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THE EFFECT OF PROPRANOLOL ON THE TRAINING RESPONSE TO
ENDURANCE EXERCISE IN NORMAL HUMAN ADULTS

The Ohio State University

Ph.D. 1984

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THE EFFECT OF PROPRANOLOL ON THE
TRAINING RESPONSE TO ENDURANCE EXERCISE
IN NORMAL HUMAN ADULTS

DISSERTATION

Presented In Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

Patrick Alan Cleary, A.B., M.A.

The Ohio State University

1984

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Patrick Alan Cleary

DEDICATION

To my great friend and loving wife, Marilyn. Her endless patience and support have allowed me to achieve far more than I could imagine. Her contributions in all aspects of my life are immeasurable.

ACKNOWLEDGEMENTS

Many thanks to my adviser, Dr. Robert L. Bartels, for his friendship, guidance, and encouragement over these many years. I consider it a sincere privilege to have worked with such an outstanding individual. Thanks also to Dr. Robert L. Hamlin. His energy and brilliance were continual sources of inspiration.

I would also like to thank Dr. Timothy E. Kirby. His good humor, willing assistance, and powerful intellect contributed immensely to this endeavor.

My sincere appreciation is extended to Dr. Stephen F. Schaal, Dr. Patricia B. Caldwell, and Dr. Daniel S. Shook. This investigation was realized only through their considerable efforts.

Special thanks to my tremendous subjects. Their time and effort had few rewards; their sacrifice made possible this study.

I would like to acknowledge Dr. Larry Sachs for the valuable statistical consultations.

SPECIAL ACKNOWLEDGEMENT

I would like to extend a special acknowledgement to the memory of the late Dr. Edward L. Fox. I had the distinct pleasure of knowing and working with this gifted, generous, self-effacing man for several years. I first met "Ed" (as he was known to his graduate students) in the mid-1970's. At that time I was visiting several academic institutions in the search of the best doctoral program in Exercise Physiology. As prestigious as was the program at The Ohio State University, it was the personal warmth and concern that Ed demonstrated during my brief visit that solidified my graduate program choice.

Accomplished as he was in the sciences, Ed treated me as a fellow colleague in his laboratory. His encouragement, keen wit and encompassing knowledge created a very pleasant and stimulating investigative environment. When my later interests in clinical medicine surfaced, Ed enthusiastically supported my application to medical school.

Ed's untimely passing left a tremendous gap in the ranks of academia and in the hearts of those who knew him. In the Laboratory of Work Physiology, we miss more than Ed's scientific acumen; we miss Ed.

A philosopher once phrased that man is no more than a collection of his memories. I am therefore especially enriched for the memories and friendship of Doctor Edward Lyle Fox.

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PUBLICATIONS

Cleary, P. A., Kirby, T., Fox, E. L., Bartels, R. L., Caldwell, P.,
and Schall, S. F. The Effect of Propranolol on the Training
Response to Endurance Exercise in Normal Human Adults.
Circulation (submitted) 1984.

Badenhop, D. T., Cleary, P. A., Schall, S. F., Fox, E. L., and
Bartels, R. L. Physiological Adjustments to Higher or Lower
Intensity Exercise in Elders. Med. Sci. Sports Exer. Vol. 15, No.
6, 1983.

VITA (cont'd)

Toner, M. M., Kirkendall, D., Chase, J. M., Delio, D. J., Cleary, P., and Fox, E. L. Metabolic and Cardiovascular Responses to Exercise with Caffeine. Ergonomics Vol. 25, No. 12, pp. 1175-1183, 1982.

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CHAPTER I

INTRODUCTION

The use of the beta-adrenergic blocking agent, propranolol, is widely established in management of several disease entities including angina pectoris, hypertension, mitral valve prolapse syndrome and migraine headaches. Propranolol, the most frequently studied compound of this class of drugs, is thus considered the prototype beta-adrenergic blocker (32).

There are many studies documenting the effects of a single dose of propranolol on the exercise response in normal man (2, 4, 5, 25, 42, 43, 57, 88, 94). In addition, there have been several training studies involving patients with coronary artery disease receiving chronic propranolol therapy (54, 63, 70). In these studies, however, it was not possible to precisely quantitate the effects of the propranolol therapy on the training response to rehabilitative exercise because of the medical necessity of maintaining such populations on uninterrupted beta-blockade.

Thus, little information is available on what effects, if any, chronic propranolol therapy exerts on the training response to endurance exercise. Indeed, the exact mechanisms by which training effects are mediated are still not well described.

A recent study (51) has suggested that sustained beta-adrenergic stimulation may be one of the key mechanisms responsible for the cardio-pulmonary conditioning. Beta-adrenergic blockade may therefore quantitatively interfere with the conditioning process.

The essence of this project was to assess the effect of propranolol on the response to endurance exercise training in normal human adults.

The Purpose of the Study

The purpose of this endeavor was to determine if there existed meaningful differences in the response to endurance training between normal human adults receiving 160 mg per day of propranolol therapy and normal individuals not receiving such therapy. This information would further our understanding of the mediators of cardiopulmonary conditioning. By recruiting normal, healthy volunteers for this project, the potentially confounding effects of drug-drug interactions or physical impairment would be minimized.

Hypothesis

In accordance with the stated purpose of the study, the following hypothesis was tested: Endurance training while receiving propranolol therapy will produce no significant differences in maximal ventilation, maximal oxygen consumption, maximal carbon dioxide production or exercise endurance time when compared to a similar group receiving no propranolol therapy.

Delimitations

1) Subjects volunteered to participate in the present study and therefore do not represent a random sample. In addition, each subject was given the option of either receiving the propranolol therapy or not receiving this treatment. Thus, each subject was fully cognizant as to which training group he or she would represent in the study.

2) The design of this investigation necessitated prescribing and then withdrawing propranolol therapy while performing a series of maximal exercise tests. This regimen would very possibly entail significant risk to a cardiac-impaired population requiring this medication. Thus, only healthy subjects in whom the drug could be safely and easily withdrawn could participate in the study.

Limitations

1) Measurement error is inherent in gas collection and analysis. The extent to which these inaccuracies occur are not known with absolute certainty.

2) Serum levels of propranolol were not determined and, therefore, the degree of variation among subjects was not known.

CHAPTER II

REVIEW OF LITERATURE

The Effects of Propranolol Administration in Normal Man

As early as 1965, Epstein et al. (25) studied the effects of beta-adrenergic blockade on the cardiac response to maximal and submaximal exercise in both normal men and in patients with heart disease. Propranolol administered I.V. (0.15 mg/kg) resulted in a 40% decrease in endurance exercise time. At maximal exercise there occurred a 22% decrease in cardiac output when compared with the non-blockaded state (both dye dilution and Fick principle), 19% decrease in heart rate, 15% decrease in mean arterial pressure, 34% decrease in left ventricular minute work and a 6% decrease in maximal oxygen consumption. In addition, propranolol increased by 12% the calculated arteriovenous difference. These changes were similar to those experienced by the subjects with heart disease. Cardiac output was still noted to increase substantially during exercise with propranolol although the increase was consistently less than without beta-blockade. During submaximal work $\dot{V}O_2$ was unchanged with propranolol even with a decreased cardiac output indicating an increased arteriovenous oxygen difference as a compensatory response. At maximal work, however, this fall in cardiac output could not be completely compensated and hence a smaller maximal $\dot{V}O_2$ was achieved.

Epstein stated that the reduced heart rate increase during exercise with beta-blockade as well as decreased contractility were both responsible for the overall decreased cardiac output during exercise. However, he remarked that there were other mechanisms besides sympathetic stimulation that were also important factors in augmenting cardiac output during exercise.

Banks et al. (5) found that 80 mg propranolol produced a 22% reduction in submaximal heart rate in nine normal males. A 12% increase in stroke volume was not sufficient to offset the 12% reduction in cardiac output as measured by carbon dioxide rebreathing (42). Total work performed during a progressive test to exhaustion was 18% less on propranolol than on placebo and oxygen consumption was reduced 3.5% over the entire work range. Carbon dioxide production and ventilation were unaffected.

Vukovich et al. (88) investigated the effects of varying doses of six different beta-blocking drugs in 25 human volunteers on the exercise double product (systolic blood pressure x heart rate). Exercise work loads were predetermined to elicit an approximate doubling of the double product for each subject. The propranolol-induced decrease in double product ranged from 25.9 to 31.8%. These changes appeared dose related to propranolol.

McSorley and Warren (57) found that 80 mg propranolol caused a reduction in skin blood flow and resting muscle blood flow in both normal and hypertensive subjects. Mean skin temperature also fell by $1.30 \pm 0.62^{\circ}\text{C}$ following propranolol administration. After an unspecified bicycle exercise session, post-exercise muscle hyperemia

was significantly reduced in the propranolol-treated group. They also found better preservation of blood flow to exercising muscle following metoprolol when compared with propranolol. The authors therefore suggested that propranolol be used with care in patients with known vascular disease.

Yin and coworkers (94) found no age-related differences in the ventricular response to either handgrip exercise or phenylephrine infusion between 17 normal young males ($\bar{x}$ = 29 years) and 11 normal older males ($\bar{x}$ = 68 years). Following propranolol administration, however, (0.15 mg/kg i.v.) the phenylephrine infusion induced a greater increase in left ventricular end-diastolic dimension in the elderly group although no age-associated differences were found during blockade at rest. The authors concluded that the normal aged heart performs as well at rest as a young heart but has a stronger dependence on beta-adrenergic drive during hemodynamic stress.

In a double blind study using 10 normal males, Anderson et al. (2) compared heart rate, $\dot{V}O_2$, $\dot{V}E$, lactate, free fatty acid and glucose levels during graded maximal exercise tests before and after oral propranolol (80 mg) dosing. Propranolol was shown to significantly inhibit exercise-induced tachycardia as well as decrease $\dot{V}O_2$ max (21%) and total work output. Subjects complained of an excessive feeling of fatigue during the work bout on propranolol. Because lactate values were lower for propranolol than for placebo, it seemed unlikely that this reported fatigue was related to lactate production. Free fatty acid levels in the blood were found to be lower at the end of the active drug exercise bout. Blood glucose

values were actually significantly higher following exercise on the drug compared with the placebo group. Anderson concluded that an alteration of the drug dose or a change in medication may be indicated in patients receiving propranolol who report undue fatigue.

Astrom and Juhlin-Dannfeldt (4, 43) reported that acute beta-receptor blockade (2 mg propranolol in 10 ml saline infused in the right femoral artery) did not interfere with exercise-induced vasodilation in the right legs of nine healthy males. However, lactate release was abolished from the blocked leg at rest and was reduced 50% during exercise. It appeared that while blood flow to the exercising leg was unaffected, metabolic changes did occur following propranolol administration.

Port and colleagues (69) studied left ventricular function before and after 2 days of oral propranolol therapy (320 mg/day) in 12 normal males. Left ventricular ejection fraction, cardiac output, stroke volume and end-diastolic volume were measured by radionuclide angiography. Following propranolol therapy, heart rate, cardiac output, left ventricular ejection fraction and systolic blood flow were all significantly depressed during exercise. Pulmonary transit time and systolic volume were increased significantly. During rest the ejection fraction, heart rate and cardiac output were again noted to be depressed ($p = 0.001$). The authors noted that at similar heart rates (different work loads) there were no differences noted in the hemodynamic measures with or without propranolol. This suggested that heart rate changes reflect the dominant influence of propranolol during exercise and rest.

Lewis and others (50) combined acute parasympathetic and beta-adrenergic blockade in order to study the mechanism of training bradycardia in ten healthy sedentary men. Heart rates were measured during rest and submaximal exercise on arm ($n = 5$) and leg ($n = 5$) ergometers with and without medication before and after an 11 week aerobic arm or leg ergometry program. Following training, the autonomic blocked subjects had no observed changes in resting heart rate. However, without blockade the resting heart rates were significantly decreased. Similar changes were noted following training during submaximal exercise in the autonomic blockade state. In addition, significant decreases in submaximal heart rate were noted in subjects without autonomic blockade. The conclusions were that non-autonomic changes, beside an intrinsic heart rate reduction, were responsible for the phenomenon of training bradycardia.

Sixteen healthy men were studied by Cathcart-Rake (12) and coworkers to assess left ventricular ejection fraction, systolic time interval and heart rate changes following oral propranolol (80 mg) and/or disopyramide (200 mg). Both drugs, when administered acutely, significantly reduced ejection fraction and increased the pre-ejection period (PEP) to left ventricular ejection time (LVET) relationship. The authors did not find these negative inotropic properties to be additive or synergistic when the drugs were given together.

Using only normal subjects ($n = 19$), Crawford and coworkers (18) studied the effects of two weeks of 160 mg/day oral propranolol therapy on left ventricular size and performance during graded supine

bicycle exercise ($n = 10$) and the effects of acute pressure loading with I.V. phenylephrine ($n = 9$). As expected, resting heart rates and systolic blood pressures decreased at rest in the propranolol group. Percent dimensional shortening (per echocardiography) was unchanged while left ventricular end-diastolic dimensions were significantly increased. During exercise, similar changes were noted except that percent dimensional shortening was reduced. During acute pressure loading with phenylephrine following atropine administration there were no significant changes in left ventricular size or performance when compared with the control data. The authors concluded that intrinsic myocardial performance in normal subjects is not affected by chronic propranolol administration and that the major effect of competitive beta-blockade is greatest during high sympathetic tone as in exercise.

In a study by Sklar et al. (78), the effects of metoprolol and propranolol were compared in normal men undergoing maximal graded treadmill exercise. Both drugs and the placebo were administered to all ten subjects at 48 hours prior to testing in a double blind protocol. A five day interval separated the randomized administration of the drugs. The oral drug dosages were: propranolol at 40 mg or 80 mg every six hours; metoprolol at 50 mg or 100 mg every six hours. The authors found no changes in maximal oxygen uptake, maximal minute ventilation, diastolic blood pressure or anaerobic threshold from either beta-blocker therapy. There was, however, a small but significant reduction in exercise duration in the higher dose propranolol group when compared with the placebo

data. He concluded that the perception of increased muscular fatigue during exercise on beta-blockers was not due to decreased perfusion of the working muscles.

More recent studies have investigated the effects of beta-blockade on the training response to endurance exercise in a normal population. Sable et al. (76) exercised normal sedentary men for five weeks of vigorous (5 x/wk) aerobic conditioning. In a double blind protocol nine subjects received propranolol (mean plasma levels 100-292 ng/ml) and eight received placebo during the conditioning period. Training intensities were reported to be similar for both groups. His study found no improvement in maximal oxygen uptake after training in the propranolol group as opposed to significant improvement in the placebo group. The authors concluded that beta-adrenergic stimulation is essential in exercise conditioning and that beta-blockade and propranolol was shown to attenuate aerobic conditioning in these normal subjects. The authors did not attempt to extrapolate these results to a cardiac rehabilitation population.

In 1983, Svendenhag and coworkers (83) reported on the influence of beta-blockade on training in healthy subjects. In his study, 16 healthy males training on bicycle ergometers for 8 weeks (40 min/day, 4 x/wk, 75% maximal $\dot{V}O_2$). Eight subjects received propranolol therapy (80 mg b.i.d.) and eight received a placebo regimen. The testing was performed in the absence of beta-blockade. Maximal $\dot{V}O_2$ improved 8% in both groups. However, oxygen pulse was noted to increase significantly only in the placebo group. Skeletal muscle

lipoprotein lipase showed significant increases in both groups as did such oxidative enzyme markers as succinate dehydrogenase, cytochrome C oxygenase and citrate synthase from biopsy samples from the vastus lateralis muscle. It was noted that these enzyme increases were quantitatively less in the beta-blocker group. The authors concluded that both central and peripheral training effects occurred following endurance training and propranolol therapy. They suggested that the sympathoadrenal system does play some as yet unspecified role in the training adaptation.

Another double-blind study (87) investigated heart rate reduction and maximal work capacity during acute (I.V. 0.15 and 0.30 mg/kg body wt.) and chronic (100 mg p.o. b.i.d. x 4 wks) beta-blockade with metoprolol. The maximal attained workload was unchanged after 0.15 mg/kg I.V. metoprolol but was significantly decreased by 5% following a 0.30 mg/kg I.V. administration. Maximal heart rate was markedly decreased in both instances. When the drug was given chronically, the maximal workload attained was significantly decreased. The maximal blood lactate levels were unaffected following the acute I.V. administrations at both dosages. It was speculated that the decrease in maximal heart rate at low doses of I.V. metoprolol are compensated by the oxygen transport system but not at the higher levels of acute blockade nor in the group receiving chronic therapy.

Tesch and colleagues (84) studied isometric endurance in 14 active normal men before and after acute propranolol (160 mg) and placebo treatment. The propranolol therapy yielded a significant decrement in endurance time for sustained isometric muscular

contractions. The authors felt that isometric work would circumvent any observed change in performance due to impaired cardiac output resulting from acute beta-blockade. Thus, the performance decrease with beta-blockade was thought to be due to mechanisms other than impaired cardiac output. No blood lactates or heart rates were reported. It would seem that the authors' conclusions were somewhat speculative in lieu of the data presented.

The Effect of Propranolol Administration in Patients with Heart Disease

Robin et al. (74) compared I.V. propranolol (0.1 mg/kg) and sublingual nitroglycerin (0.6 mg) on right ventricular fiber shortening in patients with and without coronary artery disease (C.A.D.) using a strain gauge catheter. Propranolol was found to decrease the velocity of fiber shortening, heart rate, stroke work, dp/dt and left ventricular minute work. This was accompanied by an increased peripheral resistance and tension-time index. Left ventricular and end-diastolic pressure was noted to significantly increase in patients with C.A.D.

Helfant and coworkers in 1971 (35), studied the hemodynamic effects of 5 mg intravenous infusion of propranolol on left ventricular contraction in atrial-paced subjects with and without heart disease. He found left ventricular and end-diastolic volumes increased in most instances with a reduced ejection fraction and percent circumferential fiber shortening. A propranolol-induced or

exaggerated asynergy was noted in three patients with coronary artery disease and in two normal subjects.

Armstrong et al. (3) infused 0.15 mg/kg body weight of propranolol into 19 patients with C.A.D. and 6 normal people. Atrial pacing was used as the stressing modality. Propranolol was found to reduce heart rate (78 to 69 bpm) and decrease cardiac index (3.0 to 2.6 liters/min per square meter) as well as decreasing left ventricular end-diastolic pressure. No changes were noted in myocardial oxygen uptake, LVEDP, coronary sinus flow or mean arterial pressure. Total peripheral resistance and lactate extraction both increased significantly. The propranolol also resulted in less angina during atrial-pacing stress with less S-T depression. It therefore appeared that propranolol could improve angina symptomatology without concomittant changes in coronary sinus flow or myocardial $\dot{V}O_2$. Other training studies have focused on coronary artery disease patients receiving propranolol therapy.

Reale et al. (71) studied the acute effects of 10 mg intravenous infusion of the beta-adrenergic blockers metoprolol, bunitrolol and oxyprenolol on left heart hemodynamics at rest and during exercise in patients with C.A.D. He found the bunitrolol group to manifest a significantly lower LVEDP during exercise. His group concluded that one must be cautious in prescribing beta-blockers so as not to impair cardiac function in those people with heart disease.

Campbell and coworkers in 1979 (11) investigated exercise capacity prediction in angina patients receiving propranolol therapy. They concluded that MET capacity attained after a three month

training program could be predicted using the heart rate x blood pressure product attained during the graded exercise test performed (while receiving propranolol therapy) before training commenced. Other predictors postulated were systolic blood pressure at rest with beta-blockade and the age of the patient. Regression analysis predictions using these variables correlated well with actual data obtained. It was concluded that if unacceptable effects were predicted in exercise treatment of angina patients, another modality may be considered. The authors' data also supported earlier investigations that found decreased systolic blood pressure, resting heart rate and rate pressure product (heart rate x systolic blood pressure) with propranolol therapy.

Bruce et al. (10) studied the effects of oral propranolol on the hemodynamic response to upright exercise in 3 normals and 14 patients with C.A.D. Maximal $\dot{V}O_2$, arteriovenous oxygen difference and cardiac output (direct Fick) were measured at sitting and supine rest and during upright treadmill exercise before and 90 minutes after 40 mg oral propranolol therapy. Heart rates decrease significantly during exercise and recovery. Maximal $\dot{V}O_2$ was found to decrease in normals and in patients with less than 15% left ventricular impairment. Those with greater than 15% impairment had an increased maximal $\dot{V}O_2$ following beta-blockade. This was thought to represent an enhanced peripheral extraction of oxygen.

Obma and colleagues (63) studied the effects of an eight-week aerobic conditioning program on patients with angina pectoris receiving propranolol. These patients received an average of 129 mg

of propranolol per day. No change in resting heart rate was noted after the training program. However, maximum angina-free exercise capacity improved significantly after training for almost all the patients. Obma concluded that exercise programs for C.A.D. patients were of little benefit for those patients whose aerobic capacities on propranolol were less than 2.5 METS. He also noted that exercise testing could be used to enhance the exercise prescription and also to more accurately titrate the dosage of propranolol.

Pratt et al. (70) demonstrated a 30-45% improvement in $\dot{V}O_2$ max in 21 patients with coronary artery disease (CAD) who received propranolol (30-240 mg/day) following a three month walk-jog-cycle training program. These data showed that considerable training effects were possible in CAD patients receiving propranolol therapy even though training heart rates were reduced. The latter two investigations are in disagreement with an earlier study by Malmberg et al. (54). Malmberg's subjects were angina patients receiving beta-blockers and were involved in only fifteen minutes of exercise per session four times per week. It was possible that the inadequate frequency or duration of the therapeutic exercise sessions were responsible for the lack of a demonstrable training effect.

Hossack and colleagues (39) studied the influence of 40 mg oral propranolol on exercise prescription heart rates in 14 patients with C.A.D. They noted a small but statistically insignificant change in the ratio of maximal $\dot{V}O_2$ to maximal heart rate. The authors recommended that maximal exercise tests be performed with the patient continuing to receive any cardio-active medicines that would also be

used when training in order to more accurately write the exercise prescription. The authors did note a significant reduction in carbon dioxide production (R value) during exercise with beta-blockade. The investigators hypothesized that this may have actually represented a "training" effect obtained from propranolol therapy.

Another study by Hossack (40) again noted significant decreases in carbon dioxide production during exercise (10%) following 40 mg oral propranolol in four normals and in fourteen patients with C.A.D. He also observed a decreased minute ventilation but no differences in $\dot{V}O_2$ at comparable work loads. Hossack postulated that glucose metabolism during exercise may have been inhibited by beta-blockade. This diminished carbon dioxide production was suggested responsible for the diminished minute ventilation due to the effect that the level of carbon dioxide in the blood exerts on respiratory drive. Thus, the authors stated that lower R values for exercising C.A.D. patients may actually diminish their abilities to derive training effects as it had been noted earlier that successful exercise prescriptions more commonly yielded higher levels of carbon dioxide production and R values.

Using multiple-gated equilibrium cardiac blood pool images, Marshall et al. (55) investigated the effect of oral propranolol on left ventricular performance during rest, upright bicycle ergometry and recovery. In normal subjects, different doses of propranolol (160 vs. 434 ± 99 mg/day) produced no left ventricular functional changes at rest in normal subjects nor in C.A.D. patients at 162 ± 47 mg/day. During upright bicycle exercise only the higher dose ($434 \pm$

99 mg/day) regimen caused a significant decrease in left ventricular performance in the normal subjects. Propranolol improved significantly the left ventricular performance during exercise and recovery in C.A.D. patients with previous functional ischemic exercise responses. Those C.A.D. patients without such a previous response had no such left ventricular functional changes after propranolol therapy. The authors suggested that the ischemic myocardium had greater sensitivity to beta-blockade and that left ventricular function changes noted in both normals and C.A.D. patients with ischemic dysfunction were not dependent on preload or afterload.

Squire and coworkers (81) studied the effects of propranolol on perceived exertion after myocardial revascularization surgery in three groups of patients. Heart rate and perceived exertion were also measured during exercise tests performed prior to the patient discharge from the hospital. Ratings of perceived exertion were the same for patients receiving propranolol as well as those patients not receiving propranolol and those patients who developed exertional hypotension during testing. Peak exercise MET levels (estimated) were also similar for all groups.

High density lipoprotein (HDL) levels were studied by Hoffman and others (37) in exercising cardiac patients. Two male populations were trained for three months. One group received propranolol (dose not reported) and the other population received no such therapy. This control population significantly improved their HDL levels whereas the propranolol group experienced a nonsignificant decrement in these

values. The authors felt that the use of propranolol could prevent potential HDL level improvement in a cardiac population possibly by attenuating the lipoprotein lipase activity needed to process HDL precursors.

Similar trends in HDL levels were found by Walker and coworkers (89). They noted that aerobic training (12 weeks, 3 x/wk, 70-85% max. heart rate) demonstrated no changes in total cholesterol, very low density lipoprotein, low density lipoprotein total, and in lipoprotein ratio (VLDL + LDL-C: HDL-C) in both propranolol and control populations of cardiac patients. The control group did demonstrate a significant improvement in HDL-C levels as opposed to no such findings in the propranolol group. The authors concluded that most blood lipids were not affected by beta-blockade during training.

In contrast, Smith et al. (79) compared training benefits between beta-blocked (drug and dose not reported) post-coronary bypass or post-myocardial infarction and a group of such patients not receiving beta-blocker therapy. Tests were conducted before and after a four week aerobic exercise program. No differences were noted in the significant improvements realized by both groups in $\dot{V}O_2$ max and treadmill time. There were also no differences noted in body weight, serum total cholesterol or triglyceride levels between and among groups. High density lipoprotein-cholesterol (HDL-C mg/dl) was shown however to significantly increase after training ($p < 0.01$) in the drug therapy group. The fact that a substantially larger number of patients were in the experimental group than the control group (71

versus 17 patients, respectively) may have affected this comparison. It appeared from this study that beta-blockade in post-MI or post-CABG patients did not attenuate training benefits.

Roberts (73) studied maximal $\dot{V}O_2$ changes in C.A.D. patients receiving beta-blockade therapy (drug and dose not reported) following a supervised six-month training program consisting of 45 minute sessions at 3 x/week. Training intensity was at 80% of heart rate reserve for this group ($n = 10$). The control group ($n = 15$) also received beta-blockers but exercised at only 50% of their heart rate reserve. Beta-blocker dosages were apparently similar between groups. In this study the drug was stopped three days before each treadmill test. Significant improvement was noted in the group that trained at the greater intensity (80%) of heart rate reserve. The other group that trained at a lesser intensity (and was unsupervised) showed no such improvement. It is difficult to compare the two groups in a meaningful way, however, because of the aforementioned differences in supervision between groups.

Lundstrom et al. (53) tested C.A.D. patients before and after training to determine if beta-blockade with propranolol (40-160 mg/day) interfered with a 12-16 week aerobic conditioning program. Significant improvements were noted in exercise tolerance time and maximal $\dot{V}O_2$. No changes were noted in pre- and post-training maximal heart rates. They concluded that patients with C.A.D. receiving propranolol therapy can accomplish significant gains from properly prescribed exercises.

McAllister et al. (56) also demonstrated that C.A.D. and post-myocardial infarction patients could benefit from aerobic training. After a 12 week program (70-85% maximal heart rate, 30-45 minutes at 3 days/week) submaximal systolic blood pressure and heart rate changes were similar for patients receiving propranolol and in those patients not receiving such therapy. Oxygen consumption was not measured in this study. The authors concluded that training benefits in cardiac patients were not affected by beta-blockade.

Keller and colleagues (47) also studied the aerobic training benefits in heart patients receiving a mean dose of 138 mg/day oral propranolol. Their patients exercised for a 12 week period at 5 x/week. Treadmill tests pre- and post-training showed significantly increased peak work capacity and improved estimated $\dot{V}O_2$. Heart rates at standard work loads decreased following the training regimen. The authors concluded that standard fitness variables were applicable to patients receiving propranolol therapy.

Propranolol Administration in Hypertensive Patients and Diabetic Patients

In contrast to Hossack's study with C.A.D. patients, an earlier investigation by Fagard and coworkers (26) studied the effects of combined alpha- and beta-adrenergic blockade on ventilation during exercise in twelve hypertensive men. Subjects received 2.4 g/day of labetalol, an alpha and nonspecific beta-blocking drug, following graded bicycle ergometry to exhaustion. The subjects then repeated the exercise test after receiving labetalol therapy. During maximal

exercise plasma norepinephrine increased 4.3 fold with a 2.7 fold rise in plasma epinephrine. Maximal $\dot{V}O_2$, $\dot{V}CO_2$, respiratory exchange and ventilation were not affected following labetalol therapy during both rest and exercise. The authors also found no change in anaerobic threshold. Thus, the adrenergic system was not felt to play a principle role in exercise hyperpnea.

Using hypertensive men ($n = 28$), Agre and coworkers (1) compared the hemodynamic response to static handgrip and dynamic treadmill exercise with Aldomet and propranolol therapy. They noted that while both drugs reduced the systolic blood pressure response in both exercise types, the propranolol treatment also showed a significantly reduced dynamic exercise tolerance as evidenced by lower $\dot{V}O_{2\text{ max}}$, maximal heart rate and exercise endurance time. These differences may be important when prescribing a particular type of medication for the exercising patient with uncomplicated hypertension.

In type I insulin dependent diabetics, Smith (80) found that propranolol and metoprolol both decreased submaximal endurance time at a preset workload. However, he noted a greater decrease with the nonselective beta-blocker (propranolol) when compared with the cardio-selective metoprolol. The author suggested that the nonselective nature of beta-blockade with propranolol had a greater effect on reducing glucose and free fatty acid substrate availability than the more selective blockade with metoprolol. This finding may be responsible for the phenomenon of inordinate muscle fatigue during beta-blockade therapy. He stated that diabetics who must receive beta-blockers needed to ensure an inadequate glucose ingestion prior

to exercise and may derive more benefit from a cardio-selective medication.

DeRose and colleagues (21) also studied the effects of selective and nonselective beta adrenergic blockade in eight insulin dependent diabetic patients exercising at 50% $\dot{V}O_2$ max. They found that free fatty acid mobilization was unaffected by beta-blockade. However, significantly lower lactate values were noted at the end of exercise for the patients receiving beta-blockers. Again, significant reductions in blood glucose (30 minutes post-exercise) were noted with the nonselective therapy. These authors agreed with the previous study by Smith that cardio-selective drugs may be best for exercising diabetics.

Propranolol Administration in Canines

Moss and coworkers (61) used the canine model to study myocardial oxygenation changes with propranolol (I.V. 0.25 mg/kg). Oxygen tension significantly increased with no concomitant change in coronary venous PO_2 . The authors felt that propranolol increased myocardial oxygenation and decreased the cardiac work. This explanation was consistent with the observed effectiveness of propranolol in angina pectoris.

Several recent studies using canines have investigated the effect of beta-adrenergic blockade on endurance training. Lawlor et al. (48) trained dogs for eight weeks with and without propranolol therapy (125 mg b.i.d.). Training in both groups resulted in a significantly decreased exercise heart rate. In addition, this

significant heart rate drop during exercise was also observed 4-6 days following withdrawal from the medication. It was concluded that propranolol did not inhibit the training effect as determined by heart rate response during rest and exercise.

Thomas et al. (85) studied metabolic changes using a similar protocol with canines. Blood glucose was noted to be substantially decreased during exercise in the propranolol group. Free fatty acid levels did not change following training during either rest or exercise. A similar response was noted in the blood lactate levels after training in both groups. The authors suggested that chronic beta-adrenergic blockade modified substrate utilization changes incurred from training but their abstract provided little numerical data supporting this conclusion.

In another similar study, Bove and colleagues (9) investigated changes in serum lipids in the exercise-trained canine receiving chronic beta-adrenergic blockade (250 mg propranolol/day). Serum cholesterol was similar in both control and propranolol groups before and after training. Interestingly, high-density lipoprotein cholesterol (HDL-C) dropped significantly after training in the propranolol group while incurring no change at all in the control population. These findings suggested an altered serum lipid response to exercise training due to propranolol treatment. No mechanisms were postulated to explain these observations. These HDL findings differ from those observed in studies described earlier (37, 94) in the literature review.

Summary of Review of Literature

The effects of propranolol on resting and exercising physiologic parameters have been intensely studied in normal humans, diabetics, hypertensives, and in patients with coronary artery disease. The canine model has also been used for investigation. From these studies it has been shown that blood lipid profiles after training are affected by propranolol therapy. In addition, it was suggested that diabetic patients who require beta-blockers would have greater benefit from a cardioselective regimen.

The effect of propranolol on hemodynamic variables during rest and exercise in man appear to be related to the pharmacologic dose. The aerobic capacity of the individual may also modulate the response to beta-blockers. These variables help explain the attenuation of training effects observed during propranolol therapy when other studies have reported substantial conditioning progress during beta-adrenergic blockade.

It certainly would appear that the sympatho-adrenal system does exert a substantial influence of the physiologic adaptations to exercise.

CHAPTER III

METHODS AND PROCEDURES

It was the purpose of this investigation to evaluate the acute, chronic, and withdrawal effects of propranolol therapy on the cardio-pulmonary system during exercise. This required maximal exercise testing on bicycle ergometers at four different intervals. All evaluations of metabolism and cardio-pulmonary performance were obtained in the Laboratory of Work Physiology at The Ohio State University.

Subjects

The subjects for this study consisted of volunteers responding to posted recruitment letters on the Columbus campus of The Ohio State University. To be eligible for the study, each potential subject must not have been previously engaged in a regular endurance fitness program for at least two months prior to participation. In addition, each person was required to receive permission from his or her primary-care physician in order to participate. If any subject did not have a primary-care physician, permission to enter the study was granted by the cardiologist associated with this investigation.

Consent to conduct this study was obtained from the Human Subjects Review Committee of The Ohio State University. Each subject

was carefully informed of all aspects of the experiment including risks and benefits. Written consent to participate in the study was obtained from each subject.

The subjects consisted of seven men and seven women ages 22-45 years. Of these fourteen individuals, the experimental group was made up of eight people who volunteered to receive propranolol therapy. Six subjects did not desire the drug regimen or were not able to receive propranolol due to possible drug-drug interactions with required over-the-counter medications, i.e., antihistamines. This population therefore made up the control group. The physical characteristics of the subjects are presented in Table 1 and Table 2.

Table 1
Subject Profile By Group

Variable	Control (n=6)	Propranolol (n=8)	Combined (n=14)
Age (yrs)	29.0 $\pm$ 3.1	30.8 $\pm$ 2.9	30.0 $\pm$ 3.0
Percent Fat	26.1 $\pm$ 4.2	25.5 $\pm$ 3.7	24.7 $\pm$ 3.7
Lean Body Wt (lbs)	125.7 $\pm$ 8.5	115.7 $\pm$ 6.7	121.0 $\pm$ 7.5
$\dot{V}E$ max (L/min)	71.0 $\pm$ 10.5	67.0 $\pm$ 10.1	68.7 $\pm$ 10.3
$\dot{V}CO_2$ max (L/min)	2.47 $\pm$ 0.36	2.30 $\pm$ 0.25	2.38 $\pm$ 0.30
RQ max ($\dot{V}CO_2/\dot{V}O_2$)	1.06 $\pm$ 0.17	1.08 $\pm$ 0.01	1.07 $\pm$ 0.08
$\dot{V}O_2$ max (L/min)	2.32 $\pm$ 0.33	2.2 $\pm$ 0.24	2.22 $\pm$ 0.28
$\dot{V}O_2$ max (ml/kg/min)	29.9 $\pm$ 3.6	30.9 $\pm$ 3.4	30.4 $\pm$ 3.5

Table 2
Subject Profile by Individual

Number/ Group/ Sex	Age (yrs)	Weight (lbs)	%Fat	LBW(lbs)	$\dot{V}E_{max}$ (L/min)	$\dot{V}O_{2,max}$ (L/min)	$\dot{V}CO_{2,max}$ (L/min)
1 P F	45	188	40.8	111.3	50.7	1.78	1.89
2 P M	27	150	12.9	130.6	131.9	2.91	3.15
3 P F	25	147.5	34.4	95.6	42.0	1.83	1.95
4 P M	34	174	35.7	111.9	46.4	1.36	1.53
5 P M	28	143	16.1	120.0	66.7	2.67	2.80
6 P F	22	118.8	18.4	98.2	61.0	1.81	2.00
7 P F	40	136.5	26.6	104.6	58.5	1.60	1.70
8 P M	25	185	19.1	153.2	78.9	3.20	3.41
9 C M	24	184	17.7	151.5	110.0	3.52	3.87
10 C M	27	153.5	13.2	133.3	73.8	2.40	2.64
11 C M	24	186	21.5	146.1	88.9	3.00	3.07
12 C F	25	147.5	30.8	104.0	38.6	1.46	1.53
13 C F	45	162	33.6	107.6	62.7	1.68	1.84
14 C F	28	182.5	39.5	111.6	51.9	1.85	1.87

Testing Procedures

In order to assess cardiopulmonary fitness, each subject underwent a progressive continuous exercise test to volitional exhaustion on a calibrated Monark bicycle ergometer. The pedaling frequency of fifty revolutions per minute was maintained via

metronome pacing. The metronome accuracy was previously checked against a digital chronometer. The exercise test protocol consisted of an initial three minute workload of 300 kilogram meters per minute ($\text{kg}\cdot\text{m}/\text{min}$). This load was subsequently increased by 150 $\text{kg}\cdot\text{m}/\text{min}$ every three minutes until the subject was no longer able to maintain the pedaling frequency. Strong verbal encouragement was consistently given to ensure that as near a maximal effort as possible was elicited during each test. In addition, body weight and skinfold thicknesses were recorded before and after the training period in order to determine possible changes in percent body fat and lean body mass.

Gas Collection and Analysis. Inspired gas volumes were measured with a Parkinson-Cowan Dry Gas Meter. The meter was previously checked against a 120 liter Collins spirometer for determination of the proper correction factor. All volumes were corrected to standard conditions of temperature, pressure, and humidity.

Expired gases were collected in a plastic mixing chamber and subsequently analyzed for fractional concentrations of oxygen and carbon dioxide. The Beckman OM-11 oxygen analyzer and Beckman LB-2 carbon dioxide analyzer were both calibrated with gases that were previously determined by a micro-Schollander apparatus.

The oxygen uptake, carbon dioxide production and respiratory quotient were calculated from the gases obtained during the last minute of each workload and during the final minute of the test. These methods of calculation are described by Consolazio et al. (16).

If the subject was unable to complete a full minute at the maximal workload, the gas meter value was then extrapolated to a one-minute value.

Electrocardiography and Sphygmomanometry. Heart rate was recorded for each exercise test, during the last fifteen seconds of each workload, during the final fifteen seconds of the test and then for six minutes immediately following cessation of the test. A CM5 bipolar electrode placement was utilized and a Hewlett-Packard electrocardiograph was employed to record the heart rate by way of hard wire leads. Blood pressures were recorded concurrently with heart rates using a Pymah sphygmomanometer.

Testing

The aforementioned exercise tests were performed at four different intervals for both the experimental and control groups: Test 1) Prior to propranolol therapy; Test 2) Three days following daily oral propranolol therapy of 40 milligrams every six hours; Test 3) After ten weeks of bicycle ergometry training while receiving propranolol therapy; Test 4) Four days following Test 3 during which time the propranolol therapy had been gradually withdrawn. As stated, the control group followed the same schedule but did not receive propranolol therapy.

Training

Training consisted of monitored stationary bicycle ergometry for 35 to 40 minutes per session. Three sessions per week were required for a ten week period. Exercise prescriptions were derived from the results of the second maximal exercise bout (Test 2). The workload intensity was calculated at 60-75% of each subjects maximal oxygen uptake along with the corresponding heart rate range. Heart rate and blood pressure were recorded before, during and five minutes after each session. The workloads were adjusted regularly to maintain the conditioning stimulus as determined by the heart rates obtained during exercise training.

Statistical Analysis

To evaluate the effects of propranolol on the training response to endurance exercise, a two by four analysis of variance was employed as the statistical tool. The experimental condition was compared with the control group. In addition, the effects of acute administration of propranolol and the effect of propranolol withdrawal were also evaluated. The Duncan's Multiple Range test provided an a posteriori method of accurately locating where, if any, significant changes occurred. An a priori alpha level of 0.05 was selected for all measured variables.

CHAPTER IV

RESULTS

Body Composition

There were no differences between groups in percent body fat (25.5 ± 3.7 treatment vs. 26.1 ± 4.2 control) or lean body weight (115.7 ± 6.7 treatment vs. 125.7 ± 8.5 lbs control) before training. Following training the treatment group showed a significant (25.5 ± 3.7 to 22.8 ± 3.3 percent) decrease in fat percentage as contrasted with no such change in the control group (26.1 ± 4.2 to 24.4 ± 4.0). In addition, only the treatment population increased in lean body weight (115.7 ± 6.7 to 119.5 ± 6.9 lbs, $p < 0.05$) after the exercise program. The control group neither decreased nor increased lean body weight significantly during the study (125.7 ± 8.5 lbs Test 1 to 126.6 ± 8.4 lbs Test 3).

Fat weight decreased significantly in both groups. The treatment group experienced a 4.8% loss (40.9 ± 7.3 to 36.1 ± 6.4 lbs) while the control population had a 3.5% decrease in fat (44.3 ± 7.4 to 40.8 ± 6.9 lbs). There were no statistical differences between groups.

Pressor Variables

During the four testing intervals, maximal systolic blood pressure during exercise demonstrated no significant fluctuations in

the control group ($\bar{x}$ ranges = 184 to 189 mm Hg). As expected, propranolol significantly decreased maximal systolic pressure between Test 1 and Test 2 (180 ± 4.1 to 154 ± 10.6 mm Hg). There were no changes between Tests 2 and 3. Maximal systolic pressure returned to pre-training (Test 1) levels when the drug was withdrawn during Tests 3 and 4 (157 ± 10.8 to 179 ± 9.2 mm Hg) (see Figure 1).

Heart Rate

Maximal exercise heart rate was unchanged for the control group during all testing ($\bar{x}$ ranges 181 to 186 ± 5 BPM). As with maximal systolic blood pressure, heart rate was markedly reduced from Test 1 to Test 2 in the propranolol population (189 ± 6 to 138 ± 6 BPM, $p < 0.05$). Maximal rates returned to pre-propranolol values after discontinuing the medication. However, the maximal heart rates significantly increased between Test 2 and Test 3 (138 ± 6 to 151 ± 5 BPM) following ten weeks of training in the propranolol subjects. This finding has not been demonstrated in any previous studies and may be due to possible changes in beta-receptor sensitivities (see Figure 2).

Exercise Duration

Endurance exercise test time was also measured. There were no differences in initial endurance time (Test 1) between groups (16.3 ± 1.9 treatment vs. 15.7 ± 2.3 min control). No differences were noted either between or among groups during Test 2 (15.4 ± 2.0 treatment vs. 15.9 ± 2.2 min control). Both groups significantly improved

Figure 1

EFFECT OF EXERCISE TRAINING ON MAXIMAL SYSTOLIC BLOOD PRESSURE

Brackets represent mean $\pm$ SEM.

- I = before training or drug;
- II = following acute drug administration before training;
- III = after training while receiving drug therapy;
- IV = after training following drug withdrawal

*denotes significant difference between that bar graph and the graph immediately preceding.

Figure 2

EFFECT OF EXERCISE TRAINING ON MAXIMAL HEART RATE

Brackets represent mean $\pm$ SEM.

- I = before training or drug;
- II = following acute drug administration before training;
- III = after training while receiving drug therapy;
- IV = after training following drug withdrawal

*denotes significant difference between that bar graph and the graph immediately preceding.

exercise test duration following training (Test 3). The control group improved 45% (15.9 ± 2.2 to 23.1 ± 2.8 min) and the treatment population realized a 31% (15.4 ± 2.0 to 20.2 ± 2.3 min increase. Following propranolol withdrawal, however, the treatment group experienced an additional 11% increment (20.2 ± 2.3 to 21.9 ± 2.4 min, $p < 0.05$) as contrasted with no such change in the control group. The overall improvement in both groups between Test 1 and Test 4 were statistically similar (see Figure 3).

Maximal Ventilation

Maximal minute ventilation ($\dot{V}E_{max}$) during exercise showed no significant differences between groups for Test 1 (67.0 ± 10.1 treatment vs. 71.0 ± 10.5 l/min control). It should be pointed out, however, that the treatment group did experience a fall in max $\dot{V}E$ (67.0 to 57.9 l/min) between Tests 1 and 2, though no statistical differences could be measured. A decrease in this magnitude (13%) was not observed in the control group. Both populations experienced significant increases in maximal ventilatory capacity following training between Test 2 and Test 3 (57.9 ± 6.5 to 75.8 ± 8.2 l/min treatment vs. 75.9 ± 12.7 to 88.4 ± 10.0 l/min for the control group). This calculated to an increase of 30.9% and 16.5%, respectively. There were no differences noted between Test 3 and Test 4 for the control group (88.4 ± 10.0 to 87.5 ± 9.4 l/min). However, the propranolol group increased $\dot{V}E_{max}$ an additional 16% (75.8 ± 8.2 to 87.9 ± 11.1 l/min) between Tests 3 and 4 following removal of beta-adrenergic blockade. As with the previous variable,

Figure 3

EFFECT OF EXERCISE TRAINING ON TREADMILL EXERCISE DURATION

Brackets represent mean $\pm$ SEM.

- I = before training or drug;
- II = following acute drug administration before training;
- III = after training while receiving drug therapy;
- IV = after training following drug withdrawal

*denotes significant difference between that bar graph and the graph immediately preceding.

the overall improvement in $\dot{V}E$ max as measured between Test 1 and Test 4 was statistically similar for both groups (31.2% treatment vs. 23.2% control) (see Figure 4).

Maximal Oxygen Uptake

Initial (Test 1) relative maximal oxygen consumption ($\dot{V}O_2$ max ml/kg/min) was similar for both groups (30.9 ± 3.4 treatment vs. 29.9 ± 3.6 control). No significant changes occurred between Tests 1 and 2 for either group (30.9 ± 3.4 to 29.5 ± 3.4 treatment vs. 29.9 ± 3.6 to 30.9 ± 4.0 control). However, both groups experienced significant increases in relative $\dot{V}O_2$ max between Test 2 and Test 3 (29.5 ± 3.4 to 37.1 ± 3.4 vs. 30.9 ± 4.0 to 39.0 ± 4.7 ml/kg/min). In addition, the treatment group experienced a significant 11% gain between Test 3 and Test 4 (37.1 ± 3.4 to 41.1 ± 3.4 ml/kg/min). The control group (39.0 ± 4.7 to 40.4 ± 4.0 ml/kg/min) experienced a nonsignificant 3.6% increment between Tests 3 and 4. The overall improvement for both groups were similar when measured between Test 1 and Test 4; 33.0% for the treatment and 35.1% for the control population (see Figure 5).

When interpreting the absolute maximal oxygen consumption data ($\dot{V}O_2$ max l/min) the same pattern of improvement was noted. Again, no differences were noted between Test 1 and Test 2 for either group (2.2 ± 0.2 to 2.1 ± 0.3 treatment vs. 2.3 ± 0.3 to 2.4 ± 0.4 l/min control). Significant improvements were noted between Tests 2 and 3 for both groups (2.1 ± 0.3 to 2.6 ± 0.3 treatment vs. 2.4 ± 0.4 to 3.0 ± 0.4 l/min control). This computes to 24% and 25%

Figure 4

EFFECT OF EXERCISE TRAINING ON MAXIMAL VENTILATION

Brackets represent mean $\pm$ SEM.

- I = before training or drug;
- II = following acute drug administration before training;
- III = after training while receiving drug therapy;
- IV = after training following drug withdrawal

*denotes significant difference between that bar graph and the graph immediately preceding.

Figure 5

EFFECT OF EXERCISE TRAINING ON MAXIMAL OXYGEN CONSUMPTION

Brackets represent mean $\pm$ SEM.

- I = before training or drug;
- II = following acute drug administration before training;
- III = after training while receiving drug therapy;
- IV = after training following drug withdrawal

*denotes significant difference between that bar graph and the graph immediately preceding.

increments, respectively. In addition, the treatment group showed another significant increment (9.9%) when the propranolol therapy was withdrawn (2.6 ± 0.3 to 2.9 ± 0.3 l/min). Such a change was again not shown in the control population (3.0 ± 0.4 to 3.1 ± 0.4 l/min). When overall improvement was measured between Test 1 and Test 4, both groups had similar statistical gains in aerobic fitness; 32% for the treatment subjects compared with 35% in the control category.

Maximal Carbon Dioxide Production

Absolute maximal carbon dioxide production ($\dot{V}CO_2$ max l/min) was also measured. There were no differences noted between or among both groups for Tests 1 and 2 (2.3 ± 0.3 to 2.2 ± 0.3 treatment vs. 2.47 ± 0.4 to 2.53 ± 0.4 l/min control). Both groups had significantly greater maximal carbon dioxide production after ten weeks of training (2.2 ± 0.3 to 2.9 ± 0.3 treatment vs. 2.47 ± 0.4 to 3.23 ± 0.4 l/min control) as measured between Tests 2 and 3. There were no significant changes observed for either regimen between Test 3 and 4 (2.9 ± 0.3 to 3.0 ± 0.4 treatment vs. 3.17 ± 0.4 to 3.23 ± 0.4 l/min control). The overall improvement (Test 1 to Test 4) in carbon dioxide production for the propranolol and non-drug groups was 36% and 31%, respectively (see Figure 6).

Respiratory Quotient (RQ)

The respiratory quotient ($\frac{\dot{V}CO_2}{\dot{V}O_2}$) at maximal effort demonstrated

Figure 6

THE EFFECT OF EXERCISE TRAINING ON MAXIMAL CARBON DIOXIDE PRODUCTION

Brackets represent mean $\pm$ SEM.

- I = before training or drug;
- II = following acute drug administration before training;
- III = after training while receiving drug therapy;
- IV = after training following drug withdrawal

*denotes significant difference between that bar graph and the graph immediately preceding.

no differences between or among groups for Tests 1 and 2 ($1.08 \pm .01$ to $1.06 \pm .01$ treatment vs. 1.06 ± 0.02 to 1.04 ± 0.04 control). No differences were noted between or among groups for Tests 2 and 3 either (1.06 ± 0.01 to 1.11 ± 0.03 vs. 1.04 ± 0.04 to 1.06 ± 0.04). However, the treatment group experienced a decrement ($p = 0.057$) in RQ between Test 3 and test 4 (1.11 ± 0.03 to 1.03 ± 0.04) following propranolol removal. While this change was not significant at the 0.05 level, it nonetheless needs reporting as this correlated well with the aforementioned significant increment in oxygen consumption and stable carbon dioxide production noted between Tests 3 and 4 in the treatment group. No overall differences were noted between or among either group when comparing Test 1 and Test 4 data (see Figure 7).

Figure 7

THE EFFECT OF EXERCISE TRAINING ON MAXIMAL RESPIRATORY QUOTIENT

Brackets represent mean $\pm$ SEM.

- I = before training or drug;
- II = following acute drug administration before training;
- III = after training while receiving drug therapy;
- IV = after training following drug withdrawal

*denotes significant difference between that bar graph and the graph immediately preceding.

CHAPTER V

DISCUSSION

Previous studies (66, 67, 92) have well-documented the changes in body composition after endurance training. They found that total body mass and fat weight were generally reduced while lean body weight tended to remain constant or increase slightly. In this study, significant percent body fat decreases and lean mass increases were noted for only the propranolol subjects. However, both groups significantly decreased their absolute fat weight. The reason for this observed discrepancy is not clear. Both groups exercised at the same relative intensities with frequency, duration and total work being approximately equal. Although propranolol therapy may have had an influence on substrate utilization (3, 43), it is doubtful that this was primarily responsible for the difference noted between the groups' body composition data after training.

In the present study, maximal heart rate of the treatment group significantly increased between Tests 2 and 3. This finding is contrary to a very similar study by Sable and coworkers in which maximal heart rate did not change after training while the subjects continued to receive beta-blockers (76). It is possible that changes occurred in the beta-receptors that were responsible for the increased maximal heart rates noted in our investigation.

Catecholamine-induced changes in beta-adrenergic receptors have been intensively studied in animals. Generally speaking, any regimen that chronically lowers release of catecholamines will yield an increased receptor population and enhanced receptor sensitivity to catecholamine actions. This is often termed supersensitization or hypersensitization. On the other hand, a regimen that chronically increases catecholamine release yields a receptor population with decreased density and sensitivity (desensitization) (93).

A later study by Tohmeh and Cryer (86) assessed beta-adrenergic receptors utilizing (-) [^3H] dihydroalprenolol binding to mononuclear leukocyte preparations obtained during separate administration of isoproterenol and epinephrine in normal people. They found that binding increased 88% and 98% during the first hour of isoproterenol and epinephrine infusion, respectively. However, when the isoproterenol infusion was continued to 4-6 hours, the dihydroalprenolol binding actually decreased to 48% of pre-infusion values. These findings were all statistically significant ($p < 0.05$). Scatchard plot analysis attributed these changes to the number of binding sites rather than the binding affinity and therefore to sequential increases and decreases in the number of available mononuclear leukocyte beta-adrenergic receptors during agonist administration. It is important to note that the total mononuclear cell count did not change during the isoproterenol infusion. It thus appeared that a biphasic modulation of beta-receptors occurred with an early increment and late decrement in normal human subjects. In addition, the authors noted a significant

increase in heart rate response to a ten-minute "pulse" infusion of either isoproterenol or epinephrine injections. This certainly suggested that the early increment in receptor numbers on circulating cells was somewhat paralleled by increases in extra vascular (i.e., cardiac) beta-adrenergic receptor sensitivity.

Boudoula s et al. (8) hypothesized that chronic treatment with propranolol increased the number of active beta-adrenergic receptors (i.e, hypersensitivity) as evidenced by the enhanced cardiac response to the beta-agonist isoproterenol after propranolol withdrawal in six normal subjects. Such changes could have been responsible for the more pronounced maximal chronotropic response following propranolol therapy seen in the present study. In addition, Wiegman and colleagues (90) noted that exercise training decreased vascular sensitivity to norepinephrine in rats. They postulated that the training produced either a decrease in alpha- or an increase in beta-adrenergic receptor sensitivity. These changes were thought to occur as a result of the elevation of plasma epinephrine and norepinephrine levels that occurs during bouts of heavy exercise (65). Thus, it seems reasonable that a combination of a 30 minute to 1 hour exercise period yielding increased catecholamine levels and chronic propranolol therapy would have an additive or synergistic effect on increasing cardiac beta-receptors. This could easily account for the increased maximal heart rates observed immediately after training (Tests 2 and 3) in our investigation. Future studies on the combined effects of exercise training and propranolol on beta-adrenergic receptors are certainly warranted.

In the present investigation, acute propranolol therapy (Test 1 to Test 2) did not exert a deleterious effect on maximal exercise capacity as measured by both exercise time to exhaustion and maximal oxygen consumption. This would suggest that maximal cardiac output was not adversely affected by propranolol therapy as it has been noted that cardiac output increases almost rectilinearly with oxygen uptake (6, 14, 24, 82). These findings indicate that either an increase in stroke volume or arterio-venous oxygen difference had to occur to maintain exercise capacity. These findings are in agreement with other studies (34, 49, 78). However, other reports indicate that beta-adrenergic blockade may decrease exercise tolerance and maximal oxygen consumption (10, 25, 29, 64, 72). It is possible that these differences were due to single-dose versus multiple-dose beta-adrenergic blockade or to the use of hypertensive instead of normal subjects. It is also possible that those subjects who were receiving propranolol therapy developed a temporary inability to be motivated to maximal exercise because of the possible side-effects of propranolol, i.e., lassitude and depression (32). This sensation of increased muscle fatigue during exercise on propranolol therapy has been noted in the literature in somewhat anecdotal fashion (91). In a more objective communication (33) propranolol was found to have no effect on perceived exertion during isometric and isokinetic exercise. The fact that propranolol therapy has been shown to decrease skeletal lactate (2, 4, 43) production suggests that any undue fatigue during exercise with propranolol may be mediated via the central nervous system.

Another interesting finding was the significant increase (30.9%) in maximal ventilation (noted between Test 2 and Test 3) following ten weeks of training in the subject population while they continued to receive propranolol therapy. This was not observed in an earlier report by Sable and coworkers (76). In their study, maximal ventilation increased only after propranolol therapy had been withdrawn. They suspected that propranolol may have exerted a suppressive effect on maximal ventilation via effects on bronchiolar smooth muscle. This is certainly a viable hypothesis as propranolol also possesses β_2 -receptor blockade properties. In addition, the effects of chronic propranolol administration on suppressing lactate production in skeletal muscle (4, 30) may have decreased ventilatory stimulus by maintaining a lower POO_2 blood level. Our data, however, did not show this complete attenuation of ventilatory improvement on propranolol therapy as reflected by the aforementioned 30.9% increase. In addition, following propranolol removal, maximal ventilation further improved by a significant 16%. Thus, it appears that while nonselective beta-adrenergic blockade does not attenuate the ventilatory response to exercise conditioning, it nevertheless has a significant effect on the degree to which this response is manifested in normal subjects.

The present study demonstrated significant and equal gains in endurance time and maximal oxygen uptake following training in both the control and propranolol therapy groups as determined from Test 1 and Test 4. An important finding was that the propranolol group required the washout of the drug (Test 3 to Test 4) to manifest the

full effects of training. These findings are contrary to Sable's study where he found no improvement in oxygen consumption in the propranolol group even after withdrawal of the propranolol therapy while the controls made significant fitness gains. Sable did note a small but significant improvement (9%) in exercise duration between Test 1 and Test 3 in the treatment group as compared to a greater than 20% increment in his control subjects. However, his propranolol therapy group experienced no further increase in exercise duration following drug removal in contrast to the further significant improvement observed in our treatment population following propranolol withdrawal. An earlier study (51) had shown that regular intermittent infusion of a synthetic catecholamine, dobutamine, in canines resulted in cardiovascular conditioning effects that resembled those achieved during regular intermittent aerobic exercise. Sable hypothesized that beta-adrenergic sympathetic stimulation was an important factor in exercise training and that beta-blockade had attenuated completely the effects of aerobic conditioning in his normal subjects. These discrepancies with the present investigation may be explained by the fact that individual plasma propranolol concentrations were used to determine dosages for the treatment population in Sable's study. The individual mean propranolol concentrations were 100-292 ng/ml with the total daily doses necessary to achieve such levels ranging from 166-640 mg. In our study, each subject in the drug group received precisely 160 mg. propranolol daily and plasma levels were not determined. It is therefore plausible that our subjects had relatively lower plasma

propranolol levels and were thus less apt to be completely beta-adrenergically blockaded. It would then follow that our subjects would have received some beta-adrenergic stimulation during exercise with the resultant improvement observed. Another reason for the different training responses between our study and Sable's may be due to the fact that our people trained for ten weeks at three monitored sessions per week, whereas Sables' trainees exercised for five weeks at five sessions per week. Previous studies have documented that the amount of improvement in $\dot{V}O_2$ max tends to plateau when frequency of training is increased above three days/week (31, 66, 68). This would tend to minimize any additional training benefit of Sable's five sessions/week compared with our three session/week protocol. In addition, the different lengths of the two training programs may also have been partially responsible for the aforementioned discrepancies in training effects observed. Improvement in the fitness variables discussed have been shown to continue over several months of training (19, 45, 46, 66). It is therefore reasonable to state that short-term training studies of a few weeks duration have definite limitations when interpreting training results (28, 66, 67). Thus, it is certainly plausible that Sable's five week training program was simply not of sufficient duration to chronically stimulate beta-receptor populations even though substantial receptor blockade was undoubtedly present. This is reflected by comparing the overall fitness improvement in the control groups for both studies. Our controls demonstrated a 35.1% (29.9 ± 3.6 to 40.4 ± 4.0 ml/kg/min [$\pm$ SEM]) increase in relative

$\dot{V}O_2$ max and a 46% (15.7 ± 2.3 to 22.9 ± 2.6 minutes) increase in exercise duration. In contrast, Sable's control group had a 20.9% (43.6 ± 2.9 to 52.7 ± 3.2 ml/kg/min) improvement in relative $\dot{V}O_2$ max and a 29.3% (16.4 ± 1.3 to 21.2 ± 1.5 minutes) increment in exercise duration. These findings tend to support the premise that our ten week training program was a key factor in eliciting a much higher percentage improvement in aerobic capacity compared with the five week program in the other investigation. It is reasonable to suggest that any possible fitness gains in Sable's propranolol group would less likely be manifested due to the relatively brief five week training program.

It should be noted, however, that our subjects receiving propranolol had initial lower relative maximal oxygen uptakes compared with Sable's propranolol subjects. These differences in initial fitness levels are important when assessing fitness changes as it has been shown previously that the lower the initial $\dot{V}O_2$ max, the larger the percent of improvement (7, 20, 58, 59, 60).

As noted in the Results section, both groups realized significant improvement in maximal oxygen consumption, carbon dioxide production, ventilation and exercise duration over the ten week training period. Of particular interest is the observation that not only did the propranolol group experience significant fitness gains while receiving drug therapy (Test 2 to Test 3), they also experienced further significant increments in the aforementioned variables following withdrawal of beta-blockade (Test 3 to Test 4). It would appear that even in the presence of substantial beta-adrenergic

blockade, training adaptations are expressed (albeit incompletely) until the beta-blockade is withdrawn. This withdrawal thus allowed the complete effects of training to be manifested. It is also possible that an ability to increase work capacity was perhaps effected when blockade was removed rather than affecting the degree of response. This withdrawal-mediated improvement was not observed in Sable's investigation. The end result was that the overall improvement in the aforementioned variables was statistically similar and therefore not affected adversely by propranolol therapy.

There are several hypotheses for these additional physiologic gains following propranolol withdrawal. The vasodilation in exercising muscle is locally adjusted to the workload and may be considered the fundamental determinant of cardiac output during exercise. This is supported by studies performed on canines with denervated hearts (13, 22). It is possible that chronic propranolol administration decreased the release of certain vasodilator metabolites in the skeletal muscle during exercise (2, 43). This would result in a blunted increase in cardiac output following training and hence a lower $\dot{V}O_2$ max and exercise duration in comparison with control population improvement between Tests 2 and 3. Propranolol withdrawal, by removing this blockade to vasodilator release in the muscle, would increase the cardiac output secondarily by increasing the total vasodilator metabolite production with the subsequent improvement in oxygen uptake and exercise duration noted from Test 3 to Test 4.

Another reason for the improvement in aerobic capacity following propranolol withdrawal may be related to the possible changes that may have occurred in the beta-adrenergic receptors. As mentioned earlier, beta-receptor populations were noted to increase following short term increases in catecholamine release (86) as well as during chronic administration of beta-blockade substances (93). Following beta-blockade withdrawal, this augmented receptor population may have yielded an augmented inotropic catecholamine response during exercise with a subsequent increase in cardiac output, $\dot{V}O_2$ max and exercise duration. It may also be possible that the increased heart rate following drug removal was significant in augmenting cardiac output and hence performance. Whether or not the actual sensitivity of the beta-receptors increased following propranolol withdrawal could not be ascertained with certainty in our investigation.

Lindenfeld et al. (52) found no evidence of hypersensitivity for beta-adrenergic mediated responses with epinephrine infusion following abrupt propranolol withdrawal in both normal subjects and in patients with mild to moderate angina pectoris. However, Boudoulas et al. (8) and Nattel and coworkers (62) did purport to have demonstrated hypersensitivity to isoproterenol infusions within a six day period following withdrawal of propranolol. The protocol differences between these studies makes absolute statements regarding possible hypersensitivity phenomena unfeasible.

Another reason for the increased $\dot{V}O_2$ max between Tests 3 and 4 may be gleaned from the following discussion. It is generally agreed that in the absence of pulmonary pathology, respiration is not

a limiting factor in $\dot{V}O_2$ max (13, 41) and therefore $\dot{V}O_2$ can thus be expressed using the Fick equation: $\dot{V}O_2$ max = HR max x stroke volume max X arterio-venous oxygen difference max. Approximately 50% of the increase in $\dot{V}O_2$ max following training in normal people is due to increased arterio-venous maximal systemic differences (23, 75, 77). This is most likely due to the observed mitochondrial and enzymatic changes (38) in trained muscles allowing for the greater oxygen extraction in the peripheral circulation. The other 50% improvement in $\dot{V}O_2$ max would occur as a result of increased perfusion (cardiac output) to the working muscles. It may be that beta-blockade allowed only expression of the peripheral effects of training (arterio-venous oxygen difference) during Test 3, while blockade removal allowed the additive expression of the central adaptations (i.e., increased HR x increased SV yielded an increased C.O. as seen in Test 4).

In any event, it would appear from the present investigation that substantial beta-adrenergic blockade therapy did not attenuate significant aerobic conditioning in normal subjects. Previous studies have noted significant increases in $\dot{V}O_2$ max following training in populations with coronary artery disease (15, 17, 27, 36, 44) from 18-36%. The majority of these subjects no doubt were receiving beta-blockade therapy yet still manifested improvement in $\dot{V}O_2$ max. In the present study, it would appear that for the training effect to be fully expressed, the beta-blockade needs to be withdrawn.

Summary for Discussion

Our study demonstrated significant fat loss for both groups of subjects although, for some unexplained reason, only the propranolol group increased lean mass and decreased body fat percentage. We noted no acute effects of propranolol therapy on ability to perform maximal exercise and, therefore, are in agreement with an earlier similar study by Sable (76). Our propranolol subjects, however, realized significant conditioning effects after training and even further improvement following drug removal in contrast to the lack of conditioning benefits reported by Sable. Difference in drug dose, length of training programs, and initial fitness levels may have contributed to these discrepancies.

The physiologic gains that were observed following propranolol withdrawal were probably mediated, in part, by both qualitative and quantitative changes in the beta-adrenergic receptor populations. The effect of propranolol on exercise-induced vasodilator metabolite production may have also contributed to these gains.

CHAPTER VI

SUMMARY AND CONCLUSIONS

Previous studies have shown endurance exercise to effect adaptive changes in the cardiopulmonary system in both healthy subjects as well as coronary artery disease populations. The beta-adrenergic stimulation that accompanies endurance exercise has been suggested as a key factor for this conditioning process.

To further our understanding of the mechanism of the training effect we recruited fourteen healthy men and woman, ages 22 - 45 years, to participate in a ten week training study. Eight of our subjects consented to receive 40mg of propranolol every six hours during the conditioning phase while the other six volunteers received no such treatment. We administered graded maximal exercise tests on bicycle ergometers at four different intervals in order to assess both the acute and chronic effects of propranolol on endurance capacity as well as the effects of drug removal. Each subject was tested before starting propranolol treatment or training (Test 1), following three days of oral propranolol vs. no drug therapy (Test 2) and after a ten week exercise program consisting of 40 minute sessions three times per week (Test 3). The intensity of exercise was calculated at 60-75% of each subjects' maximal oxygen uptake derived from the results of the second maximal exercise bout (Test

2). The final exercise test (Test 4) was performed following a gradual removal of propranolol therapy over a four day interval. In addition, percent body fat and lean body mass measurements were performed using skinfold calipers before and after the conditioning program. Our results were quite interesting and, in some instances, unexpected.

Only the propranolol group experienced a significant ($p < 0.05$) loss of percent body fat and an increased lean body mass. Both groups, however, did note significant decreases in absolute fat weight after training. The reason for this discrepancy between groups was not well understood.

Maximal oxygen uptake, ventilation, carbon dioxide production and exercise time to exhaustion were unaffected following acute propranolol administration (Test 1 to 2). Following ten weeks of endurance exercise training significant gains were noted in all of the aforementioned variables (Test 2 to 3). This improvement in maximal oxygen uptake and exercise time to exhaustion was less pronounced in the propranolol group than the control population. However, when the propranolol therapy was withdrawn (Test 3 to 4), further significant increments were realized in maximal oxygen consumption, ventilation and exercise time to exhaustion. Thus, the overall improvement in oxygen consumption, ventilation and exercise time to exhaustion (Test 1 to 4) was statistically identical for both propranolol and control populations.

As expected, maximal heart rate and systolic blood pressure decreased significantly following acute administration of propranolol

(Test 1 to 2). Following propranolol withdrawal (Test 3 to 4) both variables returned to pre-propranolol baseline values. However, the maximal heart rate did increase significantly following the ten week exercise regimen (Test 2 to 3) despite the presence of beta-blockade while no such observation was noted for the systolic blood pressure. There exist several hypotheses for the aforementioned physiologic gains following propranolol withdrawal. These include: 1) possible increases in the number and sensitivity of beta-adrenergic receptors secondary to both exercise-induced catecholamine release and chronic administration of beta-blocker substances (8, 62, 86, 93). Following beta-blockade withdrawal, this augmented receptor population could quite conceivably have mediated the increased cardiac output, $\dot{V}O_2$ max and exercise duration observed in our study; 2) chronic propranolol administration may have decreased the release of vasodilator metabolites responsible for increasing cardiac output (and therefore increasing $\dot{V}O_2$) during exercise (2, 43). Subsequent propranolol removal would have released this partial blockade to metabolite production thereby allowing cardiac output, $\dot{V}O_2$ max and exercise time to equal the post-training improvement observed in the control population; 3) this hypothesis would also explain the similar improvement in maximal ventilation following propranolol removal via a similar mechanism (4, 30).

Our study indicated that significant training effects do in fact occur in the presence of substantial beta-adrenergic blockade. These findings are contrary to a previous study of similar design by Sable (76). He noted no improvement in maximal ventilation, maximal oxygen

uptake or maximal heart rate following five weeks of vigorous aerobic conditioning in normal subjects receiving propranolol therapy. Reasons for the discrepancies between Sable's study and our investigation include: 1) the longer length of our conditioning program; 2) the lower initial fitness levels in our subject population; and 3) the greater doses of propranolol received by Sable's treatment group.

Conclusions

Within the limitations of this study, the following conclusions were derived:

1. Normal individuals can improve exercise endurance capacity during beta-adrenergic blockade.
2. The full expression of the improvement will not be realized until beta-blockade is withdrawn.
3. These findings are contrary to earlier reports that demonstrated beta-adrenergic blockade to completely attenuate exercise conditioning in normal subjects.
4. The results of this investigation cannot, at this time, be extrapolated to a population of patients with coronary artery disease.

Recommendations

Possibilities for further investigation are numerous and should include:

1. The use of larger and smaller doses of propranolol in order

to delineate what effect, if any, this variable would exert on the training response.

2. Comparing the effects of cardio-selective beta-adrenergic blockers with non-selective (propranolol) therapies.
3. Determination of cardiac output changes by non-invasive methodologies (i.e., carbon-dioxide rebreathing) and in so doing thereby also study changes in arterio-venous oxygen differences and how these are modulated by beta-adrenergic blockade.
4. The use of selected populations of patients with coronary artery disease in an effort to compare their training responses with and without beta-blockers to normal subjects.

APPENDIX

Analysis of Variance
for Maximal Respiratory Quotient

Source	SS	df	MS	F-ratio
Mean	62	1	61.5	5295.87
Group	0.04	1	0.004	0.31
Error	0.14	12	0.012	
R	0.02	3	0.008	2.41
RG	0.005	3	0.0016	0.53
Error	0.1	36	0.003	

Analysis of Variance for
Percent Body Fat

Source	SS	df	MS	F-ratio
Mean	33389	1	33389	86.48
Group	16	1	16	0.04
Error	4633	12	386	
R	67	3	22	11.55*
RG	4	3	1.3	0.69
Error	70	36	1.9	

* $p < 0.05$

Analysis of Variance for
Lean Body Mass

Source	SS	df	MS	F-ratio
Mean	814696	1	814696	527.14
Group	1007	1	1007	0.65
Error	18546	12	1546	
R	77	3	26	2.89*
RG	28	3	9.5	1.06
Error	321	36	8.9	

* $p < 0.05$

Analysis of Variance for
Fat Weight

Source	SS	df	MS	F-ratio
Mean	90248	1	90248	65.58
Group	225	1	225	0.16
Error	16514	12	1376	
R	236	3	79	14.04*
RG	5.8	3	1.9	0.34
Error	202	36	5.6	

* $p < 0.05$

Analysis of Variance for
Systolic Blood Pressure

Source	SS	df	MS	F-ratio
Mean	1712253	1	1712253	794.63
Group	4521	1	4521	2.10
Error	25858	12	2155	
R	2448	3	816	3.98*
RG	1807	3	602	2.94
Error	7380	36	205	

* $p < 0.05$

Analysis of Variance for
Maximal Heart Rate

Source	SS	df	MS	F-ratio
Mean	1690316	1	1690316	2937.37
Group	4449	1	4449	7.73*
Error	6905	12	576	
R	7433	3	2478	43.42*
RG	6512	3	2171	38.04*
Error	2054	36	57	

* $p < 0.05$

Analysis of Variance for
Exercise Duration

Source	SS	df	MS	F-ratio
Mean	19638	1	19638	134.31
Group	12	1	12	0.08
Error	1755	12	146	
R	536	3	179	156.20*
RG	22	3	7.3	6.40*
Error	41	36	1.1	

*p < 0.05

Analysis of Variance for
Maximal Ventilation

Source	SS	df	MS	F-ratio
Mean	319446	1	319446	137.30
Group	1059	1	1059	0.46
Error	27920	12	2327	
R	4041	3	1347	10.19*
RG	652	3	217	1.65
Error	4758	36	132	

*p < 0.05

Analysis of Variance for
Relative Maximal Oxygen Consumption

Source	SS	df	MS	F-ratio
Mean	66544	1	66544	184.61
Group	2.2	1	2.2	0.01
Error	4325	12	361	
R	1192	3	397	49.46*
RG	23	3	7.6	0.95
Error	289	36	8.0	

*p < 0.05

Analysis of Variance for
Absolute Maximal Oxygen Consumption

Source	SS	df	MS	F-ratio
Mean	360	1	360	143.94
Group	0.95	1	0.95	0.38
Error	30	12	2.5	
R	6.3	3	2.1	45.04*
RG	0.1	3	0.04	0.82
Error	1.7	36	0.05	

*p < 0.05

Analysis of Variance for
Maximal Absolute Carbon Dioxide Production

Source	SS	df	MS	F-ratio
Mean	407	1	407	122.81
Group	0.9	1	0.9	0.26
Error	40.0	12	3.3	
R	7.0	3	2.3	39.51*
RG	0.07	3	0.03	0.42
Error	2.1	36	0.06	

*p < 0.05

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