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EXERCISE RESPONSE TO ACUTE AND CHRONIC BETA BLOCKADE
IN HEALTHY MALE SUBJECTS

by

Sarah Marie Jilka

A Thesis Submitted to the Faculty of the

DEPARTMENT OF EXERCISE AND SPORT SCIENCES

In Partial Fulfillment of the Requirements
For the Degree of

MASTER OF SCIENCE

In The Graduate College

THE UNIVERSITY OF ARIZONA

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LIST OF ABBREVIATIONS

Analysis of Variance	ANOVA
Arterial-venous oxygen difference	a-vO ₂ diff
Atenolol	At
Beat	b
Beta blockade	BB
Blood pressure	BP
Beta ₁	B ₁
Beta ₂	B ₂
Cardiac output	Q
Coronary artery disease	CAD
Day	d
Electrocardiogram	EKG
Heart rate	HR
Hour	h
Intravenous	i.v.
Kilogram	kg
Liter	l
Maximal	max
Mean arterial pressure	MAP
Metoprolol	Me
Mile per hour	mph
Milligram	mg
Milliliter	ml
Minute	min
Non-selective	NS
Oxygen consumption	VO ₂
Pindolol	Pi
Placebo	Pl
Propanolol	Pr
Rating of perceived exertion	RPE
Respiratory exchange ratio	RER
Second	s
Stroke volume	SV
Systolic blood pressure	SBP
Total peripheral resistance	TPR
Trained	TR
Untrained	UT
Ventilation	V _E
Week	wk

ABSTRACT

Conflicting data on the alterations in the exercise response to beta blockade (BB) may be the result of differences in the length of time the subject has been on treatment, i.e., hours vs. days. The purpose of this study was to examine exercise responses during acute and chronic administration of BB. Twenty-eight healthy males performed maximal treadmill exercise tests after 1 day and 9 days of 3 double-blind, randomized conditions: a placebo (Pl), propranolol (Pr) 80 mg bid, and atenolol (At) 100 mg daily. Maximal heart rate (HR), oxygen consumption (VO_2), ventilation (V_E), and treadmill time (TT) were significantly reduced by Pr and At after an acute and chronic dose when compared to Pl ($p < 0.05$) in both groups of subjects. An acute dose of Pr and At caused a greater decrease in maximal HR compared to chronic administration ($143.1 \pm 5.0 \text{ b min}^{-1}$ at day 1 vs. $147.7 \pm 4.2 \text{ b min}^{-1}$ at day 9). However, the overall exercise response was not effected by the change in HR in either the TR or UT subjects. These data indicate that there is no difference in exercise response to acute and chronic BB in young healthy males.

CHAPTER 1

INTRODUCTION

Beta-adrenergic blockers are used extensively in the treatment of hypertension, angina pectoris, migraine, and cardiac arrhythmia (16,59,60). More recently they have been recognized as a viable treatment for post-myocardial infarction patients resulting in a decrease in coronary artery disease (CAD) morbidity and mortality (3,45,53,56,58,75). The potential for combining beta blocker medication and exercise as therapeutic interventions in the treatment of CAD has provoked considerable interest in research to obtain a better understanding of the interaction of these two treatments.

The first beta-adrenergic blocker suitable for clinical investigation was introduced in the early 1960's by Black with the development of pronethalol (8). Because of a number of undesirable side-effects associated with pronethalol, despite its potential clinical value, Black developed propranolol (Pr), an adrenergic beta-receptor antagonist which was ten times more active and produced fewer side effects than pronethalol. The subsequent development of other types of beta blockers, such as those

which are primarily β_1 selective, and those with intrinsic sympathomimetic properties, has led to beta-adrenergic blockers as a general classification of drugs being one of the most widely prescribed medications for cardiovascular diseases.

The pharmacological nature of beta blockers, i.e., attenuation of sympathetic nervous system activity by way of competitive inhibition, provides an ideal physiological situation for examining the influence of sympathetic activity on exercise performance. In the research conducted using beta blockers some investigators (2,5,6,18,29,41, 43,53,63,67,68) have found that in healthy males, beta blockade (BB) reduces maximal oxygen uptake ($\dot{V}O_2$ max), and/or endurance time compared to placebo or control conditions. Other researchers (58,62,78) have found a significant decrease in maximal performance time with BB in healthy individuals, but no significant impairment in $\dot{V}O_2$ max. In contrast, Reybrouck et al. (57) and Maksud et al. (44) have demonstrated maintenance of $\dot{V}O_2$ max and endurance time in similar subject populations. Reybrouck et al. also found unimpaired exercise performance in cardiac patients. In fact, it has been documented that BB actually increases endurance time and $\dot{V}O_2$ max in symptomatic populations (23).

The question of whether one can achieve a trained state while beta blocked has also been raised, since

sympathetic activity, which is considered necessary for chronic adaptation to exercise training, is attenuated with BB. While conflicting data once caused considerable confusion, it is now generally accepted that a training effect in normals (19,49,59,79) and CAD patients (17) is possible while taking beta blockade medication.

There are several factors which most likely explain the differences in results between studies for both acute exercise and prolonged exercise training while under chronic beta blockade. Factors that could account for these discrepancies include: 1) the type of beta blocker used, e.g., β_1 selective vs. non-selective; 2) the dose administered; 3) the mode of exercise testing; 4) the population examined; 5) the interval of time between the last dose and the performance test e.g., 2 h vs. 8 h; and 6) an acute (24 hour or less) vs. a chronic dose (greater than 7d).

During acute exercise, both β_1 and β_2 (B_1 and B_2) receptors are involved in the cardiovascular changes that occur to increase cardiac output: increased heart rate (HR), increased blood pressure (BP), and increased stroke volume (SV). In addition, B_2 receptors are responsible for the increase in blood flow to active skeletal muscle and the mobilization of glucose from liver and skeletal muscle glycogen, while lipolysis is mediated by both B_1 and B_2

receptors (52). A cardio-selective beta blocking agent may have less severe effects on exercise performance when compared to a non-selective blocker due to the pharmacological nature of a non-selective blocker which acts on both B_1 and B_2 receptor sites (46). However, as the dose of a B_1 selective agent is increased, that specific agent begins to lose its B_1 specific properties, i.e., it begins to antagonize B_2 receptors (26).

The dose of beta blocker given the subject varies greatly from study to study. Several investigators have used doses which are much lower than the dose normally prescribed for clinical purposes. Also, there are differences between an intravenous administration compared to an oral administration of a beta blocking agent. For example, an oral dose of propranolol (Pr) activates a metabolite, 4-hydroxypropranolol, an event which does not occur with an intravenous administration (47). The exact effects of this metabolite are not known, but will add to those of oral Pr, resulting in a two-fold difference in plasma Pr concentration when compared to an equivalent dose administered intravenously (50).

The duration of BB-mediated physiological alterations depends on the half-life and the dose administered (46,50). A water soluble beta blocker such as At has a relatively long half-life of 7-20 h, while a lipid soluble blocker such

as Pr has a shorter half-life, 2-6 h (60). Because of the short half-life of Pr, it is necessary to dose twice-a-day, while At can be taken only once-a-day.

The testing mode used may also be a factor responsible for the disparity in the data reported on the maximal exercise response under BB. Hughson et al. (30) conducted a study comparing graded exercise testing on a treadmill to graded exercise testing on a cycle ergometer in 12 male subjects 2 h after medicating with 100 milligrams (mg) of metoprolol (Me). Following beta blockade, $\dot{V}O_2$ max was found to be significantly decreased during the cycle ergometer tests (7.2%), but not in the treadmill tests (3.6%) when using a one-way analysis of variance to compare each drug experiment to the placebo test. The investigators concluded that it may not be accurate to compare studies which use different testing modes. They also found that the differences in statistical techniques used to evaluate the results of various published studies could explain some of the differences found in the literature.

The population examined will also influence the results of exercise testing during BB. For example, highly trained individuals appear to be effected to a greater extent when compared to an aged-matched untrained population (80). Angina patients however, are able to work longer and more intensely if taking beta blocking medication (17).

The time interval between the last active dose and the initiation of exercise is also a consideration concerning the disparity in results. Folgering et al. (22) indicated that peak blood levels of BB occur 1.5 h after administration. Most investigations in the literature have been conducted using a 2-4 h interval between the last dose of BB and the starting time of the exercise test. However, Kaiser et al. (37) examined the effects of Pr and atenolol (At) on submaximal and maximal exercise performance in 11 men with systemic hypertension in relation to decreases in blood pressure. The subjects received a placebo, Pr, or At for 5 weeks prior to testing. The dosing protocol was designed to achieve similar reductions in blood pressure with both drugs. The subjects were exercise tested 8 h and 24 h after ingestion of the last dose. There were no differences in systolic and diastolic blood pressures and in the maximal work rates achieved (with either Pr or At) between the 8 h and the 24 h tests. Heart rate responses were greater at 24 h at higher work rates and 4 min and 10 min post exercise in the subjects taking At. Perceived exertion ratings were higher at 24 h compared to 8 h with all treatments. If testing was performed 2 h post medication however, different results may have been revealed, since peak blood levels of either drug occur before 8 h (21).

Another factor which could explain the conflicting data reported on the maximal exercise response under BB, is the duration of the medication period prior to exercise testing. Administration lengths of 1.5 h, 1 day (d), 1 week (wk), and 4 wk have all been used in the various studies reviewed. Smyth et al. (63) and van Baak et al. (72) examined the maximal exercise responses to short-term (h) vs. long-term (d) BB. Smyth et al. studied the exercise response of healthy subjects following 3 h, 1 wk, and 4 wk of medication with low doses of Pr or Me. Compared to the placebo, HR max was significantly reduced by BB at all time intervals, however, the differences between the three time intervals were not significant, i.e., the magnitude of change over time was not significant. $\dot{V}O_2$ max was significantly reduced with Pr at 1 wk and 4 wk and with Me at 1 wk only when compared to the placebo. There was not a significant reduction in $\dot{V}O_2$ max after the initial dose (3 h) with either Pr or Me. No statistically significant drug/time effects were seen in any of the variables measured, although after 4 wk of Me, $\dot{V}O_2$ max was decreased by 2.7% compared to 8.6% at 1 wk; the difference did not achieve statistical significance. The authors concluded that acute vs. chronic doses of BB did not result in significant changes in maximal exercise performance. However, with chronic oral administration Pr accumulates in the plasma (47,50), so the

effects seen after a 3 h dose are likely to be different from responses seen after several doses of Pr.

van Baak et al. (72) used intravenous doses of Me for the acute testing phase and a daily oral dose of slow-release Me over a 4 wk period of chronic administration. The investigators concluded that there were no significant changes in exercise performance between acute and chronic BB, and therefore, no adaptations to BB had developed. However, the results may be misleading in that the authors compared intravenous (acute) doses to 4 wk of administration of slow-release tablets. Peak plasma levels after oral administration of Me are approximately 50% of plasma levels following intravenous administration of Me (55).

The studies conducted by Smyth et al. (63) and van Baak et al. (72) found that the physiological responses to exercise following short-term administration of BB did not differ significantly from those following long-term administration. However, as mentioned above, the study designs in these particular investigations may not have been completely adequate for examining potential differences between acute and chronic administration of BB.

Statement of the Problem

Much research has been done examining the effects of beta blockade on maximal and submaximal exercise capacity in

normals, trained and untrained persons, and in coronary heart diseased patients. Also, the effects of beta-adrenergic blockade (BB) in combination with exercise training in normals and coronary patients has received much attention. However, a review of the literature reveals much variability and divergency in the results of the research examining (1) the acute effects of BB on the basic physiological responses to exercise and (2) chronic physiological adaptations resulting from training while medicated with beta blocking agents.

Purpose

A careful examination of the exercise responses to both short-term (acute) and long-term (chronic) BB with normal clinical doses is needed to determine if the disparity in the results from previous investigations can be at least partially explained by the differences in the length of time the subjects were on medication prior to exercise testing and also, if the type of subject population used may influence the results. Therefore, the purpose of this study was to examine the effects of acute (24 h) and chronic (9 d) administration of BB on submaximal and maximal exercise responses in two selected populations, highly trained and healthy untrained individuals, under two different beta blocking agents, non-selective Pr and B_1 selective At . It was hypothesized that physiological

adaptations to BB would occur within 9 d of blockade, significantly altering the exercise response when compared to 1 d administration. Furthermore, because highly conditioned individuals are closer to their genetic physiological limitations, the untrained subjects would experience more of an adaptation to BB, especially with the B_1 selective blocker. The importance of this study is two-fold. First, it will provide additional insight into possible factors that would explain the differences in results from previous studies which have examined beta blockade and submaximal and maximal exercise performance. Secondly, if a 24 h dose produces the same physiological alterations as a 9 d dose, future research projects could be completed with less time and money invested by reducing the medication period prior to testing.

CHAPTER 2

REVIEW OF THE LITERATURE

Characteristics of Adrenergic Receptors and Beta Blocking Drugs

Adrenergic receptors are involved in the regulation of many metabolic, pulmonary, and renal processes, and all functions of the cardiovascular system. There are two types of adrenergic receptors: alpha and beta. Each has two subtypes designated 1 and 2 (1). Beta₁ receptors are found predominately in cardiac tissue and in adipose tissue, and they have an equal affinity for the catecholamines epinephrine and norepinephrine (66). Increases in the rate and force of cardiac contractions are the result of decreased parasympathetic and augmented sympathetic nervous system activity due to the action of catecholamines at beta₁ receptor sites (46). Beta₂ receptors are located primarily in smooth and skeletal muscle, bronchial tissue, adipose tissue, and in the liver (46,66). There is now evidence that these receptors are also present in cardiac tissue (43). B₂ receptors have a greater affinity for epinephrine, although

norepinephrine is also an agonist. Stimulation of these receptors causes bronchodilation in the lung and relaxation of smooth muscle tissue, in addition to stimulation of skeletal muscle and liver glycogenolysis (43).

An agent which antagonizes catecholamine activity at a beta-adrenergic receptor site by way of competitive inhibition is commonly referred to as a beta blocker (51). A non-selective (NS) beta blocker is a pharmacological agent which attenuates both β_1 and β_2 responses, e.g., blockers such as Pr and pindolol (Pi) act on both cardiac and smooth muscle receptors. The antagonizing action of Pr decreases inotropic and chronotropic cardiac responses and decreases peripheral vascular dilation. Through its inhibition of norepinephrine adrenergic neurons (60), Pr exerts anti-hypertensive effects by a reduction of cardiac output ($\dot{Q}$) (74) and an attenuation of tonic sympathetic nerve outflow from vasomotor centers. In addition, a NS blocker inhibits hepatic and skeletal muscle glycogenolysis and possibly lipolysis in adipose tissue which may result in hypoglycemia during exercise (52). Because of the antagonism of bronchial dilation with Pr, this drug is considered undesirable for asthmatics (57).

Pr is lipid-soluble resulting in a short half-life which varies from 3 to 6 h. This makes it necessary to medicate twice a day. Peak effects are attained in 1.5-2 h

(57). Repeated dosing leads to a lower hepatic extraction rate. The consequential increase in the amount of the drug available to the systemic circulation can increase the half-life of Pr up to 6 h (48).

A selective beta blocker, such as At or Me, is an agent which acts predominately on B_1 receptors. This is not an absolute selectivity, but is relative to the dose administered, i.e., with higher doses a B_1 selective agent will begin to antagonize B_2 receptors (3,46). A B_1 selective blocker affects the sinoatrial node by increasing both sinus cycle length and sinus node recovery time, but does not affect the reflex mechanism of vagal tone withdrawal that is characteristic of bradycardia (55). Administration of a single dose of a B_1 selective blocker results in a decreased heart rate accompanied by a reduction in Q which is compensated for by an increase in total peripheral resistance (TPR), possibly due to sympathetic vasoconstriction activity (15). Continued administration reverses the increase in systemic vascular resistance which results in the desired hypotensive effect of beta blockade (73). Administered orally, At has a plasma half-life of 7 to 20 h due to its water-soluble nature (60). This allows once-a-day dosing. Peak plasma levels usually occur within 3 h (10).

Bioavailability and the duration of action of a pharmacological agent depend on the route of distribution, absorption, amount ingested, and individual variability (47). As mentioned above, the lipid-soluble characteristic of some beta blockers can result in removal of the drug by the liver during the transport phase from the gut to the systemic circulation resulting in a greater hepatic extraction and lower plasma levels (46). However, the half-life is proportional to the amount distributed and total drug clearance is unaffected by plasma binding. The absorption of Pr from the gastrointestinal tract following an oral dose is nearly complete, i.e., 100% compared to the absorption of At which has been reported to be 63% complete (10).

Physiological Responses to Exercise as Modified by Beta Adrenergic Blockade

Hemodynamic and metabolic adaptations to acute exercise include increases in HR, SV, $\dot{Q}$, $\dot{V}O_2$, systolic blood pressure (SBP), mean arterial pressure (MAP), and muscle blood flow. These adaptations occur in response to the increasing needs of the active muscle for oxygen and are mediated, in part, by increases in sympathetic outflow through the catecholamine neural and hormonal transmitters, norepinephrine and epinephrine (66).

The mediation of sympathetic activity via catecholamines during acute exercise is attenuated by BB, decreasing certain hemodynamic and metabolic adaptations to exercise (51). Generally there is a large decrease in HR and SBP at exercise of moderate intensity, with a corresponding increase in SV and arterial venous oxygen difference ($a-vO_2$ diff) to maintain VO_2 , and little or no change in ventilation (V_E) or diastolic blood pressure (4,11,12,18,53,55,77).

Responses to an acute bout of maximal exercise under beta-adrenergic blockade are quite variable across the investigations reported to date. All previous studies report marked decreases in maximal HR ranging from approximately 20 to 50 beats min^{-1} depending on the concentration of the drug at the beta receptor site (26). It has been reported that oral administration of Pr will decrease HR to a greater extent compared to intravenous administration at high work rates (65). Significant decreases in maximal Q usually accompany the reduction in heart rate (6,18,57).

The response of VO_2 to maximal exercise while under beta blockade varies considerably from study to study. Several investigators found significant reductions in peak oxygen consumption during maximal exercise (2,4,18,28,29,43,53). Others have reported minimal or no decrease in

oxygen consumption at maximal exercise (40,61,62,77,78), and it has been noted that BB increases exercise capacity in symptomatic populations, i.e., angina patients (11). Many investigations have found BB to decrease exercise endurance time and/or work capacity (2,18,21, 22,35,61,78). However, Maksud et al. (44), Reybrouck et al. (57), and Wilmore et al. (77) did not find a reduction in endurance time and all postulated that the compensatory mechanisms of SV and a- $\dot{V}O_2$ diff are increased enough to maintain $\dot{V}O_2$ max. van Baak (70) reviewed recent literature on BB and exercise and noted that there appeared to be a relationship between the degree of decrease in max HR and the reduction in maximal work capacity; if BB decreased HR greater than 20%, maximal working capacity achieved was significantly effected. McFarlane et al. (43) exercise tested 9 healthy subjects after 48 h of Pr administration (160 mg/d in 4 doses). Work increments were added either every 30 seconds (s) or every fourth minute (min) of cycle ergometer testing. The duration of work was 3 to 4 times longer with the latter protocol in both drug and non-drug trials. Exercise time was reduced by BB with both protocols, but to a greater extent in the 4 min tests, while peak work rate achieved was greater in the 30 s tests, although $\dot{V}O_2$ max was reduced to a greater extent with this protocol.

Several investigators have found maximal $\dot{V}_E$ ($\dot{V}_E$ max) to be reduced by BB (2,4,5,22,29,73,78), while others (61,68) found no reduction in $\dot{V}_E$ max. Wilmore et al. (78) investigated changes in exercise response to BB in 47 healthy male subjects before and after 7 d of either a placebo, Pr (160 mg/d), or At (100 mg/d) and found maximal $\dot{V}_E$ to be decreased by BB with no statistically significant difference between Pr and At, although $\dot{V}_E$ max was consistently lower with Pr. A later study from this laboratory using highly trained distance runners found $\dot{V}_E$ max to be attenuated by both drugs, but significantly more with Pr compared to At (4). Petersen et al. (54) studied 6 healthy males during steady state and progressive exercise cycle ergometer tests to examine the effects of intravenous Pr hydrochloride on ventilation and gas exchange responses to graded cycle ergometer tests. The investigators concluded that despite the 20% decrease in HR and a 15% reduction in $\dot{Q}$ at maximal exercise the ventilatory system was not affected by Pr and that changes in $\dot{V}O_2$ kinetics were due to the cardiovascular changes as a result of BB. Joyner et al. (32) postulated that Pr would have a more significant effect on the ventilatory response to exercise compared to the selective blocker At due to the attenuation of B_2 receptor-mediated bronchodilation in the lung by Pr. Fourteen trained male subjects were treadmill tested during

3 separate trials of placebo, Pr (160 mg/d) and At (100 mg/d). Tidal volume was significantly reduced at several steady state and maximal work rates during the Pr trial indicating the role of B_2 receptors as airway dilators during exercise.

Probable Reasons for the Variability in the Literature

The designs of these studies reviewed above varied considerably in the type and dose of the beta blocker, the test mode used, the initial health and fitness level of the subject population, and the duration of the medication period prior to testing, i.e., acute or chronic. Each of these factors or a combination of these could account for the differences in exercise response to BB found in the literature.

There appears to be a greater impairment of exercise endurance capacity with a non-selective beta blocker, possibly because of the metabolic, peripheral, circulatory, and ventilatory responses associated with B_2 receptors (46,52). The inhibition of muscle and liver glycogenolysis and free fatty acid metabolism, in addition to the decrease in skeletal muscle blood flow with a non-selective blocker, may be responsible for the greater reduction in exercise time and maximal work capacity achieved when the non-selective blocker Pr was administered vs. a selective blocker (6,24,41,43,80). Also, as mentioned above, a

non-selective blocker Pr was administered vs. a selective blocker (6,24,41,43,80). Also, as mentioned above, a non-selective blocker has a greater inhibitory effect on ventilation due to the attenuation of B_2 receptor-mediated bronchodilation. Non-selective and selective differences are also evident in training during BB. Wilmore et al. (79) endurance-trained 47 healthy males while BB and found that although $\dot{V}O_2$ max and total test time were improved despite BB, the subjects on At had significantly greater increases in these variables compared to Pr when tested on the drug. They also noted that exercise testing performed when the subjects were off the medication resulted in even greater increases in $\dot{V}O_2$ max and treadmill time in the subjects who were taking Pr. McLeod et al. (48) found an improvement in performance after 2 months of dynamic exercise training while on Pr (80 mg bid) or At (100 mg/d). However, the change was not significant in the subjects taking Pr until drug treatment had been discontinued.

The effects of varying drug dosages have also been examined. Hughson et al. (28) compared the effects of Pr (20, 40, 80, and 160 mg) to equivalent dosages of Me (25, 50, 100, and 200 mg) and to equivalent dosages of oxprenolol (20, 40, 80, and 160 mg) on the physiological responses to cycle ergometer testing. The greatest reduction in exercise HR occurred at the highest dose of each drug and $\dot{V}O_2$ max

between the dose administered and HR and $\dot{V}O_2$ max responses, but did not find significant differences between the equipotent doses of each drug. Sklar et al. (62) examined the effects of Me and Pr on treadmill exercise responses in healthy males. The tests were conducted 4 h after dosing with 40 mg qid with Pr, 80 mg qid Pr, 50 mg qid Me, or 100 mg qid Me for 48 h. Both doses of Pr and Me decreased exercise tachycardia, however, a three times greater plasma concentration of Me was required to produce effects equivalent to Pr, i.e., a Pr concentration of 100 ng/ml resulted in a 28% decrease in exercise tachycardia, while 350 ng/ml of Me were required to produce the same effect.

Initial physiological capabilities of the subjects can affect the outcome of a maximal exercise test during BB. Wilmore et al. (80) reviewed data from a series of investigations conducted in their laboratory and found that $\dot{V}O_2$ max was unaffected during BB in relatively untrained persons, while substantial decrements were noted in highly trained subjects. Anderson et al. (4) and Tesch et al. (67) used highly trained subjects and found significant decreases in $\dot{V}O_2$ max. It has been postulated that the maintenance of exercise capacity via SV and a- $\dot{V}O_2$ diff may not be possible during BB in these highly trained individuals who have already approached their innate physiological limitations by intense training, resulting in decreased

$\dot{V}O_2$ max (4,80). Kaiser et al. (35) found that individuals with a greater percentage of slow-twitch fibers in exercising muscle are more effected by BB. They tested 9 healthy male subjects and found performance to be impaired by 20-25% in subjects with predominantly slow-twitch fibers vs. a 5% decrease in subjects with a predominance of fast-twitch muscle fibers when all subjects were BB with Pr. Conversely, maximal exercise performance in patients with angina may improve with BB due to the decrease in frequency of effort angina episodes (17).

Acute vs. Chronic Dosing

Recently, two studies in the literature have compared exercise responses between acute and chronic dosing of beta blockade. Smyth et al. (63) compared maximal exercise responses 3 h post BB (50 mg bid Me or 40 mg bid Pr) to 1 wk and 4 wk of dosing with the same drugs in healthy subjects. Beta blockade significantly decreased maximal HR and $\dot{V}O_2$ max when compared to the placebo treatment, but the degree of reduction in HR (14-18%) did not significantly differ between the three time periods with either the Pr or the Me treatment. $\dot{V}O_2$ max was decreased by 3.8%, 6.3%, and 4.5% with the 3 h, 1 wk, and 4 wk dosing respectively with Pr compared to the placebo values, although the 3 h value while on Pr did not reach statistical significance. There was a somewhat different response in $\dot{V}O_2$ max with Me: an 0.8%

decrease after 3 h, an 8.6 % reduction after 1 wk and a 2.7% decrease after 4 wk of medication; only the 1 wk value was significantly different from the corresponding placebo value.

The duration of drug administration did not have a statistically significant effect on $\dot{V}O_2$ max, although there were substantial differences between the 3 h, 1 wk and 4 wk values with both drugs, i.e., $\dot{V}O_2$ max was attenuated to a greater extent at 1 wk compared to 3 h and 4 wk, which the authors did not find to be statistically significant. Heart rate, systolic blood pressure and cardiac output were significantly reduced with both Pr and Me compared to placebo during submaximal exercise. Submaximal $\dot{V}O_2$ was maintained, despite BB, by the compensatory action of increased stroke volume and a larger a- $\dot{V}O_2$ difference. No significant effects due to differences in drug duration were observed during submaximal exercise. The authors concluded that no significant differences between acute and chronic dosing of BB had occurred. The doses administered were about half the amount normally prescribed, which could have affected the results. This is illustrated by the lack of an expected decrease in resting systolic blood pressure 3 h after Pr dosing. Also, the sample size was small; 17 subjects were divided between four treatment conditions.

This could account for the lack of significance between 3 h, 1 wk, and 4 wk of beta blockade.

van Baak et al. (72) compared intravenous (i.v.) doses of Me with a 4 wk administration of slow-release Me tablets to examine exercise responses to varying degrees of blockade and duration of medication. A progressive exercise test to exhaustion was performed by ten healthy subjects on a cycle ergometer. For the acute trial an intravenous administration of 0.15 mg/kg body weight and 0.30 mg/kg body weight were given at the start of the maximal exercise test which was performed on a cycle ergometer. Maximal HR was reduced by 13% with the 0.15 mg/kg dose and by 23% with the 0.30 mg/kg dose. $\dot{V}O_2$ max and exercise capacity, defined as the maximal workload attained, were significantly decreased only following the high i.v. dose of Me (4.7% and 5.5% respectively) when compared to the acute placebo condition. For the chronic trial, 4 wk of daily administration of 200 mg of Me in slow-release tablets, HR max was significantly reduced by 25% (44 b min^{-1}), $\dot{V}O_2$ max by 6.0% and maximal work capacity was decreased by 6.6% when compared to the 4 wk placebo treatment. There were no significant differences in exercise response between the high i.v. dose and the chronic dose of Me. The investigators concluded that chronic dosing with a B_1 blocker did not result in significant physiological adaptations and that acute and

chronic effects of BB on maximal work capacity were the same if the degree of blockade as reflected by the reduction in HR max, was the same. However, as noted earlier, comparing an i.v. dose of beta blockade to oral tablets could have caused spurious results.

CHAPTER 3

METHODS

Twenty-eight young, healthy males volunteered for this study. Fourteen of the subjects were involved in a consistent cardiorespiratory training regimine and comprised the trained group (TR). The remaining fourteen subjects were not involved in any formal exercise program and comprised the untrained group (UT). The physical characteristics of both groups are described in Table 1. Age ranged from 20 to 34 years and the mean $\dot{V}O_2$ max was $65.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and $50.2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the TR and UT groups respectively.

Prior to initiating the study, each subject received a verbal and written explanation of the study and its risks and then signed a subject consent form (Appendix A). The study protocol had been previously approved by the University of Arizona's Human Subjects Committee. A brief personal history form was completed which included questions on health status and current physical activities. A physical examination was conducted by a physician on each subject prior to testing.

Table 1 SUBJECT CHARACTERISTICS

	<u>UNTRAINED</u>	<u>TRAINED</u>
AGE, years	22.4 $\pm$ 2.2	25.7 $\pm$ 3.3
HEIGHT, cm	173.3 $\pm$ 4.9	176.7 $\pm$ 6.9
WEIGHT, kg	69.4 $\pm$ 8.6	69.7 $\pm$ 6.3
BODY FAT, %	17.5 $\pm$ 4.2	9.6 $\pm$ 2.5
LEAN BODY WEIGHT,		
kg	57.1 $\pm$ 6.2	63.0 $\pm$ 5.3
INITIAL $\dot{V}O_2$ MAX,		
ml $\cdot$ kg ⁻¹ $\cdot$ min ⁻¹	50.2 $\pm$ 4.4	65.5 $\pm$ 5.3

All values are presented as mean $\pm$ standard deviation.

Each subject completed an initial maximal treadmill test (T_1) without medication. The purpose of this initial control test was to determine each subject's $\dot{V}O_2$ max from which a rate of work equivalent to 45%, 60% and 75% of $\dot{V}O_2$ max could be determined. UT subjects began at a speed of 3.5 mph, 0% grade. At the end of 4 min, speed was increased by 1 mph every 2 min throughout 12 min. At this point, speed remained constant at 7.5 mph and grade was increased to 2.5% and was increased by 2.5% at the end of each subsequent two minute period until volitional fatigue. The TR subjects' protocol was similar except the initial speed was 5.5 mph, at 0% grade, with speed increasing by 1 mph every 2 min throughout 12 min, at which time speed remained constant at 9.5 mph and the grade was increased to 3% for 2 min and was increased by 3% at the end of each subsequent two minute period until volitional fatigue. The UT subjects had a mean maximal treadmill time of 15.5 min compared to 16.3 min for the TR group during T_1 . Twelve-lead resting and exercise electrocardiograms (EKG) were included as part of the initial test. No significant abnormalities were identified.

The standard experimental protocol used during all subsequent treatment periods consisted of an incremental maximal exercise test on the treadmill starting with a 6 min steady state period at a work rate equivalent to 45% of each

subject's $\dot{V}O_2$ max as determined from T_1 . Two additional 4 min steady state periods followed at work intensities of 60% and 75% of $\dot{V}O_2$ max respectively. The duration of these work rates was selected to ensure that steady state $\dot{V}O_2$ was attained, allowing sufficient time to account for altered $\dot{V}O_2$ kinetics with BB, without thermoregulatory factors causing significant changes. These particular intensities were chosen to limit the test duration to 20 min or less and were based on the investigator's previous experiences with test duration during BB trials. After completion of the steady state portion of the test, the subjects then continued with the protocol established for the control test at the next highest workload, continuing until the point of volitional fatigue. Verbal encouragement provided the subjects with the motivation needed to push themselves to their physiological limits. However, one test on one subject was repeated at a later time after the investigator decided that maximal exertion was not reached, i.e., the test had been terminated prematurely.

The subsequent exercise tests were conducted following both 1 d and 9 d medication periods with a placebo (Pl), oral At, and oral Pr. Clinically equivalent doses of 100 and 160 mg/day for the At and Pr trials respectively were administered along with Pl in a randomized, double-blind manner to minimize subject or investigator

have been completely achieved, since some subjects, especially the TR subjects, noticed decreases in HR and had greater feelings of fatigue when training during BB trials. The tablets were provided to the subjects in two bottles marked "A" and "B" and were physically indistinguishable among the three treatment conditions, i.e., Pl, Pr, and At. A 12 h interval between doses was followed. One tablet was taken out of each bottle for the morning dose and only one tablet out of bottle "B" for the evening dose. This ensured that two active tablets of Pr would be taken daily, with an inert placebo tablet in bottle "B" for the At trial.

For each treatment period (see Table 2) subjects began medicating 24 h before their first scheduled treadmill test; thus a morning, an evening, and a second morning dose were administered prior to testing. Two active doses of Pr taken over a 24 h period allowed the saturation effect, characteristic of Pr (46), to be more of a factor in the physiological response to the exercise tests, as opposed to providing the initial active dose only 2 to 3 h prior to testing. On the designated test day each subject took his morning dose 3 h before his test to allow for peak blood levels of the respective drug to be obtained. After the first submaximal and maximal test for each treatment period, i.e., test A, medication was continued, starting with that evening's dose, for the next 7 days through the second

Table 2. TIME-LINE OF STUDY

WEEK 1	Maximal treadmill test: Control
WEEKS 2 & 3	Trial A
Day 1	Begin medication period with drug "A", morning and evening dose
Day 2	Maximal treadmill test, 3 h post-morning medication, continue medication with drug "A" evening dose
Day 3	morning and evening dose of drug "A", continue medication through day 8
Day 4	Drug "A"
Day 5	Drug "A"
Day 6	Drug "A"
Day 7	Drug "A"
Day 8	Drug "A"
Day 9	Maximal treadmill test, 3 h post-morning medication; end of trial A
5 DAY WASHOUT PERIOD	
WEEKS 4 & 5	Trial B: same protocol noted above with drug "B"
5 DAY WASHOUT PERIOD	
WEEKS 6 & 7	Trial C: same protocol noted above with drug "C"

All drugs were distributed in a double-blind, randomized manner on day 1 of each trial.

treadmill test, test B. The treatment period totaling 9 days, was defined in this study as chronic BB, while the 24 h period was defined as acute BB. To account for all medication, any unused tablets were returned to the investigator after each medication trial, when the subject reported to the laboratory for test B. Following 5 d of drug washout, to allow for complete bio-transformation of Pr and plasma clearance of At (60), the treatment/testing schedule was repeated until each subject had completed each of the three treatment conditions. The subjects' scheduled treadmill time during a 24 h day was consistent within 1.5 h across the treatment periods for the duration of the study to reduce potential diurnal effects.

Treadmill testing was conducted in the Exercise and Sport Sciences Laboratory at the University of Arizona. Each subject had been exposed to treadmill running at least one time before the first control test. A manually controlled, motor driven treadmill, Quinton model 24-72, was used for testing. Subjects breathed through a two-way non-rebreathing Hans Rudolph valve connected to a Daniels head gear apparatus. Expired air was collected in a 10 liter (l) mixing chamber. Oxygen and carbon dioxide analyzers, Applied Electrochemistry Inc., Models S-3AS and CD-3A respectively, were used to determine O_2 and CO_2 fractions of the expired air. Calibration was conducted

after each test with a gas mixture of 16.00% O_2 and 3.95% CO_2 which had been analyzed previously by the micro-Scholander technique. A Parkinson-Cowan dry gas meter was used to measure inspired gas volumes and breathing frequencies. Analog signals from the gas analyzers and gas meter were directed into a computer which had been programmed to calculate $\dot{V}_E$ ($l \cdot \text{min}^{-1}$ BTPS), $\dot{V}O_2$ ($l \cdot \text{min}^{-1}$ and $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), $\dot{V}CO_2$ ($l \cdot \text{min}^{-1}$) and respiratory exchange ratio (RER) every 15 s, from FEO_2 , $FECO_2$, and $\dot{V}_I$ (l) values. A heart rate was calculated from the ECG which was obtained from a Hewlett Packard EKG/Phono system strip recorder with a single lead (V_5) electrode placement for all tests except T_1 during which 12-lead recordings were obtained.

Ratings of perceived exertion (RPE) were taken at the end of each steady state work rate using Borg's 15-point scale (9). Three different ratings, legs, chest, and an overall rating, were given to obtain a more accurate representation of fatigue (14).

Body composition was determined on all subjects by the hydrostatic weighing technique, correcting for residual volume via the N_2 dilution technique (7). Subject height was also recorded.

Statistical procedures involved two-way analysis of variance (ANOVA) ($p < 0.05$) to determine 1) the interaction effect between each of the trials (1 d vs. 9 d) and the P1

vs drug treatments, and 2) an interaction effect between the two drugs. Although there were obvious differences between the drug and Pl treatments, the significance of the difference from 1 d to 9 d was used as the criterion of actual acute vs. chronic responses. Duncan post hoc tests were calculated to determine 1 d and 9 d differences between the three treatments (13).

CHAPTER 4

RESULTS

The physiological effects of acute and chronic BB during submaximal and maximal exercise are described below. The initial presentation of results concerns the UT and TR subjects' responses to exercise which are illustrated in tables 3 through 6, followed by the presentation of the data comparing the effects of acute and chronic BB.

Maximal Exercise Response: Drugs vs Placebo

Untrained

The results of the maximal exercise responses to acute and chronic BB in the UT subjects are presented in Table 3. When compared to the Pl trial, the HR max reached by the UT subjects was significantly decreased by 27% and 25% in the acute Pr and At trials respectively, and by 23% and 21% in the chronic Pr and At trials respectively. Pr treatment resulted in a significantly larger decrease in HR max by $4 \text{ b} \cdot \text{min}^{-1}$ compared to the At trial for both acute and chronic trials. $\dot{V}O_2$ max was significantly reduced by

Table 3 MAXIMAL EXERCISE RESPONSES - UNTRAINED SUBJECTS

VARIABLE	DAY	PLAC	PROP	ATEN
HR, b.min ⁻¹				
	1	196.0 $\pm$ 5.3	143.2 $\pm$ 8.2 ^{ab}	147.0 $\pm$ 8.8 ^a
	9	194.3 $\pm$ 6.3	149.0 $\pm$ 8.5 ^{ab}	152.9 $\pm$ 13.2 ^a *
$\dot{V}O_2$, ml.kg ⁻¹ .min ⁻¹				
	1	50.7 $\pm$ 4.7	45.7 $\pm$ 3.6 ^{ab}	47.1 $\pm$ 5.4 ^a
	9	51.7 $\pm$ 4.9	46.8 $\pm$ 5.4 ^{ab}	48.5 $\pm$ 4.5 ^a
RER				
	1	1.11 $\pm$ 0.03	1.09 $\pm$ 0.05 ^a	1.09 $\pm$ 0.06
	9	1.11 $\pm$ 0.04	1.09 $\pm$ 0.03	1.11 $\pm$ 0.05
$\dot{V}E$, l.min ⁻¹				
	1	133.9 $\pm$ 14.0	113.9 $\pm$ 14.9 ^{ab}	119.5 $\pm$ 18.7 ^a
	9	134.7 $\pm$ 16.3	116.8 $\pm$ 15.6 ^{ab}	124.1 $\pm$ 14.7 ^a
TOTAL TIME, min				
	1	20.3 $\pm$ 0.9	18.8 $\pm$ 1.3 ^{ab}	19.1 $\pm$ 1.2 ^a
	9	20.5 $\pm$ 1.1	19.2 $\pm$ 1.2 ^{ab}	19.7 $\pm$ 1.2 ^a

"a" Significantly different from placebo (Duncan post-hocs)

"b" Significantly different from atenolol (Duncan post-hocs)

* Significant trial/drug interaction ($p < 0.05$)

All values are recorded as mean and standard deviation ($\pm$) values.

5.0 and 4.9 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the acute and chronic Pr trials respectively, and by 3.6 and 3.2 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in the acute and chronic At trials, with Pr administration resulting in a significantly greater decrease compared to At.

Ventilatory responses to maximal exercise were significantly attenuated by both BB medications at 1 d and 9 d when compared to the Pl treatment. Pr caused a decrease of 20 $\text{l} \cdot \text{min}^{-1}$ at d 1 and 18 $\text{l} \cdot \text{min}^{-1}$ at d 9 which was significantly greater than the decreases with At: 14 $\text{l} \cdot \text{min}^{-1}$ and 11 $\text{l} \cdot \text{min}^{-1}$ for the acute and chronic At trials respectively. Total time on the treadmill was significantly longer in the Pl trial vs. the beta blockade trials i.e., 1.5 and 1.2 min (1 d), and 1.3 and 0.8 min (9 d) reductions in the Pr and At trials respectively. The decrease in treadmill time compared with Pl was significantly greater with Pr than At. Maximal RER was slightly decreased from 1.11 for both Pl trials to 1.09 in both Pr trials and in the 1 d At trial. The 9 d At value was 1.11.

Trained

The TR subjects' responses to maximal exercise are illustrated in Table 4. Maximal HR was significantly reduced from 39.8 to 51.8 $\text{b} \cdot \text{min}^{-1}$ during the acute and chronic beta blocked trials compared to the Pl trials. The 1 d reduction was 28% with Pr and 22% with At. The

Table 4 MAXIMAL EXERCISE RESPONSES - TRAINED SUBJECTS

VARIABLE	DAY	PLAC	PROP	ATEN
<hr/>				
HR, b·min ⁻¹				
	1	187.9 $\pm$ 5.7	136.1 $\pm$ 8.1 ^{ab}	146.3 $\pm$ 11.2 ^a *
	9	186.1 $\pm$ 7.1	142.9 $\pm$ 9.7 ^{ab}	146.3 $\pm$ 11.3 ^a
$\dot{V}O_2$, ml·kg ⁻¹ ·min ⁻¹				
	1	64.7 $\pm$ 4.5	56.5 $\pm$ 3.3 ^{ab}	59.4 $\pm$ 4.2 ^a
	9	64.6 $\pm$ 4.2	57.9 $\pm$ 3.5 ^{ab}	60.3 $\pm$ 4.9 ^a
RER				
	1	1.11 $\pm$ 0.05	1.07 $\pm$ 0.03 ^{ab}	1.10 $\pm$ 0.03
	9	1.11 $\pm$ 0.04	1.07 $\pm$ 0.06 ^a	1.09 $\pm$ 0.05 ^a
$\dot{V}_E$, l·min ⁻¹				
	1	151.3 $\pm$ 10.1	131.3 $\pm$ 11.5 ^{ab}	142.9 $\pm$ 8.7 ^a
	9	151.9 $\pm$ 11.0	132.1 $\pm$ 12.9 ^{ab}	141.9 $\pm$ 14.1 ^a
TOTAL TIME, min				
	1	19.6 $\pm$ 1.1	17.7 $\pm$ 1.3 ^{ab}	18.4 $\pm$ 1.1 ^a
	9	19.7 $\pm$ 1.1	18.1 $\pm$ 1.3 ^{ab}	18.7 $\pm$ 1.3 ^a

"a" Significantly different from placebo (Duncan post-hocs)

"b" Significantly different from atenolol (Duncan post-hocs)

* Significant trial/drug interaction (p<0.05)

All values are recorded as mean and standard deviation ($\pm$) values.

decrease after 9 d was 23% and 21% with Pr and At respectively. The reduction was significantly greater during the Pr trials. A similar trend was seen in the $\dot{V}O_2$ response to maximal exercise under BB. Pr caused a decrease of 8.2 and 6.7 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 1 d and 9 d trials respectively and At a decrease of 5.3 and 4.3 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 1 d and 9 d respectively when compared to the Pl treatment. A significantly greater decrease was seen with the Pr treatment compared to At.

$\dot{V}_E$ max was attenuated by approximately 20 $\text{l} \cdot \text{min}^{-1}$ in both Pr trials and by 8.4 (1 d) and 10.0 (9 d) $\text{l} \cdot \text{min}^{-1}$ with At compared to the Pl treatment, with Pr producing a significantly greater attenuation. The treadmill endurance time was 19.6 and 19.7 min for the 1 d and 9 d Pl treatments respectively. The Pr test demonstrated the most significant decrease of 1.9 and 1.6 min for the 1 d and 9 d trials respectively. At also decreased treadmill time by 1.2 and 1.0 min in the 1 d and 9 d trials respectively. Maximal RER in the two Pl trials attained values of 1.11 which were significantly higher than the values of 1.07 for both Pr trials. The 9 d At RER value of 1.09 was also significantly lower than the Pl value, but not the 1 d RER of 1.10.

Submaximal Exercise Response: Drugs vs Placebo

Untrained

Responses to submaximal exercise in the UT subjects are illustrated in Table 5. At a work rate equivalent to 45% of each subject's $\dot{V}O_2$ max, HR and $\dot{V}O_2$ responses were decreased equally by both Pr and At when compared to the Pl treatment ($p < 0.05$). The decrease in HR ranged from 24 b. $\cdot$ min⁻¹ at 1 d to 29 b. $\cdot$ min⁻¹ at 9 d with both drugs. $\dot{V}O_2$ at this relative work rate was only slightly attenuated during BB by 0.8 to 1.1 ml. $\cdot$ kg⁻¹.min⁻¹. Statistically significant reductions in HR and $\dot{V}O_2$ were also observed at both 60% and 75% of $\dot{V}O_2$ max. HR was decreased by approximately 38 b. $\cdot$ min⁻¹ with both Pr and At at 1 d and by approximately 32 b. $\cdot$ min⁻¹ at the 9 d trials for the 60% rate of work, while $\dot{V}O_2$ was attenuated during BB by 1.3 to 1.6 ml. $\cdot$ kg⁻¹.min⁻¹. At 75% of $\dot{V}O_2$ max HR was decreased by approximately 27% with BB (45.6 b. $\cdot$ min⁻¹ with Pr and 46.4 b. $\cdot$ min⁻¹ with At) at 1 d. There was less of a reduction in submaximal HR during BB at 9 d: approximately 24% (39.8 b. $\cdot$ min⁻¹ with Pr and 40.5 b. $\cdot$ min⁻¹ with At). $\dot{V}O_2$ was reduced by 4.1% (1.6 ml. $\cdot$ kg⁻¹.min⁻¹) with both drugs at 1 d and by 3.6% (1.4 ml. $\cdot$ kg⁻¹.min⁻¹) at 9 d with both Pr and At.

Ventilation was reduced during steady state exercise under BB, with the largest reductions occurring at the higher intensities. Differences in response to Pr and At were seen

Table 5 SUBMAXIMAL EXERCISE RESPONSES - UNTRAINED SUBJECTS

VARIABLE	DAY	PLAC	PROP	ATEN
<u>45%</u>				
HR, b.min ⁻¹	1	123.1 $\pm$ 12.8	94.2 $\pm$ 9.4 ^a	94.1 $\pm$ 8.6 ^a
	9	117.9 $\pm$ 10.5	93.7 $\pm$ 11.4 ^a	93.9 $\pm$ 9.6 ^a
$\dot{V}O_2$, ml.kg ⁻¹ .min ⁻¹				
	1	22.5 $\pm$ 5.1	21.4 $\pm$ 5.3 ^a	21.7 $\pm$ 5.1 ^a
	9	22.2 $\pm$ 4.3	21.4 $\pm$ 5.1 ^a	21.4 $\pm$ 4.4 ^a
RER				
	1	0.89 $\pm$ 0.05	0.89 $\pm$ 0.07	0.88 $\pm$ 0.05
	9	0.87 $\pm$ 0.05	0.89 $\pm$ 0.05 ^a	0.89 $\pm$ 0.05 ^a
$\dot{V}_E$, l.min ⁻¹				
	1	42.2 $\pm$ 0.5	39.7 $\pm$ 10.8 ^a	40.0 $\pm$ 9.5 ^a
	9	40.5 $\pm$ 8.7	39.7 $\pm$ 9.7	39.1 $\pm$ 8.6 ^a
RPE LEGS				
	1	7.3 $\pm$ 1.3	7.2 $\pm$ 0.9 ^b	7.6 $\pm$ 1.1
	9	7.4 $\pm$ 1.3	7.3 $\pm$ 1.1 ^b	7.6 $\pm$ 1.1
RPE CHEST				
	1	7.2 $\pm$ 1.3	7.1 $\pm$ 1.0 ^b	7.4 $\pm$ 1.1
	9	7.3 $\pm$ 1.3	7.1 $\pm$ 1.3	7.3 $\pm$ 1.1
RPE OVERALL				
	1	7.2 $\pm$ 1.3	7.1 $\pm$ 0.9 ^b	7.4 $\pm$ 1.1
	9	7.4 $\pm$ 1.2	7.1 $\pm$ 1.3 ^a	7.3 $\pm$ 1.1
<u>60%</u>				
HR, b.min ⁻¹	1	151.7 $\pm$ 11.7	113.7 $\pm$ 7.1 ^a	113.3 $\pm$ 6.5 ^a
	9	146.1 $\pm$ 10.3	113.9 $\pm$ 8.7 ^a	114.9 $\pm$ 11.7 ^a
$\dot{V}O_2$, ml.kg ⁻¹ .min ⁻¹				
	1	32.6 $\pm$ 3.3	31.1 $\pm$ 3.3 ^a	31.3 $\pm$ 3.6 ^a
	9	32.5 $\pm$ 3.3	31.1 $\pm$ 3.8 ^a	30.9 $\pm$ 3.3 ^a
RER				
	1	0.91 $\pm$ 0.06	0.92 $\pm$ 0.05	0.92 $\pm$ 0.04
	9	0.91 $\pm$ 0.03	0.92 $\pm$ 0.02 ^a	0.92 $\pm$ 0.03

$\dot{V}_E$, l·min ⁻¹				
	1	61.5 $\pm$ 8.9	58.4 $\pm$ 9.9 ^a	59.3 $\pm$ 9.8 ^a
	9	59.1 $\pm$ 7.5	58.4 $\pm$ 9.5 ^{ab}	57.0 $\pm$ 7.9 ^a
RPE LEGS				
	1	10.3 $\pm$ 1.2	9.8 $\pm$ 1.4 ^{ab}	10.1 $\pm$ 1.1
	9	10.9 $\pm$ 1.5	9.9 $\pm$ 1.9 ^{ab}	10.8 $\pm$ 1.5
RPE CHEST				
	1	10.1 $\pm$ 1.5	10.3 $\pm$ 1.7 ^a	9.9 $\pm$ 1.8
	9	10.6 $\pm$ 1.5	9.9 $\pm$ 1.5 ^a	10.3 $\pm$ 1.6
RPE OVERALL				
	1	10.1 $\pm$ 1.3	10.2 $\pm$ 1.5 ^a	10.1 $\pm$ 1.5
	9	10.6 $\pm$ 1.7	10.0 $\pm$ 1.6 ^a	10.5 $\pm$ 1.9
$\frac{75\%}{HR}$, b·min ⁻¹				
	1	171.7 $\pm$ 8.1	126.1 $\pm$ 6.5 ^a	125.3 $\pm$ 6.7 ^a
	9	168.1 $\pm$ 6.7	128.3 $\pm$ 7.3 ^a	127.6 $\pm$ 13.7 ^a
$\dot{V}O_2$, ml·kg ⁻¹ ·min ⁻¹				
	1	38.9 $\pm$ 2.5	37.3 $\pm$ 2.3 ^a	37.3 $\pm$ 3.0 ^a
	9	38.7 $\pm$ 2.3	37.3 $\pm$ 2.8 ^a	37.3 $\pm$ 2.7 ^a
RER				
	1	0.96 $\pm$ 0.03	0.97 $\pm$ 0.03 ^a	0.97 $\pm$ 0.04 ^a
	9	0.95 $\pm$ 0.03	0.97 $\pm$ 0.03 ^a	0.97 $\pm$ 0.04 ^a
$\dot{V}_E$, l·min ⁻¹				
	1	79.1 $\pm$ 8.1	74.7 $\pm$ 7.4 ^{ab}	76.1 $\pm$ 5.9 ^a
	9	76.3 $\pm$ 7.7	73.4 $\pm$ 8.9 ^{ab}	74.0 $\pm$ 7.5 ^a
RPE LEGS				
	1	13.2 $\pm$ 1.1	13.1 $\pm$ 1.7 ^b	13.7 $\pm$ 1.2
	9	13.4 $\pm$ 1.3	13.1 $\pm$ 1.6	13.3 $\pm$ 1.3
RPE CHEST				
	1	13.1 $\pm$ 1.5	14.4 $\pm$ 1.7 ^{ab}	13.8 $\pm$ 1.5 ^a
	9	13.2 $\pm$ 1.1	13.3 $\pm$ 1.6	13.6 $\pm$ 1.5
RPE OVERALL				
	1	13.1 $\pm$ 1.5	14.3 $\pm$ 1.7 ^a	13.9 $\pm$ 1.5 ^a
	9	13.3 $\pm$ 1.1	13.4 $\pm$ 1.6	13.7 $\pm$ 1.5

"a" Significantly different from placebo (Duncan post-hocs)

"b" Significantly different from atenolol (Duncan post-hocs)

* Significant trial/drug interaction (p<0.05)

All values are recorded as mean and standard deviation ($\pm$).

only at 60% at the 9 d trial and at 75% during the 1 d trial. During all other trials, with the exception of the 9 d response at 45%, all Pr and At values were significantly decreased when compared to the Pl treatment. Minimal increases of 0.01 to 0.02 in RER with BB were found at all steady state levels.

Local (leg), central, (chest), and overall sensations of effort were measured by perceived exertion ratings from the Borg scale (see Methods). There was an increase of approximately three rating scale points with each increment in rate of work, i.e., 7 points at 45% to 10 points at 60% to 13 points at 75% for each treatment at 1 d and 9 d. There was little consistency in the drug vs. Pl interactions across the three steady state workloads, with subjects tending to rate their sense of effort lower while on Pr during the 45% and 60% intensities, yet higher at the highest intensity on 1 d. At tracked Pl very closely across all three rates of work.

Trained

The changes in submaximal treadmill exercise responses to BB compared to Pl are presented in Table 6. The TR subjects showed a trend similar to the UT subjects in HR response to steady state exercise during BB. All Pr and At trials values were significantly attenuated compared to the Pl treatment at all three rates of work at both 1 d and 9 d.

Table 6 SUBMAXIMAL EXERCISE RESPONSES - TRAINED SUBJECTS

VARIABLE	DAY	PLAC	PROP	ATEN	
<u>45%</u>					
HR, b.min ⁻¹	1	111.6 ±16.7	86.3 ±7.8 ^a	86.9 ±9.0 ^a	
	9	110.6 ±16.3	85.7 ±8.5 ^a	85.6 ±9.9 ^a	
$\dot{V}O_2$, ml.kg ⁻¹ .min ⁻¹	1	26.6 ±6.3	25.3 ±5.6 ^a	25.5 ±5.9 ^a	
	9	26.3 ±5.6	25.0 ±5.8 ^a	25.5 ±5.9 ^a	
RER	1	0.85 ±0.05	0.86 ±0.04	0.87 ±0.03	
	9	0.86 ±0.09	0.86 ±0.05	0.86 ±0.04	
$\dot{V}_E$, l.min ⁻¹	1	47.7 ±11.7	44.7 ±11.6 ^a	45.1 ±12.3 ^a	
	9	47.5 ±12.9	44.1 ±11.8 ^a	44.9 ±11.0 ^a	
RPE LEGS	1	7.1 ±1.0	7.8 ±1.4 ^a	7.8 ±1.3 ^a	*
	9	7.5 ±1.7	7.4 ±1.3	7.6 ±1.6	
RPE CHEST	1	6.9 ±0.9	8.1 ±1.2 ^{ab}	7.7 ±1.2 ^a	*
	9	7.4 ±1.9	7.5 ±1.0	7.7 ±1.4	
RPE OVERALL	1	7.0 ±1.0	8.0 ±1.4 ^{ab}	7.7 ±1.6 ^a	*
	9	7.4 ±1.6	7.4 ±1.1 ^b	7.8 ±1.6 ^a	
<u>60%</u>					
HR, b.min ⁻¹	1	138.7 ±10.9	106.2 ±3.6 ^a	105.4 ±4.9 ^a	
	9	136.4 ±10.7	104.9 ±4.9 ^a	104.3 ±5.5 ^a	
$\dot{V}O_2$, ml.kg ⁻¹ .min ⁻¹	1	38.3 ±3.9	36.3 ±3.3 ^a	36.6 ±3.5 ^a	
	9	38.9 ±3.5	36.9 ±3.3 ^a	36.8 ±3.5 ^a	
RER	1	0.87 ±0.04	0.88 ±0.03 ^b	0.89 ±0.03 ^a	
	9	0.86 ±0.04	0.88 ±0.05 ^{ab}	0.89 ±0.04 ^a	

$\dot{V}_E$, l.min ⁻¹				
	1	68.5 $\pm$ 8.8	64.8 $\pm$ 8.5 ^a	64.6 $\pm$ 9.3 ^a
	9	68.5 $\pm$ 11.5	64.4 $\pm$ 8.6 ^a	65.1 $\pm$ 9.1 ^a
RPE LEGS				
	1	9.9 $\pm$ 1.7	10.8 $\pm$ 1.7 ^a	10.6 $\pm$ 1.3 ^a
	9	10.0 $\pm$ 1.9	10.5 $\pm$ 1.8 ^a	10.8 $\pm$ 1.7 ^a
RPE CHEST				
	1	9.9 $\pm$ 1.3	11.1 $\pm$ 1.8 ^a	11.1 $\pm$ 1.5 ^a
	9	10.1 $\pm$ 1.7	10.6 $\pm$ 1.7 ^b	11.1 $\pm$ 1.5 ^a
RPE OVERALL				
	1	9.9 $\pm$ 1.4	11.2 $\pm$ 1.7 ^a	11.0 $\pm$ 1.7 ^a
	9	10.1 $\pm$ 1.7	10.5 $\pm$ 1.7 ^b	11.0 $\pm$ 1.8 ^a
$\frac{75\%}{HR}$, b.min ⁻¹				
	1	163.3 $\pm$ 10.1	120.8 $\pm$ 4.1 ^a	120.9 $\pm$ 5.7 ^a
	9	159.8 $\pm$ 9.6	121.4 $\pm$ 4.9 ^a	120.9 $\pm$ 6.9 ^a
$\dot{V}O_2$, ml.kg ⁻¹ .min ⁻¹				
	1	49.3 $\pm$ 5.1	46.6 $\pm$ 3.9 ^a	46.7 $\pm$ 4.3 ^a
	9	49.7 $\pm$ 4.5	47.4 $\pm$ 4.2 ^a	47.7 $\pm$ 4.5 ^a
RER				
	1	0.93 $\pm$ 0.05	0.96 $\pm$ 0.04 ^a	0.98 $\pm$ 0.03 ^a
	9	0.93 $\pm$ 0.05	0.95 $\pm$ 0.05 ^a	0.97 $\pm$ 0.04 ^a
$\dot{V}_E$ l.min ⁻¹				
	1	96.1 $\pm$ 15.5	93.2 $\pm$ 13.9 ^a	94.6 $\pm$ 13.7
	9	95.5 $\pm$ 15.9	93.7 $\pm$ 13.0	94.7 $\pm$ 15.1
RPE LEGS				
	1	13.4 $\pm$ 1.6	14.3 $\pm$ 2.6 ^a	14.1 $\pm$ 2.1 ^a
	9	13.5 $\pm$ 1.7	14.4 $\pm$ 1.9 ^a	14.1 $\pm$ 1.5 ^a
RPE CHEST				
	1	13.6 $\pm$ 1.4	14.5 $\pm$ 2.7 ^{ab}	15.0 $\pm$ 2.0 ^a
	9	13.7 $\pm$ 1.6	14.6 $\pm$ 1.8 ^a	14.7 $\pm$ 1.9 ^a
RPE OVERALL				
	1	13.5 $\pm$ 1.3	14.5 $\pm$ 2.5 ^a	14.7 $\pm$ 1.8 ^a
	9	13.7 $\pm$ 1.8	14.7 $\pm$ 1.9 ^a	14.5 $\pm$ 1.8 ^a

"a" Significantly different from placebo (Duncan post-hocs)

"b" Significantly different from atenolol (Duncan post-hocs)

* Significant trial/drug interaction (p<0.05)

All values are recorded as mean and standard deviation ($\pm$).

HR decreased by approximately 25 $\text{b} \cdot \text{min}^{-1}$ at 45%, 32 $\text{b} \cdot \text{min}^{-1}$ at 60%, and 38 to 42 $\text{b} \cdot \text{min}^{-1}$ at 75% of $\dot{V}\text{O}_2$ max, with both drugs giving equivalent responses. Submaximal $\dot{V}\text{O}_2$ was also decreased as a result of beta blockade when compared to the Pl treatment: 0.8 to 1.3 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at 45%, 1.7 to 2.1 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at 60%, and 2.0 to 2.7 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at 75% of $\dot{V}\text{O}_2$ max, with both drugs giving nearly equivalent responses.

The ventilatory responses to submaximal exercise were significantly and equally decreased by both Pr and At at 45% (approximately 3 $\text{l} \cdot \text{min}^{-1}$ or 6%) and at 60% (approximately 4 $\text{l} \cdot \text{min}^{-1}$ or 5.5%). The smallest decreases were seen at 75% of $\dot{V}\text{O}_2$ max (1 to 3 $\text{l} \cdot \text{min}^{-1}$ or an average of 2%). RER values were increased by BB at 60% and 75% when compared to Pl. The increase was greatest at 75%, 0.96 with Pr and 0.98 with At at 1 d and 0.95 and 0.97 with Pr and At respectively at 9 d. The Pl value for both days was 0.93.

RPE values at all sites were, with few exceptions, higher during BB. Drug differences were minimal. However, there was a trend for Pr values to be greater at 1 d and At ratings higher at 9 d at the 45% and 60% work rates.

Acute (1 day) vs Chronic (9 days) Beta Blockade

The effects of BB on exercise performance found in this investigation are consistent with the data presented in the literature to date, despite the variability among these

investigations. A closer examination was desired to note if the differences between BB and P1 changed after 9 days of medication. A two-way analysis of variance was performed which permitted examination of the interaction effect of each treatment to the acute and chronic medication periods. The HR response to BB during high intensity treadmill exercise was the only variable which was consistently and significantly affected by the treatment and dose-duration interaction. In both UT and TR subjects, the maximal HR response was less attenuated after 9 d of BB compared to the P1 responses which showed no changes over 9 days.

At maximal exercise, the UT subjects' HR response after 9 days of medication increased by 5.8 and 5.9 $\text{b} \cdot \text{min}^{-1}$ above the 1 d response in the Pr and At trials respectively. At the 75% workload the increase was approximately 2.2 $\text{b} \cdot \text{min}^{-1}$ with both drugs, although HR for P1 had decreased by 3.6 $\text{b} \cdot \text{min}^{-1}$ from the first to the ninth day.

The same trend was seen in the TR subjects, but with the Pr treatment only. Maximal HR response was 136.1 $\text{b} \cdot \text{min}^{-1}$ after 1 d and 142.9 $\text{b} \cdot \text{min}^{-1}$ after 9 d of Pr compared to 146.3 $\text{b} \cdot \text{min}^{-1}$ for both At trials. At 75%, the HR for both 1 d and 9 d At trials was 120.9 $\text{b} \cdot \text{min}^{-1}$, while the 9 d Pr trial HR increased by 4.1 $\text{b} \cdot \text{min}^{-1}$ over 1 d. However, the 9 d P1 response was 3.5 $\text{b} \cdot \text{min}^{-1}$ lower than

the 1 d Pl value which may be responsible for the statistical significance achieved.

Local, central, and overall ratings of perceived exertion at 45% in the TR subjects, showed a significant difference between the acute and chronic dose with each treatment. This appears not to be a drug related phenomenon since Pl ratings showed great variation between days and in some cases were actually higher than ratings given with the drug treatments. Pl ratings at all three sites were higher after 9 d of treatment. Also, with the exception of the 9 d overall rating with At, sensation of effort while beta blocked was perceived to be greater at 1 d. These two factors can explain the statistically significant interaction of treatment/duration.

No other variable exhibited statistically significant treatment/duration effects. However, in both groups of subjects $\dot{V}O_2$ max, $\dot{V}_E$ max and exercise endurance time showed a trend towards slight interaction effects, that is, less attenuation in exercise response after 9 d.

CHAPTER 5

DISCUSSION

The classic exercise heart rate response to BB was seen in both groups of subjects with both a selective and a non-selective blocker at all steady state and maximal work rates. Decreases in both groups of subjects ranged from 25 $\text{b} \cdot \text{min}^{-1}$ at 45% to 42 $\text{b} \cdot \text{min}^{-1}$ at the 75% work rate; Pr and At eliciting similar responses. Maximal HR was decreased by approximately 40 to 50 $\text{b} \cdot \text{min}^{-1}$, Pr resulting in a significantly larger reduction. These results are consistent with those reported in the literature (4,18,43,79).

A significant decrease was found in $\dot{V}\text{O}_2$ at all submaximal workloads. Previous investigations have reported conflicting results on the submaximal $\dot{V}\text{O}_2$ response during BB. Some investigators (53,68,69) found decreases, while others (18,29,54,77) found no change or only minimal differences in steady state $\dot{V}\text{O}_2$. Wilmore et al. (77) suggested that maintenance of $\dot{Q}$ via increases in SV allowed maintenance of $\dot{V}\text{O}_2$ during submaximal exercise with BB. Epstein et al. (18) and McFarlane et al. (43) also found

compensatory increases in SV and a-vO₂ diff. Conversely, Tesch et al. (68), found a decrease in submaximal $\dot{V}O_2$ with BB, which the authors suggested was due to improved metabolic efficiency as noted by the increase in RER values during the BB trials. The increase in the utilization of glycolytic precursors may have resulted in a reduced oxygen demand in the exercising muscle.

The ventilatory response to submaximal treadmill exercise was slightly reduced with BB. There was no consistent trend between Pr and At or between TR and UT subjects with regard to $\dot{V}_E$ attenuation. Several investigators (4,29,42,54,61,68,72) have found the ventilatory response to steady state exercise unchanged during beta blockade. Petersen et al. (54) noted that while the ventilatory response to exercise was not decreased, infused Pr resulted in a slowing of the $\dot{V}O_2$ and $\dot{V}_E$ kinetics, as evidenced by a longer time to reach steady state HR and a reduced $\dot{Q}$ response. Anderson et al. (4) indicated that maintenance of $\dot{V}_E$ may be the result of using a submaximal work rate below the subjects' anaerobic threshold.

Submaximal RER values during BB were greater compared with Pl values; statistical significance was achieved at the higher workloads with both Pr and At in TR and UT subjects. Anderson et al. (4) postulated that higher steady state RER values with BB could be a consequence, in part, of an

increased carbohydrate utilization by the working muscles due to limited free fatty acid uptake, as a result of the inhibition of lipolysis by BB. Karlsson et al. (38) reported similar results. Although statistical significance was achieved in only a few instances, At trials had higher RER values vs. Pr which would support this hypothesis, since lipolysis is predominantly mediated by B_1 receptors (37).

Submaximal RPE values consistently increased by 3 perceived exertion rating points with each increase in work rate with all three treatments at both 1 d and 9 d. The highly trained subjects reported greater feelings of fatigue during BB compared to the UT subjects at the same relative rate of work. Karlsson et al. (39) looked at local and central perceptions of fatigue during BB in alpine skiers. The skiers performed submaximal exercise on a course designed to test skill and technical ability. No significant difference in perceived exertion ratings was found in Pr, At or a placebo treatment. Tesch et al. (67) examined the effects of 80 mg Pr taken 2 h prior to submaximal and maximal cycle ergometer tests. Local (leg fatigue) and central (cardiorespiratory effort) ratings of perceived exertion were recorded. The local RPE was found to be significantly higher than the central RPE at both submaximal and maximal work rates following BB, compared to an unblocked state. The investigators also found positive

correlations between individual changes in submaximal $\dot{V}O_2$ and local and central RPE changes. This is in agreement with a study by Banks et al. (6). It is not certain why there are inconsistencies in RPE values between investigations. Several non-physiological factors can influence RPE such as, time of day, sleep deprivation, psychological mood, age, sex, environment, or the nature of the test (14) which may explain the discrepancies noted above.

$\dot{V}O_2$ max was attenuated with BB, more so by Pr than At ($p < 0.05$). In the UT subjects an approximate 10% decrease in $\dot{V}O_2$ max was seen with Pr and a 7% reduction with At was for both acute and chronic doses. Larger decreases of 13% and 10% with acute and chronic doses of Pr respectively, and 9% and 7% attenuation with the At doses respectively were found in the TR individuals. Other investigators (5,11,18,30,43,67,77) have reported similar findings. However, some investigators have not found significant reductions, but maintenance of $\dot{V}O_2$ max with BB (25,44,57,78). Reybrouck et al. (57) attributed maintenance of $\dot{V}O_2$ max to increases in SV and a- $\dot{V}O_2$ diff, despite the large decrease in HR max. In the present study, the percentage decrease in HR was greater than the percentage decrease in the $\dot{V}O_2$ response to maximal exercise under

beta blockade when compared to the Pl treatment, suggesting partial compensatory adaptations.

The decrease in $\dot{V}O_2$ max may have been a result of, in part, the decrease in $\dot{V}_E$ max. Maximal $\dot{V}_E$ was significantly decreased by Pr and At in both TR and UT subjects with acute and chronic doses. Other investigators have found similar results (5,29,43,77). However, others have reported no change in the ventilatory response to maximal exercise during BB (61,62). Although not statistically significant, there was a trend toward less attenuation after 9 d compared to 1 d for both Pr and At treatments in the UT subjects; there was an approximate $3-4 \text{ l} \cdot \text{min}^{-1}$ increase in the $\dot{V}_E$ response after chronic dosing compared to acute dosing of BB, while the TR subjects did not show this trend. There was a significant difference in maximal ventilatory responses between the two drugs. Pr resulted in significantly greater decreases in ventilation in both groups during both the acute and chronic trials, which was not evident until maximal exercise capacity was reached. The attenuation of B_2 receptor-mediated bronchodilation provides a possible explanation for the differences found between the two drugs, as recently proposed by Joyner et al. (32).

The reduction of maximal RER values with BB found in this investigation, from 1.11 with the Pl treatment to 1.07

and 1.09 with Pr in the TR and UT subjects respectively, and 1.10 with At in both groups, can be explained by the reduction in substrate availability. Total test time was significantly decreased with BB in both groups of subjects; the reductions being significantly greater with Pr. There was a trend towards less of a decrease after 9 d of BB, however, this did not reach statistical significance. Impaired exercise capacity and the change in RER can be explained by decreased utilization of free fatty acids, inhibition of hepatic glycolysis and gluconeogenesis, and a reduction in skeletal muscle blood flow. With the exception of lipolysis, these activities are predominantly B_2 receptor-mediated.

Untrained vs. Trained Subjects

The TR subjects in the present study were not able to accomodate as well to BB as the UT group. There was a greater reduction in $\dot{V}O_2$ max, $\dot{V}_E$ max, and treadmill time in the highly trained group compared to the UT group, although no formal statistical analysis was performed between the two groups. It has been suggested by Furberg (25) that because of the greater physiological capacity of highly trained individuals, they may have already maximized any compensatory mechanisms. Wilmore et al. (80) reviewed data from a series of investigations conducted in their

laboratory. They found that $\dot{V}O_2$ max was unaffected during BB in relatively untrained persons (or subjects with a $\dot{V}O_{2\text{max}}$ of less than $50 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) due to compensatory increases in SV and $a-vO_2$ diff. They noted that a highly trained person has achieved the majority of his potential for compensation through training and that the effects of BB could not be fully overridden. Karlsson et al. (39) and Koch et al. (40) examined trained and untrained persons and BB and found exercise capacity to be reduced to a greater extent in the highly trained person. The differences noted between the two groups of subjects in the present study and the above mentioned investigations provide a partial explanation for the variability in literature examining BB and exercise.

Acute vs. Chronic

The focus of the present investigation was the difference in physiological responses to a single bout of exercise between acute and chronic periods of dosing with BB. No significant differences between the two trials were noted, with one exception. A chronotropic adaptation to Pr and At did occur over a period of nine days. At the 75% work rate, the UT subjects showed a 3% increase in the chronotropic response to exercise after 9 d of BB, i.e., the HR response at 75% was decreased to a greater extent by BB

at 1 d compared to the 9 d response. Maximal HR response also showed a significant trial/drug interaction. There was a 4% increase in max HR response in both UT and TR subjects after 9 d of BB when compared to the 1 d response with both drugs. Although $\dot{V}O_2$ max, test time, and $\dot{V}_E$ max did show slight increases at 9 d vs. 1 d, statistical significance was not achieved and consequently, exercise performance was not improved after 9 d of BB when compared to the 1 d response. The studies mentioned previously by Smyth et al. (63) and van Baak et al. (72) also showed no significant differences in exercise performance between acute and chronic BB.

Physiological changes responsible for the improvement in chronotropic response may have been the result of, 1) improved sympathetic drive via greater stimulation of the adenylate cyclase system allowing improved catecholamine activity, or 2) parasympathetic withdrawal becoming more of a factor over time. While the former is more likely, HR response alone cannot determine the level of sympathetic activity (47). Changes in receptor activity could also have been a factor, and will be briefly discussed in the following paragraph.

Physiological adaptations to various stresses, such as BB, are a result of changes in receptor regulation (27). Heterogenous regulation of receptors occurs as a result of

positive or negative influences by hormones or drugs that do not normally interact with beta-adrenergic receptors and homogenous regulation is a response to chronic exposure of receptors to agonists or antagonists (66). Both types of regulation alter receptor sensitivity or affinity resulting in certain physiological changes. Williams (76) noted that receptor changes responsible for adaptations to endurance training may also be a factor in adaptations of the nervous system to BB. Evidence cited by Svedenhag (66) showed that increases in sympatho-adrenal activity are necessary for the normal response to training. The improved chronotropic response seen after 9 days of BB is likely to have been a result of improved sympatho-adrenal activity due to receptor changes.

CHAPTER 6

SUMMARY

The effects of BB on submaximal and maximal exercise performance are inconclusive in the literature to date. Five probable reasons for the variability include (1) differences in the dose and selectivity of the beta blocker used, (2) the mode of exercise testing, (3) the specific population examined, (4) the period of time between the last active dose and the start of testing, and (5) the length of time the subject has been on beta-blockade medication prior to testing. Thus, the purpose of this study was to determine the role of differences in the duration of the medication period in explaining these previous inconsistencies. It was hypothesized that alterations in exercise responses to BB would occur after 9 days of medication with a non-selective as well as a selective beta-blocking agent, when compared to short-term dosing, significantly improving exercise performance. Also, because highly trained endurance runners are closer to their genetic physiological potential as compared to more sedentary

individuals, trained persons would be likely to show less of an adjustment to long-term BB.

This investigation involved the use of three treatments: a placebo, 80 mg bid of Pr, a non-selective beta blocker, and 100 mg daily of At, a selective beta blocker. Each treatment was administered in a randomized double-blind manner. Maximal treadmill tests were conducted after both an acute (1 d) and a chronic (9 d) dose of BB. One-half of the 28 subjects did not exercise regularly (UT) and the remaining 14 were highly trained distance runners (TR).

HR max, $\dot{V}O_2$ max, $\dot{V}_E$ max, and test time were significantly reduced by both Pr and At at 1 d and 9 d in both UT and TR subjects when compared to a placebo treatment. While exercise responses to a non-selective and a selective beta blocker were similar at low and moderate work intensities, at high intensities Pr caused a greater attenuation of the physiological responses to exercise, i.e., greater decrease in HR max, $\dot{V}O_2$ max, $\dot{V}_E$ max, and total test time when compared to At.

The differences in HR max between the acute and the chronic drug trials were significant, i.e., there was a 4% increase in HR max after 9 d of Pr and At treatment in both groups of subjects suggesting a chronotropic adjustment to chronic BB. Maximal $\dot{V}O_2$, $\dot{V}_E$ max (in the UT subjects)

and treadmill time to exhaustion followed a similar trend, although not statistically significant. At 75% VO_2 max, HR response in the UT individuals demonstrated a significant interaction between the acute and chronic BB trial which was not found in the TR group. None of the other variables demonstrated significant interaction effects.

With the exception of a slight increase in HR at high intensity exercise after chronic dosing with both Pr and At, a 9 d dose of BB did not significantly alter exercise responses when compared to a 1 d dose. The lack of circulatory and metabolic adjustments to long-term BB were evident in both groups of subjects. These data indicate that the duration of BB prior to testing may not be responsible for the inconsistent findings in the literature concerning BB and exercise performance, if adequate dosing and appropriate testing procedures are used. These findings further suggest that an acute dose (24 h) of either Pr or At is sufficient for examining acute exercise responses to BB.

APPENDIX A

SUBJECT'S CONSENT FORM

University of Arizona

Effect of Acute vs. Chronic Beta-Adrenergic Blockade
During Exercise with Subjects of Two Different
Levels of Physical Fitness

I understand that I am being asked to voluntarily participate in a study titled, **Effect of Acute vs. Chronic Beta-Adrenergic Blockade During Exercise with Subjects of Two Different Levels of Physical Fitness**. 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 effects of the substance "adrenaline", which is released under stresses like exercise.

My participation in the study will include performing a series of treadmill tests to exhaustion. These tests involve running, with the speed and grade of the treadmill increasing gradually until I am too fatigued to continue. The first test will be a control test to familiarize me with normal laboratory procedures. The next series of test will occur following both one and nine days of ingesting each of three coded capsules: a placebo, propranolol, or atenolol. During the treadmill test, I will be wearing electrodes to record my heart rate, and I will be breathing through a mouthpiece so my expired air can be measured. My heart rate, oxygen consumption, and ventilation will be measured during these runs. Also, I will be weighed underwater to determine my percentage of body fat. This involves submerging me ten times after I have blown out all my air, and having the volume of air trapped in my lungs measured by breathing in a spirometer for 5-10 seconds.

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. Beta-blocking drugs can

cause stomach upset and may cause me to feel sluggish during the time I am 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, all data will be filed according to a 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 principal 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 money, and that I will receive \$150 for completing all aspects of the study.

I have read the above "Subject's Consent Form." The nature, demands, risks, 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 involvement in this project.

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

Investigator's Signature

Date

Witness' Signature

Date

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