REPRODUCIBILITY AND SENSITIVITY OF DOPPLER ECHOCARDIOGRAPHIC INDICES OF LEFT VENTRICULAR FUNCTION DURING EXERCISE

by

Alan D. Moore, Jr.

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APPROVED:

William G. Herbert, Co-Chair	Dennis E. Hinkle, Co-Chair
Don R. Sebolt	Harry H. Robertshaw
J. Michael Payne	Frank C. Gwazdauskas

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(ABSTRACT)

The two most common methods used for the assessment of left ventricular function (LVF) are two-dimensional echocardiography and nuclear ventriculography. Recent technological advances have led to the development of an inexpensive, noninvasive alternative: the stand-alone continuous wave Doppler echocardiograph. The purposes of this study were twofold: 1) to examine the repeatability of three Doppler measured indices of LVF during repeated exercise trials, and 2) to determine if induced changes in myocardial contractility would be reflected by changes in the Doppler indices. The Doppler indices of LVF were the peak acceleration of ascending aortic blood (pkA), peak velocity of ascending aortic blood (pkV), and the integral of the velocity-time waveform (SVI). The study was conducted in two phases. In the first phase, 44 young, healthy males performed similar graded cycle exercise tasks on two separate

days. Exercise levels were increased by 50 W every three minutes. PkA, pkV, SVI, blood pressure, heart rate and oxygen consumption were recorded every stage. The test was continued until the subject reached symptom-limited maximum. Pearson product-moment correlation coefficients were used to determine the reproducibility of the dependent measures between the two tests.

The second phase involved the testing of a subset of the original 44 subjects (N=18) under a placebo (control) condition, acute beta-blockade, and oral hyperhydration states. Hematocrit was measured as a means to assess blood volume changes. The subjects exercised at levels requiring 20, 40 and 60% of their maximum oxygen consumption. Each stage lasted six minutes. PkA, pkV, SVI, heart rate, blood pressure, cardiac output, and stroke volume were measured. The latter two were determined by a carbon dioxide rebreathing technique. This was a split-plot design with multiple dependent measures. The statistical analysis was a multivariate analysis of variance (MANOVA) with repeated measures. Appropriate univariate tests were utilized as post-hoc procedures.

With respect to the first phase, the correlation coefficients for pkA ranged from 0.54-0.81, for pkV,

0.65-0.77, and for SVI, 0.40-0.71. The results of the second phase indicated that alterations in contractile status by beta-blockade was reflected by changes in the Doppler measures, but the hyperhydration state did not produce a change in cardiac contractile response that was detectable. There were no documented changes in plasma volume as measured by change in hematocrit, therefore, the effectiveness of the hyperhydration procedure was judged ineffective. PkA and pkV were significantly reduced ($p<.01$) at all stages of exercise in the beta-blocked state as compared to the placebo values. Cardiac output and heart rate were significantly lower in the beta-blocked state, and stroke volume was significantly higher.

The results of this experiment indicates that continous wave Doppler echocardiographic estimates of LVF are reproducible ($r=0.40-0.81$) and reflect changes in myocardial contractility induced by acute beta-blockade.

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Chapter I

INTRODUCTION

Coronary heart disease is the leading cause of death in the United States (Cooper, Stamler, & Dyer, 1978). The American Heart Association estimates that the total incidence of myocardial infarction alone is close to 1,500,000 events annually (American Heart Association, 1981). The problem of cardiovascular disease is multifactorial and risk reduction requires intervention in many aspects of American lifestyle. In 20% of the cases, the first and only symptom of coronary disease is death (Illingworth & Connor, 1985). The most common clinical screening test for suspected ischemic heart disease is the graded exercise test (Schlant et al., 1986). During the typical graded exercise test the subject performs exercise on either a treadmill or cycle ergometer while electrocardiographic (ECG) and blood pressure responses are monitored. These variables can offer valuable information when trying to discern if coronary artery disease is present in an individual.

Often, the diagnosing physician is interested in knowing if any degree of left ventricular dysfunction exists. The routine measurements of ECG and blood pressure may offer some clues in this area but taken alone do not constitute highly

sensitive and specific diagnostic indicators of ventricular dysfunction (Lambert, Nichols, & Pepine, 1982). At present the two methods most frequently employed for the assessment of left ventricular function are two-dimensional echocardiograhy and nuclear ventriculography (Bennett, Barclay, Davis, Mannering, & Mehta, 1984). Both of these methods are very time-consuming, expensive, and require extensive personnel training to perform. In addition, nuclear ventriculography is an invasive technique that involves exposure to radioactivity as well as a higher level of acute risk than would be acceptable for "routine" assessment.

In 1964, Rushmer described a measurement he termed "initial ventricular impulse" that could be used for evaluation of left ventricular performance. At that time this measurement could only be obtained using flowmeters that were surgically implanted into the aorta. The methods of Doppler echocardiography have been developed since that time which allow non-invasive assessment of this ventricular impulse. Essentially, Doppler echocardiographic systems use ultrasonic energy to measure the flow velocity of blood cells. The concept is very similar to the use of radar for measuring the speed of automobiles on a highway. To assess left ventricular function the Doppler transducer is aimed

toward a target area, usually the ascending aorta. The ultrasonic signal produced by the transducer is transmitted at a known frequency. When the signal reaches the target, it is reflected back at a frequency that has been shifted in a manner proportional to the flow velocity in the target region (in this case blood cells in the aorta). The dynamics of blood flow in the aorta should theoretically reflect the contractile state of the left ventricle, as the blood is being ejected by the latter directly into the former.

There are two basic types of Doppler systems. The first type is the pulsed-wave (PW) Doppler. In PW Doppler systems one transducer (crystal) is used to send out a short burst of sound energy and then the same transducer is used to sense the return of the reflected sound (Labovitz & Williams, 1985). The main advantage of PW Doppler systems is the feature of selection of a discrete sample depth. This dimension of depth selection allows the operator of the PW Doppler to sample from highly localized sites; however, the PW systems have the disadvantage of "flow aliasing" (inability to measure high flow velocities such as those found in the ascending aorta during exercise). Another disadvantage is that there is no assurance that the PW Doppler signal is aimed at the correct sample depth unless an aiming device is used. The most common aiming device is

a two-dimensional echocardiograph with an aiming cursor displayed on the oscilliscope. The need for this type of sophisticated aiming device makes PW Doppler too expensive for use in most small hospitals or clinicians' offices.

The second type of Doppler echocardiographic system is the continuous wave (CW) type. The CW Doppler uses two crystals in one transducer housing. One transducer continuously generates sound waves toward the target area, the second transducer continuously receives the reflected sound waves. This method produces an analyzable signal that is reflected back from all target depths through which the transmitted signal passes. This means that a rapid scan can be used to aim the signal toward the blood vessel region which has the highest flow velocity. There is no flow aliasing problems associated with CW Doppler scans. These characteristics make it possible for the CW system to be used as a "stand alone" device which can be operated with a minimal amount of training.

EXERDOP is a CW Doppler echocardiograhic system designed specifically to measure blood flow through the ascending aorta during exercise testing. The transducer is placed in the suprasternal notch, a site which allows evaluation of aortic blood flow with minimal chance of contamination from other blood vessels (Daley, Sagar, & Wann, 1985). The

measurement obtained with the system are peak blood flow acceleration, peak blood flow velocity, and systolic velocity integral (also termed stroke distance).

One recent study by Sabbah, Khaja, Brymer, McFarland, Albert, Snyder, Goldstein, and Stein (1986) utilized EXERDOP to evaluate left ventricular performance and indicated that peak blood flow acceleration to be a useful indicator of global left ventricular performance. They based this conclusion on the finding that peak aortic acceleration was highly correlated (r=.90) with ejection fraction. They also performed in vitro evaluation of EXERDOP as a subsection of their paper and found that the velocities recorded by EXERDOP correlated highly with the known velocity of the target material. To date, in vivo studies of reproducibility of the EXERDOP measurements during exercise have not been reported.

Statement of the Problem

Stand-alone CW Doppler systems offer a method with which to assess global left ventricular performance. Considering the expense and/or invasive nature of currently utilized techniques, a stand-alone CW Doppler system such as the EXERDOP may be a valuable tool for both researchers and clinicians. The EXERDOP system has not been evaluated thoroughly in the field; therefore, an evaluation of the instrument is necessary. Questions to be considered in such

an evaluation include: 1) Are the measurements of peak blood flow acceleration, peak blood flow velocity, and systolic velocity integral repeatable when using EXERDOP? and, 2) Can alterations of the contractile state of the left ventricle be reliably detected by the instrument?

To answer these questions, evaluation of the EXERDOP system was conducted in two phases. The first phase consisted of a reproducibility study. In the study, subjects performed graded exercise on a bicycle ergometer on two separate days. The EXERDOP measurements were obtained at regular intervals throughout the test, as were heart rate and blood pressure data. The second phase of the EXERDOP evaluation consisted of a subject group tested under a control condition and under two conditions that were designed to alter their left ventricular responses to exercise. One of the experimental conditions involved the administration of atenolol, a cardioselective beta-blocker medication that has been demonstrated to cause a negative inotropic and chronotropic response. Another condition involved the administration of a placebo to obtain control data on the same subjects. The third experimental condition involved oral hyperhydration to transiently increase the blood (plasma) volume of the subjects. The increase in plasma volume was imposed to induce an increase in preload stress

on the left ventricle and result in an increased ejection fraction, without appreciably altering contractility.

Significance of the Study

This study is designed to examine two aspects of the use of a stand-alone CW Doppler system (EXERDOP) in exercise testing. The assumption currently is that the velocity measurements and the derivatives that EXERDOP is designed to evaluate are reproducible, but this assumption has not been adequately tested. Furthermore, the specificity of the system to changes in inotropic status of the heart should be explored. The results of both the reproducibility and sensitivity aspects of the study will be of interest to both practitioners and researchers who wish to quantify left ventricular function.

Research Hypothesis

1. Ho: there is no relationship between the EXERDOP derived measurements of peak blood flow acceleration, peak blood flow velocity, and systolic velocity integral collected at equivalent exertional levels on two separate days during identical graded exercise tests.
2. Ho: there are no differences between the EXERDOP derived measurements of peak blood flow acceleration, peak blood flow velocity, and systolic

velocity integral when these are obtained under three conditions: 1) Placebo; 2) a reduced inotropic state (Acute Beta-blockade); and 3) a condition with increased ventricular preload (Hyperhydration).

Delimitations

The following delimitations are inherent in the design of this study:

1. The sample size was restricted to 44 volunteers for the reproducibility phase of the study and 18 for the specificity phase;
2. Only moderately active males ($\dot{V}O_2max$ 30-55 $ml \cdot kg^{-1} \cdot min^{-1}$) were used as subjects.

Limitations

Thus, the following limitations restrict the generalizability of the findings:

1. Subjects were recruited in a non-random fashion;
2. Results from this study may be applicable to a population of people possessing similar physical characteristics and activity levels as the experimental group. Therefore, generalizations to clinical populations should be made with caution.

Basic Assumptions

The following basic assumptions were made regarding the study:

1. the angle of incidence between the direction of motion of the blood in the ascending aorta and the direction of Doppler interrogation was zero degrees (0°);
2. the blood flow in the aortic jet was laminar;
3. the subjects did not have aortic stenosis or coronary artery disease;
4. the subjects followed the instructions given regarding behavior before the tests;
5. during the preliminary tests of maximal oxygen consumption, the subjects reached a maximal level;
6. in 3 hours prior to the exercise trials involving drug administration, that the subject orally consumed the correct drug (placebo or atenolol);
7. all measurements of metabolic and cardiovascular function were performed accurately;
8. the subjects maintained the same level of fitness throughout the study.

Definitions and Symbols

Body Temperature and Pressure Saturated (BTPS) - a subscript that appears next to a volume of gas that indicates the gas was measured at 310°K, 760 mmHg, 100% humidity.

Cardiac Output (Q) - the amount of blood pumped by the heart per unit of time. Cardiac output is a product of heart rate and stroke volume, and is usually expressed in liters•min^{-1} (Brooks & Fahey, 1984).

Continuous Wave Doppler (CW) - an echocardiographic method used to measure blood velocity. CW Doppler continuously transmits and receives an ultrasonic signal for analysis (Labovitz & Williams, 1985).

Ejection Fraction (EF) - the percentage of the end-diastolic volume that is pumped from the left ventricle (Brooks & Fahey, 1984).

EXERDOP - a stand-alone CW Doppler system specifically designed for use during graded exercise testing.

Flow Velocity Integral- a synonym of systolic velocity integral.

Fraction of Expired Carbon Dioxide (F_ECO_2) - the percentage of carbon dioxide present in an individual's expired air.

Fraction of Expired Oxygen (F_EO_2) - the percentage of oxygen present in an individual's expired air.

Hematocrit (Hct) - the percentage by volume of red cells in blood.

Peak Blood Flow Acceleration (PkA) - the maximum change in blood flow velocity per unit of time. Usually expressed as $m \cdot sec^{-1} \cdot sec^{-1}$.

Peak Blood Flow Velocity (PkV) - the maximum blood flow velocity during systole. Usually expressed as $m \cdot sec^{-1}$.

Pulsed Wave Doppler (PW) - a Doppler echocardiographic method used to measure the velocity of blood. A PW Doppler uses one transducer to transmit sound energy in pulses and receive the reflected signal (Labovitz & Williams, 1985).

Plasma Volume (PV) - the fluid volume (non-cellular) within the vascular system.

Standard Temperature and Pressure Dry (STPD) - a subscript that appears next to a volume of gas that has been standardized to 273°K, 760 mmHg, 0% humidity.

Stroke Distance (SD) - a rarely used synonym of systolic velocity integral.

Stroke Volume (SV) - the amount of blood pumped from the left ventricle per beat. Usually expressed in $ml \cdot beat^{-1}$.

Systolic Velocity Integral (SVI) - the area under the curve of a plot of blood flow velocity vs. time. This is expressed in cm of distance the blood traveled during

the time of velocity measurement for a single systolic ejection.

Ventilation Expired ($\dot{V}_E$) - the volume of air expired in one minute.

Volume of Carbon Dioxide ($\dot{V}CO_2$) - the volume of carbon dioxide produced in one minute.

Volume of Oxygen Consumption ($\dot{V}O_2$) - the amount of oxygen consumed by an individual per minute.

Volume of Oxygen Comsumption (maximal) ($\dot{V}O_2max$) - the maximum volume of oxygen that can be consumed by an individual per minute under conditions of vigorous dynamic exercise. $\dot{V}O_2max$ is considered to be the criterion measurement of aerobic fitness.

Chapter II

REVIEW OF THE LITERATURE

This chapter contains a review of literature pertaining to the determination of left ventricular function. The content is organized into eight separate sections. First, invasive studies of left ventricular function are reviewed. The second section introduces the Doppler concept and identifies potential problems in Doppler measurement. The next section describes research involving Doppler velocimetry as an assessment tool for cardiac output. Doppler echocardiographic studies of left ventricular function under states of altered volume, pressure, or pharmacological state are presented next. Sections reviewing the Doppler responses of apparently healthy individuals, the detection of coronary artery disease during resting Doppler measurements, and the detection of coronary artery disease by Doppler response during exercise follow. The final section reviews reproducibility of the Doppler measurements of velocity.

Invasive Studies of Left Ventricular Function

Rushmer (1964) provided the foundation for the applications of the Doppler measurements of peak blood flow velocity and peak blood flow acceleration. He introduced the term "initial ventricular impulse." Impulse is defined in

Newtonian physics as the product of force and time ($I=F \cdot t$). Initial ventricular impulse is the net force acting over time from the beginning of systolic ejection to the attainment of peak blood flow rate. Using indwelling flow-meters, he was able to describe the characteristics of blood flow from the right and left ventricles by measuring blood flow in the aorta and the pulmonary arteries of dogs. These measurements in the aorta showed peak acceleration occurred as the flow velocity ascended to its peak value, and demonstrated that normal left ventricular ejection was characterized by the sudden imparting of momentum to the blood. One of the dogs was exercised on a treadmill. The peak flow rate of the blood increased greatly, while the ejection time was decreased. It was noted that these changes in combination only caused a slight rise in stroke volume.

Rushmer (1964) reported that these changes in ejection pattern were similar to those which were observed during stimulation of the heart by the sympathetic nerves. He also speculated that the greater force development could result from either a more synchronous excitation throughout the myocardium or a more powerful myocardial contraction. Of the two he hypothesized that the latter was more likely, as the contractile mechanism does not seem to be closely tied to the electrical activity in the myocardial cell membranes. The

study also examined the effects of ventricular premature contractions, coronary occlusion, sudden blood loss, and the administration of general anesthesia on this initial ventricular impulse. Under all of these conditions initial ventricular impulse was markedly decreased. Because animals were used as subjects, direct extrapolation to the human was not possible, although he did state that humans may respond similarly. Implantation of flowmeters for experimental purposes in the human that would allow such comparison is ethically prohibited, but development of Doppler echocardiography in later years allowed the equivalent noninvasive measurements of acceleration and velocity.

Noble, Trechard, and Guz (1966) examined aortic velocity and aortic acceleration to evaluate the potential of these indices as parameters of left ventricular function. The study was designed to determine if maximum acceleration was a sensitive measurement that would reflect changes in myocardial contractile state. Fifteen dogs had electromagnetic flowmeters surgically implanted in the ascending aorta, polyvinyl catheters were placed into the anterior descending and/or circumflex branches of the left coronary artery, and a Teflon catheter also was inserted into the left carotid artery. The tip of the catheter was advanced until it reached the ascending aorta. A snare was

placed around the left anterior descending branch of the left coronary artery so that experimental coronary occlusion could be induced. The dogs then were allowed a week of recovery before the experimental trials. The surgical preparations allowed the experimenters to measure aortic flow velocity, and left ventricular stroke volume. From the aortic flow velocity measurements, the variables of peak flow, peak acceleration, and ejection time could be calculated directly. Baseline data were obtained from the dogs after they had been allowed to rest quietly.

The first treatment the investigators imposed was coronary occlusion. The result of the induced ischemia was a reduction in maximum acceleration which was greater than the reduction of peak flow and stroke volume. Peak acceleration was the threshold variable first affected by the occlusion. The next treatment was infusion into the coronary arteries of isopropylnorepineprine or calcium gluconate. Both of these drugs are known to increase myocardial contractility. The injection of either of these produced an increase in maximum acceleration of blood through the ascending aorta. Peak blood flow and stroke volume also increased, but not as markedly. The last experimental treatment imposed was alteration of the posture of the animal from a sitting to a lying position. This change in posture

is known to cause alteration of ventricular filling. Heart rate was kept constant by right atrial pacing. The change in posture produced marked change in both stroke volume and peak blood flow. Maximum blood acceleration was affected very little by postural change.

From the results of the trials it was concluded that maximum acceleration was very sensitive to changes induced in the left ventricular muscle but insensitive to changes of velocity and ejection fraction induced by alternations in left ventricular end diastolic volume. The earlier and larger changes of maximum acceleration with induced myocardial ischemia also suggested that it was a sensitive index of myocardial contractility.

Jewitt, Gabe, Mills, Maurer, Thomas and Shillingford (1974) examined aortic blood flow measurements to determine if these were sensitive indices of left ventricular function. This research group measured both velocity and acceleration with a catheter-tip velocity probe in a group of 24 patients with coronary artery disease; these patients were candidates for either emergency or routine coronary artery bypass. They were stratified into two groups. One group (N=14) was studied during the acute phase of myocardial infarction (MI), and a second which included individuals with chronic angina pectoris who were studied prior to coronary artery bypass

graft surgery (CABG). The results of the acute MI group were of special concern; eight survived their event, six did not. A comparison of the data for survivors and non-survivors showed that the former had significantly higher maximum acceleration and peak velocity responses during the infarction. Velocity responses of $< 0.4\ m \cdot s^{-1}$ and maximum acceleration values of $< 7\ m \cdot s^{-2}$ were not associated with survival. The one patient who did exhibit values higher than these, and yet did not survive, died as a result of cerebral embolus three weeks following the MI. Interestingly, two of the CABG group had a maximum acceleration value of $< 7\ m \cdot s^{-2}$. The researchers concluded that maximum acceleration and peak aortic blood flow velocity may have prognostic value in pre- and post-operative assessment of patients before and after coronary artery surgery.

A study by Stein and Sabbah (1976) was conducted in order to examine another index for the evaluation of left ventricular function. The investigators measured the rate of change of ventricular power which is the time derivative of the product of intraventricular pressure and aortic blood flow. This indicator was hypothesized to reflect changes in inotropic state, and be independent of alterations in preload and afterload. Eighteen dogs were surgically prepared for the study by placement of left ventricular and aortic

catheters, and implantation of an electromagnetic flow transducer around the root of the aorta. The effects of drug-induced changes in contractile state were observed in a subset of nine subjects. An infusion of isoproterenol at a rate of 3.8 $ug \cdot min^{-1}$ was first. Following a recovery period of 20 min an intravenous injection of 4-5 mg of propranolol was administered. Only the first four beats after each injection were analyzed. Afterload was increased by constant infusion of angiotensin amide. Increased preload was also induced in 9 of the subjects by rapid intravenous injection of a 300 ml dextrose/water solution. This dose was administered over four min. The administration of isoproterenol caused a significant ($p<.01$) rise over control levels in the peak rate of change of ventricular power, while the administration of propranolol lowered the peak rate of change response. The augmentation of afterload did not significantly affect the peak rate of power change; however, peak power did significantly increase. Augmentation of preload did not increase the peak rate of change of power but did increase both peak flow and peak power. The investigators concluded that the peak rate of change of power was responsive to drug-induced alterations of the contractile state, yet unresponsive to changes in afterload, and was affected little by changes of the preload.

Doppler Concept and Potential Sources of Error

The first description of the physical principle known as the "Doppler effect" was written by Johann Christian Doppler (White, 1982). The Doppler effect is a shift in frequency and wave length caused by relative motion between a transducer (sonic producing source) and target, when there is a component of relative motion parallel to the direction of ultrasound interrogation (Kisslo, Adams, & Mark, 1986). The Doppler frequency shift is directly proportional to the target velocity and the frequency of the sound produced by the device used. The Doppler frequency shift is inversely proportional to the velocity of sound transmitted through the intervening medium between transducer and target. Velocity is determined from the frequency shift utilizing the Doppler equation:

$$V = \frac{\Delta F \times \text{velocity of sound}}{2Fo \times \text{Cos Theta}}$$

Where: V = velocity; ΔF = frequency shift
Fo = frequency transmitted; Theta = angle between the direction of the target and direction of interrogation

The most obvious source of error can be readily ascertained by examination of the Doppler equation. If the angle of interrogation varies greatly from 0°, error in the calculated velocity can result. An angle of greater than 25° is generally associated with a clinically unacceptable

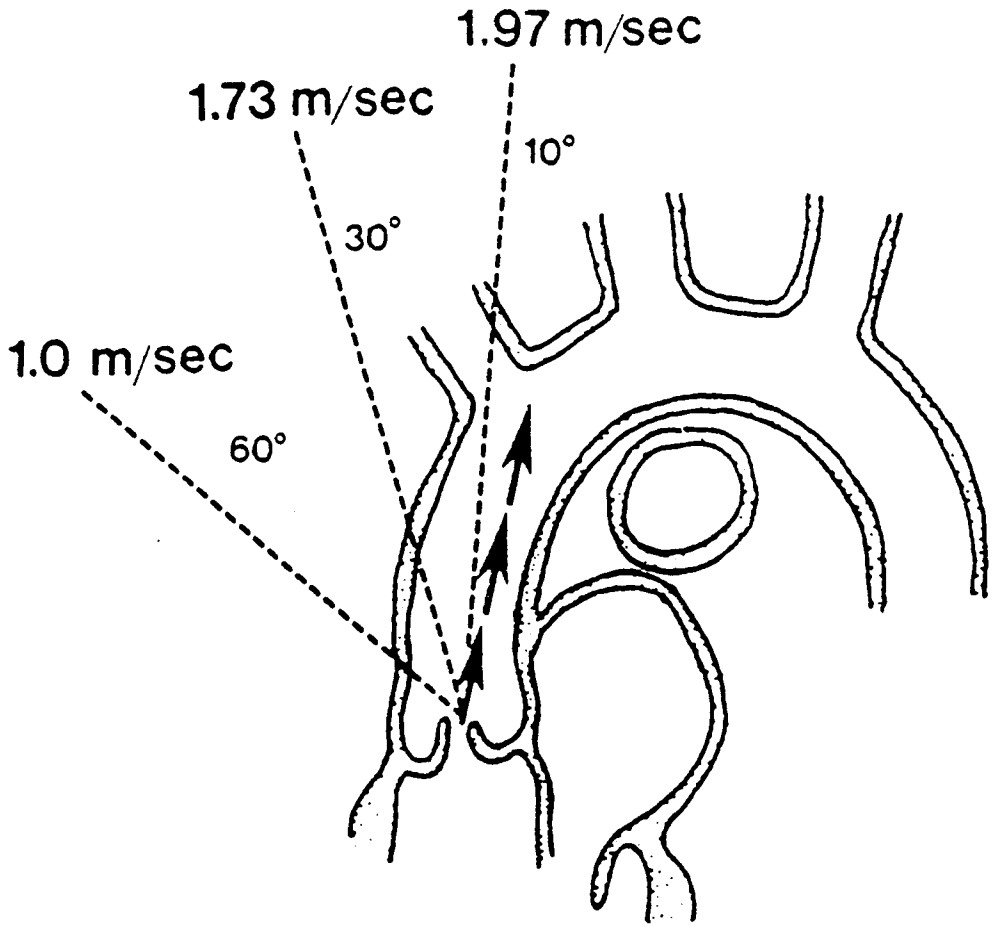

Figure 1. Error induced by angles of interrogation other than 0°. Blood velocity 2.00 $m \cdot sec^{-1}$.

estimate of velocity (Figure 1). Another source of error is due to attenuation of the transmitted signal. Attenuation is the decay of power level of the ultrasound in tissue and is directly proportional to wavelength. Thus, a 10-MHz will attenuate twice as fast as a 5-MHz signal; therefore, lower frequency ultrasound (2-3 MHz) is usually used to examine blood flow in deep vessels. Attenuation varies by tissue type with the more fluid tissues (blood or cysts) having lower attenuation than either medium attenuation fat and muscular tissue, or high attenuation gas filled space (lung tissue) or bone. Avoidance of the higher attenuation tissues is important in Doppler examinations.

Doppler Velocimetry and Estimation of Cardiac Output

The first report of Doppler echocardiography being utilized for the determination of blood flow velocity in the ascending aorta was made in two brief reports by the same author (Light, 1969a; 1969b). He reported that by the use of a transcutaneous ultrasonic Doppler technique it was possible to obtain reflections from the blood flow of the aorta which were sufficently strong to allow a flow velocity vs. time wave form to be recorded. Light (1969b) used a modified Doppler echocardiographic device originally developed for use in fetal heart monitoring. He stated that quantitative importance could be placed on such recordings

because the Doppler frequency shift should have a definitive relationship with flow velocity, which in turn should be directly related to global left ventricular function in normal individuals. He noted the values of peak blood flow acceleration and peak blood flow velocity could be derived from the Doppler recording, and an estimate of stroke volume could be obtained from the time integral of the velocity wave form (i.e., systolic velocity integral). He also stated that if the aortic diameter is known, then cardiac output estimations could be made with this technique. He concluded both works by stating that advancements in technology may lead to a Doppler echocardiographic device that would find usefulness in the fields of human physiology and medicine.

Although Rushmer (1964) had speculated on the potential of Doppler to assess changes in myocardial status, the first widespread use of Doppler velocimetry was to obtain data for the estimation of cardiac output and stroke volume. Cardiac output is the product of stroke volume and heart rate. Loeppky, Greene, Hoekenga, Caprihan and Luft (1981) utilized pulsed wave (PW) Doppler echocardiography to examine changes in stroke volume and cardiac output induced by initiation of cycle exercise in the upright and supine body positions. Aortic diameter for each subject was obtained with M-mode echocardiography. Aortic blood flow increased to a greater

extent during the initiation of upright exercise. The authors speculated that the faster rise in cardiac output was due to the rapid mobilization of pooled venous blood during exercise initiation. The values for cardiac output and stroke volume compared favorably to previous studies measuring cardiac output invasively.

Ihlen, Myhre, Amlie, Forfang and Larsen (1985) studied changes in stroke volume estimated simultaneously by Doppler echocardiography and thermodilution. The subjects of the study were 20 patients undergoing heart catheterization. Two recordings of stroke volume were obtained at each treatment level. Measurement of aortic diameter was accomplished with an M-mode echocardiograph. The treatment levels consisted of a resting basal condition, recordings taken after infusion of 2.5 $ug \cdot kg^{-1} \cdot min^{-1}$ of dobutamine, and those taken after infusion of 5.0 $ug \cdot kg^{-1} \cdot min^{-1}$ of dobutamine. Dobutamine is a synthetic catecholamine which is a direct beta-adrenergic receptor stimulating agent. The effect of administration of this drug is to induce rapid changes in stroke volume without significantly changing heart rate. Both methods demonstrated that dobutamine infusion increased stroke volume. In the study by Ihlen et al. (1985), there was no significant difference between stroke volume determined by either method and the correlation between the methods was high (r=0.92).

A study performed by a Scotch research group examined the use of SVI without measuring aortic diameter as an index of stroke volume change (Rawles, Daniel, Haites, McLellan, & Mowat, 1985). Theoretically, SVI would be expected to behave as stroke volume, assuming that aortic cross sectional area did not change appreciably during systole. SVI was measured at rest in 140 healthy subjects and norms were established. SVI was shown to be independent of sex, body surface area, and blood pressure, but declined with age. The data from the healthy group was used as a basis for comparison to other clinical groups. When corrected for age differences SVI increased 51% in 13 anemic patients, and by 43% in pregnant women (N=12). SVI was decreased by 14% in hypertensives, 31% in patients who presented with atrial fibrillation, and by 43% in patients diagnosed with cardiac (congestive heart) failure. SVI was normal in 16 patients recovering without complications from a myocardial infarction. No comparisons were made of SVI to standard measurements of stroke volume. The research group concluded that measurement of SVI without determination of aortic size met the need for a simple noninvasive method of assessing relative cardiac output and stroke volume changes.

Shaw, Johnson, Voyles, and Greene (1985) used Doppler measurements to trace stroke volume and cardiac output

changes during exercise. Subjects performed graded exercise on a cycle ergometer with work increasing 25 W/stage. The stage duration was 3 min. Aortic diameter was measured during the test using M-mode echocardiography. The authors compared the values obtained from the subject group (N=10) to those reported in literature. Absolute values at cardiac output and stroke volume were approximately 10% lower than those reported in previous studies, but the trend of changes was similar to those previously observed.

Doppler Detection of Pressure- and Pharmacologically-Induced Changes in Inotropic State

Bennett, Barclay, Davis, Mannering, and Mehta (1984), reported the results of two separate experiments on cardiovascular responses measured by a CW Doppler echocardiographic device. Among the responses examined were changes in aortic velocity and acceleration. In the first experiment six human subjects (3 males, 3 females) had control measurements collected and then were exposed to 5 different lower body pressure levels before and during infusion of dobutamine. Lower body pressure was changed with a set of "medical antishock trousers" (MAST) which are similar to the lower half of a gravitational suit worn by pilots of military aircraft to prevent blood pooling in the lower extremities during high speed turns. Pressure in the

MAST was regulated at -25, -10, 0, +10, and +15 mmHg under, at, and over atmospheric pressure. These pressure changes caused an alteration in diastolic loading condition of the heart. Dobutamine is a synthetic catecholamine whose primary activity results from stimulation of the beta one receptors of the heart causing an increased contractile state.

Dependent measures were changes in mean velocity, maximum acceleration, stroke volume, cardiac output, and left ventricular end-diastolic dimension. Doppler measurements were obtained with the transducer at the suprasternal notch. Stroke volume and cardiac output were calculated from the Doppler data. The non-invasive measurement of left ventricular dimensions with M-mode echocardiography was not technically feasible utilizing the experimental protocol outlined above. The investigators therefore designed a second experimental protocol. Nine subjects were measured at rest and at 5, 10, 20, and 40 mmHg positive pressure in the MAST. In the second experimental protocol there was no drug infusion.

The results of interest from this set of experiments relate to the independent effects of inotropic agents and changes in cardiac function due to the Frank-Starling mechanism. Application of positive pressure caused a systematic increase in preload which raised cardiac output

by 32% and stroke volume by 33%. There was no increase in maximum acceleration when the control level was compared to the highest pressure level. These results were cited as demonstrating the classic Starling function of increased contractile force with an increased pressure load. Maximum acceleration increased by 29.2% with infusion of dobutamine. Dobutamine minimally increased stroke volume. Change in acceleration without a large increase in stroke volume was taken to reflect a change in inotropic state of the myocardium. The results of this study lead the authors to conclude that the ability to measure aortic blood velocity and acceleration noninvasively allowed evaluation of changes in both inotropic state and Starling function.

Sabbah, Albert, and Snyder in 1985, reported in an abstract, an animal model used to validate CW Doppler-derived blood flow measurements against measurements obtained with an electromagnetic flow transducer placed around the root of the aorta. The experiment was performed on 16 open-chest anaesthetized dogs. The hand-held Doppler transducer was placed directly on the external surface of the aorta, with the ultrasonic beam directed along the axis of the ascending aorta. Doppler and electromagnetic maximum blood flow velocities and peak accelerations were obtained simultaneously at rest and following pharmacological

alterations of contractile state of the left ventricle. The correlation coefficents of the comparisons of acceleration and velocity were 0.96 and 0.95, respectively. The investigators concluded that CW Doppler can accurately assess peak aortic blood flow velocity (pkV) and acceleration (pkA).

Wallmeyer, Wann, Sagar, Kalbfleisch, and Klopstein (1986) conducted a study to define the relationships between the Doppler-derived indices of ascending aortic blood flow velocity and the direct flowmeter and pressure transducer measures of left ventricular function. These latter indices included: maximum intraventricular acceleration of pressure ($\Delta P/\Delta t$); maximum aortic blood flow; and maximum acceleration of aortic blood flow ($\Delta Q/\Delta t$). Comparisons were made under varying states of preload, heart rate, and inotropic state. Six dogs served as subjects. An electromagnetic flow probe was surgically placed around the ascending aorta, and pressure transducers were surgically located in the right and left atria, the ascending aorta, and the left ventricle. Pacing electrodes were sutured to the left atrium, and a hydraulic occulsion device was placed on the descending thoracic aorta; these devices aided in heart rate control and varying systemic resistance. Intravenous infusions of nitroglycerin were used to vary preload, and inotropic state was varied by infusion of either two different doses of

dobutamine (5 and 10 $ug \cdot kg^{-1} \cdot min^{-1}$) and propranolol (1 $mg \cdot kg^{-1}$). A CW Doppler transducer was applied directly to the surface of the aortic arch for the Doppler measurements.

The differences between mean values of the Doppler measurements of peak velocity and acceleration were significantly changed when the doses of dobutamine and propranolol were administered. Within an animal the Doppler measurements of pkV correlated well with maximal aortic flow ($r=.96$), $\Delta Q/\Delta t$ ($r=.95$) and $\Delta P/\Delta t$ ($r=.92$). Doppler measurements of systolic velocity integral were found to correlate less highly with the direct measures of blood flow and pressure. This may have been due to variation in the integration measurements. The investigators concluded that CW Doppler measurements of peak aortic blood flow velocity and acceleration offer an effective means to noninvasively assess short-term changes in left ventricular performance under conditions of varying preload, heart rate and inotropic state.

Boyle, Mehta, Prindle, and Bennett (1986, abstract) examined the reproducibility and range of the Doppler measured left ventricular function indices of pkV and pkA. The subjects (N=40) underwent three maximal treadmill exercise tests (Bruce protocol). The Doppler variables were measured at standing rest and the end of each stage using a

3 MHz CW Doppler system. Coefficients of variation were computed for each stage and variable. The maximum coefficient of variation was 4.4% for pkA, 3.5% for pkV and 4.9% for SVI. These results indicated that the Doppler was reproducible. A fourth test was administered with the subjects under a state of acute B-blockade (100 mg atenolol 24 and 2 hours prior to testing). The administration of atenolol reduced the peak exercise response of pkA by 50%, of pkV by 52%, and of SVI by 144%. The investigators concluded that the Doppler measurements were easily obtained, highly reproducible, and sensitive to pharmacological interventions that affect left ventricular function.

The sensitivity of Doppler-derived stroke volume, pkV, and average acceleration to changes in contractile state and loading conditions of the left ventricle was further examined by Teague, Heinsimer, and Williams (1986). Thirty male subjects had Doppler aortic velocity measurements sampled from the suprasternal notch at rest and during intravenous infusion of isoproterenol and norepinephrine. Measurements were also made during maximal upright bicycle exercise. Peak acceleration was most specifically related to changes in the contractile state. This was evidenced by a 138% increase during infusion of isoproterenol and a 183% increase in acceleration during exercise. PkV and SVI showed similar

trends, although the magnitude of the changes were less. Infusion of norepinephrine caused a nonsignificant change in acceleration, but did cause peripheral vasoconstriction as measured by increased systemic vascular resistance. The authors stated that the inotropic effects of exercise and isoproterenol were similar and concluded that Doppler velocimetry is sensitive to inotropic stimulation and relatively insensitive to the effect of afterload.

Sabbah, Albert, and Stein (1986, abstract) reported on myocardial dysfunction induced by isoproterenol in dogs with critical coronary artery stenosis. The dogs were surgically prepared by creating a stenosis of either the proximal left anterior descending coronary artery or the proximal circumflex coronary artery. PkA was measured with a CW Doppler system (Quinton EXERDOP). The transducer was placed directly over the ascending aorta. PkA at rest was not significantly different from pkA after the one vessel stenosis was induced. Isoproterenol was infused before and after the induced stenosis. PkA increased to 78±14 $m \cdot s^{-2}$ without the induced stenosis and to only 64±12 $m \cdot s^{-2}$ with the stenosis. The authors concluded that pkA is sensitive to left ventricular dysfunction induced by stenosis and that it may be useful for detecting coronary artery disease during exercise. The responses of other Doppler velocimetry

variables to the experiment were not discussed in their abstract.

Doppler Studies of Apparently Healthy Individuals

This section reviews the studies conducted to determine the Doppler echocardiographic responses of healthy individuals. Many of the studies that have examined subjects with coronary artery disease (CAD) include a control group of apparently healthy individuals. The responses of the "control" individuals will be commented upon in the section concerning Doppler detection of CAD.

Gardin, Burn, Childs, and Henry (1984) utilized Doppler echocardiography to evaluate and compare blood flow velocity in two blood vessels, the ascending aorta and the proximal main pulmonary artery. Twenty subjects (12 men and 8 women) with normal physical status and no history of cardiovascular symptoms or illness were studied. The Doppler instrument utilized was interfaced with a two-dimensional (2D) echocardiographic system. This combination allowed precise aiming of the Doppler transducer so that the scanning beam could be aligned parallel to the blood flow in the blood vessels. The transducer was placed at the suprasternal notch to measure pkV, and at the parasternal site for determination of pulmonary artery blood flow velocity. The experiment demonstrated that there was a significant ($p<.001$)

difference in the blood velocity and average acceleration of the blood ejected into the two blood vessels. PkV in the aorta was 0.92 $m \cdot s^{-1}$, vs. 0.63 $m \cdot s^{-1}$ in the pulmonary artery. Average acceleration followed the same trend with a value of 9.4 $m \cdot s^{2}$ in the ascending aorta and only 6.3 $m \cdot s^{-2}$ in the pulmonary artery. These results indicate that the blood ejected into the systemic circulation is accelerated 2-3 times as fast as the blood entering the pulmonary circulation, even though the resistance in the systemic circulation is 4-5 times higher than the pulmonary circulation. Acceleration time and deceleration time was also higher in the aorta. The ejection time compared between the two vessels was not significantly different. The main contribution of this study was the data comparing the flow characteristics between the pulmonary and systemic large vessels in normal subjects.

A recent study examined CW Doppler measurements of pkV, mean acceleration, and stroke volume during maximum supine and upright exercise (Daley, Sagar, & Wann, 1985). The Doppler transducer was placed at the suprasternal notch. Ten healthy, young adult volunteers (six males, four females) were subjects. A cycle protocol was utilized for the examination of supine exercise responses. The initial workload was 200 $kpm \cdot min^{-1}$ and was increased in 200 $kpm \cdot min^{-1}$

increments (100 kpm•min^{-1} for female subjects) every three minutes. Upright exercise responses were examined utilizing a treadmill as the exercise mode. The treadmill exercise followed the standard Bruce protocol. Test termination criterion for both supine and upright exercise was exhaustion. The investigators reported no problem obtaining high quality Doppler data in either mode. Cross sectional area of the aorta for stroke volume measurement was determined by measuring the diameter of the aortic root at the annulus with M mode echocardiography guided by cross sectional echocardiography. The area of the aorta at the annulus was calculated as: Area = pi(diameter/2). The largest aortic diameter at systole and the diameter at the end of diastole were averaged. Stroke volume was expressed as an index (ml•beat•m^{-2}).

The Doppler measures of pkV, mean acceleration, and stroke volume index were significantly different at rest as compared to exercise within each mode. PkV and stroke volume index were significantly higher at supine rest as opposed to standing. During exercise all indices of blood flow rose significantly, but at maximum exercise stroke volume index rose 66% during upright exercise as compared to a 19% rise during supine exercise. There was no difference between maximal exercise responses in mean acceleration and peak

velocity when compared between the two postures. This would seem to indicate that preload state of the heart does not differentially effect either peak acceleration or peak velocity, as preload would be higher in supine exercise.

Gardin, Koslowski, Dabestani, Murphy, Kusnick, Allfie, Russell, and Henry (1986) recently studied the aortic flow velocity response to supine bicycle exercise. Seventeen young, normal subjects exercised to volitional fatigue. Workload was increased by 25 W every 2 minutes. A PW Doppler system interfaced with an M-mode echocardiograph was utilized to measure pkV, ejection time and SVI. The Doppler transducer was placed at the suprasternal notch. PkV increased during exercise, and continued to rise until 2 min of recovery from exercise. The magnitude of this increase was from 1.09 $m \cdot s^{-1}$ at rest to 1.58 $m \cdot s^{-1}$ two min post exercise. All exercise and 2 min and 10 min post exercise aortic flow velocity values were significantly higher than rest. The ejection time decreased by 34% during exercise with the shortest ejection time occurring at peak exercise. SVI was significantly lower than all other levels at only peak exercise. The authors speculated pkV was highest at two min post exercise due to a vasodilation response of peripheral resistance vessels immediately after exercise. They noted that this velocity response was similar to the

systemic vascular resistance decrease induced by the administration of vasodilatory drugs to congestive heart failure patients. The SVI drop at peak exercise was attributed to measurement error. A possible source of error was Doppler aliasing that can occur with the use of a PW Doppler system.

Use of Doppler Velocimetry to Detect Coronary Artery Disease at Rest

Early work investigating the use of Doppler echocardiographic technique to assess left ventricular function was reported in an abstract by Chandraratna, Silveira, and Aronow (1980). Twenty-eight patients with coronary heart disease were studied at rest. A calibrated CW Doppler transducer was placed in the suprasternal notch and angled toward the ascending aorta. PkA was found to correlate well with ejection fraction (r=.83), and ranged from 9.1-19.2 $m \cdot s^{-2}$. Simply defined, ejection fraction is the volume of blood ejected from the left ventricle compared to the total end diastolic volume. The maximum acceleration value that corresponded to an ejection fraction of > 50% was > 11.6 $m \cdot s^{-2}$. The authors concluded that pkA measured with a Doppler system is a useful indicator of global left ventricular function.

Sabbah, Khaja, Brymer, McFarland, Albert, Snyder, Goldstein and Stein (1986) examined CW Doppler measurements of pkA, pkV, and SVI (also known as stroke distance) to discern whether or not ejection fraction influenced these variables at rest. The most common cause of reduced ejection fraction is myocardial infarction which causes necrosis of contractile tissues, thus rendering the heart a less efficient pump.

Thirty-six patients that were undergoing diagnostic left heart catheterization served as subjects and were stratified into three groups according to ejection fraction. Ejection fraction was measured by ventriculography. The groups were: Group A (ejection fractions of > 60%), Group B (ejection fractions = 41-60%), and Group C (ejection fractions = < 40%). Sixteen normal subjects volunteered as subjects for comparative data. All of the Doppler measurements were made under resting supine conditions with the transducer in the suprasternal notch. An additional point of interest is that the Doppler system utilized was the Quinton EXERDOP. The results of the study are below.

Group	PKA ($m \cdot s^{-1}$)	PKV ($m \cdot s^{-1}$)	SVI (cm)
Normal	20+4	0.81+0.15	14.3+4.0
Group A	19+5	0.68+0.20	10.7+5.1
Group B	12+2*	0.47+0.90*	8.2+2.7*
Group C	8+2*	0.34+0.80*	4.4+1.6*

The two groups with lower ejection fractions were significantly (values marked with asterisk) lower in all of the measured variables. Thus, the CW Doppler system could differentiate between subjects with normal vs. subjects with abnormal left ventricular performance. The investigators then correlated pkA and pkV with ejection fraction. PkA was highly correlated with ejection fraction (r=.90) in a linear regression model. A "power curve" fit of the data (second order polynomial) yielded a correlation coefficient of .93. PkV was also correlated with ejection fraction (r=.77). SVI was also examined and the correlation coefficient between it and ejection fraction was .59. In conclusion, they stated that "peak acceleration, measured noninvasively with a continuous-wave Doppler velocity meter, is a useful indicator of global left ventricular function."

Peak acceleration (pkA) as an index of global left ventricular function was also examined by Khaja, Sabbah, Brymer, Goldstein and Stein (1986). In the study, 26 patients undergoing percutaneous transluminal coronary

angioplasty had pkA measured with Doppler (Quinton EXERDOP) before, during and immediately after balloon inflation. During occlusion of a coronary vessel (balloon inflation), 15 of the patients experienced either chest pain or had ischemic electrocardiographic changes. In the patients who experienced these changes, pkA decreased from 17 to 13 $m \cdot s^{-2}$. When the balloon was deflated, pkA rose to 19 $m \cdot s^{-2}$. In patients with no ischemic type changes, pkA did not change. In the patients with no ischemic changes, collateral circulation had developed enough to supply the distal portion of the occluded coronary vessel. This was evidenced on the catheterization of these individuals. The results indicate that pkA can identify patients that have impaired left ventricular function during coronary occlusion.

Sabbah, Przybylski, Albert and Stein (1987) studied the hemodynamic changes in dogs that had induced acute ischemia produced by surgical occlusion at various locations in the coronary vasculature. PkA, pkV and SVI were measured, as were intraventricular pressure changes and ejection fraction. After the measurements were obtained the dogs were sacrificed, and Evans blue stain technique was used to determine the mass of left ventricular ischemic tissue. The correlation between percent ischemic mass and percent change in the measurements of left ventricular function were: pkA

= 0.88, ejection fraction = 0.84, SVI = 0.80, pkV = 0.77, and stroke volume = 0.71. None of these indices were capable of detecting global left ventricular dysfunction when the ischemic mass was less than 20%. The conclusion of the investigators was that of the non-invasive measures obtained by Doppler echocardiography, pkA was the most sensitive for the detection of ischemia.

Doppler Velocimetry as an Adjunct to Exercise Testing in Detection of Coronary Artery Disease

Teague, Mark, Radford, Robertson, Albert, Porter, and Waugh (1985) reported in an abstract that a study of Doppler-measured pkV and SVI in 89 patients during graded exercise tests prior to catheterization. PkV change in proportion to change in heart rate (ΔpkV/ΔHR) discriminated effectively between the patients without coronary artery disease and those with early positive stress tests (n=18), from those with negative stress tests (n=17), and from those patients who had tests termed "inadequate" but negative (n=9). Sixteen beta-blocked patients showed normal results, as did the few patients that attained the fifth stage of the Bruce protocol. The research group concluded that coronary disease impairs the normal rise in pkV and SVI during exercise stress, thus exercise Doppler examinations may improve the sensitivity of treadmill testing. The normal

results of the beta-blockade group was due to the impairment of heart rate in these individuals. This impairment was enough to make the change scores (ΔpkV/ΔHR) fall in normal range.

In another study presented in abstract form, Mehdirad, Williams, Bryg, Windhorst, Habermehl, Chaitman, and Labovitz (1985) compared left ventricular response to exercise stress as measured by two-dimensional echocardiography with change in peak velocity. Nine apparently healthy and 11 individuals with abnormal left ventricular function were studied. PW Doppler measurements were obtained at supine rest and immediately after maximal treadmill exercise. The authors observed that there was a linear relationship between the appearance of wall motion abnormalities and impairment percentage change in pkV. The conclusion of the investigators was that pkV as measured by Doppler velocimetry may provide a simple measure of left ventricular function.

A follow-up study to Mehdirad et al. (1985) examined the effect of coronary artery disease (CAD) on PW Doppler-derived parameters of aortic flow during treadmill exercise (Bryg, Labovitz, Mehdirad, Williams, & Chaitman, 1986). Twenty subjects without CAD and 17 patients were examined. PkV was lower in the CAD group (0.89±0.26 $m \cdot s^{-1}$ vs. 1.56±0.32 $m \cdot s^{-1}$). A failure of pkV to rise with increasing exercise intensity

was associated with those patients with more severe coronary artery disease. The authors concluded that changes in pkV may distinguish between healthy individuals and individuals with CAD.

The usefulness of CW Doppler measurements to detect impairment of the left ventricular function response was also examined by Mehta, Bennett, Mannering, Dawkins, and Ward (1986). PkA, pkV and SVI of ascending aorta blood flow was measured during each stage of a standard Bruce treadmill exercise test in a group of 165 subjects that were 3-4 weeks post-myocardial infarction. The subjects were grouped into those with positive electrocardiographic (N=67), and those with no ischemic electrocardiographic changes. Coronary angiography was performed on those subjects with positive changes. PkV and pkA were significantly lower in those subjects with multiple vessel disease when compared to subjects with single vessel disease. The authors concluded that assessment of left ventricular function when utilizing CW Doppler methodology may be a useful adjunct to routine exercise stress testing in the assessment of the extent of myocardial impairment after myocardial infarction.

Kelly, Rothbart, Patrone, Moore, Watson, and Gibson (1986) conducted an experiment that explored the use of a CW Doppler echocardiographic device (EXERDOP) during the Bruce

treadmill exercise test. They examined pkV and pkA changes at rest, during four stages of the treadmill protocol, and during immediate post exercise. The group of 76 subjects were stratified into two groups by age (Group 1 = 20-40 yrs, Group 2 = 40-70 yrs). Compared to Group 1, Group 2 had lower resting pkV and pkA values, and lower pkV values at all stages of exercise. There were no differences in pkA between the groups during exercise. Doppler measurements were performed on 11 additional patients who underwent thallium-201 studies for suspected ischemia. All eight patients with normal thallium reperfusion had a progressive increase in pkV despite five of which had false positive exercise electrocardiographic changes. Three patients with exercise-induced, thallium verified ischemic changes demonstrated a decrease in pkV. On the basis of these findings the investigators concluded that: 1) EXERDOP is a technically feasible adjunct to routine treadmill exercise testing, 2) older individuals have lower peak blood flow velocity and acceleration measurements at rest, and a reduced peak velocity response during exercise (this may in part be due to attenuation caused by calcification of vessels), and 3) a decreased (falling) peak velocity response during exercise appears to distinguish between true vs. false positive ECG changes during exercise testing. The finding

of no differences in pkA is contrary to the results of Mehta et al. (1986).

In another abstract, Kelly, Patrone, Rothbart, Moore, Watson, Weltman and Gibson (1986) reported the percentage change in pkA and pkV in 220 patients. These patients were divided into groups based on age and coronary artery disease status. They further subclassified their subjects by degree of exercise conditioning. The highest percentage change in pkA and pkV occurred in young, healthy, active individuals (230% pkA, 74% pkV) and the lowest in individuals that had coronary artery disease and were over 40 years of age (106% pkA, 48% pkV). There were several discrete subclassifications according to age, disease status, and condition. The investigators summarized that normal exercise Doppler values are age dependent, influenced by the degree of coronary artery disease, and are somewhat dependent on physical conditioning.

Another group that examined the utilization of CW Doppler measurements of aortic blood flow as an adjunct to exercise testing was Mehta, Bennett, Dawkins, Ward, and Mannering (1986). This group utilized 51 patients that exhibited positive ECG changes during the Bruce treadmill test as subjects. The subjects all were three weeks post myocardial infarction. The hemodynamic responses of the

subjects were monitored at rest and at peak exercise with the Doppler system. The extent of the change in peak blood flow acceleration (%ΔPkA) was noted as was time to the onset of one mm ST depression change. All of the subjects had subsequent coronary angiography and were stratified into groups according to the number of coronary vessels that exhibitied over 70% occlusion. From the data the researchers defined a poor %ΔPka response as < 25.3% increase from rest (the mean value of the three vessel group plus one standard deviation), and an abnormally brief time to onset of ST depression as less than three minutes. The researchers found that a combination of these two responses raised the specificity of the exercise test from 60% using ST changes solely to 76%. Specificity is the percentage of times a test yields a normal result when those without disease are tested. The researchers concluded that the Doppler measurements may be a useful adjunct to routine exercise stress testing in identifying high risk patients during the post myocardial infarction period.

Mehdirad, Williams, Labovitz, Bryg, and Chaitman (1987) studied the correlation of pkV during exercise with changes in ejection fraction as measured by two-dimensional echocardiography. Thirty-seven subjects with varying degrees of left ventricular function participated in the study.

Fourteen subjects had no coronary artery diease (CAD), six subjects had one vessel, five had two vessel, and three had three vessel. Nine subjects were excluded from the study because of inadequate two-dimensional echocardiographic images after exercise. In the group of normal subjects, ejection fraction and pkV increased significantly during exercise (the former by 61%, the latter by 115%). The ejection fraction of CAD patients rose by only 48% during exercise and the percent rise in pkV was only 52%. The changes in the CAD patients were significantly lower ($p<.01$). These data suggest that exercise induced changes in pkV may discriminate between individuals with normal left ventricular function and those with hemodynamic function impaired by CAD.

A very recent study compared CW Doppler velocimetry with radionuclide ejection measurements obtained during supine cycle exercise (Teague, Corn, Sharma, Prasad, Burow, Voyles, & Thadani, 1987). All 73 subjects were hospitalized for coronary angiography following chest pain. None of the patients had a history of myocardial infarction. Eighteen subjects had less than a 50% stenosis as determined by catheterization. Fifty-five patients had significant (> 70% stenosis in one or more vessels) coronary artery disease. Multigated nuclear ventriculograms were obtained at rest and throughout the exercise test, as well Doppler measurements

of pkA, pkV, and SVI. Electrocardiographic measurements were recorded. The Doppler, electrocardiographic, and ventriculographic data were compared to the catheterization data to determine sensitivity, specificity, and predictive accuracy. These values are listed below:

Instrument	Indication	Sensitivity	Specificity	Predictive Accuracy
ECG	ΔST segment (-1mm)	0.64	0.89	0.94
Ventriculography	ΔEjection Fraction (<5%)	0.85	0.78	0.92
Doppler	ΔpkA (<80%)	0.90	0.88	0.96
Doppler	ΔpkV (<20%)	0.83	0.94	0.97
Doppler	ΔSVI (<2%)	0.85	0.94	0.97

The magnitude of change in pkA and pkV from rest to peak exercise were comparable to the invasive measurement of ejection fraction changes in identifying the patients with coronary artery disease.

Two studies (both reported in abstracts) have been conducted that have failed to demonstrate an association between CAD and measures obtained by Doppler velocimetry (Harrison, Smith, Friedman, Kwan, & DeMaria, 1986; Werner, Foster, Weiland, Konstam, & Pandian, 1987). In the study by Harrison et al. (1986), six control subjects and 40 patients undergoing exercise thallium scintigraphy were examined. PkV was measured in the standing position prior to and immediately following symptom-limited maximal treadmill exercise. The thallium scan revealed that 17 subjects had a

normal response, six subjects had an old infarction (fixed defect), and 17 of the subjects demonstrated the classical reversible defect indicative of an ischemic area. PkV varied widely in each of the subject groups. PkV showed the greatest increase in the control subjects and normal patients, but 11 of the subjects who exhibited ischemia had close to comparable increases in pkV. SVI was also measured and the data showed similar trends. No statistical analyses were performed on the data. The investigators concluded that although the increases in the Doppler measures of blood flow were slightly less in the patients with either infarction or ischemia, the variability of the responses limited the application of the use of Doppler measurements to detect ischemia-induced changes in left ventricular function.

In the study conducted by Werner et al.(1987), 60 patients underwent either thallium or routine treadmill exercise stress testing. A reversible defect or ST depression during exercise were taken as a diagnosis of ischemia. There were no significant differences between the individuals that were diagnosed positive for ischemic and those who had normal responses in either peak acceleration or peak velocity. They noted that there was a significant overlap between normal and ischemic patients' responses and concluded that exercise Doppler responses were not reliable

indicators for use in the detection of coronary artery disease.

Reproducibility of Doppler Measurements of Left Ventricular Function

A previous section introduced Doppler physics and potential sources of error introduced by attenuation or an angle of interrogation that is significantly greater than zero degrees. This section will review the current literature regarding reproducibility of the Doppler measurements.

Waters, Kwan, and DeMaria (1983) studied 14 patients in whom the correlation between cardiac output measured by CW Doppler and thermodilution were low. Aortic cross sectional area was determined by three methods, A-mode (an echocardiographic imaging technique that interrogates one dimension, either length or width), two-dimensional, and left heart catheterization. Correlation between aortic cross sectional area determined by A-mode did not relate well with the area calculated using the other two methods. Correlation between Doppler-derived cardiac output and thermodilution cardiac output was low (r=.32). This correlation remained low (r=.40) even when the cross sectional areas, as determined by the three methods, was equal. This indicated that suprasternal velocity measurements were a source of

error. The investigators did not speculate on the reasons for the disparity between measurements.

A study in which the findings were in contrast to Waters et al. (1983) was reported by Gardin, Dabestani, Matin, Allfie, Russell, and Henry (1984). PW Doppler recordings obtained at rest from 10 apparently healthy subjects were made on two separate days. The sampling site was the suprasternal notch. The subjects rested for 15 min prior to measurement. The day-to-day correlation between measurements of pkV and SVI were high (r=.90 and .95, respectively). Time to peak velocity, a measure similar to but not identical to pkA, was less repeatable (r=.81). Interobserver correlation for pkV, SVI, and acceleration time were 0.97, 0.87, and 0.55. Interobserver correlation was calculated in order to compare the variables when measured by separate observers from the spectral recording obtained by the PW Doppler system. From the data, the authors found that day-to-day variability was 3.8% in SVI, of 5.2% for pkV and of 7% for time to peak velocity. Given the means ± 2 standard deviations as a criterion for significant difference, SVI would need to change by 10%, pkV by 13%, and acceleration time by 17%. The results of the study led the authors to conclude that Doppler aortic flow velocity measurements were reproducible in normal subjects.

A study conducted in 1984 examined the effects of age of human subjects on the ability to obtain a profile of aortic flow velocity with Doppler echocardiography (Vijayaraghavan, Singham, Tei, Wong, Wong, & Shah, 1984). Forty males, ages 50-95 yrs served as subjects. These subjects were examined with a CW Doppler device interfaced with a two-dimensional echocardiograph. Aortic flow velocity was determined at three sampling sites, the left ventricular apex, the suprasternal notch, and the right parasternal border. All of the measurements were made in duplicate by two independent technicians.

The pkV in the group was 1.3 ± 0.3 $m \cdot s^{-1}$ (mean ± SD). PkV was found at the left ventricular apex site in 14 (35%) of the subjects, at the suprasternal notch in 22 (55%), and in 21 (53%) at the right parasternal border site. The measurements made by the two observers were nearly identical (r=.99). Some of the subjects had the greatest pkV values in more than one site (ties existed). The site which yielded the lowest results when examined isolated was the left ventricular apex site, which yielded the highest peak velocity in only 4 (10%) of the subjects. The investigators attributed the distribution of "ideal" sampling sites to either anatomical changes which were manifested with age, or a change in the direction of the central aortic jet brought

about by atherosclerosis, and/or systemic hypertension. The investigators concluded that when Doppler aortic blood velocity measurements are being obtained in older individuals, both the suprasternal notch and the right parasternal border sites should be explored.

Shaw et al. (1985) determined the reproducibility of PW Doppler cardiac output measurements. They reported excellent reproducibility for 65 paired observations of cardiac output (r=0.98) and stroke volume (r=0.94). The investigators believed that no problem was encountered with turbulent flow in the ascending aorta, or in the assumption that the Doppler angle of interrogation was 0°. They suggested that the largest component of error in measurement of cardiac output is in the estimation of aortic diameter.

Another study which examined the variation of Doppler measurements of aortic blood flow was reported in an abstract by Christie, Wann, Sheldahl, Sagar, Tristani, and Ptacin (1986). Cardiac output was measured by thermodilution and Doppler echocardiography. Subjects exercised on upright bicycle ergometers. Pearson's product moment correlation between the two methods of cardiac output determination was 0.78. The investigators reported large intersubject variation. Thus, they concluded that cardiac output, as estimated by Doppler, provides an accurate estimate of blood

flow, but in certain individuals the flow measured by Doppler may vary from true blood flow. No speculation was offered as to the sources of variation, but the factors of attenuation and changing angle of incidence may have played a role.

Mehta, Noble, Mills, Pugh, Drake-Holland, and Bennett (1986) measured pkA and pkV with two CW Doppler systems and compared them to simultaneous recordings obtained by a catheter-tip system. Five patients undergoing cardiac catheterization were measured at rest and through a cardiac pacing protocol. Doppler variables were correlated against the catheter-tip system by means of regression analysis. Both Doppler systems were reliable and valid in the determination of pkV, pkA and SVI ($r=0.85-0.96$). These results indicated that CW Doppler at rest can accurately assess aortic blood flow velocity.

Several sources of variability in Doppler velocity measurements were examined by Gardin, Davidson, Rohan, Butman, Knoll, Garcia, Dubria, Gardin, and Henry (1987). Specifically, the effect of age, body size, gender, and blood pressure were studied. Ninety-seven subjects, both male and female (aged 21-78 years), who had no history of hypertension or cardiovascular disease were studied. Both aortic and pulmonary blood flow velocity were measured with a PW Doppler

system that was interfaced with a two-dimensional echocardiographic system. Multiple linear regression analysis revealed that there was a significant inverse relationship between aortic pkA, SVI, and mean acceleration when these variables were compared to age. Aortic ejection time showed a positive relationship with age. Age was not associated with changes in pulmonary artery Doppler measured velocities. There was no significant relation between gender, diastolic, or systolic blood pressure, and flow velocities in either vessel. Body surface area was not significantly related to any of the Doppler aortic blood flow measurements, but showed a significant positive relationship to peak pulmonary artery velocity and a negative relationship with peak pulmonary acceleration. The impairment in aortic pkV and SVI was speculated to be due to increases in aortic root diameter and perhaps may have been related to an increased angle of incidence between the Doppler signal and the flow direction. The authors did not speculate about the relationship between body surface area and pulmonary artery velocity measurements.

The reproducibility of blood flow estimates obtained by Doppler was further evaluated by Meijboom, Rijsterborgh, Bot, De Boo, Roelandt and Bom (1987). PW Doppler velocity measurements were obtained in four young, healthy subjects.

The PW system was integrated with a two-dimensional echocardiographic imaging system. Mean temporal velocity (an integration of the velocity curves) was the dependent measure. Velocity was continuously measured and examined for differences induced by respiration. A recording also was obtained during a period of breath holding. The authors did not state if the subjects were instructed not to forcefully hold their breath against a closed epiglottis. Velocity at the mitral and tricuspid valves was measured. Mean temporal velocity was significantly higher during expiration as opposed to inspiration in the mitral valve orifice (0.124 vs. 0.110 $m \cdot s^{-1}$). However, at the tricuspid orifice, velocities during expiration were smaller (0.092 vs. 0.111 $m \cdot s^{-1}$). Mean temporal volume during breath holding was smaller than during respiration. The authors concluded that measurements of mean temporal velocity were influenced by ventilatory patterns. Mitral and tricuspid valve orifice diameters also was measured with the two-dimensional echocardiograph. The diameter of both was significantly larger during diastole. The authors concluded that estimates of cardiac output obtained by PW Doppler will have variation due to both vessel diameter changes and ventilatory induced changes.

Summary

Rushmer (1964) provided the theoretical foundation for the use of Doppler echocardiography. His description of initial ventricular impulse matched the later non-invasively measured descriptions of aortic blood flow velocity. The first exploration of the use of aortic blood flow velocity measurements as a possible index for the determination of global left ventricular function was in 1966. Noble et al. (1966) determined that maximum blood flow acceleration was a sensitive measure of contractility. In 1974, the first group to study aortic blood flow in human subjects found that subnormal blood flow measurements were associated with poor prognosis following myocardial infarction (Jewitt et al., 1974).

The Doppler echocardiographic technique for measurement of aortic blood flow in humans was first described by Light (1969b). Light described the variables of pkA, pkV, SVI, and noted if aortic diameter measures could be obtained, Doppler could be used to noninvasively estimate cardiac output. Several groups have explored Doppler measurements of SVI to assess cardiac output changes, and all of these groups found Doppler estimated cardiac outputs to reliably reflect changes in cardiac output and stroke volume.

In 1984, Bennett and his associates found that an increase in preload did not significantly affect Doppler measured peak acceleration but that injection of a synthetic catecholamine produced a change in peak acceleration. This finding meant that peak acceleration was affected by changes in inotropic state of the myocardium. The finding of the association of peak acceleration with inotropic state was confirmed by Sabbah and others in 1985. However, neither Bennett's nor Sabbah's research groups studied human subjects and the Doppler measurements were made with the transducer directly on the surface of the aortic arch of the experimental animals.

The Doppler measures of pkA and pkV were found by many investigators to be sensitive to changes in global left ventricular function. Chandratatna and associates (1980) found that pkA as measured with CW Doppler correlated well with ejection fraction, a finding since confirmed by other research groups. Many studies have also examined the use of Doppler as an adjunct for the detection of coronary artery disease, and favor the usefulness of the Doppler measurements of pkA and pkV as indices of LVF. Two studies have been reported that cast doubt on the use of Doppler measures of blood flow in the detection of CAD (Harrison et al., 1986; Werner et al., 1987). Both of these studies have reported

too much variability in the data to be considered useful indices of cardiac function. Reproducibility of peak Doppler measures has been reported as excellent. Some sources of variability have been reported. These include attenuation and aging (Vijayaraghavan et al., 1984; Gardin et al., 1987) and respiration (Meijboom et al., 1987). There have been no studies that have examined the reproducibility of Doppler measures within single exercise stages.

The use of Doppler velocimetry has not become widespread to date. In the face of rising health care costs, a noninvasive, inexpensive assessment device to measure cardiac function is desirable. In general, the literature favors the use of Doppler echocardiography as a reliable and valuable tool for the assessment of left ventricular function.

Chapter III

Journal Manuscripts

REPRODUCIBILITY OF DOPPLER INDICES OF LEFT VENTRICULAR FUNCTION DURING GRADED EXERCISE

Alan D. Moore, Jr., William G. Herbert,
and Don R. Sebolt

(abbreviated title for running head)
Reproducibility of Doppler Measures During Exercise

Alan D. Moore and William G. Herbert
Laboratory for Sport, Exercise, and Work Physiology
Department of HPER
VPI & SU
Blacksburg, VA 24061
703-961-6565

ABSTRACT

The purpose of this investigation was to determine the reproducibility of three noninvasive indices of left ventricular function (LVF) obtained by a continuous wave Doppler system (EXERDOP) during exercise. Forty-four young, healthy adult male volunteers performed two maximum cycle graded exercise tests. Measures obtained by Doppler included peak ascending aortic blood flow acceleration (pkA), peak aortic blood flow velocity (pkV), and systolic velocity integral (SVI). Other dependent measures were heart rate (HR), systolic blood pressure (SBP) and oxygen consumption (VO_2). Pearson product-moment correlation coefficients and coefficients of variation were computed to determine the reproducibility of the dependent measures between the two tests. The correlation coefficients for pkA ranged from 0.54-0.84, for pkV from 0.65-0.77, and for SVI, 0.40-0.71. The ranges for test-retest correlations for the other dependent measures were: HR 0.50-0.86, SBP 0.18-0.77, and VO_2 0.35-0.79. The coefficients of variation ranged from 14.2-33.5% for pkA, from 11.4-18.9% for pkV, and from 16.3-26.7% for SVI. The ranges for HR, SBP, and $\dot{V}O_2$ were from 3.5-16.1%, 7.0-10.2%, and 9.9-17.2% for the three dependent measures, respectively. Practitioners consider the HR and

$\dot{V}O_2$ response during graded exercise testing to be reproducible; this is one of the premises for exercise prescription. These results indicate that the CW Doppler measures of pkA, pkV, and SVI possess test-retest reproducibility nearly equivalent to that for the clinically utilized measures of heart rate and blood pressure but that more variation exists in the Doppler-measured variables, particularly at lower exercise intensities.

Index Terms: CW Doppler, Maximal Exercise, Echocardiography

INTRODUCTION

The most common clinical screening test for suspected ischemic heart disease is the graded exercise test (22). During the typical graded exercise test the subject performs exercise on either a treadmill or cycle ergometer while electrocardiographic (ECG) and blood pressure responses are monitored. Often, the diagnosing physician is interested in knowing if any degree of left ventricular dysfunction exists. The routine measurements of ECG and blood pressure may offer some clues in this area, but taken alone do not constitute highly sensitive and specific diagnostic indicators of ventricular dysfunction (12). At present the two methods most frequently employed for the assessment of left ventricular function (LVF) are two-dimensional echocardiograhy and nuclear ventriculography (2). Both of these methods are very time consuming, expensive, and require extensive personnel training to perform. In addition, nuclear ventriculography is an invasive technique that involves exposure to radioactivity as well as a higher level of acute risk than would be acceptable for "routine" assessment.

Transcutaneous continous wave (CW) Doppler measurements of ascending aortic blood velocity offers a noninvasive, inexpensive alternative in the assessment of LVF (11, 21).

The correlation of peak acceleration, the first derivative of flow velocity, and ejection fraction, has been reported to be as high (r = .83-.90) (5, 19). Data concerning the day-to-day variation in Doppler measurements of blood flow are lacking. Two recent studies (9, 24) indicated that these measures are too variable to be of use in a clinical setting, but several others (3, 4, 15, 17) have concluded that the use of Doppler measurements can be a useful adjunct to exercise testing. The purpose of this investigation was to examine the reproducibility of CW Doppler measures of LVF during graded cycle exercise.

METHODS

Subjects

Forty-four males served as subjects. The subjects were volunteers, and were students and faculty members from Virginia Tech. The group was screened for coronary heart disease risk factors and judged "apparently healthy" as set forth by criteria of the American College of Sports Medicine (1). Prior to participation, each was informed of the nature of the exercise tests, the measurements collected, and the inherent risks of the protocol (Appendix A). Each gave informed consent. Individual descriptive data are contained in Table 1 (Appendix B).

Insert Table 1 about here

Experimental Protocol

Subjects performed identical graded exercise tests on two separate days (Appendix C). The tests were separated by at least three days to avoid residual leg fatigue from the first which might influence the results of the second. Each had dependent measures recorded during seated rest on a Monark cycle ergometer and during the last minute of each three minute work stage of exercise. The initial power level of 50 W was increased by 50 W a stage. Pedalling frequency was visually monitored by a technician throughout the test. The subjects were instructed to exercise until they reached their subjective limits.

Heart rate (HR) was recorded electrocardiographically and both systolic and diastolic blood pressures were measured with a sphygmomanometer. Ascending aortic blood flow velocity was measured with a 3.0 MHz CW Doppler system (EXERDOP, Quinton Instrument Co.) immediately preceding cardiac output determinations. The transducer was held at the suprasternal notch by the technician. The Doppler system measures the frequency shift of the CW signal which is reflected from blood flow being ejected from the left

ventricle via the ascending aorta. The system continuously monitors velocity and records the highest value during systole as peak velocity (pkV). Peak acceleration (pkA) corresponds to the steepest positive slope in the velocity-time relationship during systole, and systolic velocity integral (SVI) is the area under the velocity-time waveform. The Doppler system is equipped with a microprocessing unit that excludes data (beats) with a signal to raise ratio of less than 10 dB, and also excludes beats that fall outside derived acceptable limits. These limits are ±40% of the weighted average of the eight most recent measured values of pkA and SVI, and ±20% of the weighted average of the 8 most recent values of pkV. A printed report of the mean values of pkA, pkV and SVI for each sampling period was produced, as well as a report of each beat that was used in the determination of the mean values. In this study, at least 15 beats were included in each sample. Analysis of expired oxygen and carbon dioxide was performed during exercise using a standard Daniels breathing valve connected via a calibrated pneumotach (HP 47303A) to electronic gas analysers (Applied Electrochemistry SA-3, and CD3-A). The analyzers were calibrated before and after each test with reference gases previously verified by Haldane analysis.

Statistical Analysis

The test-retest data were correlated at each stage of the exercise protocol using Pearson's Product moment correlation. Coefficients of variation were computed for each stage for all dependent measures.

RESULTS

Stage Response Comparisons

The test-retest reproducibility statistics within each stage for the Doppler measures of pkA, pkV, and SVI are illustrated in Figure 1. The correlation coefficients (Pearson's r) for pkA ranged from 0.54-0.81, for pkV, 0.65-0.77, and for SVI, 0.40-0.71. The coefficients of variation for pkA ranged from 14.2-33.5%, for pkV, 11.4-18.4%, and for SVI from 16.3-26.7% (Figure 2).

Insert Figures 1 and 2 about here

As comparative indices, the correlation coefficients for HR, SBP, and $\dot{V}O_2$ are plotted in Figure 3 and the coefficients of variation in Figure 4. The correlation coefficients for HR ranged from 0.50-0.86, and for $\dot{V}O_2$, 0.35-0.79. The coefficients for SBP ranged from 0.18-0.77. The coefficients

of variation were: HR, 3.5-16.1%, SBP, 7.0-10.8%, and $\dot{V}O_2$, 9.9-17.2%.

Insert Figures 3 and 4 about here

The mean responses of pkA, pkV, and SVI to exercise are illustrated in Figure 5.

Insert Figure 5 about here

DISCUSSION

The mean responses of pkA, pkV, and SVI were within the normal responses reported for these variables (6, 7). PkA and pkV are reported as indices of myocardial contractility and were expected to systematically increase with progressively more vigorous exercise (7). In this study, however, pkV did not appreciably rise after the 200 W stage, indicating that it was less sensitive than pkA to cardiac contractile changes at high exercise intensities (14). Acute changes in SVI have been reported to be closely related to changes in stroke volume (10, 18). The normal response of stroke volume to upright exercise is an increase to intensities of 40-50% $\dot{V}O_2$max, with a maintenance or small

degradation of stroke volume beyond 85-95% $\dot{V}O_2max$ (23). The trend in measured SVI did not show this pattern, but decreased progressively beyond the third stage (Figure 5).

The correlation coefficients between the Doppler measures, compared stage-by-stage, would be interpreted by most clinicians to represent only moderate reproducibility. One study reported in the literature has examined the reproducibility of aortic blood flow at steady-state and stated it was comparable with that of HR (14). The velocity signal of this particular Doppler system has been compared to a steady-state <u>in vitro</u> flow system and was shown to compare favorably to known velocity (r = .995) (20). Barring instability of the instrument, there are other factors that may have introduced variability into the measurements. The Doppler system used in this study was a "stand-alone" unit, i.e., the technician bases the angle of interrogation solely on audio feedback and there is no visual image to enhance "aiming" of the transmitted Doppler signal. This may mean that the angle of interrogation could vary each test or stage. An attempt was made to use the optimal angulation during sampling by careful monitoring of the audio signal. Another related and potentially more serious problem could occur if the technician inadvertently interrogated different vessels. The brachiocephalic trunk is the prime example for

this source of error. The aural characteristics of the ascending aorta and brachiocephalic trunk are somewhat similar.

While the aforementioned sources of error may have played a role during the tests, it is interesting to note the test-retest correlations of HR, SBP, and $\dot{V}O_2$ are of nearly the same magnitude as the Doppler measured parameters (Figure 3). The exercise HR, SBP, and $\dot{V}O_2$ responses are accepted by practitioners to be sufficiently reproducible so as to support clinical decisions. The consistency of these cardiopulmonary measurements form the basis for exercise prescription (1). The data suggest on the basis of differences between coefficients of variation that the Doppler measures were more variable than HR, SBP, or $\dot{V}O_2$ (Figures 3 and 4). The general trend of the Doppler data was for the least variability occurring at moderate exercise intensities. This is an expected finding as the responses at lower exercise intensities are more affected by extraneous factors such as subject anxiety, and it was increasingly difficult to maintain the Doppler transducer in a steady position at higher exercise intensities. The coefficients of variation measured in this study for pkA, pkV, and SVI are higher than those reported in the sole study on reproducibility of these variables (3). The study examined

CW Doppler changes during treadmill exercise and reported the maximum coefficients of variation for pkA as 4.4%, for pkV 3.5%, and 4.9% for SVI. The reasons for the disparity between the results obtained in our study and those previously reported are not apparent. A possible explanation may be subject habituation to the cycle exercise task. One practice trial was administered to the group before the study in an attempt to alleviate this source of variance. It should be noted (Figure 5) that the mean test-retest responses are very similar, and previous studies have demonstrated that left ventricular dysfunction causes a large inhibition (> 60% for pkV), from the normal response patterns of pkA and pkV (3, 15, 17). This observation of similar mean responses in both tests in light of previous findings on the responses to left ventricular function indicate that the Doppler would most likely detect changes induced by dysfunction.

In conclusion, the correlations between the Doppler responses of pkA, pkV, and SVI were nearly as high as HR, SBP, and $\dot{V}O_2$ when compared in a stage-by-stage fashion. Some variation in pkA, pkV, and SVI may be caused by measurement inconsistencies in the CW Doppler technique utilized, but it is possible that the magnitude of the variance may simply be

the physiological variability inherent in conventional graded exercise tests of human subjects.

LITERATURE CITED

1. American College of Sports Medicine. (1986). Guidelines for graded exercise testing and prescription. 3rd ed., Philadelphia, Lea and Febiger.

2. Bennett, E. D., Barclay, S. A., Davis, A. L., Mannering, D., & Mehta, N. (1984). Ascending aortic blood velocity and acceleration using Doppler ultrasound in the assessment of left ventricular function. Cardiovascular Research, 18, 632-638.

3. Boyle, G., Mehta, N., Prindle, K., & Bennett, E. (1986). Ascending aortic blood velocity and acceleration measured by Doppler ultrasound in normal and beta-blocked subjects during treadmill exercise. Clinical Science, 71(Supplement 15), 54P (Abstract).

4. Bryg, R. J., Labovitz, A. J., Mehdirad, A. A., Williams, G. A., & Chaitman, B. R. (1986). Effect of coronary artery disease on Doppler-derived parameters of aortic flow during upright exercise. American Journal of Cardiology, 58, 14-19.

5. Chandraratna, P. A. N., Silveira, B., & Aronow, W. S. (1980). Assessment of left ventricular function by determination of maximum acceleration of blood flow in the aorta using continuous Doppler ultrasound.

The American Journal of Cardiology, 45, 398 (Abstract).

6. Daley, P. J., Sagar, K. B., & Wann, L. S. (1985). Doppler echocardiographic measurement of flow velocity in the ascending aorta during supine and upright exercise. British Heart Journal, 54, 562-567.

7. Gardin, J. M., Burn, C. S., Childs, W. J., & Henry, W. L. (1984). Evaluation of blood flow velocity in the ascending aorta and main pulmonary artery of normal subjects by Doppler echocardiography. American Heart Journal, 107, 310-319.

8. Gardin, J. M., Kozlowski, J., Dabestani, A., Murphy, M., Kusnick, C., Allfie, A., Russell, D., & Henry, W. (1986). Studies of Doppler aortic flow velocity during supine bicycle exercise. American Journal of Cardiology, 57, 327-332.

9. Harrison, M. R., Smith, M. D., Friedman, B. J., Kwan, O. L., Demaria, A. N. (1986). Doppler aortic flow velocities during exercise: Relation to evidence of myocardial ischemia by thallium perfusion scintigraphy. Journal of the American College of Cardiology, 7(2), 15A (Abstract).

10. Ihlen, H., Myhre, E., Amlie, J. P., Forfang, K., & Larsen, S. (1985). Changes in left ventricular stroke volume measured by Doppler echocardiography. British Heart Journal, 54, 378-383.

11. Khaja, F., Sabbah, H. N., Brymer, J. F., Goldstein, S., & Stein, P. D. (1986). Evaluation of left ventricular performance by continuous wave Doppler during coronary angioplasty. Free communication presented at the International Symposium on Interventional Cardiology, Houston, Texas.

12. Lambert, C. R., Nichols, W. W., & Pepine, C. J. (1982). Indices of ventricular contractile state: Comparative sensitivity and specificity. American Heart Journal, 106 (1 pt. 1), 136-144.

13. Loeppky, J. A., Greene, E. R., Hoekenga, D. E., Caprihan, A., Luft, U. C. (1981). Beat-by-beat stroke volume assessment by pulsed Doppler in upright and supine exercise. Journal of Applied Physiology: Respiratory, Environmental, and Exercise Physiology, 50(6), 1173-1182.

14. Manger, W. G. (1982). Catecholamines in normal and abnormal cardiac function. New York: Karger.

15. Mehdirad, A. A., Williams, G. A., Bryg, R. J., Windhorst, D., Habermehl, K., Chaitman, B. R., &

Labovitz, A. J. (1985). Evaluation of left ventricular function with upright exercise: Correlation of exercise Doppler with post-exercise wall motion and single plane echocardiographic ejection fraction. Circulation, 72(Supplement III), III-449 (Abstract).

16. Mehdirad, A. A., Williams, G. A., Labovitz, A. J., Bryg, R. J., & Chaitman, B. R. (1987). Evaluation of left ventricular function during upright exercise: Correlation of exercise Doppler with postexercise two-dimensional echocardiographic results. Circulation, 75(2), 413-419.

17. Mehta, N., Bennett, D., Mannering, D., Dawkins, K., & Ward, D. (1986). Usefulness of noninvasive Doppler measurement of ascending aortic blood velocity and acceleration in detecting impairment of left ventricular functional response to exercise three weeks after acute myocardial infarction. American Journal of Cardiology, 58, 879-884.

18. Rawles, J. M., Daniel, M. K., Haites, N. E., McLennon, F. M., & Mowat, D. H. R. (1985). Assessment of stroke volume and cardiac output by Doppler ultrasound alone. British Heart Journal, 53, 78 (Abstract).

19. Sabbah, H. N., Albert, D. E., Stein, P. D. (1986). Peak aortic blood acceleration is sensitive to myocardial dysfunction induced by isoproterenol in dogs with a critical coronary artery stenosis. Free communication presented at the World Congress of Cardiology, Washington, D.C.

20. Sabbah, H. N., Khaja, F., Brymer, J. F., McFarland, T. M., Albert, D. E., Snyder, J. E., Goldstein, S., & Stein, P. D. (1986). Noninvasive evaluation of left ventricular performance based on peak aortic blood acceleration measured with a continuous-wave Doppler velocity meter. Circulation, 74, 323-329.

21. Sabbah, H. N., Przybylski, J., Albert, D. E., & Stein, P. D. (1987). Peak aortic blood acceleration reflects the extent of left ventricular ischemic mass at risk. American Heart Journal, 113, 885-890.

22. Schlant, R. C., chairman. (1986). A report of the American College of Cardiology/American Heart Association Task Force on assessment of cardiovascular procedures (subcommittee on exercise testing). Journal of the American College of Cardiology, 8(3), 725-738.

23. Shaw, J. G., Johnson, E. C., Voyles, W. F., & Greene, E. R. (1985). Noninvasive Doppler determination of

cardiac output durng submaximal and peak exercise. Journal of Applied Physiology, 59(3), 722-731.

24. Werner, M., Foster, M., Weiland, D., Konstam, M., & Pandian, N. (1987). Reliability of stress Doppler echocardiography in the detection of ischemia in humans during different forms of stress. Journal of the American College of Cardiology, 9(2), 17A (Abstract).

Table 1. Subject Characteristics

Age	Weight	Predicted Body Fat*	$\dot{V}O_2max$
yr	kg	%	$ml \cdot kg^{-1} \cdot min^{-1}$
25.2	78.3	12.2	42.3
±5.6	±15.8	±4.2	±7.4

Values are means ±SD. $\dot{V}O_2max$, maximal oxygen consumption.

* Generalized skinfold equation for males (Jackson & Pollock, 1978).

Figure Legends

FIG. 1. Reproducibility of Doppler measured indices of left ventricular function.

FIG. 2. Coefficients of variation for the Doppler measured indices of left ventricular function.

FIG. 3. Reproducibility of conventionally measured cardiopulmonary variables.

FIG. 4. Coefficients of variation of conventionally measured cardiopulmonary variables.

FIG. 5. Doppler echocardiographic changes during graded exercise. Bars indicate standard error of the mean. Solid lines indicate trial 1, dashed lines trial 2.

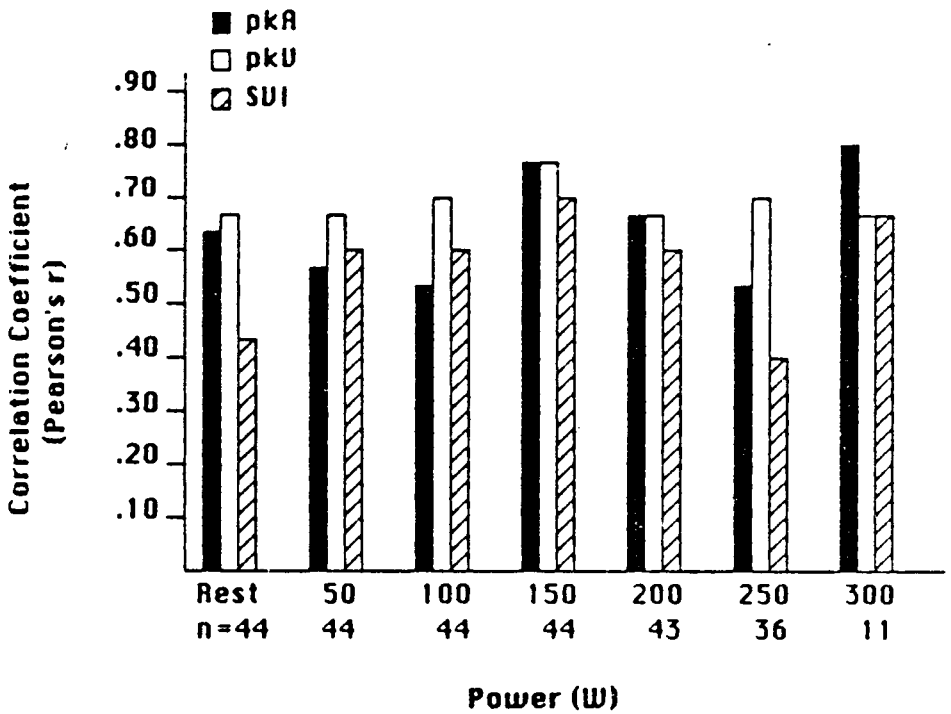

Figure 1. Reproducibility of Doppler measured indices of left ventricular function.

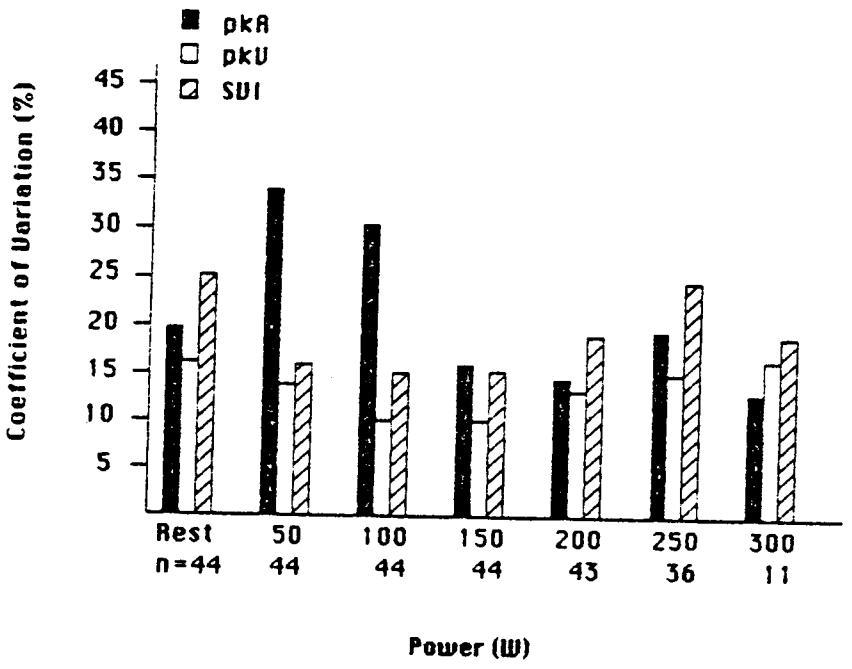

Figure 2. Coefficients of variation for the Doppler measured indices of left ventricular function.

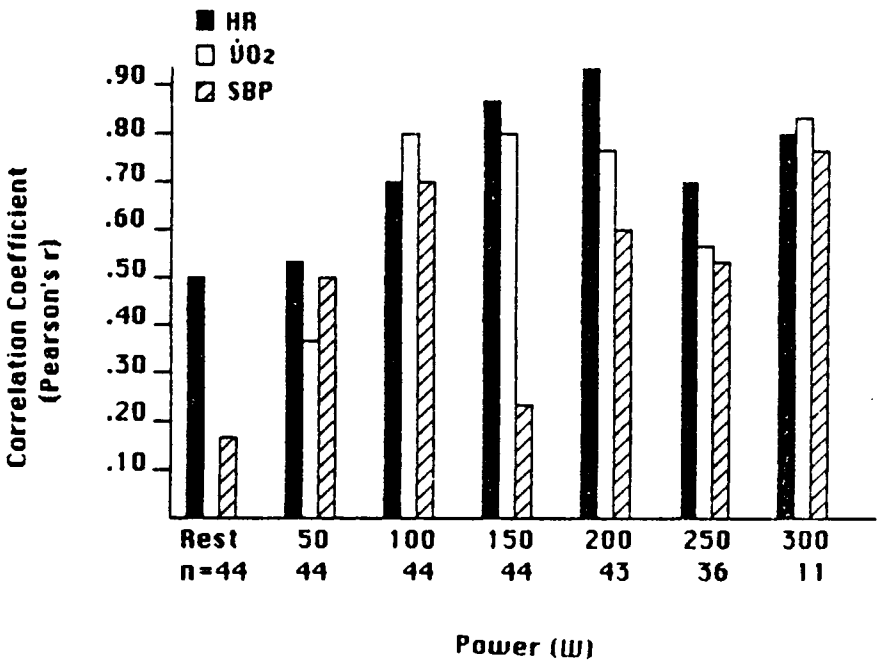

Figure 3. Reproducibility of conventionally measured cardiopulmonary variables.

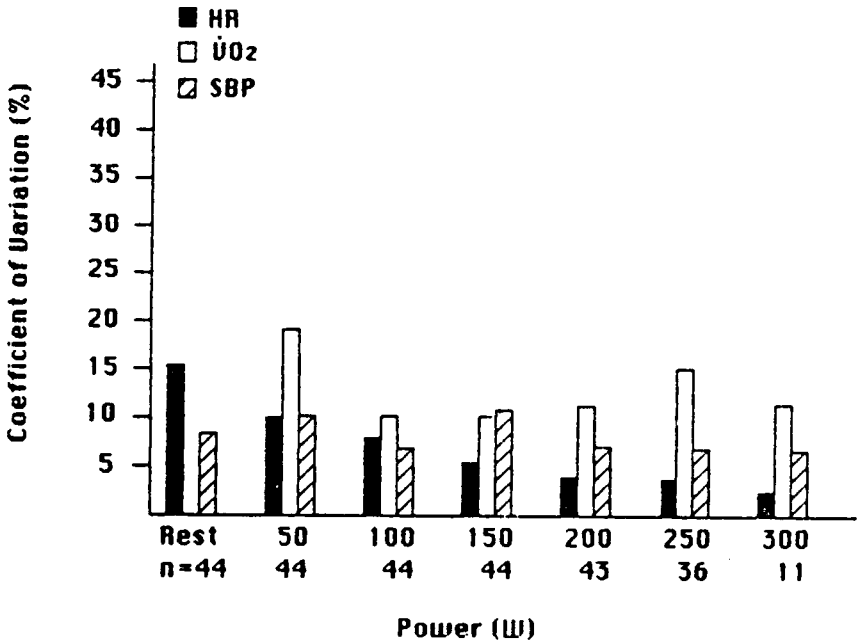

Figure 4. Coefficients of variation of conventionally measured cardiopulmonary variables.

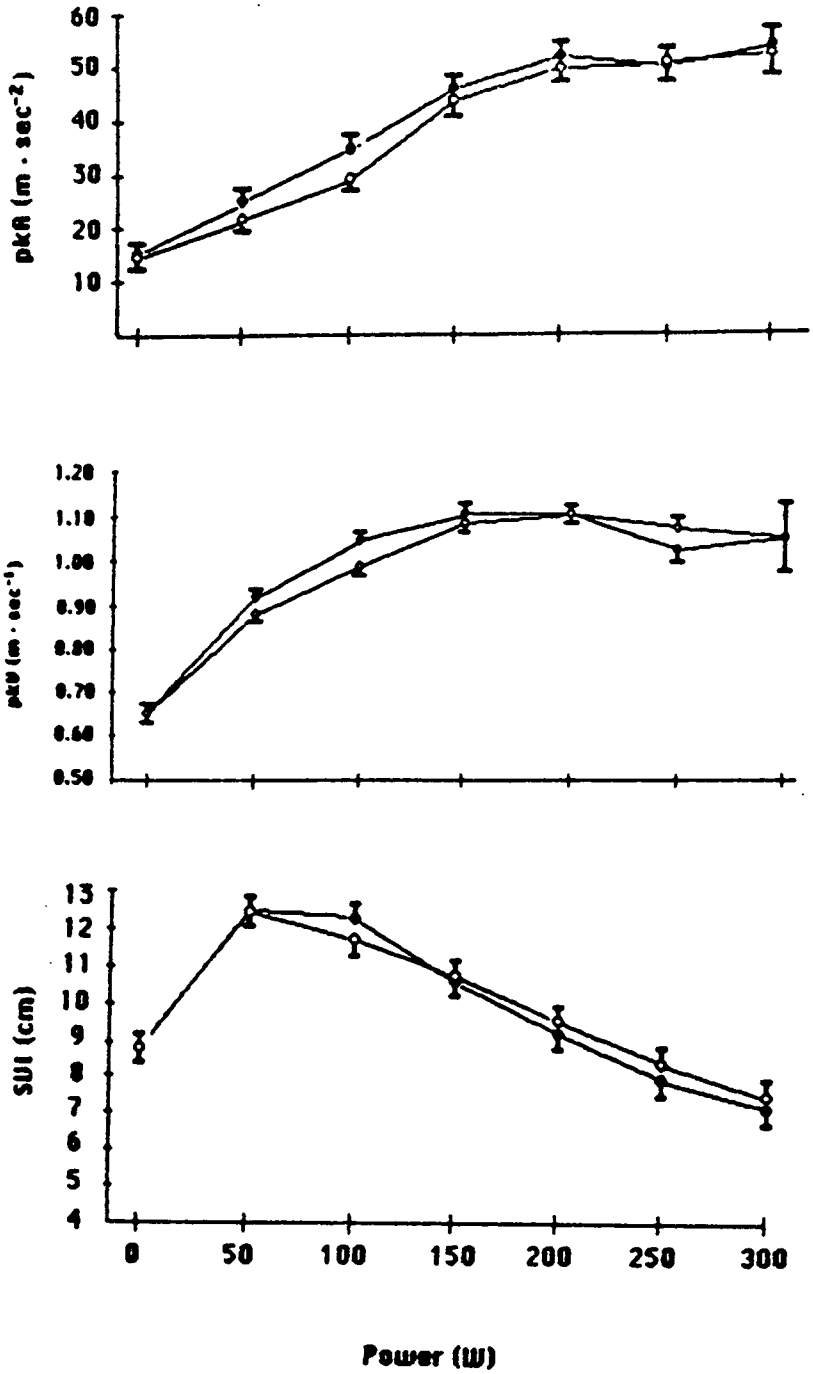

Figure 5. Doppler echocardiographic changes during graded exercise.

THE RESPONSE OF DOPPLER MEASURES TO CHANGES IN CARDIAC VENTRICULAR PRELOAD AND CONTRACTILITY DURING EXERCISE

Alan D. Moore, Jr., William G. Herbert,
Dennis E. Hinkle, and Frank C. Gwazdauskas

(abbreviated title for running head)
CW Doppler Changes During Exercise

Alan D. Moore and William G. Herbert
Laboratory for Sport, Exercise, and Work Physiology
Department of HPER
VPI & SU
Blacksburg, VA 24061
703-961-6565

ABSTRACT

Eighteen young healthy adults performed three similar cycle exercise tests under experimental conditions designed to alter their myocardial response to exercise. The purpose was to determine if a continuous wave (CW) Doppler echocardiographic system could detect the induced changes by either reducing the contractile state or increasing preload stress of the left ventricle. The graded exercise test intensities were 20, 40, and 60% $\dot{V}O_2$max for 6 minutes per stage. The tests were given: 1) 3 hr after administration of a placebo, 2) 3 hr after a 100 mg oral dose of atenolol, and 3) immediately following a 1 1/2 hour time period in which 40 ml $H_2O \cdot kg^{-1}$ was consumed (hyperhydration). Peak ascending aortic blood flow velocity (pkV), acceleration (pkA), and the systolic velocity integral (SVI) were measured with a 3.0 MHz CW Doppler system. Heart rate, systolic and diastolic blood pressures, cardiac output (CO_2 rebreathing, Collier method) and $\dot{V}O_2$ were measured at each stage. PkA was decreased ($p<.0001$) by atenolol (e.g., 46.9 $m \cdot sec^{-2}$ placebo vs 26.4 $m \cdot^{-2}$ beta blockade at 60% $\dot{V}O_2$max), and pkV demonstrated a lower magnitude but significant ($p<.0001$) decrease (e.g., 1.18 $m \cdot sec^{-1}$ placebo vs. 1.03 $m \cdot sec^{-1}$ beta blockade at 60% $\dot{V}O_2$max). SVI was increased ($p<.01$) by the

beta blockade medication at the 60% $\dot{V}O_2$max level, and stroke volume was significantly lower at all stages ($p<.05$). The hyperhydration state did not induce a change in cardiac contractile status. There were no documented changes in plasma volume as measured by changes in hematocrit, therefore, the hyperhydration procedure was judged ineffective. These data suggest that CW Doppler does reflect changes in myocardial inotropic state as induced by acute beta-blockade.

Index Terms: CW Doppler, Left Ventricular Function, Beta-blockade, Hypervolemia.

INTRODUCTION

Noninvasive measurement of blood flow velocity by Doppler echocardiography has been shown to be useful in the detection of left ventricular function changes at rest and during exercise (2, 4, 5, 8, 10, 13, 14, 15, 16, 19, 22). The majority of previous studies either used pulsed wave (PW) or continuous wave (CW) Doppler systems that were interfaced with an M-mode or two-dimensional echocardiographic system. These systems are inherently expensive, and require a considerable time investment for technical training. An alternative system, a CW Doppler system without an imaging device has recently been introduced commercially (18). This system is relatively inexpensive, requires a minimal amount of technical training, and has been demonstrated to be reliable in vitro (19).

Studies have demonstrated that acute changes in peak aortic blood flow velocity (pkV) and acceleration (pkA) are sensitive indicators of ventricular function induced by changes in inotropic state (2, 3, 13, 23), while relatively insensitive to changes in preload (2, 8). Systolic velocity integral (SVI), which is the area under the flow velocity vs time curve, has been shown primarily to be reflective of changes in stroke volume (13, 19).

The purpose of this investigation was to determine if a CW Doppler echocardiographic device would specifically detect changes in inotropic state and changes in preload stress imposed on the myocardium during graded cycle exercise in a group of healthy subjects. PkA and pkV should be supressed by beta-blockade, and SVI should increase due to an increase in stroke volume. An increase in plasma volume should increase stroke volume, thus increasing SVI; however, pkA and pkV should not be affected by this method of increased preload stress.

METHODS

Subjects. The subject group was comprised of 18 healthy, adult male volunteers. Each was screened for contraindications to exercise testing and to the administration of beta-blockade medication (1, 15). All gave informed consent prior to participation (Appendix D). In preliminary exercise trials, maximal graded exercise tests were administered to determine $\dot{V}O_2max$.

Experimental Protocol. The subjects performed cycle exercise tests consisting of three intensities; 20, 40, and 60% $\dot{V}O_2max$ (Appendix E). The duration of each exercise stage was 6 minutes, and the workload progression was continuous. The exercise tests were randomly assigned on three separate

days: 1) after placebo administration; 2) after acute beta blockade (100 mg atenolol administered 3 h prior to testing); and 3) after ingestion of a volume of cool H_2O equivalent to 40 $ml \cdot kg^{-1}$ administered in divided doses every 10 min for 90 min prior to the exercise bout (12). Atenolol is known to produce a decreased inotropic and chronotropic response to exercise and has no intrinsic sympathomimetic activity (ISA). A drug with a lack of ISA property was chosen for this experiment as a strong inhibition of inotropic response was desired. The hyperhydration trial was undertaken in an attempt to transiently expand plasma volume to increase preload. Finger-tip blood samples were collected prior to hyperhydration in that trial (90 min prior to exercise), immediately before exercise in all conditions, and after exercise cessation to assess relative plasma volume changes.

Dependent Measurements. During each test heart rate was measured electrocardiographically (Hewlett Packard 1500B) with the electrodes configured for standard clinical lead II. Blood pressure was measured with a mecurial sphygmonamometer. While exercising, the subject breathed through a Hans-Rudolph 3-way sliding valve (Model # 2770) fitted with a rubber mouthpiece. A noseclip occluded the nasal passages. Ventilation was measured on the expired side with a pneumotach (Hewlett Packard # 47303), the sensing surface of

which was connected in series with a flexible corrugated hose (I.D. 3.175 cm) leading to a baffled gas mixing chamber (volume 4.0 l). Fractions of expired oxygen and carbon dioxide were measured with electronic gas analyzers (Applied Electrochemistry SA-3, CD-3A). The ventilatory and gas exchange variables were measured continuously, except during the time the subject was rebreathing the CO_2 gas for cardiac output determination. Cardiac output was determined by the Collier method (6) during the last minute of each stage with a CO_2 analyzer interfaced with a chart recorder (Beckman Clinical Exercise Test System).

Ascending aortic blood flow velocity was measured with a 3.0 MHz CW Doppler system (EXERDOP, Quinton Instrument Co.) immediately preceding cardiac output determinations. The transducer was held at the suprasternal notch by the technician. The Doppler system measures the frequency shift of the CW signal which is reflected from blood flow being ejected from the left ventricle via the ascending aorta. The system continuously monitors velocity and records the highest value during systole as peak velocity (pkV). Peak acceleration (pkA) corresponds to the steepest positive slope in the velocity-time relationship during systole, and systolic velocity integral (SVI) is the area under the velocity-time waveform. The Doppler system is equipped with

a microprocessing unit that excludes data (beats) with a signal to raise ratio of less than 10 dB, and also excludes beats that fall outside derived acceptable limits. These limits are ±40% of the weighted average of the eight most recent measured values of pkA and SVI, and ±20% of the weighted average of the 8 most recent values of pkV. A printed report of the mean values of pkA, pkV and SVI for each sampling period was produced, as well as a report of each beat that was used in the determination of the mean values. In this study, at least 15 valid beats were included in each sample. The percentage of total beats sampled that were considered valid averaged 82.2%.

Statistical Procedures. The design is a split-plot factorial with multiple dependent measures. The statistical analysis utilized was a multivariate analysis of variance (MANOVA) with repeated measures. Appropriate univariate tests were utilized as post-hoc procedures. Any differences revealed by the univariate ANOVA were then further investigated using the Tukey post-hoc test. If the interaction was significant, tests of simple main effects were conducted followed by Tukey post-hoc tests. The level of significance for the study was set apriori at .05.

RESULTS

The subjects of the study were young adult males (Table 1). All were active and engaged in some type of regular physical conditioning activities (Appendix F).

Insert Table 1 about here

Multivariate analyses of variance revealed that the dependent measures were affected by the experimental treatment and by the imposed differences in exercise intensity ($p<.001$) (Appendix G). Two multivariate analyses were necessary as the variables requiring gas analysis ($\dot{V}O_2$, stroke volume, and cardiac output) were not measured at rest. A significant interaction between the induced changes in ventricular contractility and the changes in exercise intensity also existed (Tables 2 and 3).

Insert Tables 2 and 3 about here

The responses of the Doppler measured variables pkA and pkV were to increase with exercise intensity (Figure 1). Neither variable demonstrated a significant difference between the conditions of altered myocardial in state at

rest, and both pkA and pkV rose significantly as a result of exercise during all trials. The negative inotropic action of atenolol altered the response of both pkA and pkV by blunting the response of these indices of myocardial contractility to exercise. At 60% $\dot{V}O_2$max, pkA increased 292% over resting sitting measures, and pkV by 170% over levels measured at baseline in the placebo state. The rise in these variables during beta-blocked condition was only 150% and 160% for pkA and pkV, respectively. There was no significant difference between the placebo and hyperhydration conditions in either the pkA or pkV response.

Insert Figure 1 about here

The response of the Doppler-derived measure SVI is depicted in Figure 2. At the lowest exercise intensity SVI values were highest in the placebo condition; however, as exercise intensity increased to 60% $\dot{V}O_2$max, the greatest SVI response was noted in the beta-blockade condition. The difference in SVI response at 60% $\dot{V}O_2$max was the only statistically significant difference of SVI due to the experimentally induced changes in contractile status. Stroke volume response to exercise was significantly increased by beta blockade at all levels ($p=.0218$) (Figure 3); however,

cardiac output was highest (p=.0283) in the placebo condition (Figure 4). None of the experimental conditions affected $\dot{V}O_2$ at any exercise intensity.

Insert Figures 2-4 about here

The chronotropic response to the exercise bouts under the different states is illustrated in Figure 5. As was the case for the Doppler-measured variables pkA and pkV, heart rate was significantly ($p<.001$) lowered by the administration of atenolol throughout the exercise test, and no effect was noted as a result of the hyperhydration trial. Atenolol administration also inhibited ($p<.0001$) the increase in systolic blood pressure as compared to placebo at all levels of exercise (Figure 6).

Insert Figures 5 and 6 about here

The only differential effect induced by the hyperhydration state was that related to diastolic blood pressure. The effect of the hyperhydration trial was to raise the average diastolic pressure at the three exercise stages and at rest significantly over values observed in the other conditions. The average diastolic blood pressure observed during the

hyperhydration condition was 76.5 mmHg vs. 72.0 and 69.4 in the placebo and beta blocked trials, respectively.

DISCUSSION

Both the absolute values and relative changes in pkA and pkV for the subjects at rest and during exercise compare favorably with values previously reported (10, 11, 22). The mean values for pkA and pkV at rest during the placebo condition were 16.1 $m \cdot sec^{-1}$ and 0.70 $m \cdot sec^{-1}$, respectively. The results (Figure 1) of this study demonstrate that pkA and pkV are particularly affected by changes in inotropic state as evidenced by the clear inhibition of these values during the beta-blockade trial. The high magnitude of the blunting of pkA at the 60% $\dot{V}O_2max$ level (46.9 $m \cdot sec^{-2}$ placebo vs. 26.4 $m \cdot sec^{-2}$ at beta-blockade) indicates that it is more specific to change in myocardial contractile state than pkV (1.18 $m \cdot sec^{-1}$ placebo vs. 1.03 $m \cdot sec^{-1}$ beta-blockade). This finding is in agreement with previous studies that have examined the effect of reduced inotropic response (3, 23). Contractility is expected to increase with increasing exercise levels due to an increase in catecholamine levels (17). Atenolol inhibits the effects of catecholamines by competitive inhibition of the beta-one adrenergic receptor sites.

The effect of the experimental exercise and inotropic manipulations imposed in this study was a significantly increased SVI during exercise, and at 60% $\dot{V}O_2max$, the SVI response of the group was significantly higher in the beta-blockade condition. SVI has been used to determine stroke volume changes (13, 15, 16, 17, 22). In this experiment, stroke volume measured during beta-blockade was higher than placebo at all exercise stages (Figure 3). Thus, the finding of a higher SVI in the beta-blockade state is not unexpected if this Doppler index is specific to chronic stroke volume changes.

The responses of heart rate and systolic blood pressure to the exercise/condition combinations were as expected. Atenolol is commonly prescribed as a blood pressure medication, and the effects of this cardioselective beta-blocker on both heart rate and blood pressure have been well documented (8). Therefore, both heart rate and systolic blood pressure were lowered in the beta-blockade trial.

The only differential effect of the hyperhydration condition was an increased diastolic blood pressure. This increase may be due to the effect of an increased plasma volume level. It is probable, however, that a significant change in plasma volume was not obtained by this method. An increased plasma volume should increase cardiac output and

stroke volume by increased diastolic filling (preload stress) (2). No significant change in cardiac output or stroke volume was manifested as a result of hyperhydration, and SVI was lowered in the hyperhydration trial. The lowering of SVI with hyperhydration was the opposite of the predicted change brought about by increased plasma volume. There is no logical explanation for this result. Our measured hematocrit levels also did not indicate a change in plasma volume. These failures may have been due to postural effects that shifted plasma volume during the period of hyperhydration. Activity of the subjects was not controlled prior to entering the lab. A lengthy sitting period has been documented to reduce plasma volume (7). When the subjects entered our laboratory for the hyperhydration trial, we immediately obtained fingertip samples of blood, and the subjects then sat quietly for 90 min while drinking their assigned dosage of water. This is in contrast to the other two conditions in which blood was collected upon entering the laboratory. Vascular shifts probably occurred over the 90 min sitting period to allow redistribution of plasma and interstitial fluids. An improved approach would be to have subjects rest quietly in a supine position for 60 min before all trials, so that the first blood sample is obtained in a state of body fluid homeostasis before hyperhydration is initiated. An

improved method for inducing an acute expansion of plasma volume would be intravenous infusion of solutions that are specifically manufactured for plasma volume expansion in clinical settings such as Hespan® (6% Hetastarch in 0.9% sodium chloride).

In conclusion, the data obtained by this CW Doppler system seem to compare favorably to data found in the literature that were obtained by more sophisticated Doppler systems. The velocity and acceleration data reflected changes in inotropic state of the myocardium induced by acute beta-blockade, with pkA more influenced by these changes than pkV. SVI was reflective of increases in stroke volume induced by beta-blockade. Thus the CW Doppler system is a relatively inexpensive, noninvasive means of determining changes in myocardial contracctile status.

LITERATURE CITED

1. American College of Sports Medicine. (1986). Guidelines for graded exercise testing and prescription. 3rd ed., Philadelphia, Lea and Febiger.

2. Bennett, E. D., Barclay, S. A., Davis, A. L., Mannering, D., & Mehta, N. (1984). Ascending aortic blood velocity and acceleration using Doppler ultrasound in the assessment of left ventricular function. Cardiovascular Research, 18, 632-638.

3. Boyle, G., Mehta, N., Prindle, K., & Bennett, E. (1986). Ascending aortic blood velocity and acceleration measured by Doppler ultrasound in normal and beta-blocked subjects during treadmill exercise. Clinical Science, 71(Supplement 15), 54P (Abstract).

4. Bryg, R. J., Labovitz, A. J., Mehdirad, A. A., Williams, G. A., & Chaitman, B. R. (1986). Effect of coronary artery disease on Doppler-derived parameters of aortic flor during upright exercise. American Journal of Cardiology, 58, 14-19.

5. Chandraratna, P. A. N., Silveira, B., & Aronow, W. S. (1980). Assessment of left ventricular function by determination of maximum acceleration of blood flow in the aorta using continuous Doppler ultrasound.

The American Journal of Cardiology, 45, 398 (Abstract).

6. Collier, C. R. (1950). Determination of mixed venous CO_2 tensions by rebreathing. Journal of Applied Physiology, 9, 25-27.

7. Diaz, F. J., Bransford, D. R., Kobayashi, K., Horvath, S. M., & McMurray, R. G. (1979). Plasma volume changes during rest and exercise in different postures in a hot humid environment. Journal of Applied Physiology: Respiratory, Environmental, and Exercise Physiology, 47(4), 798-803.

8. Daley, P. J., Sagar, K. B., & Wann, L. S. (1985). Doppler echocardiographic measurement of flow velocity in the ascending aorta during supine and upright exercise. British Heart Journal, 54, 562-567.

9. Frishman, W. H. (1984). Clinical pharmacology of the beta- adrenoceptor drugs. 2nd ed., Norwalk, Connecticut, Appleton-Century-Crofts.

10. Gardin, J. M., Burn, C. S., Childs, W. J., & Henry, W. L. (1984). Evaluation of blood flow velocity in the ascending aorta and main pulmonary artery of normal subjects by Doppler echocardiography. American Heart Journal, 107, 310-319.

11. Gardin, J. M., Kozlowski, J., Dabestani, A., Murphy, M., Kusnick, C., Allfie, A., Russell, D., & Henry, W. L. (1986). Studies of Doppler aortic flow velocity during supine bicycle exercise. American Journal of Cardiology, 57, 327-332.

12. Greenleaf, J. E., & Castle, B. L. (1971). Exercise temperature regulation in man during hypohydration and hyperhydration. Journal of Applied Physiology, 30(6), 847-853.

13. Ihlen, H., Myhre, E., Amlie, J. P., Forfang, K., & Larsen, S. (1985). Changes in left ventricular stroke volume measured by Doppler echocardiography. British Heart Journal, 54, 378-383.

14. Khaja, F., Sabbah, H. N., Brymer, J. F., Goldstein, S., & Stein, P. D. (1986). Evaluation of left ventricular performance by continuous wave Doppler during coronary angioplasty. Free communication presented at the International Symposium on Interventional Cardiology, Houstin, Texas.

15. Light, L. H. (1969). Non-injurious ultrasonic technique for observing flow in the human aorta. Nature, 224, 1119-1121.

16. Loeppky, J. A., Greene, E. R., Hoekenga, D. E., Caprihan, A., Luft, U. C. (1981). Beat-by-beat

stroke volume assessment by pulsed Doppler in upright and supine exercise. Journal of Applied Physiology: Respiratory, Environmental, and Exercise Physiology, 50(6), 1173-1182.

17. Manger, W. G. (1982). Catecholamines in normal and abnormal cardiac function. New York: Karger.

18. Medical Economics Company. (1986). Physicians' Desk Reference. 40th ed., Oradell, NJ: Medical Economics Company.

19. Rawles, J. M., Daniel, M. K., Haites, N. E., McLennon, F. M., & Mcwat, D. H. R. (1985). Assessment of stroke volume and cardiac output by Doppler ultrasound alone. British Heart Journal, 53, 78 (Abstract).

20. Sabbah, H. N., Albert, D. E., Stein, P. D. (1986). Peak aortic blood acceleration is sensitive to myocardial dysfunction induced by isoproterenol in dogs with a critical coronary artery stenosis. Free communication presented at the World Congress of Cardiology, Washington, D.C.

21. Sabbah, H. N., Khaja, F., Brymer, J. F., McFarland, T. M., Albert, D. E., Snyder, J. E., Goldstein, S., & Stein, P. D. (1986). Noninvasive evaluation of left ventricular performance based on peak aortic blood

acceleration measured with a continuous-wave Doppler velocity meter. Circulation, 74, 323-329.

22. Shaw, J. G., Johnson, E. C., Voyles, W. F., & Greene, E. R. (1985). Noninvasive Doppler determination of cardiac output durng submaximal and peak exercise. Journal of Applied Physiology, 59(3), 722-731.

23. Wallmeyer, K., Wann, L. S., Sagar, K. B., Kalbfleisch, J., & Klopfenstein, H. S. (1986). The influence of preload and heart rate on Doppler echocardiographic indexes of left ventricular performance: Comparison with invasive indexes in an experimental preparation. Circulation, 74(1), 181-186.

Table 1. Subject Characteristics

Age	Weight	Predicted Body Fat*	$\dot{V}O_2max$
yr	kg	%	$ml \cdot kg^{-1} \cdot min^{-1}$
23.8	78.4	11.9	41.7
±5.3	±15.0	±4.3	±6.7

Values are means ±SD. $\dot{V}O_2max$, maximal oxygen consumption.

* Generalized skinfold equation for males (Jackson & Pollock, 1978).

Table 2. Multivariate Analysis of Variance. Dependent variables: pkA, pkV, SVI, HR, SBP, DBP. Stages: Rest Sit, 20, 40, 60% $\dot{V}O_2max$.

Source	df_H	df_E	λ	F	p
Condition	2	34	.0545	15.87	<.0001
Stage	3	51	.0076	33.54	<.0001
Condition*Stage	6	102	.1734	5.84	<.0001

df_H = degrees of freedom hypothesis

df_E = degrees of freedom error term

λ = Wilk's criterion (lambda)

Table 3. Multivariate Analysis of Variance. Dependent Variables: pkA, pkV, SVI, HR, SBP, DBP, $\dot{V}O_2$abs. Stages 20, 40, 60% $\dot{V}O_2$max.

Source	df_H	df_E	λ	F	p
Condition	2	34	.0396	10.06	<.0001
Stage	2	34	.0059	7.91	<.0001
Condition*Stage	4	68	.1133	3.96	<.0001

df_H = degrees of freedom hypothesis

df_E = degrees of freedom error term

λ = Wilk's criterion (lambda)

Figure Legends

FIG. 1. PkA and pkV responses to exercise during the conditions of placebo, hyperhydration, and acute beta blockade.

FIG. 2. The response of SVI to exercise during the experimental treatments.

FIG. 3. Stroke volume response to exercise during the experimental treatments.

FIG. 4. Cardiac output response to exercise during the three experimental conditions.

FIG. 5. Heart rate response to exercise in all conditions.

FIG. 6. Systolic blood pressure response to exercise in all conditions.

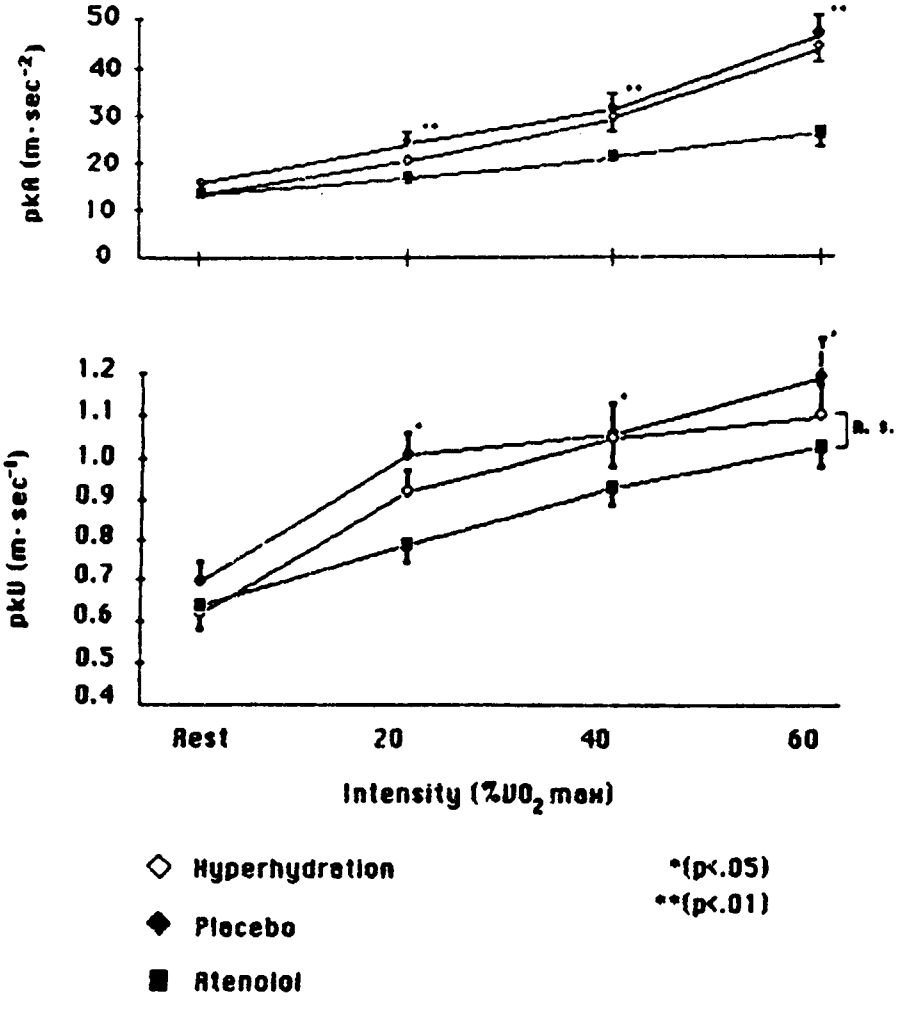

Figure 1. PkA and pkV responses to exercise during the conditions of placebo, hyperhydration, and acute beta blockade.

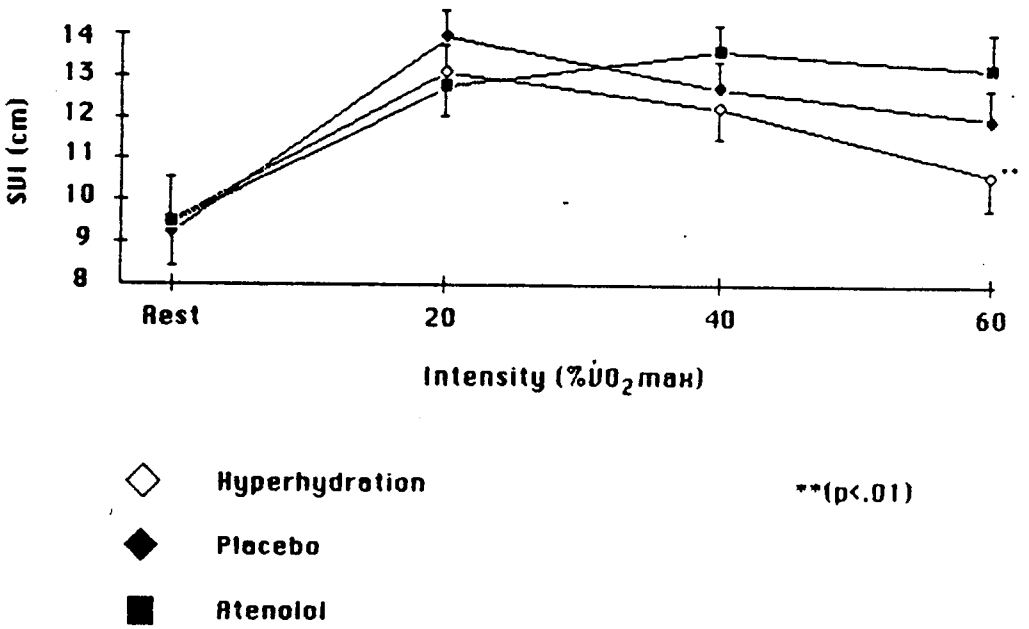

Figure 2. The response of SVI to exercise during the experimental treatments.

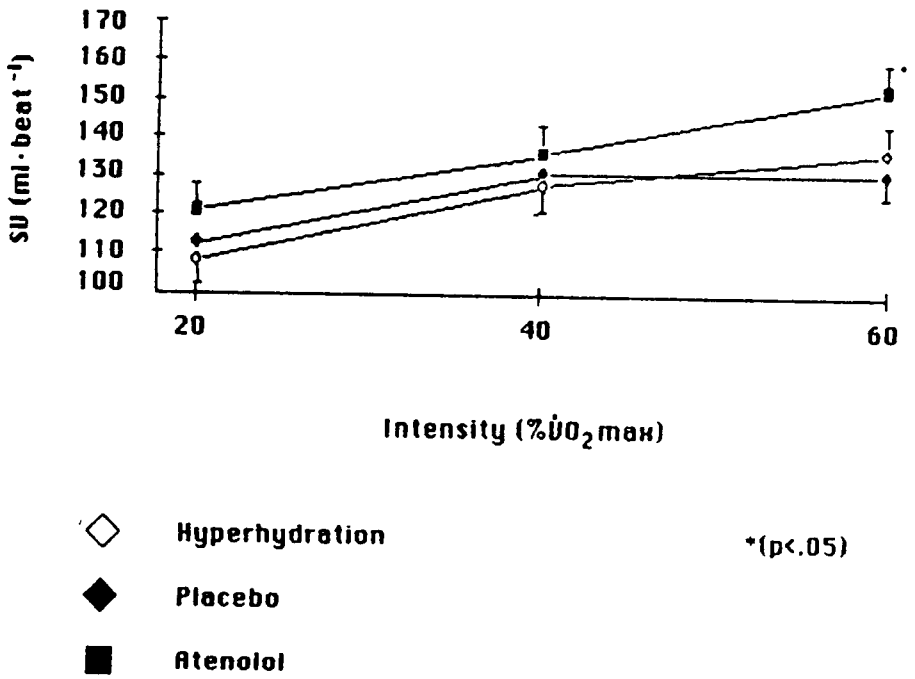

Figure 3. Stroke volume response to exercise during the experimental treatments.

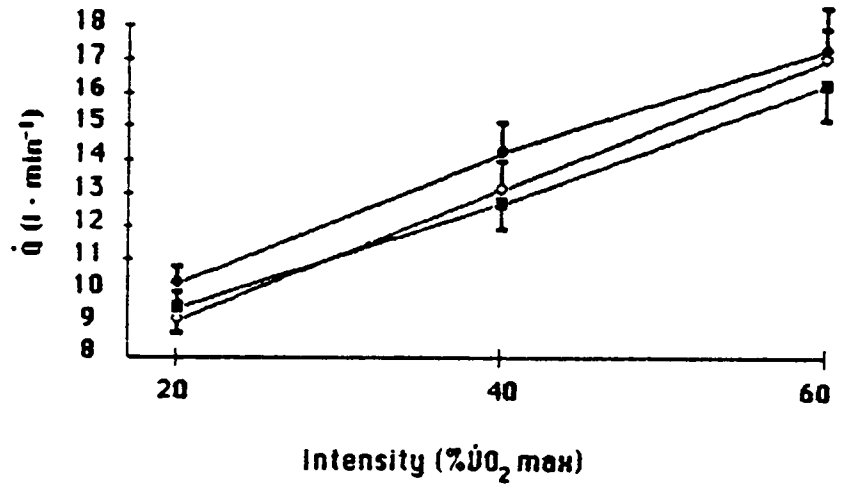

Figure 4. Cardiac output response to exercise during the three experimental conditions.

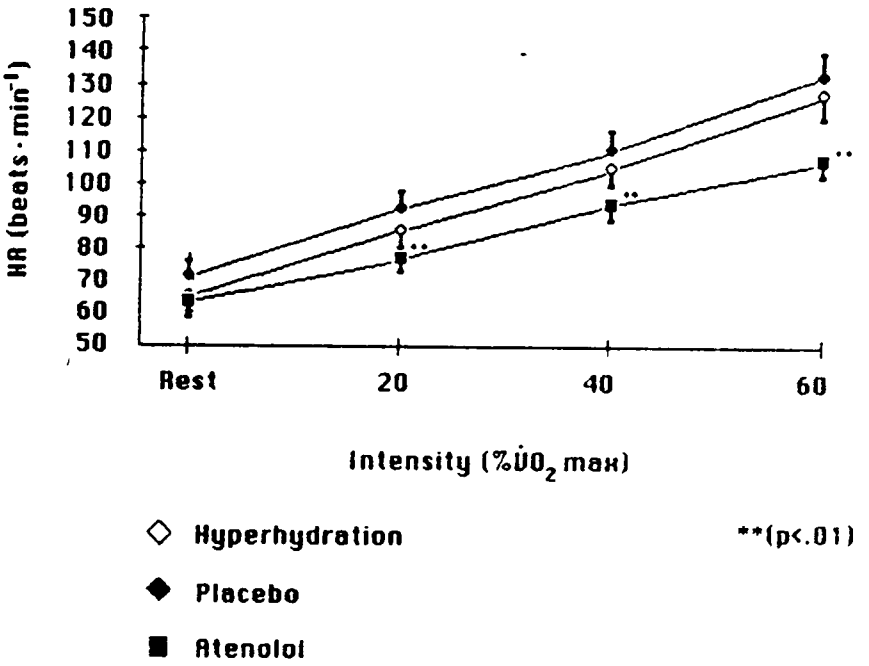

Figure 5. Heart rate response to exercise in all conditions.

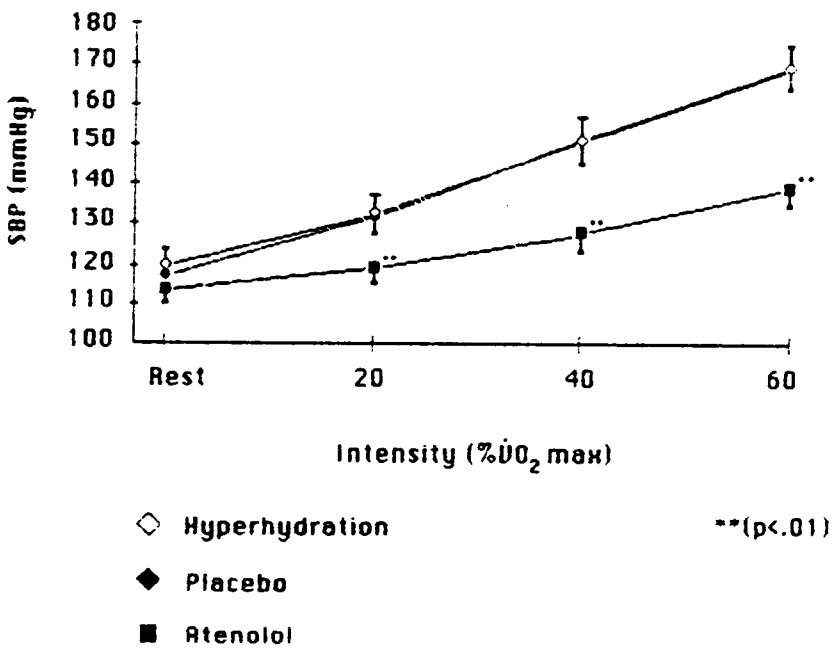

Figure 6. Systolic blood pressure response to exercise in all conditions.

Chapter IV

SUMMARY AND CONCLUSIONS

There were three purposes of this study. The first was to determine the reproducibility of the indices of left ventricular function (LVF) measured by the continuous wave (CW) Doppler unit (EXERDOP). The second was to determine if induced changes in myocardial contractile properties or in left ventricular preload were reflected in changes in the Doppler measured indices. The third purpose was to suggest improvements in the EXERDOP design. This purpose was not empirically tested, but will be discussed in this section.

The reproducibility of the Doppler measures was explored by maximal cycle testing a group of 44 young healthy adult males. The CW Doppler measures of peak acceleration (pkA), peak velocity (pkV) and systolic velocity integral (SVI) were measured during the last minute of each three minute stage. The power requirement for each stage increased 50 W. Heart rate, blood pressure, and oxygen analysis data also were sampled. The test-retest data correlated at each stage of the exercise protocol using Pearson's product-moment correlation, and coefficients of variation were computed for each stage.

The results of the reproducibility phase of the study indicated that the magnitude of the test-retest correlation averaged 0.65. The range for pkA was 0.54-0.81, for pkV 0.65-0.77 and for SVI 0.40-0.71. The range of coefficients of variation of pkA was 14.2-33.5%, of pkV was 11.4-18.4%, and for SVI, 16.3-26.7%.

These correlation coefficients would seem rather low and the coefficients of variation rather high, for a diagnostic medical instrument. The variability between the two tests, however, is likely due to variations in the physiological response of the individuals being studied or because of accommodation to the cycle exercise task. Two observations led to this speculation. The first observation is that the test-retest correlation of heart rate ranged from 0.50-0.86 and the correlation of absolute $\dot{V}O_2$ between the two tests was 0.35-0.79. Heart rate and oxygen consumption are considered by most physiologists as highly reproducible under similar exercise states. This relationship is one of the premises on which exercise prescription is based (ACSM, 1986). The Doppler indices of LVF showed reproducibility nearly comparable to the established "reproducible" exercise measures. The second observation that has been published by Sabbah et al. (1986) and confirmed by preliminary work in

this laboratory is that the EXERDOP as a unit reliably and consistently estimates blood flow velocity.

In the second phase of the study, a subset of the original 44 subjects (N=18) were tested under three conditions designed to alter the myocardial contractile responses to exercise and to examine the changes of pkA, pkV, and SVI by the EXERDOP unit. The first condition was a placebo trial; the second test was conducted after oral hyperhydration; and the third after administration of 100 mg Atenolol. The exercise tests consisted of three six minute stages, the intensity of which were 20, 40, and 60% $\dot{V}O_2$max. Comparison of the exercise responses by repeated measures multivariate analysis of variance showed that a significant interaction existed between exercise intensity and myocardial contractile condition. This was further explored by the use of repeated measures analysis of variance for each dependent variable. The univariate analyses demonstrated that pkA and pkV were significantly lowered by the administration of atenolol (reduced inotropic response) during each exercise stage. SVI was significantly increased at the 60% $\dot{V}O_2$max level. This appeared to be due to increased stroke volume induced by beta-blockade. Chronotropic and blood pressure responses followed expected trends in terms of the effects of beta-blockade. The oral hyperhydration trial appeared to

have little, if any, effect on the contractile response to exercise. It is probable that oral hyperhydration will not allow a change in plasma volume that is large enough to be detected as an increased preload force to the heart.

Suggested Improvements for the EXERDOP

In regard to improving the design of the EXERDOP, the experience of conducting over 140 exercise tests with the unit leads this investigator to offer these suggestions:

1. The EXERDOP unit should have included, when purchased, a pair of high quality headphones. The audio feedback that is generated from the speaker internal to the EXERDOP lacks clarity, is distracting to the subject/patient, and the poor sound quality potentially could lead to a technician interrogating the wrong vessel during an examination.
2. The LED display on the transducer housing was of little use during exercise evaluations, and only minimally aided in transducer placement.
3. The triggering switch that is located on the bottom of the transducer housing should be either eliminated, or better, moved to the side or top of the housing. The trigger is too difficult to press during exercise evaluation in its present location.

4. The paper drive was somewhat substandard in that there were constant problems with the paper retracting into the paper slot. An improvement to the paper drive would be to reverse the printing head surface so that the printed values could easily be seen by the technician during testing.

Implications for Clinicians and Researchers

A system such as the EXERDOP can be a valuable instrument for both research and diagnostic purposes. The present day health concerns regarding acquired immune deficiency syndrome (AIDS) may lead to less invasive research being conducted with human subjects. The containment of medical costs may lead to less invasive procedures conducted by diagnosticians. Noninvasive tools such as EXERDOP have the potential for alleviating both the aforementioned areas of concern.

The reproducibility of the Doppler responses ranged from approximately r=0.50-0.80. The study indicates that this degree of reproducibility is as high as that of the clinical measures of heart rate and blood pressure response to exercise. This study also documents that the inotropic inhibition of the myocardium as induced by acute beta-blockade can be detected with the instrument. These

findings imply that EXERDOP can be used to detect changes in left ventricular function.

Recommendations for Future Research

The results of this investigation indicate a wide spectrum of research possibilities for future investigation. Of these, the following are forwarded as feasible experiments that would enhance the knowledge of cardiac function and adaptation.

1) Further exploration of preload stress on CW Doppler responses should be undertaken. The use of an infusion of plasma volume expansion solution would be one method by which this could be accomplished. Another alternative approach would be to vary body position to increase diastolic filling. An experiment that compares supine, upright, and inverted exercise responses would be a practical approach. Inverted exercise could be accomplished using arm ergometry.

2) A study of the training adaptations to exercise and the effects of this training on the CW Doppler indices could be explored. One such study would be a comparison of the changes induced by a strength (pressure load to the left ventricle) training regimen as opposed to an endurance (volume load adaptation) regimen. Preliminary work in our laboratory indicates that the EXERDOP measures cannot be collected during isometric or slow velocity isokinetic

exercise; therefore, these comparisons may only be made during dynamic exercise such as treadmill or cycle exercise.

3) A long-term study of the change CW Doppler indices in two endurance trained groups should be performed. One group with documented coronary artery disease (CAD) and another group of subjects with no CAD should be examined for differential effects. This type of study could easily be incorporated into the routine stress testing program of the clients in the Cardiac and Intervention Center at Virginia Tech.

4) A study should be undertaken to determine if the variability that exists in EXERDOP indices of LVF are too great to allow it to be a sensitive clinical tool for routine stress testing. This type of study could be accomplished with the client population of the Cardiac and Intervention Center by comparing the Doppler responses obtained during exercise testing in clients with various degrees of left ventricular dysfunction.

Conclusions

The CW Doppler system (EXERDOP) was found to be reproducible and specific to changes in inotropic status of the left ventricle. A study of the application of EXERDOP measures in clinical groups is the next logical step in the evaluation of the usefulness of this new clinical tool.

LITERATURE CITED

American College of Sports Medicine. (1986). Guidelines for graded exercise testing and prescription. 3rd ed., Philadelphia, Lea and Febiger.

American Heart Association. (1981). Heart facts. Dallas, American Heart Association.

Bennett, E. D., Barclay, S. A., Davis, A. L., Mannering, D., & Mehta, N. (1984). Ascending aortic blood velocity and acceleration using Doppler ultrasound in the assessment of left ventricular function. Cardiovascular Research, 18, 632-638.

Boyle, G., Mehta, N., Prindle, K., & Bennett, E. (1986). Ascending aortic blood velocity and acceleration measured by Doppler ultrasound in normal and B-blocked subjects during treadmill exercise. Clinical Science, 71(Supplement 15), 54P (Abstract).

Brooks, G., & Fahey, T. (1984). Exercise physiology: Human bioenergetics and its applications. New York: John Wiley & Sons.

Bryg, R. J., Labovitz, A. J., Mehdirad, A. A., Williams, G. A., & Chaitman, B. R. (1986). Effect of coronary artery disease on Doppler-derived parameters of aortic flor during upright exercise. American Journal of Cardiology, 58, 14-19.

Chandraratna, P. A. N., Silveira, B., & Aronow, W. S. (1980). Assessment of left ventricular function by determination of maximum acceleration of blood flow in the aorta using continuous Doppler ultrasound. The American Journal of Cardiology, 45, 398 (Abstract).

Christie, J. L., Wann, L. S., Sheldahl, L., Sagar, K. B., Tristani, F. E., & Ptacin, M. J. (1986). Doppler estimates of ascending aortic flow during exercise show substantial inter-subject variation. Circulation, 74(Supplement II), II-229.

Collier, C. R. (1950). Determination of mixed venous CO_2 tensions by rebreathing. Journal of Applied Physiology, 9, 25-27.

Cooper, R., Stamler, J., & Dyer, S. (1978). The decline in mortality from coronary artery disease, USA, 1968-1975. Journal of Chronic Disease, 31, 709-720.

Costill, D. L., & Fink, W. J. (1974). Plasma volume changes following exercise and thermal dehydration. Journal of Applied Physiology, 37(4), 521-525.

Daley, P. J., Sagar, K. B., & Wann, L. S. (1985). Doppler echocardiographic measurement of flow velocity in the ascending aorta during supine and upright exercise. British Heart Journal, 54, 562-567.

Diaz, F. J., Bransford, D. R., Kobayashi, K., Horvath, S. M., & McMurray, R. G. (1979). Plasma volume changes during rest and exercise in different postures in a hot humid environment. Journal of Applied Physiology: Respiratory, Environmental, and Exercise Physiology, 47(4), 798-803.

Frishman, W. H. (1984). Clinical pharmacology of the beta-adrenoceptor drugs. 2nd ed., Norwalk, Connecticut, Appleton-Century-Crofts.

Gardin, J. M., Burn, C. S., Childs, W. J., & Henry, W. L. (1984). Evaluation of blood flow velocity in the ascending aorta and main pulmonary artery of normal subjects by Doppler echocardiography. American Heart Journal, 107, 310-319.

Gardin, J. M., Dabestani, A., Matin, K., Allfie, A., Russell, D., & Henry, W. L. (1984). Reproducibility of Doppler aortic blood flow measurements: Studies on intraobserver, interobserver, and day-to-day variability in normal subjects. American Journal of Cardiology, 54, 1092-1098.

Gardin, J. M., Kozlowski, J., Dabestani, A., Murphy, M., Kusnick, C., Allfie, A., Russell, D., & Henry, W. L. (1986). Studies of Doppler aortic flow velocity during supine bicycle exercise. American Journal of Cardiology, 57, 327-332.

Gardin, J. M., Davidson, D. M., Rohan, M. K., Butman, S., Knoll, M., Garcia, K., Dubria, S., Gardin, S. K., & Henry, W. L. (1987). Relationship between age, body size, gender and blood pressure and Doppler flow

measurements in the aorta and pulmonary artery. American Heart Journal, 113, 101.

Greenleaf, J. E., & Castle, B. L. (1971). Exercise temperature regulation in man during hypohydration and hyperhydration. Journal of Applied Physiology, 30(6), 847-853.

Harrison, M. R., Smith, M. D., Friedman, B. J., Kwan, O. L., Demaria, A. N. (1986). Doppler aortic flow velocities during exercise: Relation to evidence of myocardial ischemia by thallium perfusion scintigraphy. Journal of the American College of Cardiology, 7(2), 15A (Abstract).

Ihlen, H., Myhre, E., Amlie, J. P., Forfang, K., & Larsen, S. (1985). Changes in left ventricular stroke volume measured by Doppler echocardiography. British Heart Journal, 54, 378-383.

Illingworth, D. R., & Connor, W. E. (1985). Hyperlipidemia and coronary heart disease. In Coronary heart disease, Connor, W. E., & Bristow, J. D. (Eds.), 21-42.

Jackson, A. S., & Pollock, M. W. (1978). Generalized equations for predicting body density in men. British Journal of Nutrition, 40, 497-504.

Jewitt, D., Gabe, I., Mills, C., Maurer, B., Thomas, M., & Shillingford, J. (1974). Aortic velocity and acceleration measurements in the assessment of coronary heart disease. European Journal of Cardiology, 113, 299-305.

Kelly, T. A., Patrone, V. J., Rothbart, R. M., Moore, J. C., Watson, D. D., Weltman, A., & Gibson, R. S. (1986). The utility of exercise Doppler in normals and patients with coronary artery disease. Circulation, 74(Supplement II), II-230 (Abstract).

Kelly, T. A., Rothbart, R. M., Patrone, V. J., Moore, J. C., Watson, D. D., & Gibson, R. S. (1986). Suprasternal exercise Doppler (EXERDOP): Feasibility and results in normals and patients with suspected coronary disease. Journal of the American College of Cardiology, 7(2), 15A (Abstract).

Khaja, F., Sabbah, H. N., Brymer, J. F., Goldstein, S., & Stein, P. D. (1986). Evaluation of left ventricular performance by continuous wave Doppler during coronary angioplasty. Free communication presented at the International Symposium on Interventional Cardiology, Houstin, Texas.

Kisslo, J., Adams, D., & Mark, D. B. (1986). Basic Doppler echocardiography. New York, Churchill Livingstone.

Labovitz, A. J., & Williams, G. A. (1985). Doppler Echocardiography, Philadelphia, Lea and Febiger.

Lambert, C. R., Nichols, W. W., & Pepine, C. J. (1982). Indices of ventricular contractile state: Comparative sensitivity and specificity. American Heart Journal, 106 (1 pt. 1), 136-144.

Light, L. H. (1969a). Transcutaneous observation of blood velocity in the ascending aorta in man. Journal of Physiology (London), 204, 1P-2P (Abstract).

Light, L. H. (1969b). Non-injurious ultrasonic technique for observing flow in the human aorta. Nature, 224, 1119-1121.

Loeppky, J. A., Greene, E. R., Hoekenga, D. E., Caprihan, A., Luft, U. C. (1981). Beat-by-beat stroke volume assessment by pulsed Doppler in upright and supine exercise. Journal of Applied Physiology: Respiratory, Environmental, and Exercise Physiology, 50(6), 1173-1182.

Manger, W. G. (1982). Catecholamines in normal and abnormal cardiac function. New York: Karger.

Medical Economics Company. (1987). Physicians' Desk Reference. 41st ed., Oradell, NJ: Medical Economics Company.

Mehdirad, A. A., Williams, G. A., Bryg, R. J., Windhorst, D., Habermehl, K., Chaitman, B. R., & Labovitz, A. J. (1985). Evaluation of left ventricular function with upright exercise: Correlation of exercise Doppler with post-exercise wall motion and single plane echocardiographic ejection fraction. Circulation, 72(Supplement III), III-449 (Abstract).

Mehdirad, A. A., Williams, G. A., Labovitz, A. J., Bryg, R. J., & Chaitman, B. R. (1987). Evaluation of left ventricular function during upright exercise: Correlation of exercise Doppler with postexercise two-dimensional echocardiographic results. Circulation, 75(2), 413-419.

Mehta, N., Bennett, D., Dawkins, K., Ward, D., & Mannering, D. (1986). Doppler monitored hemodynamic response and early ischemia in exercise stress testing predicts triple vessel disease. Journal of the American College of Cardiology, 7(2), 16A (Abstract).

Mehta, N., Bennett, D., Mannering, D., Dawkins, K., & Ward, D. (1986). Usefulness of noninvasive Doppler measurement of ascending aortic blood velocity and acceleration in detecting impairment of left ventricular functional response to exercise three weeks after acute myocardial infarction. American Journal of Cardiology, 58, 879-884.

Mehta, N., Noble, M. I. M., Mills, C. J., Pugh, S., Drake-Holland, A., & Bennett, E. D. (1986). Validation of Doppler measured ascending aortic blood velocity and acceleration in humans against an electromagnetic catheter-tip system. Clinical Science, 71(Supplement 15), 54P-55P.

Meijboom, E. J., Rijsterborgh, H., Bot, H., De Boo, J. A. J., Roelandt, J. R. T. C., & Bom. N. (1987). Limits of reproducibility of blood flow measurements by Doppler echocardiography. American Journal of Cardiology, 59, 133-137.

Noble, M. I. M., Trenchard, D., & Guz, A. (1966). Left ventricular ejection in conscious dogs: Measurement and significance of the maximum acceleration of blood from the left ventricle. Circulation Research, 19, 139-147.

Rawles, J. M., Daniel, M. K., Haites, N. E., McLennon, F. M., & Mowat, D. H. R. (1985). Assessment of stroke volume and cardiac output by Doppler ultrasound alone. British Heart Journal, 53, 78 (Abstract).

Rushmer, R. F. (1964). Initial ventricular impulse - A potential key to cardiac evaluation. Circulation, 29, 280-283.

Sabbah, H. N., Albert, D. E., & Snyder, J. E. (1985). Blood velocity and acceleration: Comparison of continuous wave Doppler with electromagnetic flowmetry. Federation Proceedings, 44(5), 1565 (Abstract).

Sabbah, H. N., Albert, D. E., Stein, P. D. (1986). Peak aortic blood acceleration is sensitive to myocardial dysfunction induced by isoproterenol in dogs with a critical coronary artery stenosis. Free communication presented at the World Congress of Cardiology, Washington, D.C.

Sabbah, H. N., Khaja, F., Brymer, J. F., McFarland, T. M., Albert, D. E., Snyder, J. E., Goldstein, S., & Stein, P. D. (1986). Noninvasive evaluation of left ventricular performance based on peak aortic blood acceleration measured with a continuous-wave Doppler velocity meter. Circulation, 74, 323-329.

Sabbah, H. N., Przybylski, J., Albert, D. E., & Stein, P. D. (1987). Peak aortic blood acceleration reflects the extent of left ventricular ischemic mass at risk. American Heart Journal, 113, 885-890.

Schlant, R. C., chairman. (1986). A report of the American College of Cardiology/American Heart Association Task Force on assessment of cardiovascular procedures (subcommittee on exercise testing). Journal of the American College of Cardiology, 8(3), 725-738.

Shaw, J. G., Johnson, E. C., Voyles, W. F., & Greene, E. R. (1985). Noninvasive Doppler determination of cardiac output durng submaximal and peak exercise. Journal of Applied Physiology, 59(3), 722-731.

Stein, P. D., & Sabbah, H. N. (1976). Rate of change of ventricular power: An indicator of ventricular performance during ejection. American Heart Journal, 91, 219-227.

Teague, S. M., Mark, D. B., Radford, M., Robertson, J., Albert, D., Porter, J. A., & Waugh, R. A. (1985). Doppler ejection dynamics during ischemic exercise responses. Circulation, 72(Supplement III), III-448 (Abstract).

Teague, S. M., Heinsimer, J. A., & Williams, R. S. (1986). Doppler left ventricular ejection dynamics: Influence

of afterload, exercise, and introphy. Circulation, 74(Supplement II), II-228 (Abstract).

Teague, S. M., Corn, C., Sharma, M., Prasad, R., Burow, R., Voyles, W. F., & Thadani, V. (1987). A comparison of Doppler and radionuclide ejection dynamics during ischemic exercise. American Journal of Cardiac Imaging, 1(2), 145-151.

Vijayarghavan, G., Singham, K. T., Tei, C., Wong, A.L., Wong, M., & Shah, P. M. (1984). Aortic flow velocity in older subjects using continuous-wave Doppler echocardiography. American Heart Journal, 107(6), 1275-1276 (Brief Communications).

Wallmeyer, K., Wann, L. S., Sagar, K. B., Kalbfleisch, J., & Klopfenstein, H. S. (1986). The influence of preload and heart rate on Doppler echocardiographic indexes of left ventricular performance: Comparison with invasive indexes in an experimental preparation. Circulation, 74(1), 181-186.

Waters, J. S., Kwan, O. L., & DeMaria, A. N. (1983). Sources of error in the measurement of cardiac output by Doppler techniques. Circulation, 68(Supplement III), III-229 (Abstract).

Werner, M., Foster, M., Weiland, D., Konstam, M., & Pandian, N. (1987). Reliability of stress Doppler echocardiography in the detection of ischemia in humans during different forms of stress. Journal of the American College of Cardiology, 9(2), 17A (Abstract).

White, D. N. (1982). Johann Christian Doppler and his effect: A brief history. Ultrasound Medicine and Biology, 8, 583.

APPENDIX A

INFORMED CONSENT (REPRODUCIBILITY PHASE)

CERTIFICATE
OF
APPROVAL FOR RESEARCH
INVOLVING HUMAN SUBJECTS

Division of HPER

The Human Subjects Committee of the Division of Health, Physical Education and Recreation has reviewed the research proposal of:

Alan D. Moore, Jr.

entitled: Reliability of a Stand Alone Continuous-Wave Doppler Echocardiographic System (EXERDOP) During Maximal Graded Cycle Exercise Tests.

The members have judged the subjects participating in the related experiment (not to be at risk) as a result of their participation.

(If a risk proposal) Procedures have been adopted to control the risks at acceptably low levels. The potential scientific benefits justify the level of risk to be imposed.

Members of Divisional
Human Subjects Committee

Chairman	Date
	Date
	Date

REQUEST FOR APPROVAL OF RESEARCH PROPOSAL
IN THE DIVISION OF HPER

Submitted to

Charles Baffi
Chairman, Division Human Subjects Committee and/or
Chairman, Institutional Review Board

by

Alan D. Moore, Jr.
Principal Investigator

and

William G. Herbert
Faculty Sponsor

TITLE: Reliability of a Stand Alone Continuous-Wave Doppler Echocardiographic System (EXERDOP) During Maximal Graded Cycle Exercise Tests.

BACKGROUND/SCIENTIFIC JUSTIFICATION: At present the two methods most frequently employed for the assessment of left ventricular function are two-dimensional echocardiography and nuclear ventriculography (Bennett, et al, 1984). Both of these methods are extremely expensive, require extensive technician training, and in the latter method the use of radioisotopes. Recent technological advances have led to the development of a Doppler echocardiographic system designed for use during exercise testing that avoids the problems associated with the above mentioned methods. If found to be reliable this system (EXERDOP) may find use in clinicial and research settings. The EXERDOP system uses ultrasonic energy to measure the blood flow in the ascending aorta. No adverse effects have been documented with the use of ultrasonic devices, and it is considered to be a technique that is even safe enough for routine prenatal examinations.

PURPOSE(S): The purpose of the study is to determine the reliability of the EXERDOP system during maximal cycle tests held on separate days.

EXPERIMENTAL METHODS & PROCEDURES: The subjects of the experiment will be males less than 35 years of age that are in the category of "apparently healthy" as set forth by the American College of Sports Medicine (ACSM, 1986; see attached), and will be students and faculty/staff members from Virginia Tech. During the initial visit to the laboratory subjects will be screened for contraindications to exercise testing, and will be measured for percentage body fat with skinfold calipers.

During the experimental test the subject will exercise on a cycle ergometer. The workloads will advance 50 Watts every 3 min. Heart rate will be continuously monitored and blood pressure will be recorded each stage. Expired respiratory gasses will be collected through a one-way non-rebreathing valve for calculation of oxygen comsumption. Measurements of aortic blood flow will be conducted during the final minute of each stage with the EXERDOP system.

The subject will be requested to exercise until they are unable and/or unwilling to continue. At this time a monitored cool down period will be administered.

STATEMENT DESCRIBING LEVEL OF RISK TO SUBJECTS: The subjects will be screened according to the ACSM guidelines. The level of risk inherent in exercise testing subjects in the "apparently healthy" category under the age of 35 is minimal, however the following may occur: 1)abnormal changes in heart rate and rhythm, 2) extreme change in blood pressure, 3) fainting, 4) very rare instances of heart attack, 5) leg fatigue, 6) skin irritation caused by electrode preparation for ECG, and/or 7) minor soreness above the sternum where the EXERDOP transducer is positioned.

PROCEDURES TO MINIMIZE SUBJECT RISK (IF APPLICABLE): The subjects will be screened prior to any participation in the study. The primary investigator and two of the technicians are certified by ACSM for exercise testing and supervision. All of the laboratory technicians are certified in CPR. Heart rate and rhythm will be continuously monitored electrocardiographically to permit rapid detection of abnormalities if they should arise. A telephone will be available for the investigators to phone the rescue squad if necessary.

RISK/BENEFIT RATIO (IF RISK PROJECT): The risk to the subjects is minimal. The subjects will learn their oxygen comsumption which is the criterion measurement of aerobic fitness. The benefit to the research and medical community will be great if the EXERDOP proves to be a reliable indicator of left ventricular function.

LABORATORY FOR EXERCISE, SPORTS, AND WORK PHYSIOLOGY

Division of Health, Physical Education and Recreation
Virginia Polytechnic Institute and State University

INFORMED CONSENT

I, _____, do hereby voluntarily agree and consent to participate in a testing program conducted by the personnel of the Human Performance Laboratory of the Division of Health, Physical Education and Recreation of Virginia Polytechnic Institute and State University.

Title of Study: Reliability of a Stand Alone Continuous-Wave Doppler Echocardiographic System (EXERDOP) During Maximal Graded Cycle Exercise Tests.

The purposes of this experiment include: To examine the reliability of a new Continuous-Wave echocardiographic device during maximal cycle testing.

I voluntarily agree to participate in this testing program. It is my understanding that my participation will include: Two tests on a cycle ergometer to maximal exercise levels. Each test will last from 12-18 min. During these tests the investigators will constantly monitor heart rate and rhythm, will measure blood pressure once every 3 min., will continuously collect my expired respiratory gasses, and will determine aortic blood flow with an echocardiographic device every 3 min. The blood flow determintation will be made by a technician placing a hand-held probe above my sternum (the area where my neck and chest meet).

I understand that participation in this experiment may produce certain discomforts and risks. These discomforts and risks include: Abnormal changes in heart rate and/or rhythm, abnormal changes in blood pressure, fainting, very rare instances of heart attack, leg fatigue, skin irritation due to skin preparation for ECG monitoring, and minor soreness above the sternum from the pressure of the technician holding the probe in place for the blood flow measurements.

These risks will be minimized by screening for contraindications for me to exercise. The primary investigator and two of the laboratory technicians are certified by the American College of Sports Medicine for exercise testing and supervision, and all of the technicians are certified in CPR.

Certain personal benefits may be expected from participation in this experiment. These include: The subjects' maximal oxygen uptake, which is the criterion measure of aerobic fitness.

Appropriate alternative procedures that might be advantageous to you include: The subject will be excluded from the study if any changes occur during the exercise tests that make it hazardous to continue.

I understand that any data of a personal nature will be held confidential and will be used for research purposes only. I also understand that these data may only be used when not identifiable with me.

I understand that I may abstain from participation in any part of the experiment or withdraw from the experiment should I feel the activities might be injurious to my health. The experimenter may also terminate my participation should he feel the activities might be injurious to my health.

I understand that it is my personal responsibility to advise the researchers of any preexisting medical problem that may affect my participation or of any medical problems that might arise in the course of this experiment and that no medical treatment or compensation is available if injury is suffered as a result of this research. A telephone is available which would be used to call the local hospital for emergency service.

I have read the above statements and have had the opportunity to ask questions. I understand that the researchers will, at any time, answer my inquiries concerning the procedures used in this experiment.

Scientific inquiry is indispensable to the advancement of knowledge. Your participation in this experiment provides the investigator the opportunity to conduct meaningful scientific observations designed to make significant educational contribution.

If you would like to receive the results of this investigation, please indicate this choice by marking in the appropriate space provided below. A copy will then be distributed to you as soon as the results are made available by the investigator. Thank you for making this important contribution.

_____ I request a copy of the results of this study.

Date _____ Time _____a.m./p.m.

Participant Signature _____

Witness _____
HPL Personnel

Project Director _____ Telephone _____

HPER Human Subjects Chairman Dr. Charles Baffi
Telephone 961-6561.

Dr. Charles Waring, Chairman, International Review Board for Research Involving Human Subjects. Phone 961-5283.

APPENDIX B

RAW DATA, CORRELATION MATRICES, AND COEFFICIENTS OF VARIATION FOR REPRODUCIBILITY PHASE

Subject Characteristics

Subject	Age yr	Weight kg	Body Fat %	$\dot{V}O_2max$ $ml \cdot kg^{-1} \cdot min^{-1}$
01	30	70.0	13.6	43.5
02	22	53.6	9.8	39.1
03	23	82.3	10.4	41.0
04	19	82.5	8.9	42.8
05	21	66.9	12.5	37.0
06	23	88.8	10.4	42.3
07	21	84.0	14.3	33.8
08	34	65.2	5.8	52.8
09	19	77.2	-	51.1
10	22	78.6	12.5	45.1
11	24	74.8	13.1	41.1
12	30	75.0	10.9	32.1
13	22	67.1	8.9	40.3
14	22	73.2	8.9	43.2
15	20	73.2	6.1	47.8
16	-	80.6	-	27.7
17	20	62.0	15.1	45.3
18	19	71.1	8.9	46.4
19	22	77.0	13.4	48.2
20	25	75.0	10.4	35.9
21	24	86.0	12.2	35.4
22	22	82.2	8.9	46.3
23	19	74.7	13.4	37.7
24	23	70.6	5.7	55.9
25	27	85.5	12.2	44.6
26	23	73.7	14.8	48.3
27	26	95.9	14.8	38.2
28	43	90.1	23.8	41.1
29	20	60.0	8.0	39.5
30	28	86.1	14.5	33.8
31	34	69.9	8.7	49.5
32	23	95.6	13.1	33.4
33	24	78.0	13.9	36.0
34	22	80.2	8.0	42.7
35	20	70.0	11.6	40.6
36	20	68.2	5.1	47.0
37	24	128.4	23.8	28.5
38	19	64.0	8.9	40.7
39	25	129.4	16.7	32.5
40	18	73.1	8.9	56.4
41	23	76.2	14.8	39.9
42	21	65.4	8.0	54.1
43	18	108.0	22.4	38.8
44	38	71.7	12.0	39.5
45	27	65.6	13.9	41.6
X	23.84	78.39	11.91	41.74
SD	5.30	15.00	4.28	6.68
Range	18-43	62-129.4	5.1-23.8	27.7-56.4

Index of Terms for Raw Data Set

ID = subject identification
Stg = 0 = sitting rest
1 = 50 W
2 = 100 W
3 = 150 W
4 = 200 W
5 = 250 W
6 = 300 W
pkA = peak acceleration
pkV = peak velocity
SD = systolic velocity integral
HR = heart rate
SBP = systolic blood pressure
DBP = diastolic blood pressure
$\dot{V}O_2$abs = oxygen consumption in liters•min^{-1}
perpnt = percentage of Doppler data points considered valid
vpoints = number of valid points in sample

* number following variable name refers to the trial in which the data was collected.

OBS	ID	STG	PKA1	PKA2	PKV1	PKV2	SD1	SD2	HR1	HR2	SBP1	SBP2	DBP1
1	1	0	11	13	0.48	0.55	5.6	6.4	68	76	118	130	90
2	1	1	23	22	0.85	0.83	12.8	13.4	91	92	150	148	70
3	1	2	34	25	1.14	0.88	15.2	8.8	115	118	187	164	74
4	1	3	50	56	1.06	1.01	9.8	8.8	150	136	210	180	86
5	1	4	50	61	0.88	1.07	7.6	7.2	166	176	210	208	86
6	1	5	50	55	0.88	0.96	7.6	7.0	166	188	210	220	86
7	2	0	13	12	0.48	0.50	9.4	5.4	87	91	120	126	80
8	2	1	20	20	0.86	0.73	11.6	11.8	125	120	130	142	80
9	2	2	32	27	0.96	0.92	10.6	11.6	166	162	168	156	90
10	2	3	36	33	0.99	0.95	9.0	8.8	187	188	190	170	86
11	3	0	9	11	0.39	0.43	4.2	7.2	81	75	118	130	100
12	3	1	19	30	0.74	0.89	12.2	13.8	94	98	138	160	80
13	3	2	27	50	0.94	1.04	13.2	13.8	107	130	156	164	82
14	3	3	42	48	1.05	0.95	12.6	10.4	130	152	166	188	80
15	3	4	52	52	0.99	0.97	10.8	10.2	160	172	210	194	80
16	3	5	49	50	0.87	0.82	8.4	6.8	181	188	200	206	80
17	4	0	11	9	0.44	0.39	5.8	5.0	78	88	114	110	86
18	4	1	15	15	0.66	0.58	10.4	8.8	85	111	140	116	74
19	4	2	23	21	0.89	0.80	12.0	10.2	120	122	162	156	72
20	4	3	27	31	0.79	1.05	8.8	12.2	160	150	186	196	60
21	4	4	44	53	0.84	1.01	7.0	10.2	175	171	214	196	72
22	4	5	35	52	0.64	1.13	5.4	10.6	187	188	210	200	80
23	5	0	14	17	0.60	0.77	8.8	12.2	62	67	118	112	86

OBS	DBP2	VO2ABS1	VO2ABS2	PERPNT1	PERPNT2	VPOINTS1	VPOINTS2
1	88	.	.	50.0000	84.615	28	33
2	70	1.08305	0.95190	77.7778	100.000	21	25
3	72	1.25873	1.39079	90.6250	84.615	29	33
4	80	2.04883	2.00931	76.9231	87.179	30	34
5	84	3.08403	2.21870	66.1290	85.366	41	35
6	86	3.08403	2.85091	66.1290	56.757	41	21
7	94	.	.	47.6190	60.000	20	21
8	90	1.17169	0.92001	68.9655	64.865	20	24
9	90	1.53455	1.49269	83.3333	77.778	35	35
10	86	1.82774	2.12828	79.2453	59.615	42	31
11	88	.	.	67.3469	44.000	33	11
12	80	1.04222	1.19399	57.5758	61.538	19	16
13	90	1.50907	1.48874	72.5000	51.613	29	16
14	90	2.12747	2.23391	57.3333	68.966	43	20
15	86	2.54457	2.60521	77.2727	78.125	51	25
16	80	3.23464	3.40419	57.6471	44.444	49	12
17	84	.	.	69.7674	67.213	30	41
18	86	0.90897	1.22134	73.9130	63.889	34	23
19	78	1.45852	1.75422	87.1795	93.023	34	40
20	70	2.17984	1.97970	66.6667	74.359	28	29
21	70	2.57137	2.69406	48.3871	73.913	30	51
22	78	3.13706	3.56114	76.1905	67.857	32	38
23	70	.	.	70.9091	30.435	39	21

OBS	ID	STG	PKA1	PKA2	PKV1	PKV2	SD1	SD2	HR1	HR2	SBP1	SBP2	DBP1
24	5	1	21	23	0.83	0.99	13.6	16.2	100	100	126	118	80
25	5	2	33	26	1.09	0.86	13.0	10.0	140	132	134	142	80
26	5	3	60	55	1.26	1.25	11.8	13.8	170	164	160	168	74
27	5	4	55	60	1.11	1.20	9.0	9.4	181	188	186	180	80
28	5	5	55	59	1.11	1.15	9.0	5.6	181	195	186	180	80
29	6	0	17	11	0.83	0.50	12.0	6.0	75	67	140	126	86
30	6	1	16	20	0.71	0.83	9.2	10.6	100	102	154	138	90
31	6	2	21	20	0.86	0.79	10.2	9.0	120	125	160	156	96
32	6	3	34	27	0.99	0.93	9.6	8.8	148	148	194	162	96
33	6	4	41	42	1.05	1.03	9.2	9.2	168	167	200	174	94
34	6	5	36	33	0.80	0.97	5.8	9.0	200	188	212	190	90
35	7	0	11	11	0.49	0.49	7.8	8.2	88	88	124	120	86
36	7	1	18	20	0.81	0.75	13.6	13.2	102	90	130	130	86
37	7	2	24	25	0.75	0.83	9.8	12.2	140	120	154	142	80
38	7	3	44	38	0.99	0.96	11.4	11.4	152	150	174	186	86
39	7	4	43	45	0.99	0.93	8.2	8.8	188	180	176	196	80
40	7	5	40	38	0.78	0.69	6.6	5.0	200	188	186	204	80
41	8	0	13	13	0.61	0.58	10.0	11.4	52	56	110	110	84
42	8	1	17	19	0.80	0.85	13.4	14.2	73	78	130	112	70
43	8	2	23	24	1.03	1.00	15.8	14.6	110	108	140	134	64
44	8	3	36	40	1.07	1.25	12.8	14.2	138	136	160	150	70
45	8	4	44	50	1.08	0.99	10.8	8.6	162	160	168	164	70
46	8	5	50	54	0.80	1.16	5.6	9.4	185	177	170	182	64

OBS	DBP2	VO2ABS1	VO2ABS2	PERPNT1	PERPNT2	VPOINTS1	VPOINTS2
24	80	0.92532	0.88456	86.111	96.4286	31	27
25	84	1.45780	1.27654	90.000	61.7647	36	21
26	70	1.83076	1.69778	80.000	90.4762	32	38
27	70	2.47859	2.40748	64.063	73.6842	41	42
28	70	2.47859	2.38057	64.063	50.0000	41	22
29	84	.	.	88.095	77.1429	37	27
30	86	1.21260	1.10526	52.500	74.2857	21	26
31	84	1.46937	1.54021	87.692	49.1803	57	30
32	80	1.98862	2.15092	61.364	71.4286	27	30
33	78	2.27150	2.54557	58.696	56.2500	27	27
34	80	2.92482	3.75629	33.708	50.0000	30	26
35	78	.	.	64.706	60.3774	22	32
36	90	1.12766	1.00763	75.000	80.0000	27	28
37	90	1.46822	1.40738	61.111	60.7843	22	31
38	90	2.08155	2.06150	46.774	83.7209	29	36
39	90	2.47397	2.81823	47.458	53.3333	28	32
40	90	2.48603	2.76991	43.182	22.2222	19	8
41	74	.	.	60.417	43.3962	29	23
42	70	0.98775	0.95713	65.854	86.2069	27	25
43	70	1.45319	1.54563	89.744	79.4118	35	27
44	66	2.20746	2.12866	68.333	81.3953	41	35
45	66	2.81271	2.54783	46.939	42.8571	46	27
46	60	3.44565	3.36701	42.857	76.9231	30	40

OBS	ID	STG	PKA1	PKA2	PKV1	PKV2	SD1	SD2	HR1	HR2	SBP1	SBP2	DBP1
47	8	6	50	43	0.80	0.75	5.6	5.6	185	187	170	184	64
48	9	0	24	.	0.93	.	11.2	.	68	.	140	.	88
49	9	1	34	.	1.33	.	15.2	.	100	.	160	.	84
50	9	2	64	.	1.71	.	16.0	.	110	.	188	.	90
51	9	3	75	.	1.53	.	12.2	.	150	.	224	.	88
52	9	4	80	.	1.49	.	10.2	.	170	.	230	.	80
53	9	5	75	.	1.37	.	8.0	.	185	.	226	.	80
54	9	6	56	.	1.11	.	6.0	.	188	.	234	.	80
55	10	0	17	15	0.76	0.64	11.4	6.2	67	78	106	116	64
56	10	1	24	25	1.07	1.02	16.0	15.0	87	115	140	134	60
57	10	2	32	32	1.27	1.10	17.4	13.4	115	125	146	142	54
58	10	3	55	62	1.54	1.32	17.0	12.6	150	150	174	180	60
59	10	4	68	74	1.45	1.37	12.6	9.6	175	188	188	200	70
60	10	5	73	80	1.41	1.49	9.2	9.6	207	200	208	208	70
61	11	0	21	16	0.84	0.84	10.0	12.0	90	78	130	118	64
62	11	1	57	25	1.11	1.09	13.6	17.8	105	97	140	122	62
63	11	2	64	32	1.16	1.27	12.6	16.8	127	118	164	166	66
64	11	3	65	53	1.26	1.36	10.4	15.4	158	137	180	170	60
65	11	4	68	64	1.18	1.41	8.2	13.6	174	167	190	200	60
66	11	5	55	45	1.02	0.81	7.2	6.4	194	190	200	210	60
67	12	0	9	14	0.42	0.56	4.0	5.6	85	91	118	118	36
68	12	1	15	17	0.64	0.76	6.2	7.8	115	107	122	140	90
69	12	2	27	38	0.84	1.04	6.8	8.6	136	150	156	152	94

OBS	DBP2	VO2ABS1	VO2ABS2	PERPNT1	PERPNT2	VPOINTS1	VPOINTS2
47	60	3.44565	3.20094	42.857	19.512	30	16
48	.	.	.	75.000	.	36	.
49	.	1.03696	.	90.909	.	30	.
50	.	1.70875	.	85.294	.	29	.
51	.	2.07171	.	63.235	.	43	.
52	.	2.96223	.	70.588	.	36	.
53	.	3.00837	.	82.609	.	38	.
54	.	3.94709	.	29.787	.	14	.
55	70	.	.	73.529	71.795	25	28
56	70	0.98144	0.86211	100.000	83.871	33	26
57	70	1.56656	1.51127	94.286	64.706	33	33
58	66	1.99777	2.10071	69.697	87.500	23	35
59	70	2.35098	2.49672	72.581	80.000	45	36
60	70	3.54569	2.72792	79.032	81.633	49	40
61	70	.	.	93.548	84.091	29	37
62	60	1.06338	0.82242	80.000	75.610	24	31
63	58	1.51030	1.39460	72.500	67.797	29	40
64	50	2.20430	1.86746	70.370	55.405	38	41
65	54	2.50627	2.27185	56.604	60.784	30	31
66	60	2.85301	2.98876	50.000	70.492	30	43
67	84	.	.	77.551	97.917	38	47
68	76	0.91274	0.93076	78.571	80.000	33	24
69	74	1.33637	1.29762	67.647	58.065	23	18

OBS	ID	STG	PKA1	PKA2	PKV1	PKV2	SD1	SD2	HR1	HR2	SBP1	SBP2	DBP1
70	12	3	46	45	0.92	0.91	5.4	5.2	167	165	170	164	90
71	12	4	42	43	0.75	0.86	4.0	4.6	188	188	190	176	90
72	13	0	14	17	0.62	0.74	10.2	9.2	85	83	120	158	74
73	13	1	52	39	0.98	0.76	9.8	7.4	100	130	170	160	74
74	13	2	55	45	1.08	0.98	9.8	9.0	150	150	180	170	80
75	13	3	42	49	0.84	1.00	7.4	8.2	176	170	184	170	80
76	13	4	30	45	0.71	0.95	6.0	7.4	185	176	188	190	80
77	14	0	18	16	0.70	0.68	8.2	7.8	65	62	124	122	76
78	14	1	24	26	0.91	1.00	11.4	12.4	96	83	142	142	70
79	14	2	37	34	1.14	1.18	12.6	13.4	110	114	160	164	70
80	14	3	66	58	1.31	1.26	12.6	10.8	160	148	194	180	80
81	14	4	51	61	1.09	1.63	8.4	15.4	188	167	208	196	80
82	14	5	71	47	1.54	1.17	13.6	9.2	188	177	210	196	86
83	15	0	11	14	0.54	0.65	6.6	7.6	86	75	120	114	74
84	15	1	22	20	0.96	0.81	11.0	8.6	91	100	124	132	70
85	15	2	23	24	0.94	0.95	9.0	9.4	110	113	150	160	70
86	15	3	28	30	1.04	0.98	8.4	8.2	145	142	170	166	66
87	15	4	42	51	1.03	1.13	6.2	6.6	167	166	184	172	64
88	15	5	41	47	1.02	1.09	6.4	7.0	185	182	192	190	64
89	16	0	12	15	0.49	0.61	5.0	6.8	83	75	118	100	82
90	16	1	21	20	0.85	0.88	9.8	11.2	98	92	132	122	88
91	16	2	32	23	1.06	0.71	12.0	8.4	113	122	142	142	88
92	16	3	49	40	1.20	1.13	11.2	11.6	136	136	174	154	84

OBS	DBP2	VO2ABS1	VO2ABS2	PERPNT1	PERPNT2	VPOINTS1	VPOINTS2
70	66	1.81440	2.02659	72.727	64.516	24	20
71	70	2.40639	2.19560	48.000	60.526	24	23
72	90	.	.	94.595	58.333	35	28
73	90	1.08204	1.00833	100.000	50.000	29	21
74	84	1.54822	1.62600	90.323	82.857	28	29
75	76	2.22026	2.01893	59.524	90.000	25	27
76	84	2.70476	2.44425	46.809	69.565	22	32
77	74	.	.	74.468	60.000	35	21
78	80	0.92126	0.88040	52.381	100.000	22	27
79	76	1.41815	1.38370	75.000	82.353	21	28
80	80	2.20383	1.94861	71.429	94.118	25	32
81	74	2.70150	2.64347	68.293	64.706	28	33
82	70	3.13608	3.16573	64.706	45.333	22	34
83	74	.	.	88.889	71.875	32	23
84	74	1.14130	1.05688	65.789	51.220	25	21
85	70	1.79018	1.59637	76.596	85.714	36	24
86	70	2.37583	2.10692	70.588	91.304	24	42
87	66	2.02983	2.85506	73.333	53.846	22	21
88	66	3.50094	2.94782	38.095	40.000	16	12
89	72	.	.	88.889	45.763	24	27
90	78	1.01292	0.99276	65.714	85.294	23	29
91	70	1.62788	1.52137	50.000	49.180	18	30
92	78	1.91564	2.11058	80.000	81.818	28	36

OBS	ID	STG	PKA1	PKA2	PKV1	PKV2	SD1	SD2	HR1	HR2	SBP1	SBP2	DBP1
93	16	4	51	40	1.12	1.13	9.6	11.6	150	136	188	154	70
94	17	0	16	18	0.69	0.82	9.0	13.8	94	71	122	130	88
95	17	1	29	23	1.09	0.91	14.0	14.6	110	89	154	140	76
96	17	2	59	31	1.42	1.10	14.0	11.4	130	122	174	160	84
97	17	3	66	60	1.33	1.28	11.2	11.6	165	143	194	180	80
98	17	4	59	58	1.26	1.18	9.4	9.6	188	176	200	192	76
99	18	0	22	19	0.75	0.62	7.4	6.6	125	100	152	140	70
100	18	1	29	29	1.05	1.10	15.8	15.8	115	107	162	164	70
101	18	2	47	42	1.26	1.23	14.0	15.9	150	125	176	160	70
102	18	3	78	84	1.28	1.46	12.0	14.2	167	158	180	170	74
103	18	4	80	88	1.31	1.32	11.6	12.4	182	179	176	172	70
104	18	5	48	69	1.00	1.17	9.6	10.8	190	195	184	188	80
105	19	0	11	12	0.50	0.59	5.4	7.2	55	79	130	130	80
106	19	1	14	14	0.64	0.74	7.6	10.8	111	97	156	132	90
107	19	2	21	17	0.88	0.72	10.4	6.8	130	118	168	140	86
108	19	3	33	27	0.94	0.94	8.4	8.8	150	142	174	164	82
109	19	4	39	34	0.94	1.05	8.2	9.2	170	167	188	170	80
110	19	5	42	42	0.88	1.01	7.6	8.6	177	187	190	184	84
111	20	0	16	12	0.58	0.48	6.2	5.6	94	72	104	103	64
112	20	1	23	19	0.76	0.69	8.8	9.2	96	86	120	116	66
113	20	2	52	39	0.84	0.74	9.0	9.0	140	109	140	150	60
114	20	3	61	56	0.97	0.99	7.8	9.4	136	140	152	160	58
115	20	4	57	51	0.88	1.00	6.8	8.2	160	168	160	170	60

OBS	DBP2	VO2ABS1	VO2ABS2	PERPNT1	PERPNT2	VPOINTS1	VPOINTS2
93	78	2.22881	2.11058	79.487	81.818	31	36
94	86	.	.	78.947	90.909	30	30
95	70	1.17523	0.92941	81.818	85.000	27	17
96	74	1.55684	1.48585	64.706	68.182	22	30
97	80	2.19581	2.01819	75.472	84.000	40	21
98	86	2.80787	2.48422	68.254	79.310	43	46
99	76	.	.	62.069	77.273	18	17
100	78	1.12918	0.71496	89.286	87.097	25	27
101	80	1.46113	1.57648	76.316	89.655	29	26
102	80	2.15250	1.94647	97.059	100.000	33	44
103	70	2.59350	2.55248	86.000	80.556	43	29
104	70	2.90249	3.29745	47.222	71.429	17	30
105	60	.	.	60.000	96.875	18	31
106	70	1.06145	1.32390	60.606	90.323	20	28
107	70	1.38505	1.66431	87.097	70.213	27	33
108	70	2.06453	2.02478	83.333	78.431	20	40
109	70	2.74801	2.71073	86.667	73.469	26	36
110	74	3.00111	3.71820	70.270	73.077	26	38
111	76	.	.	63.636	77.049	35	47
112	68	0.82365	0.88681	89.655	92.500	26	37
113	60	1.43544	1.37828	92.000	80.769	23	42
114	62	1.86382	1.98732	96.875	90.769	31	59
115	64	2.60794	2.71355	86.667	76.000	26	38

OBS	ID	STG	PKA1	PKA2	PKV1	PKV2	SD1	SD2	HR1	HR2	SBP1	SBP2	DBP1
116	21	0	15	10	0.67	0.43	10.2	4.4	83	82	128	126	80
117	21	1	17	16	0.76	0.75	14.4	12.2	122	106	132	110	70
118	21	2	27	27	0.84	0.89	10.4	11.6	136	125	150	130	80
119	21	3	39	39	0.89	0.93	8.0	8.0	170	163	170	152	90
120	21	4	39	43	0.88	0.96	6.4	8.0	187	180	180	180	90
121	21	5	39	35	0.73	0.80	4.2	4.6	194	182	190	200	86
122	22	0	13	14	0.54	0.61	5.8	6.4	82	75	132	124	80
123	22	1	32	20	1.19	0.87	12.2	9.6	93	85	170	130	80
124	22	2	38	30	1.23	1.13	12.0	13.0	120	99	170	152	74
125	22	3	57	36	1.48	1.20	12.4	10.8	130	121	210	160	80
126	22	4	61	45	1.43	1.27	9.2	9.8	150	139	220	190	80
127	22	5	63	57	1.41	1.34	8.2	8.8	180	166	228	212	80
128	22	6	50	38	1.29	0.86	8.0	5.2	200	186	230	224	80
129	23	0	24	16	0.68	0.74	8.2	12.6	75	71	124	132	72
130	23	1	25	19	0.91	0.83	10.2	13.4	78	78	150	136	62
131	23	2	30	28	1.10	1.08	12.8	12.0	98	109	162	144	66
132	23	3	42	35	1.19	1.14	11.4	11.0	136	138	190	168	70
133	23	4	59	51	1.17	1.17	8.8	9.6	175	169	230	200	74
134	23	5	37	51	0.84	1.17	6.6	9.6	206	169	228	200	70
135	24	0	18	15	0.80	0.70	8.6	9.8	62	110	146	70	74
136	24	1	37	21	1.25	0.97	12.6	13.2	105	88	174	120	66
137	24	2	63	26	1.37	1.13	10.8	13.0	125	100	170	152	60
138	24	3	70	39	1.40	1.14	9.4	11.2	152	125	190	162	60

OBS	DBP2	VO2ABS1	VO2ABS2	PERPNT1	PERPNT2	VPOINTS1	VPOINTS2
116	80	.	.	87.179	87.7551	34	43
117	80	0.89125	0.89162	87.805	76.4706	36	26
118	84	1.31644	1.57504	52.778	78.1818	19	43
119	88	1.81706	1.91012	82.000	70.2703	41	26
120	82	2.08793	2.47260	68.293	83.0189	28	44
121	80	3.04209	2.73064	50.000	51.1628	18	22
122	84	.	.	100.000	96.9697	35	32
123	70	1.03498	0.92182	95.833	96.4286	23	27
124	76	1.44345	1.38643	96.429	47.3684	27	18
125	60	2.04941	1.99614	81.081	77.5510	30	38
126	64	2.64159	2.59822	82.353	67.4419	28	29
127	68	3.16424	3.88860	71.795	72.9167	28	35
128	70	3.81312	3.50588	38.636	54.2857	17	19
129	80	.	.	82.759	55.5556	24	30
130	70	1.00019	0.78316	68.085	61.1111	32	22
131	66	1.30723	1.35107	64.706	55.0000	33	22
132	60	1.99502	1.75199	66.667	65.8537	24	27
133	74	2.46483	2.65240	86.047	66.0714	37	37
134	74	2.81662	2.65240	45.455	66.0714	15	37
135	68	.	.	83.871	77.7778	26	35
136	60	1.16889	0.31735	85.366	91.6667	35	33
137	58	1.73996	1.50366	93.478	89.4737	43	34
138	60	2.41321	1.90192	80.000	68.5714	24	24

OBS	ID	STG	PKA1	PKA2	PKV1	PKV2	SD1	SD2	HR1	HR2	SBP1	SBP2	DBP1
139	24	4	60	31	1.25	0.97	7.4	7.6	166	136	208	194	70
140	24	5	67	46	1.26	1.12	9.0	8.6	180	155	206	204	70
141	24	6	50	59	1.03	1.20	8.8	7.2	181	170	220	220	70
142	25	0	12	9	0.48	0.42	7.8	7.0	52	59	120	114	82
143	25	1	18	20	0.81	0.84	13.4	14.6	100	85	140	128	74
144	25	2	22	19	0.95	0.87	14.8	14.0	105	99	150	154	80
145	25	3	30	23	1.00	0.90	14.6	13.0	115	115	188	160	74
146	25	4	42	34	1.05	1.09	12.0	13.0	140	142	184	164	80
147	25	5	39	34	0.84	0.97	9.2	10.0	166	153	200	176	80
148	26	0	17	14	0.70	0.57	8.0	7.8	83	98	136	122	78
149	26	1	28	23	1.12	0.90	15.2	11.8	120	101	162	148	68
150	26	2	33	29	1.05	0.97	10.4	10.0	136	143	158	164	80
151	26	3	51	48	1.08	1.02	11.2	9.0	158	169	166	172	78
152	26	4	50	50	0.98	1.01	8.8	8.0	188	188	174	170	80
153	26	5	38	52	0.77	0.98	5.6	7.2	200	204	194	180	76
154	27	0	22	19	0.86	0.87	9.6	11.4	91	65	130	132	66
155	27	1	53	30	1.16	1.17	13.8	15.4	107	92	140	130	72
156	27	2	63	57	1.28	1.26	11.0	12.4	115	105	164	140	64
157	27	3	55	60	1.16	1.26	7.4	10.0	130	130	168	174	80
158	27	4	54	54	0.95	1.08	5.6	6.2	150	140	166	174	66
159	27	5	64	57	1.06	1.18	5.6	7.4	167	162	166	190	70
160	27	6	54	60	0.94	1.13	4.6	6.2	185	178	172	202	70
161	28	0	15	12	0.64	0.54	7.0	6.0	60	60	124	120	80

OBS	DBP2	VO2ABS1	VO2ABS2	PERPNT1	PERPNT2	VPOINTS1	VPOINTS2
139	70	2.92897	2.43681	62.745	58.140	32	25
140	76	3.79807	2.69686	67.213	38.710	41	24
141	80	3.79807	3.98822	34.043	20.253	16	16
142	80	.	.	69.697	61.765	23	21
143	76	1.04557	0.99332	59.091	95.652	26	22
144	74	1.55728	1.57934	93.750	96.154	30	25
145	70	2.05654	1.94336	81.481	74.074	22	20
146	74	2.38480	2.46581	58.537	78.125	24	25
147	76	2.52422	3.86107	65.909	55.814	29	24
148	78	.	.	36.508	87.500	23	35
149	80	0.93626	0.87058	90.244	84.906	37	45
150	74	1.49574	1.53387	80.435	61.905	37	26
151	72	2.14667	1.75902	72.917	62.821	35	49
152	70	2.56304	2.60874	67.273	54.717	37	29
153	78	3.10578	3.52756	48.438	51.685	31	46
154	80	.	.	86.667	97.619	26	41
155	70	1.05216	1.07844	68.750	86.486	22	32
156	80	1.65273	1.53692	100.000	97.222	29	35
157	70	2.04286	1.95100	52.174	76.667	24	46
158	70	2.51500	2.62177	72.222	29.231	26	19
159	66	2.97402	3.26099	68.571	40.909	24	18
160	60	3.67259	3.46849	49.153	53.968	29	34
161	80	.	.	90.909	70.732	30	29

OBS	ID	STG	PKA1	PKA2	PKV1	PKV2	SD1	SD2	HR1	HR2	SBP1	SBP2	DBP1
162	28	0	15	12	0.64	0.54	7.0	6.0	60	60	124	120	80
163	28	1	20	16	0.79	0.70	9.2	9.0	81	75	134	140	72
164	28	2	22	16	0.81	0.64	9.4	7.6	94	95	142	154	80
165	28	3	27	28	0.95	0.84	10.4	8.4	120	115	146	162	70
166	28	4	41	35	1.08	0.97	9.0	8.8	134	136	176	180	72
167	28	5	45	60	1.07	1.18	8.6	9.0	153	150	198	180	74
168	28	6	55	46	0.99	0.84	6.8	6.2	167	165	210	210	70
169	29	0	18	17	0.73	0.70	8.2	8.6	75	65	132	130	90
170	29	1	34	24	1.05	0.98	10.4	10.6	107	97	168	130	82
171	29	2	36	29	1.05	1.02	8.8	9.6	140	123	178	160	88
172	29	3	36	29	0.92	0.62	7.2	5.8	180	159	214	170	84
173	29	4	41	27	0.84	0.67	10.0	5.0	187	181	220	200	84
174	30	0	18	17	0.86	0.70	17.0	10.2	72	71	114	100	74
175	30	1	15	23	0.70	0.84	10.6	13.0	99	105	116	120	64
176	30	2	36	27	0.98	0.99	11.8	13.8	117	123	118	116	73
177	30	3	43	46	0.92	1.05	6.8	12.2	144	143	146	142	72
178	30	4	60	44	1.12	0.87	7.2	7.6	160	156	156	154	74
179	30	5	54	60	1.01	1.13	5.2	9.6	179	143	169	170	72
180	31	0	18	16	0.72	0.72	10.0	10.0	62	53	110	116	80
181	31	1	19	18	0.84	0.80	13.8	13.2	71	82	110	122	84
182	31	2	31	27	1.01	0.93	12.0	10.0	102	101	134	134	68
183	31	3	38	41	1.10	1.06	11.0	11.4	110	122	162	164	74
184	31	4	46	54	1.08	1.19	9.2	11.8	148	155	194	180	74

OBS	DBP2	VO2ABS1	VO2ABS2	PERPNT1	PERPNT2	VPOINTS1	VPOINTS2
162	80	.	.	90.9091	70.732	30	29
163	78	1.01418	1.07952	72.7273	64.706	24	22
164	70	1.44772	1.56462	91.1765	68.293	31	28
165	74	1.77375	2.06382	82.3529	56.000	28	28
166	76	2.63506	2.79639	56.4103	70.732	22	29
167	70	3.10118	3.21637	56.3380	84.000	40	42
168	70	3.46564	3.73804	47.9167	52.174	23	24
169	88	.	.	96.5517	65.854	28	27
170	64	0.95902	0.90386	84.8485	94.231	28	49
171	70	1.43857	1.34253	71.7949	60.526	28	23
172	60	1.94580	1.93074	54.5455	18.750	18	12
173	70	2.37182	1.95417	18.1818	26.415	6	14
174	68	.	.	90.6250	92.308	29	36
175	78	0.85391	0.88143	55.7377	68.085	34	32
176	55	1.54296	1.36701	51.3158	58.621	39	34
177	70	1.63216	1.78668	61.9718	77.049	44	47
178	74	2.32818	2.28733	49.4505	52.703	45	39
179	74	2.91440	2.66728	25.8065	53.571	8	45
180	70	.	.	75.6757	82.759	28	24
181	80	1.04879	0.86524	62.7907	78.261	27	18
182	76	1.51290	1.31536	55.7692	100.000	29	29
183	78	2.05526	1.97839	78.3784	76.471	29	26
184	82	3.08009	2.45199	72.5000	72.727	29	24

OBS	ID	STG	PKA1	PKA2	PKV1	PKV2	SD1	SD2	HR1	HR2	SBP1	SBP2	DBP1
185	31	5	52	55	0.93	1.06	6.8	9.0	184	180	204	210	72
186	32	0	12	15	0.53	0.63	9.6	6.8	83	88	140	138	90
187	32	1	18	22	0.81	0.87	13.8	11.2	103	111	160	150	92
188	32	2	20	23	0.85	0.91	14.6	12.4	113	115	172	174	96
189	32	3	26	29	0.94	0.98	11.0	11.8	132	139	180	194	104
190	32	4	34	37	1.01	1.07	11.8	11.8	151	157	200	212	100
191	32	5	37	45	0.96	1.12	10.4	9.8	180	180	218	224	98
192	33	0	14	13	0.58	0.58	9.2	6.8	78	74	112	116	74
193	33	1	21	22	0.99	1.07	14.6	17.8	103	96	134	140	70
194	33	2	26	27	1.11	1.18	16.4	15.8	120	106	140	148	68
195	33	3	36	34	1.19	1.10	12.8	11.8	132	136	152	180	66
196	33	4	51	46	1.49	1.16	14.0	11.0	151	154	170	190	60
197	33	5	54	49	1.17	1.14	9.2	8.2	186	182	170	200	66
198	34	0	20	26	0.89	1.13	10.4	15.6	86	95	130	122	80
199	34	1	25	34	1.12	1.27	16.0	17.4	111	107	148	140	80
200	34	2	30	36	1.18	1.44	12.8	19.0	120	125	150	152	78
201	34	3	53	67	1.34	1.56	14.6	16.6	137	143	180	170	76
202	34	4	69	77	1.53	1.59	14.2	14.2	159	161	198	184	82
203	34	5	63	68	1.56	1.34	14.4	9.6	176	181	210	200	76
204	34	6	64	68	1.32	1.34	9.4	9.6	193	181	220	200	80
205	35	0	16	18	0.63	0.80	9.4	11.6	92	93	130	130	84
206	35	1	23	25	1.01	1.08	14.6	14.2	112	109	174	154	86
207	35	2	34	36	1.26	1.28	14.2	12.8	135	138	176	170	90

OBS	DBP2	VO2ABS1	VO2ABS2	PERPNT1	PERPNT2	VPOINTS1	VPOINTS2
185	80	3.45875	2.80073	57.3171	48.485	47	16
186	88	.	.	54.7170	86.842	29	33
187	90	1.02940	1.28504	96.4286	72.093	27	31
188	90	1.60060	1.60121	79.3103	85.714	23	36
189	90	2.18327	2.18350	70.2128	54.054	33	20
190	94	2.45737	2.35746	74.3590	61.818	29	34
191	80	3.19615	3.16112	52.9412	55.932	27	33
192	84	.	.	59.4595	84.848	22	28
193	80	0.86883	0.89804	90.9091	96.667	20	29
194	66	1.39859	1.28702	87.5000	70.455	28	31
195	66	1.94835	1.93571	48.2759	58.000	14	29
196	72	2.24646	2.63211	65.1163	60.000	28	42
197	74	2.66121	2.79343	63.3333	51.111	38	46
198	76	.	.	96.6667	91.525	29	54
199	74	1.07489	1.01538	96.6667	100.000	29	29
200	76	1.68389	1.49315	96.6667	96.875	29	31
201	78	2.24915	2.09749	81.0811	78.378	30	29
202	82	2.44157	2.67463	84.2105	86.538	32	45
203	74	3.22468	2.94756	83.3333	85.185	35	46
204	74	3.42630	2.94756	66.1290	85.185	41	46
205	84	.	.	63.1579	80.556	24	29
206	90	0.89459	1.05339	84.2105	98.333	32	59
207	72	1.21169	1.43593	88.8889	98.333	24	59

OBS	ID	STG	PKA1	PKA2	PKV1	PKV2	SD1	SD2	HR1	HR2	SBP1	SBP2	DBP1
208	35	3	57	50	1.54	1.45	12.4	12.2	151	155	200	196	80
209	35	4	64	56	1.67	1.43	12.8	10.8	172	182	208	200	84
210	35	5	71	56	1.62	1.43	11.6	10.8	189	182	230	200	70
211	36	0	12	12	0.55	0.55	7.2	7.2	74	83	138	136	90
212	36	1	19	19	0.82	0.82	9.6	9.6	99	112	140	146	80
213	36	2	22	22	0.87	0.84	9.4	9.4	130	128	152	146	74
214	36	3	34	34	0.94	0.94	8.4	8.4	166	163	108	182	76
215	36	4	37	37	0.95	0.95	7.8	7.8	186	186	192	180	70
216	36	5	37	62	0.95	1.00	7.8	7.2	186	194	192	210	70
217	37	0	12	13	0.51	0.59	7.6	9.4	83	80	110	138	86
218	37	1	37	22	0.92	0.76	12.4	10.8	95	95	150	130	90
219	37	2	43	25	0.94	0.59	12.2	8.8	102	102	160	170	80
220	37	3	31	35	0.92	0.91	10.8	11.2	113	110	190	184	80
221	37	4	49	50	1.05	1.11	9.8	11.0	127	125	194	210	74
222	37	5	55	57	1.16	1.30	7.2	10.2	150	145	212	230	60
223	37	6	75	64	1.26	1.24	6.4	7.4	177	168	220	230	68
224	37	7	75	54	1.26	0.94	6.4	5.0	177	179	220	236	68
225	38	0	19	18	0.77	0.71	7.8	7.4	94	84	110	110	70
226	38	1	39	21	1.10	0.85	12.2	8.4	112	100	140	120	74
227	38	2	40	40	0.95	1.05	7.2	6.4	139	140	150	138	70
228	38	3	58	65	1.05	1.38	6.8	7.2	190	176	162	150	80
229	38	4	78	55	1.44	1.25	6.6	6.6	194	194	164	150	84
230	39	0	14	12	0.61	0.45	10.4	7.2	86	70	134	120	86

OBS	DBP2	VO2ABS1	VO2ABS2	PERPNT1	PERPNT2	VPOINTS1	VPOINTS2
208	70	1.88292	2.02858	92.8571	87.5000	26	56
209	70	2.33650	2.88262	89.3617	88.8889	42	72
210	70	2.78107	2.88262	83.3333	88.8889	30	72
211	86	.	.	75.0000	75.0000	21	21
212	70	1.04661	0.86563	93.7500	93.7500	30	30
213	64	1.50248	1.19748	93.5484	93.5484	29	29
214	64	1.81289	2.10972	67.1875	67.1875	43	43
215	70	2.63669	2.35945	54.9296	54.9296	39	39
216	70	2.63669	3.22803	54.9296	80.0000	39	24
217	84	.	.	35.7143	76.7442	40	33
218	70	1.26471	1.15024	73.9130	53.6585	34	22
219	80	1.75381	1.55841	73.3333	61.8182	22	34
220	80	2.11010	2.07987	65.8537	73.8095	27	31
221	78	2.51963	2.60859	76.2712	83.3333	45	40
222	76	3.11611	3.15000	50.0000	88.4615	17	46
223	70	3.66102	3.51346	48.7805	45.1613	20	28
224	70	3.66102	3.65826	48.7805	50.0000	20	23
225	70	.	.	62.9630	82.9787	34	39
226	68	1.04318	0.98179	58.5366	77.4194	24	48
227	70	1.44744	1.55098	83.0769	40.0000	54	20
228	68	2.07410	1.96499	77.2727	63.0137	34	46
229	70	2.60629	2.39113	46.6667	35.0000	21	21
230	80	.	.	62.7119	39.7260	37	29

OBS	ID	STG	PKA1	PKA2	PKV1	PKV2	SD1	SD2	HR1	HR2	SBP1	SBP2	DBP1
231	39	1	25	17	0.90	0.86	14.2	14.8	100	91	164	140	94
232	39	2	36	21	1.02	0.90	13.6	15.4	105	100	170	160	90
233	39	3	47	37	0.97	0.94	10.6	13.6	126	118	174	168	80
234	39	4	55	56	1.05	1.21	11.0	13.6	148	145	184	198	80
235	39	5	51	46	1.09	1.01	10.0	10.2	172	167	186	208	80
236	39	6	37	40	0.70	0.86	6.6	8.0	189	183	190	192	80
237	40	0	23	17	0.99	0.84	11.4	10.8	72	59	146	106	70
238	40	1	27	24	1.22	1.00	19.4	12.6	95	87	140	142	70
239	40	2	43	26	1.31	1.10	18.2	11.6	113	113	174	146	80
240	40	3	45	47	1.36	1.38	17.0	14.0	134	127	170	160	80
241	40	4	65	54	1.39	1.11	11.0	9.6	149	147	142	170	70
242	40	5	65	58	1.23	1.42	8.4	12.4	172	156	174	170	70
243	40	6	72	70	1.51	1.39	12.0	11.2	187	190	190	174	70
244	41	0	16	18	0.74	0.78	9.4	9.4	75	100	126	132	80
245	41	1	18	22	0.88	0.97	13.4	11.0	98	102	120	124	80
246	41	2	25	27	1.03	1.05	12.2	12.2	118	121	132	140	84
247	41	3	40	58	1.26	1.25	12.0	12.0	144	154	150	146	76
248	41	4	48	55	1.30	1.23	10.4	9.4	178	177	170	170	70
249	41	5	46	51	1.22	1.26	9.0	9.4	194	204	170	180	70
250	41	6	45	51	1.01	1.26	6.8	9.4	201	204	180	180	70
251	42	0	16	18	0.67	0.78	11.0	12.0	54	75	118	116	66
252	42	1	23	20	0.93	0.85	14.4	11.2	93	94	130	130	70
253	42	2	23	29	0.94	1.03	11.8	12.0	110	124	160	162	74

OBS	DBP2	VO2ABS1	VO2ABS2	PERPNT1	PERPNT2	VPOINTS1	VPOINTS2
231	80	1.27653	1.06860	36.1702	75.6757	17	28
232	84	1.55835	1.55969	33.3333	78.0488	20	32
233	72	2.24002	1.97680	64.2857	59.4595	36	22
234	70	2.99752	2.90623	71.1538	75.0000	37	33
235	70	4.20404	3.56104	67.7778	71.0145	61	49
236	80	4.17573	4.15800	53.4884	47.3684	46	36
237	68	.	.	77.7778	97.3684	28	37
238	66	0.98763	1.00600	83.7209	75.0000	36	21
239	70	1.30397	1.47131	69.0476	96.0000	29	24
240	60	1.81063	2.07589	66.6667	90.0000	28	27
241	68	2.53279	2.47207	74.4681	68.7500	35	33
242	70	3.00042	2.95502	75.3846	82.5000	49	33
243	66	3.16607	4.12387	60.8696	70.0000	42	49
244	80	.	.	96.2963	29.8246	52	17
245	74	0.94480	0.95443	86.2745	72.3404	44	34
246	80	1.53240	1.40796	95.1220	80.3922	39	41
247	74	1.94258	2.12180	85.1064	89.5833	40	43
248	80	2.32967	2.67599	75.8621	82.3529	44	42
249	74	3.04339	3.07814	51.2821	70.8861	20	56
250	74	2.88668	3.07814	53.6585	70.8861	22	56
251	60	.	.	60.6061	76.8116	20	53
252	70	0.76330	1.15258	74.4186	72.9730	32	27
253	70	1.37879	1.27695	82.9268	75.6757	34	28

OBS	ID	STG	PKA1	PKA2	PKV1	PKV2	SD1	SD2	HR1	HR2	SBP1	SBP2	DBP1
254	42	3	36	46	0.97	1.13	9.2	10.4	143	151	170	180	74
255	42	4	44	51	1.13	1.29	9.2	10.0	176	175	170	190	70
256	42	5	40	46	0.85	1.07	6.0	7.4	189	190	190	196	70
257	43	0	18	18	0.54	0.74	6.2	11.2	78	62	128	120	78
258	43	1	28	23	0.91	0.83	12.2	12.6	93	87	158	158	70
259	43	2	41	39	0.96	0.92	12.0	11.4	112	98	166	160	82
260	43	3	43	33	0.91	0.96	9.0	8.4	135	121	180	174	78
261	43	4	39	40	0.86	0.87	7.4	7.4	146	146	188	200	80
262	43	5	50	42	1.03	0.84	7.2	5.6	165	169	202	200	76
263	43	6	39	40	0.75	0.76	4.6	6.0	175	180	208	210	70
264	44	0	12	15	0.48	0.52	5.8	7.2	64	56	122	112	70
265	44	1	16	19	0.62	0.81	10.0	14.6	76	80	140	120	70
266	44	2	23	24	0.83	0.81	13.2	11.4	121	101	144	140	80
267	44	3	46	46	0.93	0.88	11.6	10.2	125	125	172	162	80
268	44	4	53	40	1.06	0.90	10.4	8.8	155	151	180	166	80
269	44	5	29	32	0.70	0.70	6.0	5.6	179	176	190	170	80
270	45	0	18	18	0.82	0.82	13.6	13.6	78	78	110	110	70
271	45	1	24	24	0.91	0.91	13.4	13.4	90	90	118	118	80
272	45	2	32	32	1.28	1.28	18.2	18.2	115	115	146	146	76
273	45	3	43	43	0.96	0.96	11.0	11.0	135	135	174	174	70
274	45	4	58	58	1.03	1.03	10.4	10.4	160	160	188	188	74
275	45	5	41	41	0.71	0.71	6.6	6.6	178	178	200	200	70

OBS	DBP2	VO2ABS1	VO2ABS2	PERPNT1	PERPNT2	VPOINTS1	VPOINTS2
254	78	1.97824	1.92977	74.4681	77.7778	35	42
255	70	2.51362	2.52148	52.7273	77.0833	29	37
256	74	3.40300	3.58486	19.5122	40.0000	8	16
257	80	.	.	65.0000	95.0000	26	38
258	76	1.28333	1.13880	67.7419	90.6250	21	29
259	68	2.13764	1.60857	72.2222	66.6667	26	30
260	70	2.18544	1.61874	76.7442	70.5882	33	36
261	70	2.60975	2.69415	69.8113	61.6438	37	45
262	62	3.14483	3.24166	68.4211	49.1228	39	28
263	64	3.80402	4.23467	26.0000	62.5000	13	15
264	80	.	.	48.5294	50.0000	33	17
265	74	1.02534	0.78451	91.6667	87.0968	33	27
266	70	1.42177	1.37082	89.1892	65.2174	33	30
267	70	1.81494	2.17796	79.0698	68.9655	34	40
268	74	2.32290	2.62704	78.7234	42.1053	37	32
269	74	2.32307	2.86449	42.5926	71.6981	23	38
270	70	.	.	75.9259	75.9259	41	41
271	80	0.85645	0.85645	59.6154	59.6154	31	31
272	76	1.42329	1.42329	73.5294	73.5294	25	25
273	70	1.87577	1.98856	48.8889	48.8889	22	22
274	74	2.63509	2.63509	77.3585	77.3585	41	41
275	70	2.73077	2.73077	45.2381	45.2381	19	19

STG=0

PEARSON CORRELATION COEFFICIENTS
/ PROB > |R| UNDER HO:RHO=0 / NUMBER OF OBSERVATIONS

	PKA1	PKV1	SD1	HR1	SBP1	DBP1
PKA2	0.62365 0.0001 44	0.60321 0.0001 44	0.33244 0.0275 44	0.24519 0.1087 44	0.14640 0.3430 44	-0.35286 0.0188 44
PKV2	0.63759 0.0001 44	0.66726 0.0001 44	0.40520 0.0064 44	0.09373 0.5451 44	0.13177 0.3939 44	-0.35727 0.0173 44
SD2	0.51459 0.0004 44	0.50900 0.0004 44	0.42933 0.0036 44	-0.06234 0.6877 44	0.01137 0.9416 44	-0.18228 0.2363 44
HR2	-0.05446 0.7255 44	-0.00328 0.9831 44	-0.06850 0.6586 44	0.46061 0.0017 44	0.29898 0.0487 44	0.04259 0.7837 44
SBP2	-0.07642 0.6220 44	-0.17458 0.2570 44	-0.09795 0.5270 44	0.32472 0.0315 44	0.15980 0.3001 44	0.28635 0.0595 44
DBP2	-0.33929 0.0243 44	-0.42866 0.0037 44	-0.27853 0.0671 44	0.33199 0.0277 44	0.07740 0.6175 44	0.55249 0.0001 44

STG=1

PEARSON CORRELATION COEFFICIENTS
/ PROB > |R| UNDER HO:RHO=0 / NUMBER OF OBSERVATIONS

	PKA1	PKV1	SD1	HR1	SBP1	DBP1	VO2REL1
PKA2	0.56653 0.0001 44	0.48509 0.0008 44	0.34184 0.0231 44	0.19482 0.2051 44	0.27931 0.0663 44	-0.16622 0.2809 44	0.14812 0.3373 44
PKV2	0.39196 0.0085 44	0.65415 0.0001 44	0.59394 0.0001 44	0.25318 0.0973 44	0.21983 0.1516 44	-0.15537 0.3139 44	0.03280 0.8326 44
SD2	0.10341 0.5041 44	0.26611 0.0808 44	0.61132 0.0001 44	0.02710 0.8614 44	0.01597 0.9180 44	-0.22491 0.1422 44	-0.01502 0.9229 44
HR2	0.08217 0.5959 44	-0.00813 0.9582 44	-0.00655 0.9664 44	0.53803 0.0002 44	0.14212 0.3574 44	0.16235 0.2924 44	0.16721 0.2780 44
SBP2	0.10502 0.4975 44	0.17295 0.2616 44	0.11156 0.4709 44	0.24211 0.1133 44	0.51104 0.0004 44	0.13781 0.3723 44	0.14160 0.3592 44
DBP2	-0.37243 0.0128 44	-0.40835 0.0059 44	-0.04158 0.7887 44	0.13541 0.3808 44	-0.03384 0.8274 44	0.41635 0.0049 44	-0.08734 0.5729 44
VO2REL2	-0.16363 0.2885 44	-0.18756 0.2228 44	-0.11721 0.4486 44	0.08952 0.5634 44	-0.15710 0.3085 44	0.19728 0.1993 44	0.35372 0.0185 44

STG=2

PEARSON CORRELATION COEFFICIENTS
/ PROB > |R| UNDER H0:RHO=0 / NUMBER OF OBSERVATIONS

	PKA1	PKV1	SD1	HR1	SBP1	DBP1	VO2REL1
PKA2	0.54784 0.0001 44	0.33557 0.0260 44	-0.08985 0.5619 44	0.25745 0.0916 44	0.17579 0.2537 44	-0.23117 0.1311 44	0.13722 0.3744 44
PKV2	0.36770 0.0141 44	0.71370 0.0001 44	0.33910 0.0243 44	0.10379 0.5026 44	0.17152 0.2656 44	-0.28181 0.0638 44	0.24845 0.1039 44
SD2	0.12587 0.4156 44	0.45685 0.0018 44	0.61090 0.0001 44	-0.13299 0.3895 44	-0.05885 0.7043 44	-0.22471 0.1425 44	-0.02440 0.8751 44
HR2	-0.03994 0.7969 44	-0.05476 0.7241 44	-0.29484 0.0520 44	0.71551 0.0001 44	0.13966 0.3659 44	0.32506 0.0313 44	0.39234 0.0084 44
SBP2	0.17590 0.2534 44	0.10552 0.4954 44	0.02214 0.8866 44	0.04287 0.7823 44	0.68788 0.0001 44	0.30004 0.0478 44	-0.01193 0.9387 44
DBP2	-0.25056 0.1009 44	-0.19438 0.2061 44	0.01978 0.8986 44	0.17172 0.2650 44	0.21944 0.1524 44	0.51244 0.0004 44	-0.14672 0.3419 44
VO2REL2	0.10913 0.4807 44	0.23786 0.1200 44	-0.05809 0.7080 44	0.55356 0.0001 44	0.20763 0.1762 44	-0.08099 0.6012 44	0.78986 0.0001 44

STG=3

PEARSON CORRELATION COEFFICIENTS
/ PROB > |R| UNDER HO:RHO=0 / NUMBER OF OBSERVATIONS

	PKA1	PKV1	SD1	HR1	SBP1	DBP1	VO2REL1
PKA2	0.77489 0.0001 44	0.48827 0.0008 44	0.17830 0.2469 44	0.27617 0.0696 44	-0.04290 0.7822 44	-0.16601 0.2815 44	0.26847 0.0781 44
PKV2	0.63296 0.0001 44	0.77159 0.0001 44	0.45881 0.0017 44	0.10884 0.4819 44	0.02090 0.8929 44	-0.25839 0.0904 44	0.26697 0.0798 44
SD2	0.28748 0.0585 44	0.50943 0.0004 44	0.69786 0.0001 44	-0.34094 0.0235 44	-0.00457 0.9765 44	-0.33512 0.0262 44	-0.04583 0.7677 44
HR2	0.11526 0.4563 44	-0.07615 0.6232 44	-0.31403 0.0379 44	0.86761 0.0001 44	-0.09808 0.5265 44	0.20822 0.1750 44	0.46419 0.0015 44
SBP2	-0.05651 0.7156 44	0.03014 0.8460 44	0.15299 0.3215 44	0.00587 0.9698 44	0.25329 0.0971 44	0.07278 0.6387 44	0.03076 0.8429 44
DBP2	-0.21120 0.1688 44	-0.25931 0.0892 44	0.01630 0.9164 44	-0.00016 0.9992 44	0.07668 0.6208 44	0.58707 0.0001 44	-0.10920 0.4804 44
VO2REL2	0.09314 0.5476 44	0.13223 0.3922 44	-0.01073 0.9449 44	0.51627 0.0003 44	0.01943 0.9004 44	-0.01564 0.9197 44	0.81867 0.0001 44

STG=4

PEARSON CORRELATION COEFFICIENTS
/ PROB > |R| UNDER HO:RHO=0 / NUMBER OF OBSERVATIONS

	PKA1	PKV1	SD1	HR1	SBP1	DBP1	VO2REL1
PKA2	0.67830 0.0001 43	0.43882 0.0032 43	0.28951 0.0597 43	0.18907 0.2246 43	-0.08036 0.6085 43	-0.22614 0.1448 43	0.14175 0.3646 43
PKV2	0.55713 0.0001 43	0.67767 0.0001 43	0.41645 0.0055 43	0.05345 0.7335 43	0.09472 0.5457 43	-0.15454 0.3224 43	0.04880 0.7560 43
SD2	0.27564 0.0736 43	0.40166 0.0076 43	0.61972 0.0001 43	-0.27694 0.0722 43	0.14309 0.3600 43	-0.07915 0.6139 43	-0.15128 0.3329 43
HR2	0.06353 0.6857 43	-0.04658 0.7668 43	-0.15523 0.3202 43	0.88660 0.0001 43	0.04616 0.7688 43	0.22394 0.1489 43	0.40192 0.0075 43
SBP2	-0.12846 0.4117 43	-0.05173 0.7418 43	0.17220 0.2695 43	-0.03606 0.8184 43	0.62322 0.0001 43	0.17585 0.2593 43	-0.05833 0.7102 43
DBP2	-0.34016 0.0256 43	-0.15568 0.3188 43	0.14589 0.3506 43	-0.01762 0.9107 43	0.18021 0.2475 43	0.52556 0.0003 43	-0.07409 0.6368 43
VO2REL2	0.22113 0.1541 43	0.26736 0.0830 43	0.04245 0.7869 43	0.53104 0.0002 43	-0.03508 0.8233 43	-0.24386 0.1151 43	0.73517 0.0001 43

STG=5

PEARSON CORRELATION COEFFICIENTS
/ PROB > |R| UNDER HO:RHO=0 / NUMBER OF OBSERVATIONS

	PKA1	PKV1	SD1	HR1	SBP1	DBP1	VO2REL1
PKA2	0.55270 0.0005 36	0.52283 0.0011 36	0.32622 0.0522 36	-0.02001 0.9078 36	-0.00047 0.9973 36	-0.31520 0.0611 36	0.24955 0.1422 36
PKV2	0.63654 0.0001 36	0.72859 0.0001 36	0.45307 0.0055 36	-0.04668 0.7869 36	0.14050 0.4137 36	-0.24583 0.1484 36	0.20807 0.2233 36
SD2	0.33532 0.0456 36	0.40765 0.0136 36	0.40469 0.0144 36	-0.11740 0.4953 36	0.15090 0.3797 36	-0.07469 0.6651 36	0.08924 0.6047 36
HR2	-0.21644 0.2048 36	-0.13788 0.4226 36	0.02505 0.8847 36	0.67010 0.0001 36	-0.01101 0.9492 36	0.17623 0.3039 36	0.31655 0.0600 36
SBP2	0.14962 0.3838 36	0.14602 0.3955 36	0.16681 0.3309 36	-0.03747 0.8282 36	0.55962 0.0004 36	0.03807 0.8255 36	-0.03886 0.8220 36
DBP2	-0.34010 0.0424 36	-0.31737 0.0593 36	-0.09034 0.6003 36	0.13154 0.4444 36	0.17894 0.2964 36	0.51164 0.0014 36	-0.14479 0.3995 36
VO2REL2	-0.18981 0.2675 36	-0.18381 0.2832 36	-0.06836 0.6920 36	0.31157 0.0643 36	-0.02214 0.8980 36	0.00273 0.9872 36	0.59381 0.0001 36

STG=6

PEARSON CORRELATION COEFFICIENTS
/ PROB > |R| UNDER H0:RHO=0 / NUMBER OF OBSERVATIONS

	PKA1	PKV1	SD1	HR1	SBP1	DBP1	VO2REL1
PKA2	0.80829 0.0026 11	0.67810 0.0218 11	0.55578 0.0759 11	-0.00742 0.9827 11	0.04845 0.8875 11	-0.12891 0.7056 11	-0.00165 0.9962 11
PKV2	0.66136 0.0267 11	0.70528 0.0153 11	0.62066 0.0416 11	0.28784 0.3907 11	0.06652 0.8459 11	0.02704 0.9371 11	-0.03813 0.9114 11
SD2	0.42141 0.1968 11	0.52177 0.0997 11	0.71115 0.0141 11	0.31760 0.3412 11	-0.11327 0.7402 11	0.14995 0.6599 11	-0.13301 0.6966 11
HR2	-0.25888 0.4421 11	0.04482 0.8959 11	0.15052 0.6587 11	0.79812 0.0032 11	-0.49284 0.1235 11	0.09609 0.7787 11	0.12014 0.7249 11
SBP2	0.10271 0.7638 11	0.06984 0.8383 11	-0.23438 0.4879 11	-0.34363 0.3008 11	0.77230 0.0053 11	0.14324 0.6744 11	-0.13111 0.7008 11
DBP2	-0.17393 0.6090 11	0.04355 0.8988 11	0.36364 0.2716 11	0.20732 0.5408 11	0.45479 0.1599 11	0.53917 0.0870 11	-0.05644 0.8691 11
VO2REL2	0.03035 0.9294 11	0.21042 0.5346 11	0.54819 0.0808 11	0.02542 0.9409 11	-0.11230 0.7424 11	-0.30414 0.3632 11	0.81691 0.0021 11

Coefficients of Variation (Doppler Measures) Values Expressed as Percentages

Power (W)	n	PkA	PkV	SVI
Rest Sitting	44	19.4	16.9	26.7
50	44	33.5	13.9	16.3
100	44	30.3	11.5	17.3
150	44	17.9	11.4	17.4
200	43	16.5	14.7	19.5
250	36	20.0	17.2	26.3
300	11	14.2	18.4	22.6

Coefficients of Variation (HR, SBP, $\dot{V}O_2$)

Values Expressed as Percentages

Power (W)	n	HR	SBP	$\dot{V}O_2$
Rest Sitting	44	16.1	9.0	-
50	44	10.7	10.2	17.2
100	44	8.9	7.0	9.9
150	44	6.6	10.8	10.1
200	43	4.8	7.8	13.1
250	36	5.4	7.3	14.6
300	11	3.5	7.1	11.8

APPENDIX C

DETAILED METHODOLOGY (REPRODUCIBILITY PHASE)

Appendix C

DETAILED METHODOLOGY (REPRODUCIBILITY PHASE)

This appendix consists of descriptive information concerning subjects, general design of the study, test procedures, instrumentation, techniques used to sample the dependent measures, and statisical analysis of the data for the first phase of the study. The appendix is divided into sections that correspond to each of the above mentioned areas.

Subjects

Forty-four males served as subjects for this experiment. Each was a volunteer, and either students or faculty members from Virginia Tech. The subjects were screened for cardiac risk factors and met the criteria for the "apparently healthy" category as set forth by the American College of Sports Medicine (ACSM, 1986). The range for $\dot{V}O_2max$ among these individuals was 27.7-55.9 $ml \cdot kg^{-1} \cdot min^{-1}$ and for a predicted body composition, the range was 5.1-23.8% fat. Individual descriptive data for the subjects is contained in Appendix E. Prior to participation, each subject was informed of the nature of the exercise tests, about the measurements to be collected, and the inherent risks of the

tests. Each gave informed consent prior to participation (Appendix C).

General Design

Two graded exercise tests were administered to the same group of subjects on separate days (test-retest design). There were no differences between the test protocols. The dependent measures were examined for reproducibility between the two exercise tests.

Experimental Testing Procedures

The subjects underwent two graded exercise tests on a stationary bicycle ergometer. The second test was given no sooner than three days after the first to avoid possible residual leg soreness which might confound the results of the second. Each subject had initial measures for each variable taken at supine rest. Dependent measures were next recorded with subjects in a seated posture at rest on the cycle ergometer (Monark No. 868, mechanically braked by a friction belt). The subject was then asked to pedal the ergometer at 50 rpm. An audio cue (metronome) was used to pace the subject. The power setting for the initial load was 50 W, and the load was increased by 50 W every 3 min. The average test lasted approximately 12-15 min. Each test was terminated when the subject reached volitional fatigue, or if the pedalling rate was no longer maintained.

Instrumentation and Sampling of Dependent Measures

While exercising, the subject breathed through a Daniel's low resistance - low deadspace valve fitted with a rubber mouthpiece. A nose clip was used to insure that no ventilatory gas escaped through the nasal passages. Ventilation was measured on the expired side with a digital pneumotach (Hewlett Packard Model 47303A), the sensing head surface of which was connected in series with a flexible corrugated hose (I.D. 1.25 in) leading to a baffled gas mixing chamber. The total dead space of the system on the expired side, including the mixing chamber was 4.5 liters. FEO_2 and $FECO_2$ was sampled from the mixing chamber. Oxygen analysis was accomplished with an Applied Electrochemistry SA-3 analyzer, while carbon dioxide concentrations were determined by an Applied Electrochemistry CD-3A analyzer. All ventilatory and gas exchange measurements were continuously sampled throughout the test. These values were visually obtained from LED displays on the instruments. FEO_2 and $FECO_2$ were visually averaged within the 15-20 s interval after minute ventilation was recorded; this delay compensated for transit time of the expirate through the system. Barometric pressure and wet and dry bulb temperatures were recorded before each trial.

The pneumotach was calibrated periodically during the study with a 100 l volume of air pumped with a 3.0 l volumetric syringe. The gas analyzers were calibrated before and after each trial with two known gas fractions previously verified by Haldane analysis. The cycle ergometer was calibrated before each day of testing.

The blood flow measurements were determined with a CW Doppler system (Quinton EXERDOP). A hand-held transducer was placed on the suprasternal notch and positioned inferiorly toward the ascending aorta. Audio feedback in the instrument, the intensity of which correlated with the Doppler signal strength, guided the technician to aim at the proper location. The highest blood flow velocity of the ascending aorta was the target area, and when the audio signal produced a sharp and distinct high pitched noise with each systolic ejection it was accepted that proper transducer positioned was achieved. An LED display on the handle of the transducer was also available to aid in aiming, but this was found to be of minimal value. The Doppler measurements of peak blood flow acceleration, peak blood flow velocity, and systolic velocity integral were recorded during the last minute of each stage of exercise, and at rest before exercise.

Blood pressure was recorded with a mercurial sphygmonamometer at both resting positons, and once each stage during exercise. Heart rate was recorded electrocardiographically (Hewlett Packard 1500B) at the end of each exercise stage, and during rest prior to exercise. Heart rhythm was observed continuosly with an oscilliscope. The electrodes were configured for a standard clinical Lead II.

Statistical Analysis

The test-retest reproducibility of all dependent measures at each stage of exercise was computed using the Pearson product-moment correlation coefficient, and a standard estimate of variation (coefficient of variation) was computed.

APPENDIX D

INFORMED CONSENT (INTERVENTION PHASE)

CERTIFICATE
OF
APPROVAL FOR RESEARCH
INVOLVING HUMAN SUBJECTS

Division of HPER

The Human Subjects Committee of the Division of Health, Physical Education and Recreation has reviewed the research proposal of:

Alan D. Moore, Jr.

entitled: Sensitivity of a Stand Alone Continuous-Wave Doppler Echocardiographic System (EXERDOP) to Induced Changes in Cardiac Response During Graded Cycle Exercise.

The members have judged the subjects participating in the related experiment (not to be at risk) as a result of their participation.

(If a risk proposal) Procedures have been adopted to control the risks at acceptably low levels. The potential scientific benefits justify the level of risk to be imposed.

Members of Divisional
Human Subjects Committee

_____	_____
Chairman	Date
_____	_____
	Date
_____	_____
	Date

REQUEST FOR APPROVAL OF RESEARCH PROPOSAL
IN THE DIVISION OF HPER

Submitted to

Charles Baffi
Chairman, Division Human Subjects Committee and/or
Chairman, Institutional Review Board

by

Alan D. Moore, MS
Principal Investigator

and

William G. Herbert, PhD and J. Michael Payne, MD
Faculty Sponsors

TITLE: Sensitivity of a Stand Alone Continuous-Wave Doppler Echocardiographic System (EXERDOP) To Induced Changes in Cardiac Response During Graded Cycle Exercise Tests.

BACKGROUND/SCIENTIFIC JUSTIFICATION: At present the two methods most frequently employed for the assessment of left ventricular function are two-dimensional echocardiography and nuclear ventriculography (Bennett, et al, 1984). Both of these methods are extremely expensive, require extensive technician training, and in the latter method the use of radioisotopes. Recent technological advances have led to the development of a Doppler echocardiographic system designed for use during exercise testing that avoids the problems associated with the above mentioned methods. If found to be sensitive to subtle changes in myocardial contractile status this system (EXERDOP) may find use in clinical and research settings. The EXERDOP system uses ultra-sonic energy to measure the blood flow in the ascending aorta. No adverse effects have been documented with the use of ultrasonic devices, and it is considered to be a technique that is even safe enough for routine prenatal examinations.

PURPOSE(S): The purpose of the study is to determine the sensitivity of the EXERDOP system to detect subtle changes

in myocardial contractile status during cycle exercise tests held on separate days.

EXPERIMENTAL METHODS & PROCEDURES: The subjects of the experiment will be males less than 35 years of age that are in the category of "apparently healthy" as set forth by the American College of Sports Medicine (ACSM, 1986; see attached), and will be students and faculty/staff members from Virginia Tech. All of the subjects will have already performed two maximal graded cycle tests as they will be recruited from the subject groups that completed a reliability study in our laboratory (proposal approved by IRB, Jan. 1987). These subjects have been screened for contraindications to exercise testing.

The subjects will be requested to perform exercise tests under the three experimental conditions as follows: 1) 120 minutes after the administration of one oral dose of 100 mg Atenolol (Tenormin), 2) 90 minutes after the initiation of a hyperhydration protocol in which the subjects will be asked to consume approximately a total of 40 ml/kg body weight of cool water; the dose will be split into a small volume of water every 10 min, and 3) Two hours after the administration of a placebo. The first two conditions are designed to slightly alter either the contractile force or volume load of the heart.

During the experimental test the subject will exercise on a cycle ergometer. The workloads will advance 25% of the subject's capacity every 6 min. Maximum capacity was determined in the reliability study referred to above. Heart rate will be continuously monitored and blood pressure will be recorded each stage. Expired respiratory gasses will be collected through a one-way non-rebreathing valve for calculation of oxygen comsumption. Measurements of aortic blood flow will be conducted during the fourth minute of each stage with the EXERDOP system. Cardiac output will be non-invasively estimated using a carbon dioxide rebreathing technique. Information on relative changes in plasma volume will be obtained by the use of four blood samples, obtained by finger-tip lancet. These samples will be taken 2 hrs before, immediately prior to, and immediately following the exercise test.

The subject will be requested to exercise the full duration of each workload. The test is designed so that the heaviest workload will be perceived by the subject as moderately hard, i.e., <u>not</u> maximal exercise. There will be three

workloads, therefore the most difficult workload will be only 75% of the subject's capacity. The total time of the exercise portion of the test will be 18 min.

STATEMENT DESCRIBING LEVEL OF RISK TO SUBJECTS: The subjects will have screened according to the ACSM guidelines, and will have performed two maximum cycle exercise tests prior to participation in this experiment. The level of risk inherent in exercise testing subjects in the "apparently healthy" category under the age of 35 is minimal for the study as designed, however the following may occur: 1)abnormal changes in heart rate and rhythm, 2) extreme change in blood pressure, 3) fainting, 4) very rare instances of heart attack, 5) leg fatigue, 6) skin irritation caused by electrode preparation for ECG, 7) minor soreness above the sternum where the EXERDOP transducer is positioned, 8) slight risk of infection through the finger(s) from which the blood samples are collected, and/or 9) the occurrence of side effects from Atenolol admintistration. These side effects are outlined in the subsequent paragraph.

Atenolol is a commonly prescribed cardioselective beta-blocking drug that is used most commonly in the treatment of hypertension. Use of atenolol is contraindicated in subjects exhibiting sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. In addition, subjects with broncospastic disease should not receive atenolol even though it is cardioselective. Most adverse effects of the drug are mild and transient. The most common side effects which have been observed to occur at rates > 1% in U.S. studies are: bradycardia (3%), postural hypotension (2%), dizziness (4%), vertigo (2%), fatigue (3%), diarrhea (2%), and nausea (3%). Other adverse effects are rare (see attached information from the Physician's Desk Reference, 1986).

PROCEDURES TO MINIMIZE SUBJECT RISK (IF APPLICABLE): The subjects will be screened prior to any participation in the study. The screening procedure will be directed by a physician and adjunct faculty member, J. Michael Payne, MD. The subjects will have a resting 12-lead ECG recorded to screen for heart block greater than first degree, and other electrocardiographically determined contraindications to atenolol administration. Other information that will be considered when taking the case history of the subjects will include: 1) History of broncospastic disease, 2) Any

respiratory illness, 3) Information on smoking behavior, 4) History of any renal problems (rheumatic fever, kidney disease), and 5) Any recent illness or fever.

The absolute contraindications for participation in the study will include: 1) any of the contraindications for exercise testing as outlined by the American College of Sports Medicine Guidelines (see attached), and 2) any of the contraindicating conditions listed in the previous paragraph.

Dr. Payne will prescribe and administer the drug for use in the experiment, and meet with the subjects (in a group session) to explain the drug's actions, the expected effects, and the potential side effects. He will obtain the drug for use in the experiment.

The primary investigator and two of the technicians are certified by ACSM for exercise testing and supervision. All of the laboratory technicians are certified in CPR. Heart rate and rhythm will be continuously monitored electrocardiographically to permit rapid detection of abnormalities if they should arise. A telephone will be available for the investigators to phone the rescue squad if necessary during the testing sessions, and a nurse will be present during all drug trials.

The peak action and effect of the drug is 2-6 hrs. after administration, however the effects will persist (with gradual resolution to a "normal" state) for 24 hrs. The subjects will be monitored by a phone call approximately 2 hr after leaving the laboratory; this would be at about 6 hr post-administration. The subjects will also be given the number at which they can contact a licensed nurse who is employed for this study, if they have any problems or questions. They will also have a telephone number to contact the primary investigator or the faculty advisors if the need arises.

Accepted sanitary techniques will be utilized during the finger-tip blood sampling to minimize the probability of infection.

RISK/BENEFIT RATIO (IF RISK PROJECT): The risk to the subjects is minimal. Atenolol is a commonly prescribed drug with a low occurrence of side-effects. The side effects that are experienced by a low percentage of the population are transient and mild. The subjects will not be

financially compensated for participation in the study. The subjects will learn their oxygen comsumption which is the criterion measurement of aerobic fitness, will obtain a copy of a physician interpreted clinical-quality ECG, and will learn their cardiac output response profile to exercise. Approximately half of the subjects will view the tests as a valuable learning experience as they are currently working in an exercise program for cardiac patients, many of whom are prescribed beta-blocking medication. The benefit to the research and medical community will be great if the EXERDOP proves to be a reliable and sensitive indicator of left ventricular function.

LABORATORY FOR EXERCISE, SPORTS, AND WORK PHYSIOLOGY

Division of Health, Physical Education and Recreation
Virginia Polytechnic Institute and State University

INFORMED CONSENT

I, _____, do hereby voluntarily agree and consent to participate in a testing program conducted by the personnel of the Human Performance Laboratory of the Division of Health, Physical Education and Recreation of Virginia Polytechnic Institute and State University.

Title of Study: Sensitivity of a Stand Alone Continuous-Wave Doppler Echocardiographic System (EXERDOP) To Induced Changes in Cardiac Response During Graded Cycle Exercise Tests.

The purposes of this experiment include: To examine the sensitivity of a new Continuous-Wave echocardiographic device during cycle testing.

I voluntarily agree to participate in this testing program. It is my understanding that my participation will include: Three tests on a cycle ergometer at submaximal exercise levels. Each test will last 18 min. During these tests the investigators will constantly monitor heart rate and rhythm, will measure blood pressure once every 6 min., will continuously collect my expired respiratory gases, and will determine aortic blood flow with an echocardiographic device every 6 min. In addition, they will estimate cardiac output by having me rebreathe a high oxygen, high carbon dioxide containing gas once every 6 min. (this procedure lasts for about 20 sec) and will collect 4 fingertip samples of my blood before and after the tests. The blood flow determination will be made by a technician placing a hand-held probe above my sternum (the area where my neck and chest meet).

I also understand that participation in the study will involve the administration of one dose of a commonly prescribed prescription drug to me (atenolol). I understand that it is my responsibility to follow the instructions that the physician gives me regarding the use of atenolol, and that although the peak effect of the drug will be from 2-6 hours after I take it, the effects will persist (in declining intensity) for about a day.

I understand that participation in this experiment may produce certain discomforts and risks. These discomforts and risks include: Abnormal changes in heart rate and/or rhythm, abnormal changes in blood pressure, fainting, very rare instances of heart attack, leg fatigue, skin irritation due to skin preparation for ECG monitoring, slight risk of infection through the finger(s) on which the blood samples are collected, rare occurrence of side effects from the drug administration (most commonly these are slow heart rate, lowering of blood pressure, dizziness, vertigo, fatigue, nausea, and diarrhea), and minor soreness above the sternum from the pressure of the technician holding the probe in place for the blood flow measurements.

These risks will be minimized by screening for contraindications for me to exercise, and for contraindications for the administration of the drug that I will be asked to take as part of this study. The primary investigator and two of the laboratory technicians are certified by the American College of Sports Medicine for exercise testing and supervision, and all of the technicians are certified in CPR. A nurse will be available during my testing sessions, and I will be phoned 2 hours following the test. I will also be provided the telephone nembers of the nurse, the primary investigator, and the faculty advisors if I wish to have any questions answered.

Certain personal benefits may be expected from participation in this experiment. These include: The subjects' maximal oxygen uptake, which is the criterion measure of aerobic fitness, a profile of the subjects' cardiac output responses to exercise, and a copy of a physician interpreted 12-lead electrocardiogram.

Appropriate alternative procedures that might be advantageous to you include: The subject will be excluded from the study if any changes occur during the exercise tests that make it hazardous to continue or if any contraindications to the administration of the drug are found.

I understand that any data of a personal nature will be held confidential and will be used for research purposes only. I also understand that these data may only be used when not identifiable with me.

I understand that I may abstain from participation in any part of the experiment or withdraw from the experiment

should I feel the activities might be injurious to my health. The experimenter may also terminate my participation should he feel the activities might be injurious to my health.

I understand that it is my personal responsibility to advise the researchers of any preexisting medical problem that may affect my participation or of any medical problems that might arise in the course of this experiment and that no medical treatment or compensation is available if injury is suffered as a result of this research. A telephone is available which would be used to call the local hospital for emergency service.

I have read the above statements and have had the opportunity to ask questions. I understand that the researchers will, at any time, answer my inquiries concerning the procedures used in this experiment.

Scientific inquiry is indispensable to the advancement of knowledge. Your participation in this experiment provides the investigator the opportunity to conduct meaningful scientific observations designed to make significant educational contribution.

If you would like to receive the results of this investigation, please indicate this choice by marking in the appropriate space provided below. A copy will then be distributed to you as soon as the results are made available by the investigator. Thank you for making this important contribution.

_____ I request a copy of the results of this study.

Date _____ Time _____a.m./p.m.

Participant Signature _____

Witness _____
HPL Personnel

Project Director Alan D. Moore Telephone 961-5006, 951-1505

Faculty Advisors William G. Herbert Telephone 961-6565
J. Michael Payne Telephone 951-3311

HPER Human Subjects Chairman Dr. Charles Baffi Telephone 6561

Dr. Charles Waring, Chairman, International Review Board for Research Involving Human Subjects. Phone 961-5283.

APPENDIX E

DETAILED METHODOLOGY (INTERVENTION PHASE)

Appendix E

DETAILED METHODOLOGY (INTERVENTION PHASE)

This appendix consists of descriptive information regarding subjects, general design, test procedures, instrumentation, techniques used to sample the dependent measures, special screening/monitoring considerations for the intervention trials, and statistical analysis for this phase of the study. The appendix is divided into sections that correspond to each of the above mentioned areas.

Subjects

Eighteen males served as subjects. They were volunteers, and either students or faculty/staff members from Virginia Tech. This group was a subset of those from the reproducibility phase of the study. The subjects, therefore, met the criteria for inclusion that the investigator had set for the reproducibility study. In addition to the screening performed prior to the reproducibility phase, each was further screened for contraindications to the administration of beta-blockade medication. The primary concern was to screen out any subjects who might demonstrate significant bradycardia, atrio-ventricular heart block greater than first degree, or bronchospastic disease (Physicians' Desk Reference, 1987). Prior to participation, each was informed

of the nature of the exercise tests, the nature of the experimental interventions, the measurements that were to be collected, and the inherent risks of these procedures. Each gave informed consent to acknowledge their understandings of the risks and their decision to proceed or withdraw at any time (Appendix D).

General Design

The design of the study required that the subjects undergo three similar exercise tests. One involved a control (placebo) condition. Another was administered while the subjects were under acute beta-blockade, and the third was done under a hyperhydrated state. The results of these tests were compared to determine if the experimental manipulations of cardiac state influenced the dependent measures.

Experimental Testing Procedures

The subjects participated in three cycle exercise tests. These tests were submaximal in nature, and consisted of three stages. The stages were performed at loads of 20, 40, and 60% $\dot{V}O_2$peak. $\dot{V}O_2$peak was established during the reproducibility phase of the study. These stages were designed to provide a graduated "spectrum" of exercise intensities and related physiological responses. The stage duration was 6 min, the loads were applied in a positive progression and exercise was continuous. A stage was

extended for an additional 4 min if the initial cardiac output determination was inadequate, i.e., inadequate plateauing of CO_2 rebreathing curve. Prior to each test subjects had the dependent measures recorded in supine and seated postures after 5 min of rest. Cardiac output, stroke volume, and oxygen consumption were only measured during exercise. The subject was asked to maintain a pedal frequency of 50 rpm during cycling and an audio cue (metronome = 100 $bt \cdot min^{-1}$) was used for pacing. Dependent measures were collected according to the timelime below:

Min 0.00-2.50	Physiological adaptation of subject to the load.
Min 2.50-3.25	Blood Pressure Determination.
Min 3.25-3.50	Heart Rate Determination.
Min 3.50-4.50	EXERDOP Measurements.
Min 4.50-6.00	Cardiac Output determination by CO_2 rebreathing.

Instrumentation and Sampling of Dependent Measures

While exercising, the subject breathed through a Hans-Rudolph 3-way sliding valve (Model #2770) fitted with a rubber mouthpiece. A noseclip was used to insure that no ventilatory gas escaped through the nasal passages. Ventilation was measured on the expired side with a digital pneumotach (Hewlett Packard Model 47303A), the sensing head

surface of which was connected in series with a flexible corregated hose (I.D. 1.25 in) which lead to a baffled gas mixing chamber (volume). The total dead space of the system on the expired side, including the mixing chamber was approximately 4.6 liters. The FEO_2 and $FECO_2$ were sampled from the mixing chamber. Oxygen analysis was accomplished with an Applied Electrochemistry SA-3 analyzer, while carbon dioxide concentrations were determined with an Applied Electrochemistry CD-3A analyzer. All ventilatory and gas exchange measurements were continuously sampled while the subject was exercising, except during the time that the subject rebreathed CO_2 for the cardiac output measurements. The ventilatory and gas exchange measurements were obtained visually by a technician who monitored the LED displays on each instrument. Gas fractions were obtained during the interval 15-20 sec after ventilation was measured; this delay compensated for transit times of the expirate in the system.

Cardiac output was determined by the CO_2 rebreathing method at the end of each exercise stage (Collier, 1950). Measurement of carbon dioxide concentration of the rebreathing gases at equilibrium and of end tidal CO_2 were accomplished with a Beckman LB-2 analyzer interfaced with a chart recorder (Beckman Clinical Exercise Test System). Two rebreathing gases were available to use: Gas 1 (10% CO_2,

balance O_2), and gas 2 (14.5% CO_2, balance O_2). These concentrations allowed exercise evaluation of cardiac output, but were too high in CO_2 concentration for use in determining cardiac output under resting metabolic conditions.

The blood flow measurements were determined with a CW Doppler system (EXERDOP, Quinton Instruments). A hand-held transducer was placed on the suprasternal notch and positioned inferiorly toward the heart. Audio feedback assisted the technician in locating the target area, the ascending aorta. The maximum flow in the vessel will be located when the audio signal produces a sharp and distinct high pitched noise with each systolic ejection. A LED display on the transducer housing assisted the technician in the location of the proper angle. The Doppler measurements included peak blood flow velocity, peak blood flow acceleration, and systolic velocity integral (also known as stroke distance).

Blood pressure was obtained with a mercurial sphygmonamometer, and heart rate was recorded electrocardiograhically (Hewlett Packard 1500B). Heart rhythm was observed continuously with an oscilliscope. The electrodes were configured for standard Lead II.

Special Considerations Beta Blockade trial

Three hours before two of the exercise trials, the subject was orally administered either a 100 mg dose of atenolol or a placebo. Neither the subject and investigator knew at the time of testing which was administered (double-blind). The placebo and atenolol were not similar in appearance, thus the subjects knew that there was some type of difference between the two. Atenolol is a beta-one cardioselective drug, and the dose used is twice the normal initial dose of the drug (Physician's Desk Reference, 1986). This drug has been demonstrated to have the same negative inotropic properties as those possessed by propranolol, without some of the side effects usually attributed to propranolol administration (Frishman, 1984). Atenolol has no intrinsic sympathomimetic activity (partial agonist activity).

Plasma Volume Expansion Trial

The subjects reported to the laboratory 1.5 hours prior to exercise testing. During the hyperhydration trial, blood hematocrit measurements were taken for purposes of estimating plasma volume change. These measurements started before hyperhydration so a "euhydration baseline" was established (Costill & Fink, 1974). After initial hematocrit measurements, the subjects were asked to consume 40 ml

$H_2O \cdot kg^{-1}$ of cool water (approximately 4°C). The fluid was administered at 10 min intervals to avoid the sudorific effect and possible gastric problems potentially caused by the ingestion of this large volume (Greenleaf & Castle, 1971). The hematocrit values were measured prior to the initiation of fluid ingestion, immediately prior to exercise, and after exercise. Blood was collected via a finger-tip lancet and heprinized micropipets. Blood was also collected prior to and after the other exercise trials.

Statistical Analyses

The design is a split-plot factorial with multiple dependent measures. The statistical analysis utilized was a multivariate analysis of variance (MANOVA) with repeated measures. Appropriate univariate tests were utilized as post-hoc procedures. Any differences revealed by the univariate ANOVA were then further investigated using the Tukey post-hoc test. If the interaction was significant, tests of simple main effects were conducted followed by Tukey post-hoc tests. The level of significance for the study was set apriori at .05.

APPENDIX F

RAW DATA FOR INTERVENTION PHASE

Subject Characteristics

Subject	Age yr	Weight kg	Body Fat %	$\dot{V}O_2max$ $ml \cdot kg^{-1} \cdot min^{-1}$
01	30	70.0	13.6	43.5
12	30	75.0	10.9	32.1
13	22	67.1	8.9	40.3
20	25	75.0	10.4	35.9
24	23	70.6	5.7	55.9
25	27	85.5	12.2	44.6
26	23	73.7	14.8	48.3
27	26	95.9	14.8	38.2
28	43	90.1	23.8	41.1
29	20	60.0	8.0	39.5
30	28	86.1	14.5	33.8
34	22	80.2	8.0	42.7
35	20	70.0	11.6	40.6
39	25	129.4	16.7	32.5
40	18	73.1	8.9	56.4
41	23	76.2	14.8	39.9
42	21	65.4	8.0	54.1
45	27	65.6	13.9	41.6
X	25.2	78.3	12.2	42.3
SD	5.62	15.80	4.25	7.35

Index of Terms for Raw Data Set

Stage=2 = sitting rest
3 = 20% $\dot{V}O_2max$
4 = 40% $\dot{V}O_2max$
5 = 60% $\dot{V}O_2max$

Cond=1 = placebo
2 = hyperhydration
3 = beta-blockade

---------- STAGE=2 COND=1 ----------

OBS	SUBJECT	PKA	PKV	SVI	HR	SBP	DBP	Q	SV	VO2ABS	VPOINTS	TPOINTS
1	1	14	0.58	5.8	77	104	78	.	.	.	30	30
2	9	19	0.80	8.8	89	118	68	.	.	.	33	43
3	12	14	0.60	6.2	94	112	68	.	.	.	31	33
4	13	17	0.71	10.8	63	122	86	.	.	.	43	54
5	20	13	0.53	7.2	68	110	80	.	.	.	34	42
6	24	15	0.72	9.4	75	118	78	.	.	.	47	55
7	25	14	0.58	8.4	61	126	86	.	.	.	27	42
8	26	15	0.55	8.0	88	110	78	.	.	.	35	78
9	27	18	0.84	10.8	71	120	80	.	.	.	29	32
10	28	13	0.63	7.6	63	122	74	.	.	.	34	38
11	29	15	0.65	7.4	60	110	66	.	.	.	38	40
12	30	11	0.53	6.8	71	104	64	.	.	.	18	32
13	34	21	0.89	10.8	61	124	68	.	.	.	38	41
14	35	29	1.23	16.0	85	124	86	.	.	.	34	44
15	39	12	0.59	10.2	68	122	80	.	.	.	37	78
16	40	16	0.76	9.4	66	118	70	.	.	.	28	30
17	43	17	0.69	11.2	52	120	76	.	.	.	23	50
18	45	16	0.71	12.0	71	116	68	.	.	.	50	57

---------- STAGE=2 COND=2 ----------

OBS	SUBJECT	PKA	PKV	SVI	HR	SBP	DBP	Q	SV	VO2ABS	VPOINTS	TPOINTS
19	1	12	0.51	9.0	58	122	88	.	.	.	24	60
20	9	16	0.75	10.2	75	124	80	.	.	.	15	15
21	12	10	0.48	5.4	74	112	80	.	.	.	32	45
22	13	13	0.58	10.0	71	108	80	.	.	.	37	38
23	20	12	0.45	5.4	68	108	82	.	.	.	27	44
24	24	15	0.75	11.6	53	116	84	.	.	.	30	30
25	25	11	0.48	8.0	50	116	82	.	.	.	21	26
26	26	13	0.67	10.8	65	122	78	.	.	.	28	44
27	27	14	0.70	11.4	52	124	86	.	.	.	28	31
28	28	11	0.50	5.4	63	122	84	.	.	.	39	45
29	29	14	0.61	7.0	56	122	86	.	.	.	34	35
30	30	12	0.57	8.0	71	112	84	.	.	.	33	61
31	34	16	0.70	10.0	78	120	80	.	.	.	48	61
32	35	17	0.74	11.6	88	144	92	.	.	.	39	49
33	39	13	0.52	10.0	75	136	96	.	.	.	15	51
34	40	13	0.64	10.6	63	116	84	.	.	.	23	31
35	43	18	0.74	13.4	47	114	72	.	.	.	25	26
36	45	18	0.79	14.0	65	110	78	.	.	.	27	31

---------- STAGE=2 COND=3 ----------

OBS	SUBJECT	PKA	PKV	SVI	HR	SBP	DBP	Q	SV	VO2ABS	VPOINTS	TPOINTS
37	1	12	0.52	8.0	57	120	88	.	.	.	37	54
38	9	14	0.66	8.2	60	112	88	.	.	.	27	30
39	12	13	0.60	7.0	73	110	66	.	.	.	32	41
40	13	13	0.64	10.6	60	118	78	.	.	.	33	33
41	20	13	0.52	6.6	65	100	64	.	.	.	34	44
42	24	17	0.82	11.6	64	122	72	.	.	.	41	43
43	25	12	0.56	9.8	48	106	70	.	.	.	39	45
44	26	11	0.59	9.6	75	110	70	.	.	.	40	48
45	27	16	0.84	14.0	45	110	68	.	.	.	36	38
46	28	12	0.59	7.6	55	116	68	.	.	.	35	42
47	29	16	0.71	8.4	58	118	70	.	.	.	31	36
48	30	10	0.51	8.0	70	96	64	.	.	.	14	16
49	34	14	0.66	9.0	75	124	78	.	.	.	42	92
50	35	12	0.56	8.2	93	114	84	.	.	.	38	60
51	39	12	0.59	10.6	75	124	80	.	.	.	31	51
52	40	14	0.66	8.2	68	110	64	.	.	.	27	64
53	43	20	0.83	13.2	47	120	80	.	.	.	27	28
54	45	13	0.69	12.4	56	106	74	.	.	.	49	69

---------- STAGE=3 COND=1 ----------

OBS	SUBJECT	PKA	PKV	SVI	HR	SBP	DBP	Q	SV	VO2ABS	VPOINTS	TPOINTS
55	1	21	0.84	11.4	95	124	70	11.5	120.6	0.96542	27	31
56	9	23	1.04	13.6	107	112	72	10.8	100.5	1.03092	36	43
57	12	20	0.86	10.0	107	132	66	9.5	88.5	0.85556	41	47
58	13	24	1.01	15.4	107	154	70	7.9	73.1	0.94346	25	36
59	20	19	0.79	11.6	83	120	70	8.7	104.3	0.84715	35	45
60	24	19	0.86	11.8	94	122	70	10.5	111.9	1.33898	49	49
61	25	19	0.81	13.2	77	130	80	11.0	142.3	1.21846	39	45
62	26	26	1.05	14.4	107	140	76	11.1	103.1	0.81338	28	36
63	27	25	1.14	16.0	81	124	78	8.8	108.7	1.24739	23	28
64	28	21	0.96	11.4	71	132	60	9.2	130.2	0.94401	37	38
65	29	21	0.95	11.4	88	130	70	9.8	110.8	0.83620	29	40
66	30	17	0.82	10.4	95	116	62	9.0	94.4	0.90795	36	40
67	34	33	1.38	20.8	88	140	74	14.0	159.3	1.29814	40	52
68	35	56	1.39	13.8	106	144	70	11.7	110.7	1.14453	65	73
69	39	18	0.86	16.6	90	146	80	13.1	145.8	1.19257	38	42
70	40	32	1.22	15.6	96	142	60	10.6	110.0	1.19728	20	27
71	43	24	1.10	17.6	91	142	70	9.5	104.6	0.90959	30	35
72	45	20	1.03	16.0	81	120	70	8.4	104.3	0.80049	35	40

STAGE=3 COND=2

OBS	SUBJECT	PKA	PKV	SVI	HR	SBP	DBP	Q	SV	VO2ABS	VPOINTS	TPOINTS
73	1	21	0.83	14.6	68	130	70	8.4	123.1	0.90863	24	26
74	9	23	1.09	14.0	110	140	80	11.5	104.3	1.19358	44	45
75	12	17	0.79	9.6	86	132	80	9.2	106.7	1.00128	28	43
76	13	21	0.83	14.4	86	122	66	7.5	86.9	0.95506	39	48
77	20	16	0.75	10.5	84	112	80	8.4	100.1	0.90547	32	37
78	24	16	0.76	10.0	76	136	78	9.9	129.7	1.27372	29	29
79	25	15	0.67	12.0	79	128	80	10.2	129.4	0.90631	33	48
80	26	29	1.22	17.4	107	146	70	9.1	84.4	1.01568	34	37
81	27	23	0.95	11.4	80	132	70	10.0	124.8	1.34503	30	50
82	28	17	0.70	7.8	75	126	74	9.3	123.3	0.95462	29	34
83	29	21	0.87	9.6	71	130	70	6.8	96.3	0.71770	35	38
84	30	13	0.58	8.2	81	120	80	7.7	94.7	0.82424	39	73
85	34	24	1.07	14.6	107	136	84	9.9	92.5	1.11847	32	32
86	35	21	1.02	15.0	107	154	80	8.7	81.2	0.99585	35	37
87	39	17	0.86	17.4	79	148	96	9.6	121.2	1.23369	27	34
88	40	27	1.26	10.6	81	140	70	10.2	126.2	1.19277	44	46
89	43	27	1.14	20.2	79	130	68	10.2	128.9	1.06375	44	47
90	45	23	1.16	18.4	86	120	78	7.9	92.3	0.86565	31	34

STAGE=3 COND=3

OBS	SUBJECT	PKA	PKV	SVI	HR	SBP	DBP	Q	SV	VO2ABS	VPOINTS	TPOINTS
91	1	16	0.66	12.8	74	118	82	10.2	137.7	0.88591	33	35
92	9	17	0.84	11.2	82	118	60	8.3	100.9	0.90782	42	54
93	12	14	0.71	10.8	80	110	60	7.8	97.1	0.84149	29	37
94	13	14	0.65	10.2	78	122	66	8.8	113.2	0.77507	36	39
95	20	15	0.69	11.0	76	108	56	11.9	158.0	1.16891	28	31
96	24	18	0.80	11.4	78	130	66	11.7	149.9	1.24312	31	39
97	25	15	0.70	12.6	62	112	70	8.9	124.9	0.91575	30	58
98	26	22	1.00	16.8	90	118	60	9.9	110.2	1.01621	30	33
99	27	18	0.88	13.2	75	122	66	8.6	116.2	1.08154	31	50
100	28	15	0.76	11.8	64	116	62	11.1	173.0	1.21379	26	30
101	29	16	0.78	11.0	75	108	70	8.7	115.8	0.88568	26	35
102	30	12	0.57	9.6	84	108	76	7.3	86.7	0.88987	37	47
103	34	21	0.86	11.0	75	128	80	10.8	144.3	1.05871	34	34

STAGE=3 COND=3

OBS	SUBJECT	PKA	PKV	SVI	HR	SBP	DBP	Q	SV	VO2ABS	VPOINTS	TPOINTS
104	35	18	0.88	14.2	93	126	70	11.0	81.3	1.09623	37	43
105	39	15	0.79	15.6	71	134	80	7.6	106.3	1.02906	27	42
106	40	19	0.89	14.8	84	118	58	14.3	170.4	1.26850	30	34
107	43	22	0.85	14.8	73	132	80	7.4	101.4	1.07730	26	37
108	45	19	0.93	16.2	73	110	70	6.7	91.4	0.84524	32	36

STAGE=4 COND=1

OBS	SUBJECT	PKA	PKV	SVI	HR	SBP	DBP	Q	SV	VO2ABS	VPOINTS	TPOINTS
109	1	27	0.97	12.4	105	160	66	15.4	146.3	1.48376	37	46
110	9	32	1.27	13.8	130	144	80	13.8	106.1	1.50512	31	41
111	12	25	0.98	9.2	120	142	70	10.8	90.1	1.13198	27	32
112	13	35	0.89	10.6	122	154	82	13.2	108.0	1.30991	36	44
113	20	33	0.88	11.2	94	134	68	15.0	159.3	1.22816	39	45
114	24	27	1.12	13.8	120	140	70	16.4	136.7	1.81513	46	53
115	25	20	0.79	10.6	92	156	70	15.7	170.7	1.77679	54	57
116	26	33	1.07	12.0	136	156	80	15.5	113.8	1.44695	32	50
117	27	45	1.18	11.8	103	150	80	15.0	145.3	1.69493	45	54
118	28	28	1.13	12.4	94	160	60	14.9	158.8	1.78906	41	48
119	29	27	1.06	11.0	103	144	70	12.7	125.6	1.13536	37	59
120	30	22	0.90	10.8	110	130	62	10.2	92.7	1.33115	37	41
121	34	61	1.33	16.6	111	158	74	20.2	181.7	1.98481	28	42
122	35	21	0.87	10.6	122	160	74	12.0	98.1	1.82037	38	40
123	39	23	0.75	11.2	100	172	86	13.9	139.0	1.70064	25	42
124	40	36	1.36	15.4	120	150	66	16.1	135.0	2.08457	38	45
125	43	34	1.28	15.8	107	180	70	14.3	133.7	1.54162	29	35
126	45	31	1.29	19.0	97	138	64	10.9	112.2	1.41050	32	40

STAGE=4 COND=2

OBS	SUBJECT	PKA	PKV	SVI	HR	SBP	DBP	Q	SV	VO2ABS	VPOINTS	TPOINTS
127	1	23	0.87	9.8	97	154	74	13.4	138.1	1.48814	39	44
128	9	39	1.30	13.2	127	154	78	15.8	124.7	1.52135	58	63
129	12	25	0.95	9.8	112	114	80	10.3	91.9	1.13985	28	32
130	13	49	1.07	11.6	107	150	66	12.4	115.6	1.50898	55	55
131	20	20	0.75	9.4	92	138	80	11.4	123.4	1.30039	45	47
132	24	22	0.94	10.8	91	154	72	18.9	207.3	2.38761	37	38
133	25	18	0.73	11.8	84	140	80	11.4	135.5	1.21533	18	24
134	26	42	1.11	13.6	136	166	70	13.9	102.1	1.59094	36	54
135	27	42	1.03	12.0	88	150	66	14.3	162.8	1.91731	34	48
136	28	26	1.04	11.4	90	148	66	12.8	141.7	1.56344	32	35
137	29	24	0.97	9.8	99	150	68	10.7	108.0	1.18441	39	41
138	30	21	0.67	8.2	107	132	82	9.5	88.4	1.30837	29	59
139	34	33	1.34	18.4	118	164	74	15.2	129.1	1.55104	34	42
140	35	29	1.22	16.4	136	170	80	13.9	102.4	1.55093	45	47
141	39	22	0.96	17.6	91	196	88	16.3	179.0	1.83896	33	47
142	40	35	1.43	10.6	107	140	76	12.6	118.1	1.97279	29	36
143	43	32	1.24	15.2	107	166	66	13.0	121.3	1.48425	44	46
144	45	31	1.34	10.4	100	134	78	10.6	105.7	1.20769	46	48

STAGE=4 COND=3

OBS	SUBJECT	PKA	PKV	SVI	HR	SBP	DBP	Q	SV	VO2ABS	VPOINTS	TPOINTS
145	1	23	0.84	14.4	83	132	70	13.4	152.6	1.36968	31	33
146	9	21	1.01	13.2	97	120	60	12.2	126.2	1.28537	40	51
147	12	15	0.79	11.0	91	120	58	10.6	116.2	1.22494	34	59
148	13	22	1.07	16.8	97	136	70	11.9	122.4	1.21979	34	35
149	20	18	0.70	8.8	83	108	54	11.6	139.4	1.27683	35	47
150	24	20	0.89	11.6	94	138	60	12.8	136.2	1.89407	31	33
151	25	15	0.65	11.8	79	122	64	11.0	139.3	1.38559	31	51
152	26	26	1.07	15.3	115	138	60	12.6	109.5	1.31033	28	34
153	27	24	1.00	14.0	94	128	66	10.0	106.0	1.34762	37	53
154	28	23	1.12	15.0	88	126	58	14.3	162.4	1.76459	30	41
155	29	19	0.80	10.0	88	128	70	10.5	119.3	1.07276	20	55
156	30	16	0.82	13.8	90	114	80	10.6	117.6	1.31127	39	50
157	34	27	1.03	12.8	100	132	86	15.0	149.8	1.83417	42	45

STAGE=4 COND=3

OBS	SUBJECT	PKA	PKV	SVI	HR	SBP	DBP	Q	SV	VO2ABS	VPOINTS	TPOINTS
158	35	22	1.02	15.8	105	128	84	19.1	182.3	1.66375	46	52
159	39	18	0.92	18.0	85	140	80	14.1	165.5	1.77473	34	43
160	40	21	0.93	11.4	94	110	50	15.9	168.6	1.77028	42	52
161	43	26	0.99	13.0	115	160	80	12.7	110.5	2.03346	47	60
162	45	26	1.08	17.8	88	114	70	10.3	116.6	1.27410	30	30

STAGE=5 COND=1

OBS	SUBJECT	PKA	PKV	SVI	HR	SBP	DBP	Q	SV	VO2ABS	VPOINTS	TPOINTS
163	1	44	1.11	9.6	140	190	70	17.1	121.8	1.91372	37	56
164	9	62	1.36	12.4	150	150	74	17.4	116.3	2.02968	40	50
165	12	44	0.92	5.6	143	170	70	12.9	89.9	1.60852	40	52
166	13	44	1.18	11.6	146	174	80	15.8	108.2	1.90337	56	62
167	20	50	1.03	10.0	115	160	68	14.5	126.2	1.73353	48	56
168	24	44	1.02	8.4	136	188	60	17.9	131.4	2.44041	48	66
169	25	46	1.00	10.0	125	180	72	20.0	165.2	2.96902	40	55
170	26	63	1.24	11.4	167	170	70	17.2	103.1	2.02780	63	77
171	27	50	1.06	9.0	125	190	80	19.6	135.5	2.58128	49	62
172	28	43	1.41	13.8	125	176	66	20.3	162.1	2.51309	44	55
173	29	30	1.14	10.6	125	150	66	10.6	84.9	1.53013	56	65
174	30	36	1.04	10.8	132	138	64	12.5	94.7	1.74493	41	58
175	34	85	1.75	18.2	136	172	68	23.2	170.6	2.50147	38	41
176	35	15	0.65	8.6	146	180	74	18.9	129.1	2.11852	40	41
177	39	47	1.10	15.8	110	180	80	27.2	246.9	2.47007	31	55
178	40	60	1.61	17.2	135	158	68	16.9	125.2	2.53483	47	60
179	43	43	1.34	13.2	130	180	70	16.5	126.9	1.96016	35	45
180	45	39	1.44	18.6	107	148	70	12.2	114.2	1.73563	31	51

STAGE=5 COND=2

OBS	SUBJECT	PKA	PKV	SVI	HR	SBP	DBP	Q	SV	VO2ABS	VPOINTS	TPOINTS
181	1	45	0.82	6.4	115	172	72	19.2	166.7	2.34512	43	47
182	9	48	1.29	11.4	149	164	70	17.3	116.0	1.99289	44	51
183	12	40	1.00	8.4	136	170	80	13.3	97.4	1.80861	54	57
184	13	48	1.07	9.6	136	178	66	14.4	105.9	2.13031	68	81
185	20	42	0.85	10.0	107	146	70	13.4	125.6	1.63588	50	53
186	24	42	0.96	7.0	115	184	74	22.2	193.3	3.20849	40	62
187	25	30	0.74	8.4	107	180	74	18.6	173.6	2.33255	28	53
188	26	42	0.92	8.4	167	184	72	18.1	108.2	2.15512	45	79
189	27	50	1.07	7.8	120	170	76	18.5	154.5	2.70401	25	49
190	28	27	1.04	9.8	115	158	66	16.5	144.1	2.18001	40	49
191	29	27	1.05	9.2	125	160	60	13.3	106.0	1.56615	35	47
192	30	41	0.82	8.6	125	140	78	11.7	93.5	1.61155	46	57
193	34	54	1.53	14.4	143	178	68	17.5	122.3	2.08049	42	51
194	35	67	1.44	14.0	158	180	76	19.0	120.0	2.17806	49	52
195	39	53	1.15	16.4	107	190	80	23.3	217.5	2.72623	37	60
196	40	71	1.45	10.6	130	142	72	16.4	126.2	2.70987	42	51
197	43	39	1.35	14.4	115	190	64	19.2	166.8	2.42575	36	44
198	45	32	1.22	16.0	120	158	80	14.3	119.3	1.80249	48	66

STAGE=5 COND=3

OBS	SUBJECT	PKA	PKV	SVI	HR	SBP	DBP	Q	SV	VO2ABS	VPOINTS	TPOINTS
199	1	22	0.84	10.8	97	148	70	15.3	157.4	1.83036	44	55
200	9	25	1.03	11.6	110	136	60	14.4	130.8	1.73031	36	38
201	12	18	0.84	10.6	100	122	60	12.9	128.8	1.75704	39	44
202	13	31	1.11	14.2	115	140	70	14.2	118.2	1.67087	33	55
203	20	19	0.70	8.4	100	118	60	15.4	153.6	1.76583	40	47
204	24	32	1.26	16.0	111	154	60	18.8	169.5	2.62046	41	50
205	25	20	0.90	14.4	94	140	70	19.0	201.7	2.26156	37	62
206	26	36	1.19	14.6	135	144	60	15.2	112.6	2.13545	36	56
207	27	36	1.04	12.6	100	138	72	16.3	168.0	1.09185	36	49
208	28	28	1.22	15.4	94	140	58	18.8	200.2	2.74446	51	55
209	29	22	0.92	9.8	105	142	74	13.2	125.4	1.44870	38	41
210	30	20	0.78	9.6	105	128	82	12.8	121.5	1.71211	30	56
211	34	36	1.22	16.2	110	142	84	18.7	169.9	2.40623	31	44
212	35	28	1.10	11.2	121	150	70	21.8	180.2	2.14987	47	48
213	39	23	1.02	18.2	100	160	84	19.9	199.6	2.53412	37	73
214	40	24	1.00	11.8	111	126	56	16.3	146.8	2.37395	38	48
215	43	30	1.08	12.0	115	150	62	16.3	141.6	2.51149	33	41
216	45	26	1.27	19.4	107	124	70	12.5	116.7	1.94198	43	48

APPENDIX G

DATA ANALYSIS FOR INTERVENTION PHASE

Multivariate Analysis of Variance. Dependent variables: pkA, pkV, SVI, HR, SBP, DBP. Stages: Rest Sit, 20, 40, 60% $\dot{V}O_2$max.

Source	df_H	df_E	λ	F	p
Condition	2	34	.0545	15.87	<.0001
Stage	3	51	.0076	33.54	<.0001
Condition*Stage	6	102	.1734	5.84	<.0001

df_H = degrees of freedom hypothesis
df_E = degrees of freedom error term
λ = Wilk's criterion (lambda)

Multivariate Analysis of Variance. Dependent Variables: pkA, pkV, SVI, HR, SBP, DBP, $\dot{V}O_2$abs., Stages: 20, 40, 60% $\dot{V}O_2$max.

Source	df_H	df_E	λ	F	p
Condition	2	34	.0396	10.06	<.0001
Stage	2	34	.0059	7.91	<.0001
Condition*Stage	4	68	.1133	3.96	<.0001

df_H = degrees of freedom hypothesis
df_E = degrees of freedom error term
λ = Wilk's criterion (lambda)

ANOVA Table with Tests of Simple Main Effects - Peak Acceleration

Source	SS	df	MS	F	p
Subjects	4038.33	17	273.55		
Condition (C)	3940.11	2	1970.06	47.71	<.0001
C at Rest	68.94	2	34.47	0.77	.4709
C at 20% $\dot{V}O_2max$	484.03	2	242.02	5.40	.0092
C at 40% $\dot{V}O_2max$	1022.48	2	511.24	11.40	.0002
C at 60% $\dot{V}O_2max$	4482.49	2	2241.25	50.00	<.0001
Condition*Subject	1524.56	34	44.84		
Stage (S)	18221.24	3	6073.75	120.30	<.0001
S at Placebo	9257.45	3	3085.82	61.12	<.0001
S at H_2O	9411.83	3	3137.28	62.14	<.0001
S at B-blockade	1669.79	3	556.60	11.02	<.0001
Stage*Subject	2574.93	51	50.49		
Condition*Stage	2117.81	6	352.97	8.55	<.0001
Condition*Stage* Subject	4211.52	102	41.29		

H_2O = Hyperhydration

ANOVA Table with Tests of Simple Main Effects - Peak Velocity

Source	SS	df	MS	F	p
Subjects	3.84	17	0.23	17.42	<.0001
Condition (C)	30.72	2	0.36	17.03	<.0001
C at Rest	0.06	2	0.03	1.50	.2375
C at 20% $\dot{V}O_2max$	0.43	2	0.21	10.50	.0003
C at 40% $\dot{V}O_2max$	0.20	2	0.10	5.00	.0125
C at 60% $\dot{V}O_2max$	0.23	2	0.11	5.50	.0085
Condition*Subject	0.72	34	0.02		
Stage (S)	6.17	3	2.06	144.44	<.0001
S at Placebo	2.33	3	0.77	38.50	<.0001
S at H_2O	2.49	3	0.83	41.50	<.0001
S at B-blockade	1.54	3	0.51	25.50	<.0001
Stage*Subject	0.92	51	0.02		
Condition*Stage	0.19	6	0.03	2.44	.0303
Condition*Stage* Subject	1.32	102	0.01		

H_2O = Hyperhydration

ANOVA Table with Tests of Simple Main Effects - Systolic Velocity Integral

Source	SS	df	MS	F	p
Subjects	883.34	17	51.96	16.16	
Condition (C)	29.07	2	14.54	2.34	0.1113
C at Rest	0.82	2	0.41	0.07	0.9325
C at 20% $\dot{V}O_2max$	33.13	2	16.57	2.67	0.0837
C at 40% $\dot{V}O_2max$	18.05	2	9.03	1.46	0.2464
C at 60% $\dot{V}O_2max$	68.33	2	34.17	5.51	0.0085
Condition*Subject	210.85	34	6.20		
Stage (S)	473.52	3	157.85	32.78	<.0001
S at Placebo	210.75	3	70.25	14.57	<.0001
S at H_2O	138.27	3	46.09	9.56	<.0001
S at B-blockade	206.25	3	68.75	15.26	<.0001
Stage*Subject	245.58	51	4.82		
Condition*Stage	62.72	6	10.45	3.25	.0058
Condition*Stage* Subject	327.97	102	3.22		

H_2O = Hyperhydration

ANOVA Table with Tests of Simple Main Effects - Heart Rate

Source	SS	df	MS	F	p
Subjects	20922.97	17	1230.76		
Condition (C)	9790.95	2	4895.47	39.73	<.0001
C at Rest	600.48	2	300.24	2.44	.1023
C at 20% $\dot{V}O_2$max	2141.45	2	1075.73	8.73	.0009
C at 40% $\dot{V}O_2$max	2511.82	2	1255.91	10.19	.0003
C at 60% $\dot{V}O_2$max	6566.27	2	3283.13	26.65	<.0001
Condition*Subject	4189.05	34	123.21		
Stage (S)	92891.94	3	30963.98	361.81	<.0001
S at Placebo	707992.51	3	235997.50	2751.62	<.0001
S at H_2O	130342.04	3	43447.35	507.68	<.0001
S at B-blockade	20411.68	3	6803.89	79.50	<.0001
Stage*Subject	4364.64	51	85.58		
Condition*Stage	2029.05	6	338.17	10.90	<.0001
Condition*Stage* Subject	3165.62	102			

H_2O = Hyperhydration

ANOVA Table with Tests of Simple Main Effects - Systolic Blood Pressure

Source	SS	df	MS	F	p
Subjects	17493.25	17	1029.01		
Condition (C)	15732.70	2	7866.35	83.44	<.0001
C at Rest	350.81	2	175.40	1.86	.1712
C at 20% $\dot{V}O_2max$	2102.20	2	1051.10	11.15	.0002
C at 40% $\dot{V}O_2max$	6849.94	2	3424.97	36.33	.0001
C at 60% $\dot{V}O_2max$	11084.62	2	5542.31	58.79	<.0001
Condition*Subject	3205.29	34	94.27		
Stage (S)	56680.66	3	18893.55	186.67	<.0001
S at Placebo	28884.66	3	9628.22	95.13	<.0001
S at H_2O	25586.34	3	8528.78	84.27	<.0001
S at B-blockade	6864.17	3	2288.05	22.60	<.0001
Stage*Subject	5162.00	51	101.21		
Condition*Stage	4654.55	6	775.75	17.01	<.0001
Condition*Stage* Subject	4652.77	102	45.61		

H_2O = Hyperhydration

ANOVA Table - Diastolic Blood Pressure

Source	SS	df	MS	F	p
Subjects	3742.00	17	220.12		
Condition	1868.44	2	934.22	8.06	.0014
Condition*Subject	3941.55	34	115.93		
Stage	1640.44	3	546.81	19.60	.0001
Stage*Subject	1422.88	51	27.89		
Condition*Stage	255.11	6	42.52	2.02	.0695
Condition*Stage* Subject	2145.55	102	21.03		

ANOVA Table - Cardiac Output

Source	SS	df	MS	F	p
Subjects	546.50	17	32.15		
Condition	35.90	2	17.95	3.97	.0283
Condition*Subject	153.94	34	4.53		
Stage	1398.69	2	699.35	130.72	<.0001
Stage*Subject	181.85	34	5.35		
Condition*Stage	8.78	4	2.19	1.21	.3159
Condition*Stage* Subject	128.66	68	1.82		

ANOVA Table - Stroke Volume

Source	SS	df	MS	F	p
Subjects	71030.92	17	417.87		
Condition	5198.96	2	2599.40	4.29	.0218
Condition*Subject	20587.00	34	605.50		
Stage	18951.40	2	9475.70	20.51	<.0001
Stage*Subject	15711.32	34	462.09		
Condition*Stage	1491.15	4	372.79	1.59	.2120
Condition*Stage* Subject	16902.78	68	248.57		

ANOVA Table - Absolute Oxygen Consumption

Source	SS	df	MS	F	p
Subjects	9.121	17	0.536		
Condition	0.174	2	0.087	1.02	0.3710
Condition*Subject	2.901	34	0.085		
Stage	32.768	2	16.384	275.08	<.0001
Stage*Subject	2.025	34	0.059		
Condition*Stage	0.118	4	0.029	1.36	0.2565
Condition*Stage* Subject	1.478	68	0.021		

ANOVA Table with Tests of Simple Main Effects -
RPP (Rate Pressure Product)

Source	SS	df	MS	F	p
Subjects	73000.69	17	4294.15	34.62	<.0001
Condition (C)	81046.56	2	40523.28	79.00	<.0001
C at 20% $\dot{V}O_2max$	546.08	2	4273.04	8.33	.0011
C at 40% $\dot{V}O_2max$	22433.79	2	11216.89	21.87	.0001
C at 60% $\dot{V}O_2max$	62072.16	2	31036.08	60.50	<.0001
Condition*Subject	17441.33	34	512.98		
Stage (S)	208103.72	2	104051.86	322.90	<.0001
S at Placebo	97446.87	2	48723.43	151.20	<.0001
S at H_2O	93110.60	2	46555.30	144.47	<.0001
S at B-blockade	29987.86	2	14993.93	46.53	<.0001
Stage*Subject	10956.24	34	322.24		
Condition*Stage	12442.30	4	3110.57	25.08	<.0001
Condition*Stage* Subject	8434.25	68	124.03		

H_2O = Hyperhydration

Summary of Tukey Tests of Main Effect Stage: Dependent Doppler Measures Collected from Rest Sitting - 60% $\dot{V}O_2$peak

Source	Q
Peak Acceleration	
Difference between Rest & 60% $\dot{V}O_2$peak	25.62**
Difference between Rest & 40% $\dot{V}O_2$peak	13.28**
Difference between Rest & 20% $\dot{V}O_2$peak	6.39**
Difference between 20 & 60% $\dot{V}O_2$peak	19.23**
Difference between 20 & 40% $\dot{V}O_2$peak	6.89**
Difference between 40 & 60% $\dot{V}O_2$peak	12.33**
Peak Velocity	
Difference between Rest & 60% $\dot{V}O_2$peak	24.02**
Difference between Rest & 40% $\dot{V}O_2$peak	19.23**
Difference between Rest & 20% $\dot{V}O_2$peak	13.37**
Difference between 20 & 60% $\dot{V}O_2$peak	10.65**
Difference between 20 & 40% $\dot{V}O_2$peak	10.65**
Difference between 40 & 60% $\dot{V}O_2$peak	4.79**
Systolic Velocity Integral	
Difference between Rest & 60% $\dot{V}O_2$peak	8.23**
Difference between Rest & 40% $\dot{V}O_2$peak	11.38**
Difference between Rest & 20% $\dot{V}O_2$peak	12.77**
Difference between 20 & 60% $\dot{V}O_2$peak	4.54**
Difference between 20 & 40% $\dot{V}O_2$peak	1.39
Difference between 40 & 60% $\dot{V}O_2$peak	3.14

** $p<.01$ $Qcv(.01) = 4.35$ for $df=51$
* $p<.05$ $Qcv(.05) = 3.42$ for $df=51$

Summary of Tukey Tests of Main Effect Stage: Dependent Hemodynamic Measures from Rest Sitting - 60% $\dot{V}O_2$peak

Source	Q
Heart Rate	
Difference between Rest & 60% $\dot{V}O_2$peak	44.34**
Difference between Rest & 40% $\dot{V}O_2$peak	28.93**
Difference between Rest & 20% $\dot{V}O_2$peak	14.62**
Difference between 20 & 60% $\dot{V}O_2$peak	29.71**
Difference between 20 & 40% $\dot{V}O_2$peak	14.31**
Difference between 40 & 60% $\dot{V}O_2$peak	15.40**
Systolic Blood Pressure	
Difference between Rest & 60% $\dot{V}O_2$peak	30.74**
Difference between Rest & 40% $\dot{V}O_2$peak	19.35**
Difference between Rest & 20% $\dot{V}O_2$peak	8.07**
Difference between 20 & 60% $\dot{V}O_2$peak	22.69**
Difference between 20 & 40% $\dot{V}O_2$peak	11.31**
Difference between 40 & 60% $\dot{V}O_2$peak	11.38**
Diastolic Blood Pressure	
Difference between Rest & 60% $\dot{V}O_2$peak	9.94**
Difference between Rest & 40% $\dot{V}O_2$peak	8.25**
Difference between Rest & 20% $\dot{V}O_2$peak	7.77**
Difference between 20 & 60% $\dot{V}O_2$peak	2.17
Difference between 20 & 40% $\dot{V}O_2$peak	0.47
Difference between 40 & 60% $\dot{V}O_2$peak	1.69

** $p<.01$ $Qcv(.01) = 3.85$ for $df=34$
* $p<.05$ $Qcv(.05) = 2.88$ for $df=34$

Summary of Tukey Tests of Main Effect Stage: Dependent Measures Collected During Exercise Only

Source	Q
Cardiac Output	
Difference between 20 & 60% $\dot{V}O_2$peak	22.84**
Difference between 20 & 40% $\dot{V}O_2$peak	11.78**
Difference between 40 & 60% $\dot{V}O_2$peak	11.05**
Stroke Volume	
Difference between 20 & 60% $\dot{V}O_2$peak	15.00**
Difference between 20 & 40% $\dot{V}O_2$peak	10.06**
Difference between 40 & 60% $\dot{V}O_2$peak	4.94**
Absolute Oxygen Consumption	
Difference between 20 & 60% $\dot{V}O_2$peak	33.15**
Difference between 20 & 40% $\dot{V}O_2$peak	15.38**
Difference between 40 & 60% $\dot{V}O_2$peak	17.76**
Rate Pressure Product	
Difference between 20 & 60% $\dot{V}O_2$peak	35.88**
Difference between 20 & 40% $\dot{V}O_2$peak	16.24**
Difference between 40 & 60% $\dot{V}O_2$peak	19.64**

** $p<.01$ $Qcv(.01) = 3.85$ for $df=34$

Summary of Tukey Tests on Simple Main Effects of Stage - Peak Acceleration

Source	Q
Placebo	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	18.43**
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	8.98**
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	4.93**
Difference between 20 & 60% $\dot{V}O_2$peak	13.50**
Difference between 20 & 40% $\dot{V}O_2$peak	5.83**
Difference between 40 & 60% $\dot{V}O_2$peak	7.66**
Hyperhydration	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	18.21**
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	9.45**
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	4.07*
Difference between 20 & 60% $\dot{V}O_2$peak	14.13**
Difference between 20 & 40% $\dot{V}O_2$peak	5.37**
Difference between 40 & 60% $\dot{V}O_2$peak	8.78**
Beta Blockade	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	7.69**
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	4.57**
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	2.05
Difference between 20 & 60% $\dot{V}O_2$peak	5.63**
Difference between 20 & 40% $\dot{V}O_2$peak	2.51
Difference between 40 & 60% $\dot{V}O_2$peak	3.11

** $p<.01$ $Qcv(.01) = 4.35$ for $df=51$
* $p<.05$ $Qcv(.05) = 3.42$ for $df=51$

Summary of Tukey Tests on Simple Main Effects of Stage - Peak Velocity

Source	Q
Placebo	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	15.96**
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	11.85**
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	10.02**
Difference between 20 & 60% $\dot{V}O_2$peak	5.94**
Difference between 20 & 40% $\dot{V}O_2$peak	1.93
Difference between 40 & 60% $\dot{V}O_2$peak	4.11*
Hyperhydration	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	14.58**
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	14.09**
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	9.72**
Difference between 20 & 60% $\dot{V}O_2$peak	5.84**
Difference between 20 & 40% $\dot{V}O_2$peak	4.37**
Difference between 40 & 60% $\dot{V}O_2$peak	1.46
Beta Blockade	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	12.63**
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	9.39**
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	4.89**
Difference between 20 & 60% $\dot{V}O_2$peak	7.73**
Difference between 20 & 40% $\dot{V}O_2$peak	4.50**
Difference between 40 & 60% $\dot{V}O_2$peak	3.23

** $p<.01$ $Qcv(.01) = 4.35$ for $df=51$
* $p<.05$ $Qcv(.05) = 3.42$ for $df=51$

Summary of Tukey Tests on Simple Main Effects of Stage - Systolic Velocity Integral

Source	Q
Placebo	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	5.14**
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	6.58**
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	9.02**
Difference between 20 & 60% $\dot{V}O_2$peak	3.88*
Difference between 20 & 40% $\dot{V}O_2$peak	2.43
Difference between 40 & 60% $\dot{V}O_2$peak	1.44
Hyperhydration	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	2.05
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	5.17**
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	6.86**
Difference between 20 & 60% $\dot{V}O_2$peak	4.81**
Difference between 20 & 40% $\dot{V}O_2$peak	1.68
Difference between 40 & 60% $\dot{V}O_2$peak	3.13
Beta Blockade	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	7.07**
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	7.94**
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	6.22**
Difference between 20 & 60% $\dot{V}O_2$peak	0.85
Difference between 20 & 40% $\dot{V}O_2$peak	1.71
Difference between 40 & 60% $\dot{V}O_2$peak	0.86

** $p<.01$ $Qcv(.01) = 4.35$ for $df=51$
* $p<.05$ $Qcv(.05) = 3.42$ for $df=51$

Summary of Tukey Tests on Simple Main Effects of Stage - Heart Rate

Source	Q
Placebo	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	28.25**
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	17.88**
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	9.67**
Difference between 20 & 60% $\dot{V}O_2$peak	18.57**
Difference between 20 & 40% $\dot{V}O_2$peak	8.20**
Difference between 40 & 60% $\dot{V}O_2$peak	10.36**
Hyperhydration	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	28.48**
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	18.25**
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	9.44**
Difference between 20 & 60% $\dot{V}O_2$peak	19.03**
Difference between 20 & 40% $\dot{V}O_2$peak	8.80**
Difference between 40 & 60% $\dot{V}O_2$peak	10.22**
Beta Blockade	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	19.99**
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	13.89**
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	6.14**
Difference between 20 & 60% $\dot{V}O_2$peak	13.85**
Difference between 20 & 40% $\dot{V}O_2$peak	7.75**
Difference between 40 & 60% $\dot{V}O_2$peak	6.09**

** $p<.01$ $Qcv(.01) = 4.35$ for $df=51$
* $p<.05$ $Qcv(.05) = 3.42$ for $df=51$

Summary of Tukey Tests on Simple Main Effects of Stage - Systolic Blood Pressure

Source	Q
Placebo	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	12.49**
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	8.22**
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	3.53*
Difference between 20 & 60% $\dot{V}O_2$peak	8.95**
Difference between 20 & 40% $\dot{V}O_2$peak	4.68**
Difference between 40 & 60% $\dot{V}O_2$peak	4.26*
Hyperhydration	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	11.73**
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	7.49**
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	3.06
Difference between 20 & 60% $\dot{V}O_2$peak	8.66**
Difference between 20 & 40% $\dot{V}O_2$peak	4.42**
Difference between 40 & 60% $\dot{V}O_2$peak	4.24*
Beta Blockade	
Difference between Sitting Rest & 60% $\dot{V}O_2$peak	6.10**
Difference between Sitting Rest & 40% $\dot{V}O_2$peak	3.37
Difference between Sitting Rest & 20% $\dot{V}O_2$peak	1.17
Difference between 20 & 60% $\dot{V}O_2$peak	4.76**
Difference between 20 & 40% $\dot{V}O_2$peak	2.04
Difference between 40 & 60% $\dot{V}O_2$peak	2.72

** $p<.01$ $Qcv(.01) = 4.35$ for $df=51$
* $p<.05$ $Qcv(.05) = 3.42$ for $df=51$

Summary of Tukey Tests on Simple Main Effects of Stage - Rate Pressure Product

Source	Q
Placebo	
Difference between 20 & 60% $\dot{V}O_2$peak	24.52**
Difference between 20 & 40% $\dot{V}O_2$peak	10.65**
Difference between 40 & 60% $\dot{V}O_2$peak	13.86**
Hyperhydration	
Difference between 20 & 60% $\dot{V}O_2$peak	23.99**
Difference between 20 & 40% $\dot{V}O_2$peak	10.65**
Difference between 40 & 60% $\dot{V}O_2$peak	13.33**
Beta Blockade	
Difference between 20 & 60% $\dot{V}O_2$peak	13.64**
Difference between 20 & 40% $\dot{V}O_2$peak	6.86**
Difference between 40 & 60% $\dot{V}O_2$peak	6.81**

** $p<.01$ $Qcv(.01) = 3.85$ for $df=51$
* $p<.05$ $Qcv(.05) = 2.88$ for $df=51$

Summary of Tukey Tests of Main Effect Condition: Dependent Measures Collected from Rest Sitting - 60% $\dot{V}O_2$peak

Source	Q
Peak Acceleration	
Difference between Placebo & Beta-blockade	13.50**
Difference between Placebo & Hyperhydration	3.20*
Difference between Hyperhydration & Beta-blockade	9.54**
Peak Velocity	
Difference between Placebo & Beta-blockade	8.28**
Difference between Placebo & Hyperhydration	3.85**
Difference between Hyperhydration & Beta-blockade	4.43**
Heart Rate	
Difference between Placebo & Beta-blockade	12.47**
Difference between Placebo & Hyperhydration	4.60**
Difference between Hyperhydration & Beta-blockade	7.86**
Systolic Blood Pressure	
Difference between Placebo & Beta-blockade	16.07**
Difference between Placebo & Hyperhydration	0.51
Difference between Hyperhydration & Beta-blockade	15.55**
Diastolic Blood Pressure	
Difference between Placebo & Beta-blockade	2.01
Difference between Placebo & Hyperhydration	5.60**
Difference between Hyperhydration & Beta-blockade	3.58*

** $p<.01$ $Q_{cv}(.01) = 3.85$ for df=34
* $p<.05$ $Q_{cv}(.05) = 2.88$ for df=34

Summary of Tukey Tests of Main Effect Condition: Dependent Measures Collected During Exercise Only

Source	Q
Cardiac Output	
Difference between Placebo & Beta-blockade	3.83*
Difference between Placebo & Hyperhydration	2.86
Difference between Hyperhydration & Beta-blockade	0.96
Stroke Volume	
Difference between Placebo & Beta-blockade	3.49*
Difference between Placebo & Hyperhydration	0.17
Difference between Hyperhydration & Beta-blockade	3.67*
Rate Pressure Product	
Difference between Placebo & Beta-blockade	16.62**
Difference between Placebo & Hyperhydration	2.85
Difference between Hyperhydration & Beta-blockade	13.76**

** $p<.01$ $Qcv(.01) = 3.85$ for $df=34$
* $p<.05$ $Qcv(.05) = 2.88$ for $df=34$

Summary of Tukey Tests on Simple Main Effects of Condition - Rate Pressure Product

Source	Q
20% $\dot{V}O_2$max	
Difference between Placebo and Beta-blockade	5.71**
Difference between Placebo and Hyperhydration	1.50
Difference between Hyperhydration and Beta-Blockade	4.20**
40% $\dot{V}O_2$max	
Difference between Placebo and Beta-blockade	8.75**
Difference between Placebo and Hyperhydration	1.51
Difference between Hyperhydration and Beta-Blockade	7.24**
60% $\dot{V}O_2$max	
Difference between Placebo and Beta-blockade	14.33**
Difference between Placebo and Hyperhydration	1.93
Difference between Hyperhydration and Beta-Blockade	6.78**

** $p<.01$ $Qcv(.01) = 3.85$ for $df=34$
* $p<.05$ $Qcv(.05) = 2.88$ for $df=34$

Summary of Tukey Tests on Simple Main Effects of Condition - Peak Acceleration

Source	Q
20% $\dot{V}O_2$max	
Difference between Placebo and Beta-blockade	4.64**
Difference between Placebo and Hyperhydration	2.35
Difference between Hyperhydration and Beta-Blockade	2.28
40% $\dot{V}O_2$max	
Difference between Placebo and Beta-blockade	6.26**
Difference between Placebo and Hyperhydration	0.95
Difference between Hyperhydration and Beta-Blockade	5.31**
60% $\dot{V}O_2$max	
Difference between Placebo and Beta-blockade	12.99**
Difference between Placebo and Hyperhydration	1.65
Difference between Hyperhydration and Beta-Blockade	11.33**

** $p<.01$ $Q_{cv}(.01) = 3.85$ for $df=34$
* $p<.05$ $Q_{cv}(.05) = 2.88$ for $df=34$

Summary of Tukey Tests on Simple Main Effects of Condition - Peak Velocity

Source	Q
20% $\dot{V}O_2max$	
Difference between Placebo and Beta-blockade	6.28**
Difference between Placebo and Hyperhydration	2.54
Difference between Hyperhydration and Beta-Blockade	3.74*
40% $\dot{V}O_2max$	
Difference between Placebo and Beta-blockade	3.88*
Difference between Placebo and Hyperhydration	0.26
Difference between Hyperhydration and Beta-Blockade	3.62*
60% $\dot{V}O_2max$	
Difference between Placebo and Beta-blockade	4.70*
Difference between Placebo and Hyperhydration	2.65
Difference between Hyperhydration and Beta-Blockade	2.04

** $p<.01$ $Qcv(.01) = 3.85$ for $df=34$
* $p<.05$ $Qcv(.05) = 2.88$ for $df=34$

Summary of Tukey Tests on Simple Main Effects of Condition - Systolic Velocity Integral

	60% $\dot{V}O_2max$
Source	Q
Difference between Placebo and Beta-blockade	2.09
Difference between Placebo and Hyperhydration	2.29
Difference between Hyperhydration and Beta-Blockade	4.36**

** p<.01 Qcv(.01) = 3.85 for df=34
* p<.05 Qcv(.05) = 2.88 for df=34

Summary of Tukey Tests on Simple Main Effects of Condition - Systolic Blood Pressure

Source	Q
20% $\dot{V}O_2$max	
Difference between Placebo and Beta-blockade	3.19*
Difference between Placebo and Hyperhydration	0.15
Difference between Hyperhydration and Beta-Blockade	3.03*
40% $\dot{V}O_2$max	
Difference between Placebo and Beta-blockade	5.68**
Difference between Placebo and Hyperhydration	0.10
Difference between Hyperhydration and Beta-Blockade	5.57**
60% $\dot{V}O_2$max	
Difference between Placebo and Beta-blockade	7.22**
Difference between Placebo and Hyperhydration	0.12
Difference between Hyperhydration and Beta-Blockade	7.09**

** $p<.01$ $Qcv(.01) = 3.85$ for $df=34$
* $p<.05$ $Qcv(.05) = 2.88$ for $df=34$

Summary of Tukey Tests on Simple Main Effects of Condition - Heart Rate

Source	Q
20% $\dot{V}O_2$max	
Difference between Placebo and Beta-blockade	5.84**
Difference between Placebo and Hyperhydration	2.56
Difference between Hyperhydration and Beta-Blockade	3.28*
40% $\dot{V}O_2$max	
Difference between Placebo and Beta-blockade	6.38**
Difference between Placebo and Hyperhydration	2.06
Difference between Hyperhydration and Beta-Blockade	4.20**
60% $\dot{V}O_2$max	
Difference between Placebo and Beta-blockade	9.82**
Difference between Placebo and Hyperhydration	2.10
Difference between Hyperhydration and Beta-Blockade	7.64**

** $p<.01$ $Qcv(.01) = 3.85$ for $df=34$
* $p<.05$ $Qcv(.05) = 2.88$ for $df=34$

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