Obtaining a Trained State", J. Cardiac Rehab., (1983), 3: 27.

52. Svedenhag, J., Henriksson, J., Juhlen-Dannfelt, A., Assono, K., and Lithell, H. "Training Under the Influence of B-Blockade - Effects on Healthy Subjects", Abs. Med. Sci. in Sports, (1983), 15: 166.

53. von Baak, M., Jennen, W., and Verstappen, F. "Heart Rate Reduction and Maximal Work Capacity During Acute and Chronic Beta Receptor Blockade", Abs. Med. Sci. in Sports, (1983), 15: 166.

54. Tesch, P.A., Kaiser, P. "Effects of B-Adrenergic Blockade on O_2 Uptake During Submaximal and Maximal Exercise", J. Appl. Physiol., (1983), 54: 901.

55. Ambrosioni, E., Costa, F.V., Montebugnoli, L., Bassein, L., Marchesini, B., and Magnani, B. "Comnparison of Antihypertensive Efficacy of Atenolol, Oxprenolol and Pindolol at Rest and During Exercise", Drugs, (1983), 25 (Sup. 2): 30.

56. Magnani, B., Mantovani, B., Brancaleoni, M., Gubelli, S., and Ambrosioni, E. "Cardioselectivity and Partial Agonist Activity in the Antianginal Efficacy of the B-Adrenoreceptor Antagonists", Drugs, (1983), 25 (Sup. 2): 166.

57. Schwartz, J.B. "Atenolol in the Treatment of Angina", Drugs, (1983), 25 (Sup. 2): 160.

58. Petrie, J.C., Jeffers, T.A., Scott, A.K., and Webster, J. "Dose and Duration of Response to B-Blockers in the Treatment of Hypertension", Drugs, (1983), 25 (Sup. 2): 26.

59. Folgering, H., and van Bussel, M. "Maximal Exercise Power After a Single Dose of Metaprolol and of Slow Release Metaprolol", Eur. J. of Clin. Pharmaco., (1980), 18: 225.

60. Sucec, A.A. "A Horizontal Treadmill Protocol for Concurrent Determination of Anaerobic Threshold and $\dot{V}O_2$ max for Male and Female Distance Runners", Abs. Med. Sci. in Sports, (1981), 13: 69.

61. Kasch, F.W., Wallace, J.P., Hurn, R.R., Krogh, L.A., and Hurl, P.M. "$\dot{V}O_2$ max During Horizontal and Inclined Treadmill Running", J. Appl. Physiol., (1976), 40: 982.

62. Whipp, B.J., and Wasserman, K. "Oxygen Uptake Kinetics for Various Intensities of Constant Load Work", J. Appl. Physiol., (1972), 33: 351.

63. Linnarsson, D. "Dynamics of Pulmonary Gas Exchange and Heart Rate Changes at Start and End of Exercise", Acta Physiol. Scand., (1974), 415 (Sup.): 1.

64. Wilmore, J.H., Davis, J.A., and Norton, A.C. "An Automated System of Measuring Metabolic and Respiratory Function During Exercise", J. Appl. Physiol., (1976), 40: 619.

65. Astrand, P.O., and Rodahl, K. Textbook of Work Physiology 2, (1977), 297, 485.

66. Borg, G.A.V. "Perceived Exertion. A Note on History and Methods", Med. Sci. in Sports, (1973), 5: 90.

67. Behnke, A.R., and Wilmore, J.H. Evaluation and Regulation of Body Build and Composition, Englewood Cliffs, Prentice-Hall, (1974), 21-24.

68. Wilmore, J.H. "A Simplified Method for the Determination of Residual Lung Volumes", J. Appl. Physiol., (1969), 27: 96.