UNIVERSITY OF CALGARY

Comparison and Reliability of Non-Invasive Acetylene Uptake Techniques for the Measurement of Cardiac Output

by

Daniel William Dibski

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

FACULTY OF KINESIOLOGY

CALGARY, ALBERTA

MAY, 2003

UNIVERSITY OF CALGARY

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Comparison and Reliability of Non-Invasive Acetylene Uptake Techniques for the Measurement of Cardiac Output" submitted by Daniel Dibski in partial fulfillment of the requirements for the degree of Master of Science.

Supervisor, Dr. David J. Smith
Faculty of Kinesiology, University of Calgary

Dr. Stephen R. Norris
Faculty of Kinesiology, University of Calgary

Dr. Gordon T. Ford
Faculty of Medicine, University of Calgary

Dr. Robert Jensen
Pulmonary Division, LDS Hospital, Salt Lake City

Dr. Mark Haykowsky
Faculty of Rehabilitation Medicine, University of Alberta

Dr. Yagesh Bhambhani,
Faculty of Rehabilitation Medicine, University of Alberta

May 9, 2003
Date

Abstract

Thirteen trained male cyclists performed carbon dioxide rebreathing (CO_2RB) at intensities from rest to 200W, and open-circuit acetylene uptake (OpCirc) and single-breath acetylene uptake (SB) at intensities from rest to 300W, with all procedures using 50W increments. Oxygen consumption ($\dot{V}O_2$), cardiac output ($\dot{Q}$), and heart rate (HR), were measured at each stage, and the values for each variable were compared within each intensity to determine reliability of the measuring technique. Both the OpCirc and SB techniques were shown to be reliable measures of $\dot{Q}$ ($r = 0.95$ and $r = 0.92$, respectively) with decreasing coefficients of variation as intensity increased, and were similar to published data. The $\dot{Q}$-$\dot{V}O_2$ relationship using the SB technique diverged from the regression line for OpCirc and CO_2RB. Linear regression of the $\dot{Q}$-$\dot{V}O_2$ relationship for CO_2RB was $y = 6.18 \times \dot{V}O_2 + 2.59$, for OpCirc was $y = 6.12 \times \dot{V}O_2 + 2.98$, and for SB was $y = 5.05 \times \dot{V}O_2 + 3.76$. The OpCirc and SB techniques were both shown to be reliable techniques for measuring $\dot{Q}$, comparable to previously reported $\dot{Q}$ measurements, and suitable for use in exercise testing. The SB technique, requiring a constant, slow exhalation rate, was more difficult to perform at higher exercise intensities.

Acknowlegements

I would like to express heartfelt thanks to each of the following:

- Dr. David Smith, my supervisor, who provided an education that went far beyond scholastic learning, and who taught me as much about life as he did about physiology.
- Dr. Gordon Ford, my "co-supervisor", who opened many doors for me personally and professionally, and who made innumerable contributions to my education.
- Dr. Robert Jensen, for extensive contributions to this project, and for going the extra mile providing both the equipment and the knowledge necessary for this to be successful.
- Dr. Stephen Norris, for reviewing manuscripts and ideas, and for helping me maintain a "non-isolationist" view of human physiology.
- Dr. Mark Haykowsky and Dr. Yagesh Bhambhani, who provided valuable feedback and encouragement as members of my examination committee.
- Rosie Neil, for making this project work, and for keeping me humble. ☺
- For the hospital staff and lab technicians who had a hand in helping with this project: Shirley Bryan, Marta Kozlowska, Cindy Kelly, Jamie Howell, Heather Philpot, Maura Hooper, Stephanie McCallum – Thank You!
- My fellow graduate students, for helping out as subjects, and lending a hand in so many other ways. Special thanks to Tim Butterfield and Matt Black – Subject Extraordinaire!
- The subjects in this project, who endured months of testing, and who were as great a group of guys as I could have hoped for.
- My God, for the strength to make it through this.

Dedication

This thesis is dedicated to my wife and best friend, Kerri, who was my rock through this entire process, and to my parents, who instilled in me a love of knowledge and learning and always made me believe that I could do it.

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CHAPTER 1: INTRODUCTION

The primary function of the circulatory system is to deliver the metabolic requirements necessary for tissue metabolism and growth, and to remove metabolic waste products. When the body begins to exercise, the working skeletal muscles must increase their level of metabolism to provide sufficient energy required to sustain the work. This elevated metabolism requires greater delivery of oxygen to and removal of waste products from the working muscles (Dowell, 1983). The abilities to utilize oxygen in skeletal muscle (peripheral factors) and provide blood and oxygen to that exercising muscle (central factors) are critical components of health and performance. Consequently, the monitoring of the cardiovascular adaptations that occur during exercise can yield valuable information. An important measure of central cardiovascular function during exercise is cardiac output ($\dot{Q}$), as it provides a useful indication of ventricular efficiency over time (Karpman, 1987). Cardiac output is the volume of blood pumped by each ventricle per minute, and it is usually expressed as liters per minute.

Measurement and monitoring of $\dot{Q}$ at different basal and exercising conditions is not an easy task. Traditional techniques and standards of measurement are difficult to perform, and are, with the possible exception of echocardiography, for the most part indirect valuations of blood flow. Short of diverting aortic flow, or inserting a flexible aortic turbine, measurement of cardiac output is generally limited to utilizing variables involved in the Fick equation to derive a calculated value of cardiac output. The Fick equation,

$$\dot{Q} = \dot{V}O_2 / (a - \bar{v}O_2 diff)$$

where:

$\dot{Q}$ = cardiac output in liters per minute ($l \cdot min^{-1}$)

$\dot{V}O_2$ = oxygen consumption in liters per minute ($l \cdot min^{-1}$)

$a - \bar{v}O_2 diff$ = mixed arterial-venous oxygen content difference in $ml \cdot l^{-1} \cdot 100^{-1}$

was developed by Adolph Fick in 1870 for the calculation of blood flow. This equation is the basis for cardiac catheterization today (Lawrence, 1996). The Fick principle is an application based upon the law of conservation of mass. It is derived from the fact that the quantity of oxygen delivered to the pulmonary capillaries via the pulmonary artery, plus the quantity of oxygen that enters the pulmonary capillaries from the alveoli must equal the quantity of oxygen that is carried away by the pulmonary veins.

The standards for measuring cardiac output are traditionally invasive techniques involving the use of catheterization of peripheral and pulmonary arteries. Cardiac catheterization was performed as early as 1844, with experiments by Claude Bernard on horses. In 1912, Bliechroeder, Unger, and Loeb were the first to insert catheters into blood vessels of dogs without using X-rays to guide the procedure. The first human cardiac catheterization was performed in 1929, when a surgical student, Werner Forssmann, inserted urological catheters into cadavers, guiding the catheter from a vein in the arm into the right atrium. Encouraged by the ease of this in cadavers, he inserted a urological catheter into his own arm and heart and walked to the X-ray room to have his chest X-rayed. He did not experience any harmful effects of the procedure, and won the Nobel Prize for this experiment (Lawrence, 1996). Between the 1940's and 1950's, there were only a few laboratories specialized enough to perform catheterized cardiovascular

research. By the late 1960's, medical advances and need for increased number of cardiac laboratories eventually brought about large-scale growth in the number of laboratories and clinics capable of performing the procedure.

The direct Fick method is considered as the gold standard for measurement of cardiac output. This technique involves the catheterization of the radial artery and the pulmonary artery for arterial and venous blood sampling, measurement of $\dot{V}O_2$ during steady-state conditions, and then calculating cardiac output utilizing the Fick equation. Mixed venous blood is sampled from the right pulmonary artery, reflecting the site of total body venous mixing, and therefore requires a balloon-tipped flexible catheter to be inserted through the anticubital vein and through the right heart. This technique was first used experimentally in the 1940's (Cournand et al., 1945), and is the standard by which all other techniques are compared. The standard error of measurement for the direct Fick technique is low at rest (5%) and has been shown to decrease in submaximal exercise (Holmgren & Pernow, 1960). Its use during near-maximal exercise has been questioned, as its reliability may be compromised due to the difficulty of achieving steady-state conditions at these higher exercise intensities (Warburton et al., 1999a).

The standards of measurement in the clinical setting are dye-dilution and thermodilution, which are also invasive, catheter-involving techniques. These techniques offer advantages over the direct Fick technique in that they do not require direct cardiac catheterization, or in the case of thermodilution, do not require an arterial catheter (Hamilton et al., 1948; Eliasch et al., 1954; Grevnik, 1966; Miller et al., 1966; Branthwaite & Bradley, 1968). The validity and accuracy of the thermodilution method has been questioned (Branthwaite et al., 1968; Mackenzie et al., 1986, Espersen et al.,

1995), and several studies have shown that this method tends to over-predict true cardiac output by as much as 39% (van Grondelle et al., 1983; Mackenzie et al., 1986; Russell et al., 1990; Moore et al., 1991). As it is, many studies have used this method as a reference for validating non-invasive measures. Dye-dilution has been reported to have low measurement error with coefficients of variation generally within 5 to 10% (Grevnik, 1966; Hillis et al., 1985; Ekblom et al., 1968) during rest and submaximal exercise, though few studies have reported coefficients of variation during maximal exercise. The dye-dilution technique is relatively easier to use than the direct Fick and thus has been used more readily in exercise studies. However, its invasive nature makes it difficult to warrant its use in healthy subjects, particularly during near maximal exercise, and thus many exercise physiologists have chosen to pursue other techniques to measure cardiac output in healthy individuals (Warburton et al., 1999a).

Research trends in this area have been towards the use of non-invasive measures of cardiac output, minimizing discomfort and risk to the subject. The advantages of such techniques are primarily for the subject's benefit, but also in the ability to measure cardiac output at differing intensities of exercise without the cumbersome and somewhat risk-involved methods of catheterization. Three techniques in particular have gained broad acceptance and use in the field of exercise physiology. These include foreign gas (acetylene) rebreathing methods, indirect Fick carbon dioxide (CO_2) rebreathing methods, and echocardiography.

Investigations into the use of CO_2 rebreathing for the measurement of cardiac output began in the early 20th century (Klausen et al., 1965). With increased availability of direct techniques, CO_2 rebreathing fell out of favor, until interest was again piqued in

the 1950's and 1960's, coinciding with the advent of rapid CO_2 analysis using infrared meters. The CO_2 rebreathing technique has been shown to be a valid and reproducible method for measuring cardiac output with relatively low methodological errors (CV = 3-5%, Clausen et al., 1970). Correlation coefficients when compared to direct techniques range from r = 0.65 at rest to r = 0.96 during submaximal exercise (Klausen et al., 1965; Wigle et al., 1979; Beekman et al., 1984; Marks et al., 1985; Reybrouk & Fagard, 1990). The reproducibility of the technique has been studied in individuals of varying age and gender, and a high correlation (r = 0.93) has been reported between tests done on two different days in both males and females (Klausen, 1965; Ferguson et al, 1968; Muiesan et al., 1968; Clausen et al., 1970; Wigle et al., 1979; Wilmore et al., 1982; Reybrouk & Fagard, 1990). However, the CO_2 rebreathing technique requires that subjects achieve steady-state conditions, which can become problematic near maximal exercise. Also, the technique is uncomfortable to perform during exercise due to rebreathing high concentrations of CO_2 (Muiesan et al., 1968). Rebreathing high CO_2 concentrations can result in increases in arterial P_{CO_2} (Pa_{CO_2}) and changes in arterial P_{O_2} (Pa_{O_2}), which can lead to fluctuations in cardiac output (Barker et al., 1999). Thus, the CO_2 rebreathing technique is limited in use to submaximal exercise below ventilatory threshold II.

The acetylene (C_2H_2) rebreathing technique was developed by Grollman (1929). It is based upon the Fick principle applied to physiologically inert gases, where the rate of alveolar-capillary transfer of a soluble gas is assumed to be proportional to pulmonary capillary blood flow (Borstein, 1910; Krogh & Lindhard, 1912). This technique has been shown to give accurate and reliable measurements of cardiac output from rest to maximal exercise, with correlation coefficients ranging from r = 0.78 to 0.95 when compared to

direct methods (Chapman et al., 1950; Asmussen & Nielsen, 1952, Triebwasser et al., 1977; Smyth et al., 1984; Nystrom et al., 1986; Hsia et al., 1995; Liu et al, 1997). However, as in CO_2 rebreathing, the C_2H_2 rebreathing technique can result in to increases in Pa_{CO_2} and changes in Pa_{O_2} which may in themselves alter cardiac output. As well, during high intensities of exercise, the change in Pa_{CO_2} and Pa_{O_2} can lead to subject discomfort and dyspnea. Thus, the use of rebreathing techniques during exercise, be it CO_2 or C_2H_2, can be problematic, particularly at near-maximal levels.

Doppler echocardiography has been used to measure cardiac output at all levels of intensity, from rest to maximal exercise. The use of echocardiography for measuring cardiac output began in the 1950's, with the introduction of the Doppler technique in the 1980's (Huonker et al., 1996). The Doppler method has been compared with invasive measures of cardiac output and has been reported to provide reasonable estimates at rest. Lewis et al. (1984) reported correlations of $r = 0.95$ when comparing Doppler echocardiography with thermodilution. However, difficulties in using the Doppler technique other than at rest become manifest with progressive intensities of exercise (Warburton et al., 1999b). The technique requires trained personnel, and there can be high inter-rater variability. It is also applicable for only 80-90% of the population (Shaw et al., 1985) due to factors such as aortic stenosis, tortuous aortas, chronic pulmonary disease, and obesity, among others. Huntsman et al. (1983) found that successful measurements could be made in only 85-90% of their patient population, even after excluding for aortic stenosis, aortic insufficiency, and prosthetic valves. During exercise, it is often difficult to achieve quality ultrasound signals due to interference from rapid lung movement (Shaw et al., 1985). Thus, for researchers intending to investigate

cardiac output in a minimally invasive manner during exercise to maximal intensities, a need has been established for a procedure that is valid, reliable, and imposes minimal to no encumbrance to the subject or patient. Recently, hope of fulfilling this need has been seen in the development of non-rebreathing acetylene techniques for the determination of cardiac output.

The acetylene breathing measures do not require the attainment of steady-state, a benefit at near-maximal levels, such that simultaneous readings of cardiac output and $\dot{V}O_2$ can be obtained during a test, leading to a more concise picture of how an athlete or patient is functioning during exercise. These new techniques examine the rate of uptake of acetylene by the lungs into the blood stream. This rate of uptake can provide an estimate of pulmonary blood flow, which is equal to the volume of blood ejected by the left ventricle during the same unit of time.

There are two non-rebreathing techniques currently being used. The first (open-circuit acetylene uptake) involves subjects breathing a mixture of known gases and the rate of uptake of acetylene is measured with a mass spectrometer. In the second technique (single-breath constant exhalation acetylene uptake) subjects inhale a known concentration of gases to vital capacity, exhale at a constant rate, and the rate of acetylene uptake is measured.

Initial investigations of the open-circuit method have produced accurate measurements of cardiac output in humans at all levels of exercise when compared to the direct Fick method, without requiring the subjects to rebreathe a gas mixture (Barker et al., 1999; Card et al., 1996; Johnson et al., 2000). Barker et al. (1999) reported no statistically significant difference between measures of cardiac output by the Fick and

C_2H_2 uptake techniques (r = 0.93). Johnson et al. (2000), using two different methods of open circuit analysis (called OpCirc1 and OpCirc2) showed R^2 values for each technique of 0.90 and 0.89, respectively, when compared to direct Fick measurements. The mean differences (±SD) between the techniques were −1.5 ± 2.0 and −0.5 ± 1.9 $l \cdot min^{-1}$ for OpCirc1 vs. Fick and OpCirc2 vs. Fick, respectively. When compared to acetylene rebreathing, the open circuit technique was highly correlated (r = 0.974, Card et al., 1996).

Investigations of the single-breath constant exhalation acetylene uptake have reported high correlations with both direct Fick and thermodilution at rest (Elkayam et al., 1981; Zenger et al., 1993). Elkayam et al. (1981) reported mean differences between the single-breath technique and thermodilution at rest of 0.03 ± 0.76 $l \cdot min^{-1}$, and a single-breath coefficient of variation of 9%. Similar values were obtained by the single-breath technique when compared to acetylene rebreathing (Thomas et al., 1997). However, the authors found that the single-breath technique tended to underestimate cardiac output at rest, and some subjects were unable to perform the constant flow exhalation at higher intensities. Despite these issues it was concluded that the single-breath technique reliably measured cardiac output across moderate to heavy intensities.

Statement of Problem

At present, few studies have investigated the use of non-rebreathing, acetylene uptake techniques to determine cardiac output. Both the open-circuit acetylene uptake technique and the single-breath constant exhalation technique show promise in being both non-invasive and non-intrusive measures. Additional research is required to confirm the

validity of the techniques, as well as assess the reliability of the measures. Thus, further research should be conducted to quantify the sensitivity of both acetylene uptake methods, and the reliability of the resultant data. There has been limited research comparing the two new acetylene uptake methods with other non-invasive measures of cardiac output.

Statement of Purpose

The purposes of this study were: 1) to assess the reliability of the two acetylene uptake techniques for the measurement of cardiac output; and 2) to compare the two non-invasive, non-rebreathing acetylene uptake methods with previously established CO_2 rebreathing.

Statement of Research Hypothesis

a. It was hypothesized that there would be no difference between measures of cardiac output using open-circuit acetylene uptake, single-breath constant exhalation acetylene uptake, and carbon dioxide rebreathing at any level of intensity. Furthermore, with the additional measure by echocardiography, there would be no differences between the measures at rest.
b. It was hypothesized that there would be no intra-variation in the repeated measures of open-circuit acetylene uptake and single-breath constant exhalation acetylene uptake at any level of intensity.

CHAPTER 2: REVIEW OF LITERATURE

2.1 Cardiac Output Physiology

Cardiac output is precisely adjusted so that peripheral tissues receive an adequate circulatory supply under a variety of conditions. Cardiac output is controlled by four factors: heart rate (HR), myocardial contractility, preload, and afterload. Heart rate and myocardial contractility may be termed *cardiac factors*, in that they are characteristics of the cardiac tissues. Heart rate is defined as the number of contractions by the heart per unit time, usually expressed as beats per minute ($b \cdot min^{-1}$). Myocardial contractility is an expression of cardiac performance at a given preload and afterload. It is the change in peak isometric force at a given initial fiber length (Fozzard et al., 1986). Preload is the stretch of the myocardial fiber by the venous return during ventricular filling, and afterload is the aortic pressure against which the left ventricle ejects the blood (Thompson, 1984). Preload and afterload are important determinants of cardiac output, but are in themselves influenced by cardiac output. Thus, preload and afterload are designated *coupling factors*, as they constitute a functional coupling between the heart and blood vessels (Berne & Levy, 1992). Myocardial contractility, preload, and afterload are essentially the contributing factors to stroke volume (SV – the volume of blood ejected per beat), thus, the two major determinants of cardiac performance can be simplified to stroke volume and heart rate (i.e., $\dot{Q} = SV \times HR$) and the quantity of blood pumped by the heart can be varied by changing either of these two factors. When necessary, stroke volume in a normal heart can almost double, and heart rate can increase by up to 250 percent. Therefore, an investigation of cardiac output can be subdivided

into a review of the pacemaker activity and the regulation of myocardial performance (Berne & Levy, 1992).

Heart Rate

The control of heart rate (chronotropic regulation) is performed principally by the autonomic nervous system, further broken down into the sympathetic and parasympathetic divisions (Dampney, 1994). The myocardium is unique in the sense that it will regularly depolarize in rhythmical fashion in the absence of outside neural influence. The natural pacemaker region of the heart, the sinoatrial (SA) node has an intrinsic depolarization rate on average of 100 $b \cdot min^{-1}$. The SA node is usually under the tonic influence of both divisions of the autonomic nervous system. Simply put, the sympathetic system enhances heart rate, and the parasympathetic inhibits it, by affecting the electrochemical properties of the pacemaker potential. Control of heart rate involves the reciprocal action of the two divisions: an increase in heart rate is accomplished by an increase in sympathetic tone, and a concomitant decrease in parasympathetic tone. Decrease in heart rate is accomplished by the reverse mechanism.

Cardiac sympathetic fibers originate in the intermediolateral columns of the upper five or six thoracic and lower one or two cervical segments of the spinal cord. The postganglionic cardiac sympathetic fibers are distributed to the various chambers of the heart from the base, penetrating the myocardium. This arrangement allows the sympathetic system to have an influence on both heart rate and myocardial contractility. The sympathetic system utilizes adrenergic neurotransmitters (e.g. norepinephrine and epinephrine), which have a relatively slow removal process compared to acetylcholine

utilized by the parasympathetic system. Thus, sympathetic activity alters heart rate much more slowly than vagal activity, and cannot exert a beat-by-beat control of cardiac function (Karpman, 1987).

Cardiac parasympathetic fibers originate on the medulla oblongata, and are communicated to the heart via the vagus nerve. The right branch of the vagus predominantly affects the SA node, while the left vagus branch mainly affects atrioventricular (AV) tissue conduction. The neurotransmitter utilized is acetylcholine. As both the SA and AV nodes are high in cholinesterase, and the potassium ion (K^+) channels activated by acetylcholine are very prompt, the vagus nerve can potentially provide a beat-by-beat control of SA and AV nodal function (Berne & Levy, 1992).

Stroke Volume

Stroke volume control is mitigated by altering either preload or afterload of the heart, or by affecting myocardial contractility. An increase in preload increases stroke volume; an increase in afterload results in a decrease in stroke volume; and an increase in contractility produces an increase in stroke volume (Berne & Levy, 1992). Changes in preload may be accomplished by affecting venous return to the heart. This is a product of the functional relationship between cardiac output and central venous pressure. Increases in right atrial pressure increase ventricular filling, which results in increases in the load on the myocardial fibers just prior to contraction (preload). This increase in preload results in a more forceful contraction by the cardiac muscle, and the measurable force increase is known as the Frank-Starling mechanism (Berne & Levy, 1992).

Increases in preload are accomplished by increases in blood volume, which can cause increased end-diastolic filling of the ventricles (Krip et al., 1997). Any factor that increases venous return or slows the heart produces greater ventricular filling during the diastolic phase of the cardiac cycle (Karpman, 1987). Hypervolemia is associated with increased ventricular filling and increased stroke volume (Hopper et al., 1988). Greater ventricular filling is referred to as an increase in end-diastolic volume (EDV). Increased EDV causes increases in stroke volume by the Frank-Starling effect (Convertino, 1991), where pre-stretch of the myocardial fibers initiates a powerful contraction during ejection. The effect of the Frank-Starling effect was demonstrated by Coyle et al. (1986), where detraining that resulted in a relative loss in blood volume (hypovolemia) caused a concomitant decrease in stroke volume and increase in heart rate to maintain the same cardiac output at the same level of exercise.

Changes in afterload are accomplished by affecting total peripheral resistance, arterial compliance, and peripheral arterial pressure. Chronic and acute hypertension (produced by vasoconstriction and/or decreased compliance of the vessels) can lead to increases in diastolic pressure, creating a greater load against which the ventricle needs to contract. Further increases in afterload can lead to a situation of decreased volume ejection, and ultimately heart failure.

Augmentation of contractility is observed by the administration of certain drugs, such as norepinephrine or digitalis, and with increases in contraction frequency (tachycardia). This increased contractility is termed a *positive inotropic effect* (Berne & Levy, 1992). The postganglionic cardiac sympathetic fibers that are distributed to the various chambers of the heart from the base, penetrating the myocardium, utilize

epinephrine and norepinephrine as neurotransmitters. Thus, the sympathetic system has an influence on both heart rate and myocardial contractility. These adrenergic neurotransmitters bind to β_1 receptors on the sarcolemma of the myocardial fibers and cause an increase in cyclic adenosine monophosphate (cAMP), which in turn increases lipolysis, the phosphorylation of myosin light chains, and the increased cycling velocity of the myosin-actin contraction mechanism (Robergs & Roberts, 1997). Additionally, stimulatory G proteins simultaneously increase the conductance of calcium across the membrane, which further aids myocardial contraction velocity and force. Clinically, the ratio of the volume of blood ejected from the left ventricle per beat to the volume of blood in the left ventricle at the end of diastole (known as ejection fraction) is widely used as an index of contractility.

Cardiac Output During Exercise

Cardiac output may double or triple in volume during moderate levels of exercise, and these higher levels of cardiac output are sustained throughout the duration of the exercise bout. Thus, the processes activated during physical exercise elicit a substantial and sustained volume overload challenge to the heart (Dowell, 1983). Cardiac output increases in a linear relationship with exercise intensity, as blood flow increases in proportion to the intensity of exercise. Average resting levels for cardiac output have been described as being approximately 5 $l \cdot min^{-1}$ for males, with ratio increases being in the range of 5:1 to 6:1 when being plotted vs. oxygen consumption (Astrand et al., 1964; Barker et al., 1999). Figure 1 shows the relationship between cardiac output and oxygen consumption.

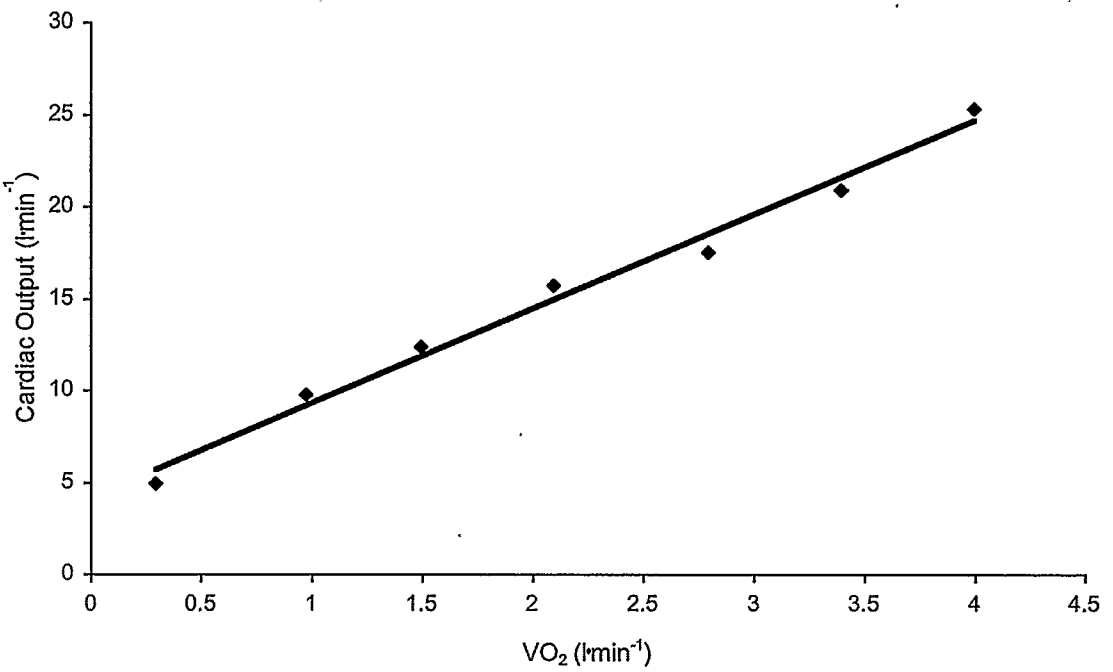

Figure 1. Linear relationship between oxygen consumption and cardiac output (Astrand et al., 1964).

The cardiovascular adjustments that occur during exercise arise from the combination of both neural and local (chemical) factors (Berne & Levy, 1992). The neural factors consist of (a) central command; (b) reflexes originating in contracting muscles; and (c) baroreceptor reflexes. Central command originates from cerebralcortical activation of the sympathetic nervous system. Activation of the sympathetic nervous system results in an increase in heart rate (HR), an increase in contractile force of the myocardium (contractility), and an increase in peripheral vasoconstriction. The increased vasoconstriction of the resistive vessels of the skin,

splanchnic regions, and non-working muscles provides a shunting effect, diverting blood away from these areas and making it available for the working muscles.

The reflexes originating in the contracting muscles are activated by stimulation of mechanoreceptors (stretch and tension sensitive), and chemoreceptors (sensitive to the byproducts of metabolism). These reflexes further serve to increase sympathetic activity (Karpman, 1987).

The baroreceptor reflex originates in stretch receptors located in the carotid sinus and aortic arch. When activated by stretch of the vessel (induced by increased arterial pressure), receptors in the carotid sinus send an afferent signal conducted up the nerve of Hering to the glossopharangeal nerve, by which it is conducted to the nucleus of tractus solitarius (NTS). Baroreceptors in the aortic arch act in a similar manner, conducting information to the NTS by way of the afferent fibers of the vagus nerve. Stimulation of the NTS results in a decrease in sympathetic activity and an increase in vagal activity. This activation serves to result in vasodilation and bradycardia.

Metabolic (or local chemical) regulation asserts that local blood flow is governed by the metabolic activity of the tissue. That is, if O_2 supply is inadequate for tissue demands, vasodilator metabolites are released. These vasodilator metabolites act locally to dilate the resistance vessels. Though the exact mechanism by which this accomplished is unknown, proposed contributors to this increased blood flow (active hyperemia) include potassium ions, inorganic phosphate, interstitial fluid osmolarity, decreased pH, and adenosine (Karpman, 1987).

Heart rate during exercise

The onset of exercise is associated with a near simultaneous sympathetic stimulation of the SA node, AV node, and ventricular myocardium (Robergs & Roberts, 1997). Heart rate is also affected by increased metabolic activity, though in the early stages increases in HR are predominantly due to sympathetic activity (Hollander & Bouman, 1975). The increase in heart rate accompanies an increase in sympathetic tone to the SA node, and a concomitant decrease in parasympathetic tone. This is a feed-forward, central-command mediated, vagal withdrawal. Heart rate may also be increased immediately prior to the onset of exercise due to the anticipatory effect. The increase in HR, combined with increases in stroke volume, increases arterial blood pressure, which may invoke the baroreceptor response, leading to a decrease in HR. However, the baroreceptor reflex is temporarily reset to a higher threshold, allowing HR and blood pressure to increase without opposition (Brown, 1980). When heart rate is plotted vs. intensity, the relationship appears to be linear at submaximal workloads, though on the whole, the relationship tends to be curvilinear with a flattening of the curve at near maximal levels. There can be wide individual variation in the slope of the heart rate-intensity curve.

Stroke Volume during exercise

In physical exercise, significant increase of muscular blood flow, together with the forcing work of "the muscular pump", the decrease of the intrathoracic pressure, and the increased tone of the capacitive vessels results in the increased and quickened venous return. This is categorized as an increase in preload. As a result of this, during the diastolic period the widening of the ventricular cavity takes place, and due to this the

ventricular contraction becomes more intensive and stroke volume increases according to the Frank-Starling mechanism (Karpman, 1987).

During dynamic exercise, the total peripheral resistance decreases, and diastolic blood pressure remains relatively unchanged. Thus, afterload does not have a great influence on stroke volume in a healthy individual. However, the remarkable plasticity of the heart can be demonstrated during periods of increased afterload. The Anrep phenomenon (Sarnoff et al., 1960, as cited in Karpman, 1987) is characterized by the fact that stroke volume will adapt to remain unchanged despite an increase of blood ejection resistance. This phenomenon will occur without a change in ventricular dimension, though the mechanism is not clear.

Increases in myocardial contractility (characterized by strengthening cardiac contractions at a given initial fiber length) can be seen in response to a quickening of the heart rate, called the Bowditch effect (Karpman, 1987). In essence, this phenomenon of a stronger cardiac contraction is postulated to occur because of "post-systolic potentiation". In tachycardia, where heart rate exceeds 170-180 $b \cdot min^{-1}$, relaxation of the myocardium can be incomplete (i.e., the increased tension of the myocardial fibers remains) and each successive contraction of the ventricles appears to be relatively strengthened. The mechanism of intensification may be explained by the shortened diastolic period resulting in an incomplete calcium yield from the muscular fibers, and this increased concentration of calcium in the myoplasma causes an inotropic effect.

Stroke volume responses during exercise may be generally classified into one of three categories: (1) initial increase followed by sustained plateau; (2) initial increase, followed by decrease at higher intensities, and; (3) continual increase up to max (Gledhill

et al., 1994; Zhou et al., 2001) (Figure 2). It has been widely accepted that during incremental work, stroke volume reaches a plateau at submaximal heart rates (Gledhill et al., 1994), and the majority of healthy individuals tested would fall into category (1). This plateau of stroke volume has been demonstrated to occur between 40-60% of $\dot{V}O_2$ max (Astrand et al., 1964; Ekblom & Hermansen, 1968; Hopper et al., 1988; Zeidfard et al., 1972; Di Bello et al., 1996). Physiologically, the basis for this phenomenon is the presence of a large basal-reserve volume of blood (Karpman, 1987). As exercise intensity increases to approximately 40-60% of maximum, the basal-reserve volume of the blood is consecutively included into the stroke volume. At higher intensities, the progressively diminishing time available for diastolic filling limits stroke volume, causing it to plateau. A further increase in intensity above 40-60% is either not accompanied by an increase in stroke volume, or the increase is insignificant.

In some conditions, a decrease in stroke volume may be observed at higher workloads (category 2). At low intensities, the stroke volume increases in accordance with increases in workload. However, with a further increase of the intensity, the value of the stroke volume begins to fall, approaching initial values. This type of adaptation is not favourable in athletes. Generally, this condition would occur in situations of poor fitness or cardiovascular disease. Spina et al. (1992), measuring cardiac output by the C_2H_2 rebreathing method, showed that stroke volume declined during incremental exercise in sedentary adults, whereas endurance training prevented the decline in stroke volume in the same subjects following a 12-week exercise program. In situations of low total blood or plasma volumes, the diminished diastolic filling time at high heart rates

leads to the decrease in stroke volume. Increases in myocardial contractility are either not present, or not sufficient to compensate for the poor end-diastolic volume.

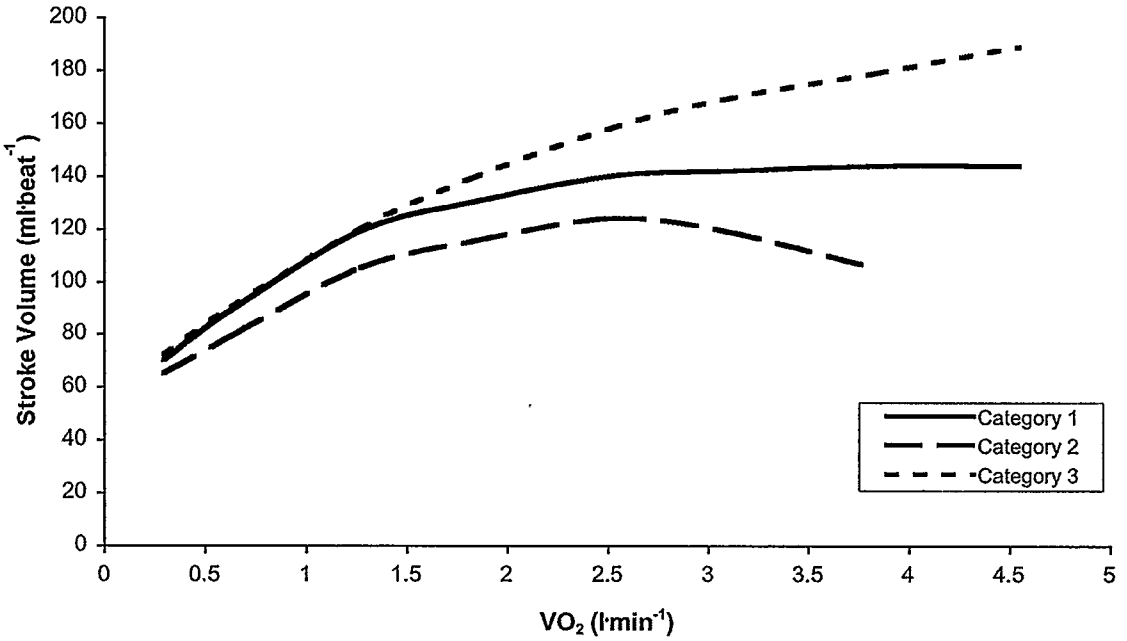

Figure 2. Three typical responses of stroke volume to increases in exercise intensity. Category 1 demonstrates the classic model of increase and plateau. Category 2 demonstrates the case where stroke volume may decrease at higher intensities. Category 3 demonstrates the recent research that in elite endurance athletes stroke volume does not plateau, but continues to increase up to maximal levels of exercise (Janicky, 1990; Gledhill et al., 1994).

Recently, research has been conducted which has shown evidence of stroke volume continuing to increase all the way to maximal levels in elite endurance athletes (Gledhill et al., 1994, Zhou et al., 2001). Despite the recent attention to this area, this is not a new phenomenon, as work by Ekblom & Hermansen in 1968 showed that in highly trained endurance athletes, 9 out of 13 subjects reached maximal stroke volume at maximal exercise. Gledhill et al. (1994) demonstrated that in elite cyclists, there was no plateau of stroke volume, while active males in the same study showed the classic plateau

at 40-60% of max. This finding was also shown by Zhou et al. (2001) using elite male distance runners. The proposed mechanism for this phenomenon was that the elite athletes rely on augmentations in both ventricular emptying and, perhaps more importantly, ventricular filling (Gledhill et al., 1994). However, what remains unclear is whether the continued increase in stroke volume with increasing intensity of exercise in elite endurance athletes is an adaptation to training, a consequence of genetics, or a combination of both (Zhou et al., 2001). The studies in this area have been cross-sectional, and thus causality of the adaptation is unknown.

Cardiovascular adaptations to exercise

Prolonged and repeated exposures to exercise cause structural and functional changes in the cardiovascular system. The type and magnitude of change is dependent upon the training stimulus, with differing results occurring for endurance training vs. strength training. Several cardiovascular adaptations have been identified and attributed to the influence of endurance exercise training. These effects are summarized in Figure 3.

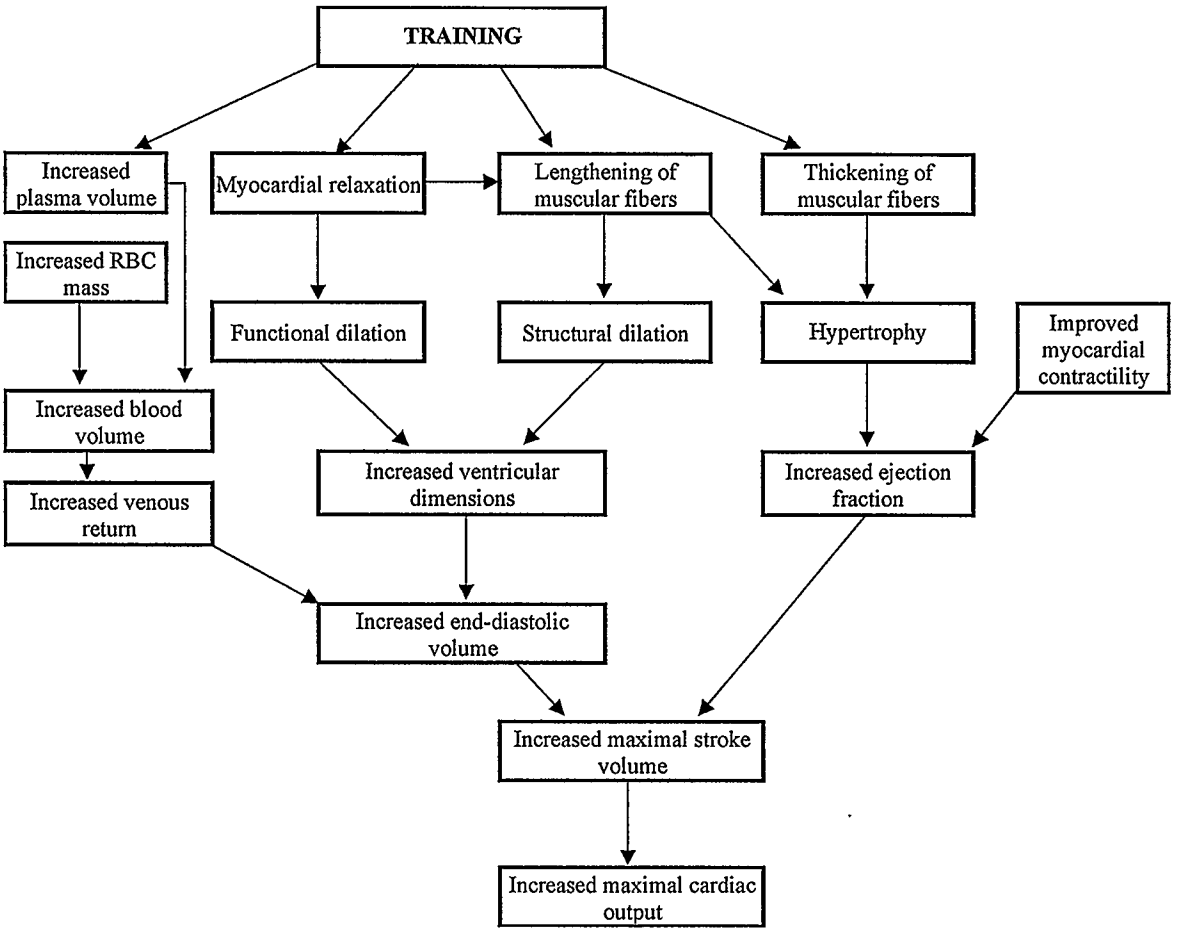

Figure 3. Summary of the effects of endurance training on the cardiovascular system.

When sedentary subjects have been compared to endurance-trained athletes, significant differences can be seen in maximal cardiac output, heart rate and stroke volume. In sedentary individuals, cardiac output increases on average about four times the resting level to a value of 20 to 22 $l \cdot min^{-1}$, and heart rate in these young adults usually averages about 195 $b \cdot min^{-1}$ (Saltin, 1969). Therefore, the stroke volume is generally in the range of 100-120 $ml \cdot beat^{-1}$ in maximal exercise. However, world-class endurance athletes have had maximal cardiac output values measured at 35 to 40 $l \cdot min^{-1}$ (Ekblom & Hermansen, 1968; Gledhill et al., 1994). These cardiac outputs are generally reached

with heart rates slightly lower than the untrained individuals. Therefore, the large increases in cardiac output achieved by endurance training are most often due to significant increases in stroke volume. When plotting cardiac output vs. oxygen consumption, the comparison between normal populations and elite endurance athletes has shown that for a given $\dot{V}O_2$, cardiac output is higher for the endurance athlete (Barker et al., 1999; Gledhill et al., 1994). This relationship is shown in Figure 4.

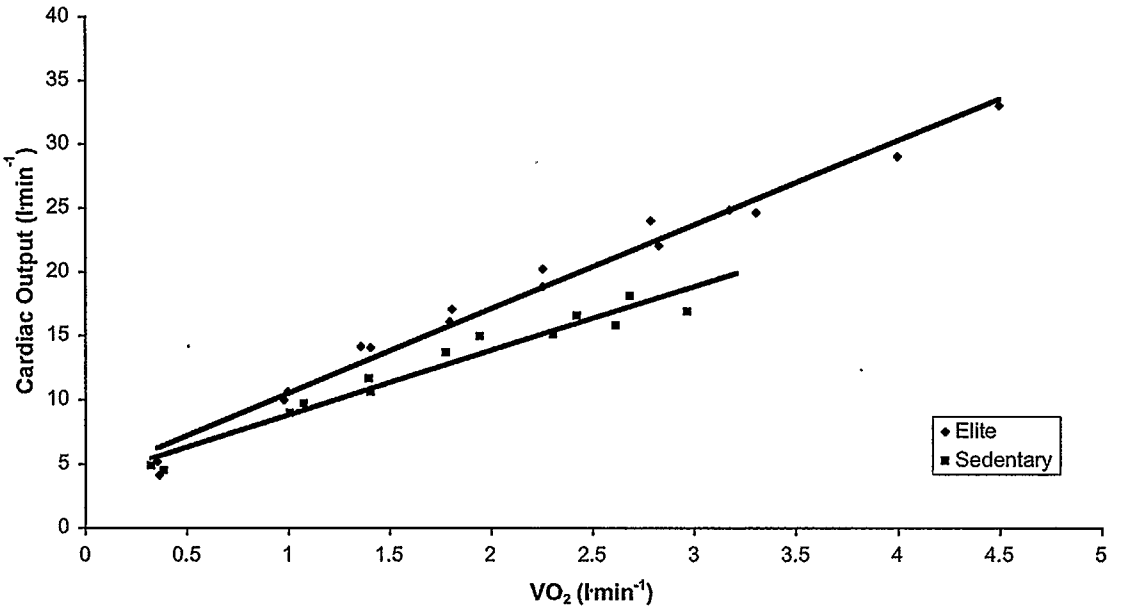

Figure 4. Differences in the cardiac output-oxygen consumption relationship between sedentary subjects and elite endurance athletes (Barker et al., 1999; Gledhill et al., 1994).

Heart rate response to endurance training

Training effects of chronic endurance exercise are noted by a decrease in exercising heart rate at a given workload. The relationship between heart rate and oxygen consumption is illustrated in Figure 5.

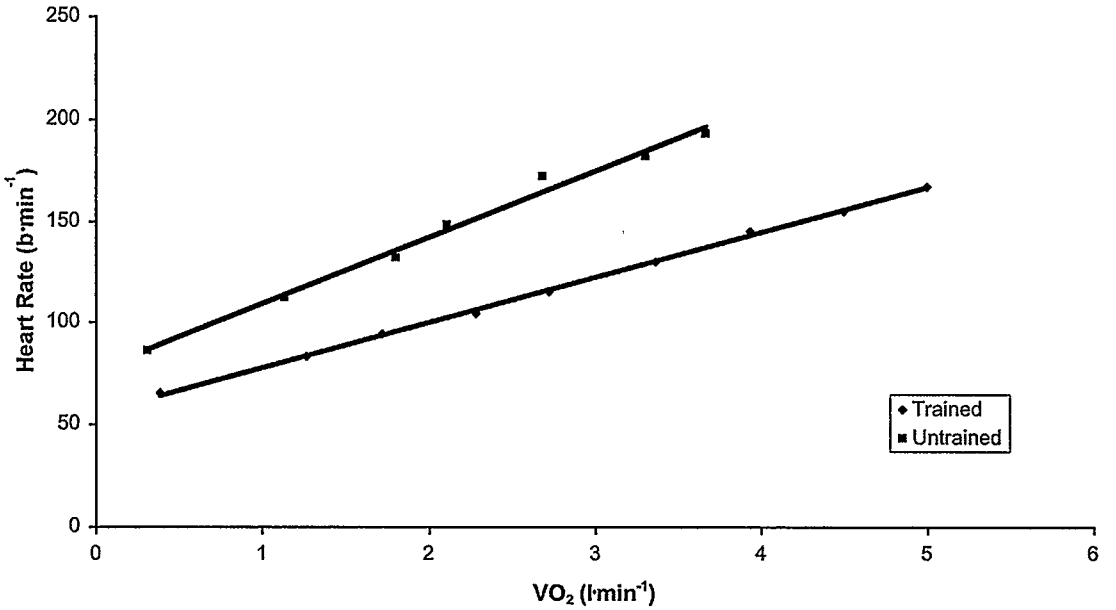

Figure 5. Heart rate-oxygen consumption relationship showing post-training adaptation. Heart rate is lower at any given intensity for trained vs. untrained subjects (Coyle et al., 1986).

These relationships are essentially linear for both groups throughout the major portion of the work range, though tending towards a curvilinear relationship at near maximal levels. Wilmore et al. (2001), in the HERITAGE family study of 631 subjects, found that heart rate decreased significantly at the same workload after approximately 20 weeks of endurance training. Of interest, the heart rate response for elite athletes is not only lower in magnitude than their sedentary counterparts, but the *rate* of increase (that is, the slope of the rate of change) is lower as well. Change in the slope of the HR-$\dot{V}O_2$ relationship is an area that is generally not well understood, though contributors may involve the efficiency and economy of movement, as well as interplay between cardiac output and the arterial-venous oxygen difference (a-$\overline{v}O_2$diff). Sunagawa et al. (1984) suggested that the slope of the HR-$\dot{V}O_2$ relationship was related to the inotropic state of cardiac function.

Stroke volume response to endurance training

Endurance training has been shown to increase stroke volume. The endurance athlete's heart has a considerable larger stroke volume during both rest and exercise than an untrained person of the same age (Figure 6).

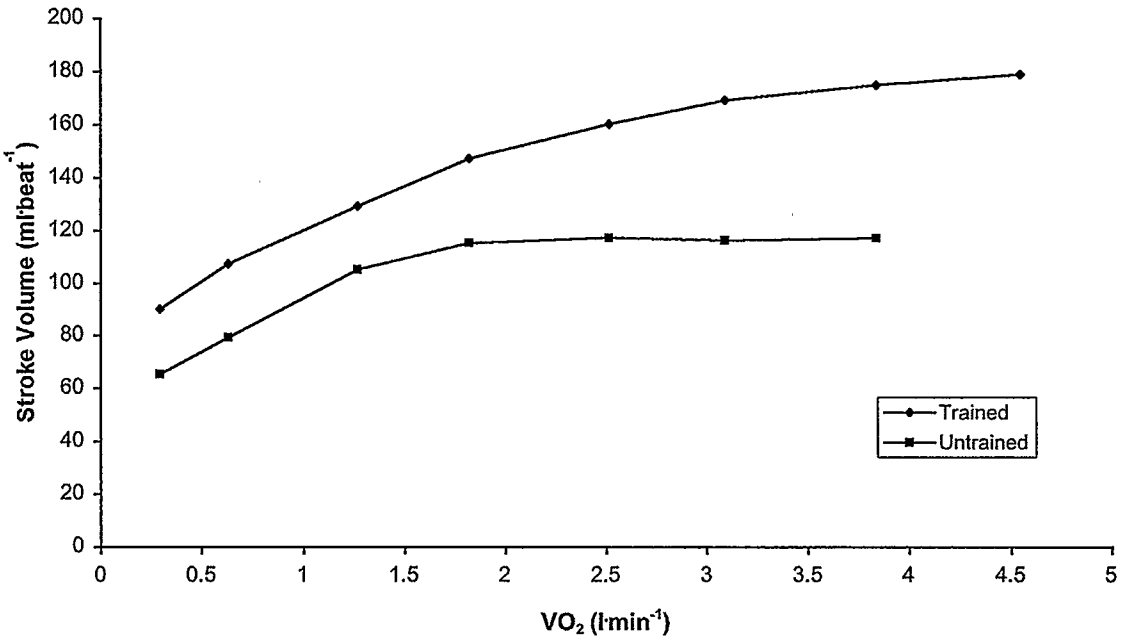

Figure 6. Effect of training on stroke volume. Endurance training can lead to chronic increases in stroke volume for any given intensity (Schairer et al., 1992).

Wilmore et al. (2001) showed a significant increase in stroke volume at the same workload after 20 wks of endurance training, as well as an increased maximal stroke volume. Data from cross-sectional studies of cardiac dimension and capacities indicate that heart dimensions and end-diastolic volumes are greater in endurance athletes than sedentary subjects or athletes involved in activities of a short duration (Robergs & Roberts, 1997; Spirito et al., 1994; Fagard, 1997). Endurance training has been shown to elicit increases in cardiac mass and function in previously sedentary individuals (Shapiro,

1997; Spirito et al., 1994; Fagard, 1997), and left ventricular end-diastolic volume (LVEDV) can increase after 9-weeks of endurance training (Cox et al., 1986). This larger LVEDV is associated with an increased stroke volume for a given submaximal exercise intensity (Robergs & Roberts, 1997).

To capitalize on increases in left ventricular dimension, increases in blood volume (specifically plasma volume) also occur as a result of endurance training. Increases in red blood cell counts and total hemoglobin also occur, but their concentration relative to the total blood volume actually decreases, due to the diluting effects of the relatively larger increases in plasma volume (Robergs and Roberts, 1997; Manning & Guyton, 1982). Increases in plasma volume have been shown to occur after just one intense intermittent exercise session. Gillen et al. (1991) reported that a single high intensity exercise session induced a 10% increase in plasma volume after 24 hours. Chronically, training induced increases in plasma volume have been attributed to an increase in plasma albumin, and these increases have been reported between 300-800 ml (Coyle et al., 1986; Convertino, 1991). The primary benefit of an increase in plasma volume is an increase in venous return to the heart, resulting in a greater end-diastolic volume. This increased end-diastolic volume (i.e., greater preload) increases stroke volume as predicted by the Frank-Starling mechanism. Gledhill et al. (1994) suggested that the increase in blood volume of elite endurance athletes was the major contributor to their enhanced ventricular function. Also assisting venous return in elite athletes is a decrease in intrathoracic pressure as a result of higher ventilation rates.

Elite endurance athletes also show a greater systolic emptying rate when compared to normal and sedentary subjects (Gledhill et al., 1994). It is generally

accepted that both sedentary and trained subjects increase stroke volume during exercise by greater ventricular emptying during systolic contraction. This is accomplished by the action of the sympathetic neurotransmitters epinephrine and norepinephrine, which produce an augmented contraction. In endurance-trained subjects, the contractile state of the myocardium itself is enhanced, and this improves its capabilities for achieving a larger stroke volume (Karpman, 1987).

As outlined previously, recent research has been conducted which has shown evidence of stroke volume continuing to increase all the way to maximal levels in elite endurance athletes (Gledhill et al., 1994, Zhou et al., 2001). This was proposed to occur by augmentations in both ventricular emptying and ventricular filling (Gledhill et al., 1994). It should be noted that these studies investigating this area have been based upon cross-sectional design, and this type of design is biased by potential genetic differences that have caused individuals to select certain exercise modes and intensities (Robergs & Roberts, 1997). Thus the cause-and-effect relationship may not been fully explained – that is, does elite level endurance training produce these adaptations, or does the genetic ability to increase stroke volume up to maximal intensities of exercise naturally select individuals for elite performance?

2.2 Cardiac Output Measurement

There can be significant intervariation in cardiac output from person to person as a result of health, genetics, and training status, as well as intravariation of cardiac output within an individual depending on fitness and/or disease. This, combined with the knowledge that cardiac output is a key determinant of arterial blood pressure and systemic oxygen

transport, leads to the conclusion that the ability to measure cardiac output precisely and reliably is often of critical importance to provide insight into the regulation of human cardiovascular and metabolic functions (Hunt et al., 1997).

Gold Standard Measurements of Cardiac Output

The "gold standard" for measurement of cardiac output is the direct Fick method, based upon the Fick principle. This principle is an application based upon the law of conservation of mass. It is derived from the fact that the quantity of oxygen delivered to the pulmonary capillaries via the pulmonary artery, plus the quantity of oxygen that enters the pulmonary capillaries from the alveoli must equal the quantity of oxygen that is carried away by the pulmonary veins.

As outlined by Berne & Levy (1992), the rate, r_1, of oxygen (O_2) delivery to the lungs equals the O_2 concentration in the pulmonary arterial blood, $[O_2]_{pa}$, times the pulmonary arterial blood flow, $\dot{Q}$, which equals cardiac output; that is:

$$r_1 = \dot{Q}\,[O_2]_{pa}$$

Then, when r_2 is the rate of O_2 uptake by the pulmonary capillaries from the alveoli, at equilibrium, r_2 equals the oxygen consumption of the body. Thus:

$$r_2 = \dot{V}O_2$$

The rate at which O_2 is carried away by the pulmonary veins, r_3, is equal to the O_2 concentration in the pulmonary venous blood, $[O_2]_{pv}$, multiplied by the total pulmonary venous flow, which is essentially equal to the pulmonary arterial blood flow, $\dot{Q}$; that is:

$$r_3 = \dot{Q}\,[O_2]_{pv}$$

From the law of conservation of mass:

$$r_1 + r_2 = r_3$$

Therefore,

$$\dot{Q}[O_2]_{pa} + \dot{V}O_2 = \dot{Q}[O_2]_{pv}$$

Solving for cardiac output:

$$\dot{Q} = \dot{V}O_2 / ([O_2]_{pv} - [O_2]_{pa})$$

The equation is also commonly seen as:

$$\dot{Q} = \dot{V}O_2 / (a - \bar{v}O_2 diff)$$

where:

$\dot{Q}$ = cardiac output in liters per minute ($l \cdot min^{-1}$)

$\dot{V}O_2$ = oxygen consumption in liters per minute ($l \cdot min^{-1}$)

$a - \bar{v}O_2 diff$ = arterial-venous oxygen content difference in $ml \cdot l^{-1} \cdot 100^{-1}$

Clinically, cardiac output is determined by direct measurements of these variables. $\dot{V}O_2$ is computed by direct, open circuit measurement of oxygen consumption by the body during steady-state conditions, as equilibrium is required for the assumption that the rate of O_2 uptake by the pulmonary capillaries from the alveoli is equal to $\dot{V}O_2$. This is accomplished using a metabolic measuring cart or Douglas bag technique. Arterial O_2 concentration is determined by a sample of peripheral arterial blood drawn by needle puncture. O_2 concentration in the peripheral arteries is essentially identical to that in the pulmonary veins (Berne & Levy, 1992). The mixed venous O_2 concentration is determined by a blood sample taken from within the pulmonary artery. This is the point where true venous mixing occurs, since venous blood levels of O_2 vary in different

regions of the body, due to differences in metabolic activity (Warburton et al., 1999a). Previously, this was accomplished by using a very stiff catheter and fluoroscopic guidance, though now a very flexible catheter with a small balloon near the tip can be inserted into a peripheral vein. Blood flow advances the tube towards the heart. By following pressure changes, the tester is able to advance the catheter tip into the pulmonary artery without the aid of fluoroscopy.

The direct Fick method is an invasive and risk-involved technique, and it is cumbersome for use during exercise. The necessity to achieve steady-state makes its use at near maximal levels very difficult, not to mention the difficulties of exercising with a central line in place. The technique requires highly trained personnel to perform what is a very precise technique, and if not meticulously carried out, the accuracy of its estimates is generally worse than that achieved by other methods (Darovic, 1995, as cited in Warburton et al., 1999a). When performed correctly, the direct Fick technique is highly repeatable, with the standard error of measurement on repeated tests 5% or lower (Holmgren & Pernow, 1960). The risks associated with cardiac catheterization, though relatively low, include ventricular arrhythmias and fibrillation, and perforation of the pulmonary artery or right ventricle. It has been postulated that if true steady-state conditions can be achieved the direct Fick method will give exact measures of cardiac output (Warburton et al., 1999a). As these conditions are rarely achieved during incremental to maximal exercise, a certain amount of error in estimation can occur with this technique (Warburton et al., 1999a).

The two other standards of measurement fall under the category of indicator dilution techniques, and include the dye-dilution method and the thermodilution method.

Both these methods are invasive, and involve catheterization. However, these techniques offer advantages over the direct Fick in that they do not require direct cardiac catheterization (Branthwaite & Bradley, 1968). The indicator dilution techniques for measuring cardiac output are based on the law of conservation of mass (Warburton et al., 1999a). That is, if a liquid is flowing through a tube at a given flow rate, and a known mass of dye is injected into the steam at point *A*, mixing occurs at some point downstream. If a small sample of liquid is continually withdrawn from point *B* farther downstream and passed through a densitometer, a curve of the dye concentration can be recorded as a function of time. If no dye is lost between points, the flow may be measured by dividing the amount of indicator injected upstream by the area under the downstream concentration curve.

The dye-dilution technique has been widely used to estimate cardiac output. With this method, a bolus of dye, usually 1 ml indocyanine green, is injected into a large central vein or the right side of the heart through a catheter. The downstream concentration of dye is sampled from a systemic artery, and the curve of indicator concentration is recorded as a function of time (Grevnik, 1966).

Because of indicator recirculation, the entire concentration curve is not inscribed. Therefore, to compute the area under the concentration curve, the downslope of curve beyond the point of recirculation is extrapolated to zero concentration (Figure 7). This extrapolation induces some error into the estimation of cardiac output (Berne & Levy, 1992).

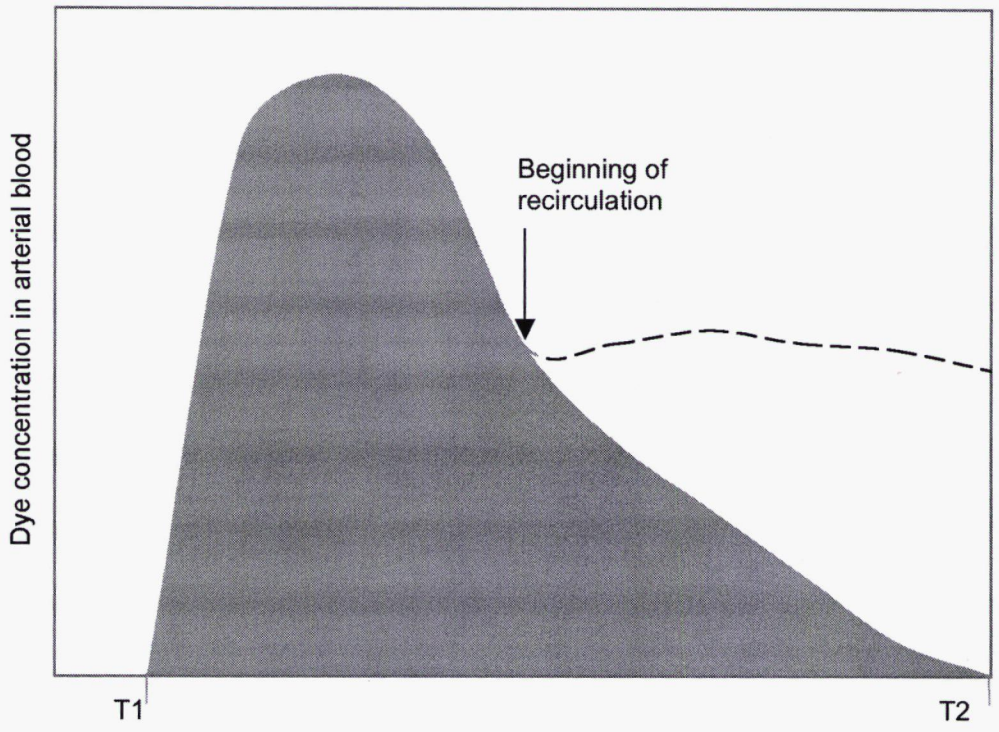

Figure 7. Typical dye concentration curve recorded. Because of recirculation, the concentration does not return to 0 (dashed line). The solid line on the descending limb below recirculation represents the semilogarithmic extrapolation of the upper portion of the descending limb prior to the beginning of recirculation. (Adapted from Berne & Levy, 1992).

The thermodilution method is based on the same principle as dye-dilution, except that, instead of dye, a cold fluid (usually saline) is injected through the venous catheter (Warburton et al., 1999a). The flexible catheter is inserted into a peripheral vein and advanced so that the tip lies in the pulmonary artery. A small thermister at the catheter tip records the changes in temperature. An opening in the catheter is a few inches proximal to the tip. When the tip is in the pulmonary artery, the opening lies in or near the right atrium (Branthwaite & Bradley, 1968). The cold saline injected rapidly into the right atrium through the catheter, and the resultant change in temperature downstream is recorded by the thermister in the pulmonary artery (Branthwaite & Bradley, 1968;

Mackenzie et al., 1986). The thermodilution technique has several advantages over the direct Fick and dye-dilution methods: (1) an arterial puncture is not necessary; (2) the small volumes of saline used in each determination are innocuous, allowing repeated determinations to be made; and (3) recirculation is negligible (Mackenzie et al., 1986).

The validity and accuracy of the thermodilution method has been questioned (Branthwaite et al., 1968; Mackenzie et al., 1986, Espersen et al., 1995), and several studies have shown that this method tends to over-predict true cardiac output by as much as 39% at rest (van Grondelle et al., 1983; Mackenzie et al., 1986; Russel et al., 1990; Moore et al., 1991). Thermodilution has also been reported to consistently overestimate cardiac output by as much as 43% during exercise (Hsia et al., 1995). Moore et al. (1991) reported that thermodilution at best predicts cardiac output with a 10% error. Therefore, its use as a gold standard for comparison is circumspect. As it is, many studies have used this method as a reference for investigating non-invasive measures.

Dye-dilution has been reported to have low measurement error with coefficients of variation generally within 5 to 10% (Grevnik, 1966; Hillis et al., 1985; Ekblom et al., 1968) during rest and submaximal exercise, though few studies have reported coefficients of variation during maximal exercise. The dye-dilution technique is relatively easier to use than the direct Fick and thus has been used more readily in exercise studies, even though the extrapolation of the concentration curves in dye-dilution can lead to errors in measurement, and tendencies to underpredict cardiac output (Berne & Levy, 1992). The invasive nature of the dye-dilution technique makes it difficult to warrant its use in healthy subjects, particularly during near maximal exercise (Warburton et al., 1999a).

The direct Fick and dye-dilution methods are still today considered as the gold standards of measurement of cardiac output, though their use for exercise physiology is limited (Warburton et al., 1999a). The invasive nature of cardiac catheterization, and its associated risks, make it impractical for use in healthy, active subject populations or for the monitoring of athletes. Thermodilution is most often used in clinical situations, as it does not require an arterial catheter, and the cold saline injected is innocuous to the subject. However, the problems associated with thermodilution, in particular the tendency to overestimate cardiac output during exercise, make it unsuitable for use in exercise physiology. Thus many exercise physiologists have chosen to pursue other non-invasive techniques to measure cardiac output in healthy individuals.

Carbon Dioxide Rebreathing

Background

Much of the initial work with CO_2 rebreathing began in the early 1900's. Some of the more popular experiments were carried out by Christiansen, Douglas and Haldane in 1914 using direct alveolar sampling for determination of the partial pressure of CO_2 in the arterial blood. The partial pressure of CO_2 in the mixed venous blood was estimated from the rise of the partial pressure of CO_2 in the lungs either during rebreathing in a closed system or during breath holding (as cited in Klausen, 1965). With the advent of acetylene rebreathing by Grollman (1929), and increased use of the direct Fick and dye-dilution techniques, CO_2 rebreathing as a measure of cardiac output gradually fell out of favor. A new interest in the method was piqued in the 1950's and early 1960's with the development of rapid CO_2 analysis using infrared CO_2 meters (Klausen, 1965). Since

that time, the CO_2 rebreathing technique has undergone extensive testing and comparison versus other measurement techniques (Klausen et al., 1965; Wigle et al., 1979; Beekman et al., 1984; Marks et al., 1985; Reybrouk & Fagard, 1990).

The determination of cardiac output from the CO_2 rebreathing technique is based on a variation of the Fick equation:

$$\dot{Q} = \frac{\dot{V}CO_2}{C\bar{v}_{CO_2} - Ca_{CO_2}}$$

Where:

$\dot{Q}$ = cardiac output in liters/min

$\dot{V}CO_2$ = CO_2 output in liters/min STPD

$C\bar{v}_{CO_2}$ = milliliters of CO_2 per liter of mixed venous blood, and

Ca_{CO_2} = milliliters of CO_2 per liter of arterial blood

Resting Measurements

The "gold standard" of comparison for CO_2 rebreathing is the direct Fick technique. It has generally been found that the CO_2 rebreathing method tends to underestimate measurements by the direct Fick measurement at rest. Correlation coefficients have been shown to vary anywhere from 0.22 to 0.94 (Warburton et al., 1999a). Wigle et al. (1979) found that the CO_2 rebreathing method underestimated the direct Fick measurement by 22.4% at rest, though the authors concluded that overall, the CO_2 rebreathing method is an accurate predictor of cardiac output. An underestimation of only 6% was found by Muiesan et al. (1968) at rest, a difference that was not significant. Nugent et al. (1994) reported that, at rest, the CO_2 rebreathing technique

gave consistently lower values than the direct Fick method. At rest, the CO_2 rebreathing method was lower by 0.72 $l \cdot min^{-1}$, but again the difference was not significant at the 0.05 level.

When compared to the dye-dilution method of cardiac output determination, much of the same evidence has been found. Fergusen et al. (1968) found a low correlation between the two methods ($r = 0.22$), though they admitted that their low finding required further investigation. Wigle et al. (1979) similarly found a low correlation ($r = 0.27$), and an overestimation by CO_2 rebreathing of 10.2%. Generally, when compared to both the direct Fick method and dye-dilution, the CO_2 rebreathing technique has been shown to be relatively ineffective at predicting cardiac output at rest.

Exercising Measurements

The CO_2 rebreathing sampling technique requires the subject achieve steady state at the time of measurement. This is true for rest and also different exercise levels. Thus, if a subject is to have cardiac output measured at a particular exercise intensity, they must have achieved steady-state conditions at that exercise intensity. This becomes increasingly difficult for heavy loads, especially close $\dot{V}O_2$ max. Vanhees et al. (2000) recommend that CO_2 rebreathing be performed only at rest and lower levels of exercise. With that in mind, most measurements of cardiac output during exercise using the CO_2 rebreathing method are at a submaximal level below ventilatory threshold II.

Despite the limitations of the CO_2 rebreathing method during high load exercise, results at the submaximal level tend to correlate well with direct measures of $\dot{Q}$. As

exercise intensity increases, the relationship between $\dot{Q}$ measured by CO_2 rebreathing and direct Fick appears to be more robust. Wigle et al. (1979) reported an increase in accuracy with higher cardiac output, concluding that the method is useful for exercise studies, and correlation coefficients when compared to direct techniques range from $r = 0.65$ at rest to $r = 0.96$ during submaximal exercise (Klausen et al., 1965; Wigle et al., 1979; Marks et al., 1985; Reybrouk & Fagard, 1990) Ferguson et al. (1968) stated that the CO_2 method was found to be as reliable as the direct Fick and thermodilution methods during exercise, and similar results were found by Nugent et al. (1994) in their comparisons. Thus, at lower steady-state exercise intensities, the CO_2 rebreathing technique correlates well to direct measures when measuring exercising cardiac output.

Reproducibility

Many studies have shown that the CO_2 rebreathing method has high reproducibility during exercise, but the validity at rest, as previously discussed, is subject to scrutiny (Vanhees et al., 2000). Zeidfard et al. (1972) found that at workloads of 25% and 75% of maximum working capacity, there was a low coefficient of variation. With subjects exercising at two different submaximal loads, Knowlton & Adams (1974) found significant repeatability for both workloads. Wigle et al. (1979) showed repeatability within 10% of the average over three different test days, though the resting scores showed substantial variability from day to day. Finally, Reybrouck and Fagard (1990) found the validity of CO_2 rebreathing when compared to dye-dilution was acceptable during exercise, but not at rest.

Conclusions

The CO_2 rebreathing technique has been extensively studied and validated against direct techniques for measuring cardiac output. The strengths of CO_2 rebreathing are in its non-invasiveness, ease of use, and reliable output at sub-threshold exercise intensities. The weaknesses of the CO_2 rebreathing technique are that it requires steady-state conditions, is difficult to tolerate at near-maximal exercise intensities, and can generate variable results at rest. During sub-maximal exercise the CO_2 rebreathing technique is similar in validity and reliability to the invasive techniques, and provides an adequate alternative to the direct Fick and dye-dilution methods. However, it is not appropriate for measuring maximal values of cardiac output.

Doppler Echocardiography

Background

The history of echocardiography finds its roots in the initial work of Curie and Curie, who discovered piezoelectricity in the 1880's. Further investigations produced the first patent for ultrasound in 1937 by Sokolov (Feigenbaum, 1996). Developments in this area occurred quickly during World War II, when the application of ultrasound technology was used for naval sonar. Following the war, peaceful uses for wartime technology produced crude, two-dimensional ultrasound scanning techniques. Early uses for this technology focused on the brain, and the first use of ultrasound to examine the heart was by Keidel in 1950 (Feigenbaum, 1996). Initially termed "ultrasound cardiology," the term echocardiography became attached to the technique in the 1960's.

The use of echocardiography for determination of cardiac output began with work in the area of the Doppler technique in the 1950's (Feigenbaum, 1996), and the Doppler technique was introduced as a routine diagnostic tool in the early 1980's (Huonker et al., 1996). According to the Doppler principle, an ultrasound wave is transmitted through blood moving through the ascending aorta during systole (Huntsman et al., 1983). Theoretically, by placing the Doppler transducer in the suprasternal notch, the ultrasound signal passes parallel to the blood flow through the ascending aorta. The movement of erythrocytes causes a shift in the frequency of the ultrasonic transmission. This shift (referred to as the Doppler frequency shift) is proportional to the flow of blood (Warburton et al., 1999b), and can be calculated by using the Doppler formula:

$$V = \frac{(\Delta f)(c)}{(2f)(\cos\theta)}$$

where:

V = blood flow velocity (cm/sec)

Δf = the Doppler frequency shift (Hz)

f = the known frequency of the discharged ultrasound (Hz)

c = the velocity of sound in tissue (1540 $m \cdot sec^{-1}$)

θ = the angle between the direction of blood flow and the direction of the signal

Stroke volume is then calculated by averaging the blood flow velocity and multiplying it by the cross-sectional area of the vessel where the measurement was taken (Christie et al., 1987). The product of stroke volume and heart rate is then used to calculate cardiac output.

There are two types of Doppler systems used in the assessment of cardiac output: continuous-wave Doppler; and pulsed-wave Doppler (Warburton et al., 1999b). Continuous Doppler systems, as the name implies, measure flow velocity all the way through the Doppler beam. However, because of this, velocity information can come from all along the beam, instead of just the area of interest (Nishimura, 1984). Continuous-wave systems also assume an angle of 180° between the sound beam and the direction of blood flow, an assumption that may be erroneous (Warburton et al., 1999b).

Pulsed-wave Doppler systems measure flow velocity at a particular point along the Doppler beam (Nishimura, 1984). When used in conjunction with M-mode or two-dimensional echocardiography to determine specific vessel diameter, Doppler information can be determined for a selected area (Goldberg et al., 1982). The primary disadvantage with pulsed wave echocardiography is its large transducer, which is difficult to place on the suprasternal notch, and may become cumbersome during exercise (Goldberg et al., 1982). Recent advances in technology have helped to minimize this problem.

Resting Measurements

When the Doppler method has been compared to invasive measures of cardiac output, it has been reported to provide reasonable estimates at rest (Warburton et al., 1999b). Most investigations involving Doppler methods at rest involved cardiac patients, and the standard of comparison was thermodilution (Lewis et al., 1984; Huntsman et al., 1983; Nishimura et al., 1984). Lewis et al. (1984) found a correlation of 0.91 when comparing pulsed Doppler echocardiography to thermodilution, and concluded that

cardiac output can be measured accurately by left ventricular outflow measurements. Similar conclusions were found by Huntsman et al. (1983), though the authors noted that the echocardiographic technique was not suitable for all patients (or subjects). Certain cardiac and/or thoracic conditions – such as aortic stenosis, tortuous aortas, chronic pulmonary disease, and obesity, among others – may prohibit the use of echocardiography. Nishimura et al. (1984) found that accurate measures of cardiac output using the Doppler method were only possible in 70% of the patients examined. Thus, Doppler echocardiography can provide a good estimate of cardiac output at rest.

Exercising Measurements

Studies investigating Doppler echocardiography during exercise have reported reasonably high correlation values (Rowland & Obert, 2002). The non-invasive nature of the Doppler technique, combined with the ability to measure beat-to-beat changes, makes it promising for physiologists hoping to study cardiac output during exercise. Initially, the technique was thought to be very hard to perform during exercise. Excessive subject movement would lead to recording artifact, and a situation called alaising could occur during high intensity exercise with pulsed-wave Doppler. Alaising occurred when the highest peak velocities of blood exceeded the maximum velocity that the pulsed-wave recording instrument could measure (Leoppky et al., 1984). This situation has been corrected by improvements in the technology.

Though the number of studies examining the Doppler technique during exercise is relatively small, the few studies done have shown the technique to evidence good correlation with other invasive measures (Daley et al., 1985; Huonker et al., 1996; Di

Bello et al., 1994). Daley et al. (1985) found high quality Doppler signals could be obtained in all subjects during exercise. Similar findings were reported by Huonker et al. (1996) and Di Bello et al. (1994) when exercising at both submaximal and maximal levels. These authors concluded that the Doppler technique is a capable method of determining cardiac output during exercise.

In study comparing the Doppler method with thermodilution, Christie et al. (1987) reported high correlation ($r = 0.86$), though that coefficient was for measurements taken from rest to maximal exercise. Generally, the Doppler technique has been shown to underpredict cardiac output during exercise. Espersen et al. (1995) found that Doppler echocardiography underpredicted thermodilution measures by 32% (4.0 $l \cdot min^{-1}$), direct Fick measures by 11% (1.1 $l \cdot min^{-1}$), and Fick oximetry (CO_2 rebreathing) by 16% (1.6 $l \cdot min^{-1}$) during submaximal exercise. In a study by Shaw et al. (1985), the Doppler technique underpredicted thermodilution measures from 14% to 19%. Generally, however, it has been suggested that the Doppler technique is a suitable measure of cardiac output during submaximal exercise (Warburton et al., 1999).

Very few studies have examined Doppler echocardiography during maximal exercise. Gardin et al. (1986) noted that despite mild alaising, increased spectral dispersion, faster heart rates, and increased respiratory rate during maximal exercise, aortic flow velocity measurements could be recorded by the suprasternal technique. Similarly, Di Bello et al. (1996) reported no difficulty recording Doppler information during maximal exercise.

As with submaximal exercise, Doppler measurements taken at maximal intensities tend to underpredict invasive measures. Christie et al. (1987) found that at maximal

exercise, the Doppler method underestimated cardiac output by approximately 15% (3.2 $l \cdot min^{-1}$). Shaw et al. (1985) found by extrapolation that Doppler echocardiography underestimates maximal cardiac output by approximately 17%. These results indicate that the Doppler method may tend to underestimate cardiac output compared to invasive measures (Warburton et al., 1999b).

Reproducibility

Coefficients of variation for Doppler methods are generally lower at rest than during exercise (Warburton et al., 1999b). At rest, coefficients of variation are within 10-15% (Espersen et al., 1995). A difficulty with the Doppler technique is that for high reproducibility and low intra-observer variability, it requires the services of trained personnel. With untrained personnel, intra-observer variability is less than that between observers, and the interobserver variability decreases with repeated trials (Shaw et al., 1985). However, repeated trials are not often available or feasible in exercise studies. When performed by trained personnel, good reproducibility has been reported ($r = 0.98$) (Shaw et al., 1985), and it appears that if performed by trained personnel, the Doppler technique can provide reasonably reproducible and reliable measurements of cardiac output during rest and exercise (Warburton et al., 1999b).

Conclusions

Of all non-invasive measures of cardiac output, Doppler echocardiography is the only one that is relatively simple to perform, reliable over repeated measurements, accurate, useful during low-intensity exercise, and truly non-invasive. However, difficulties in

obtaining readings during strenuous exercise, particularly in high movement exercise like running, as well as its limitation to use in only 80-90% of the population, make it unsuitable for use in maximal exercise studies. The Doppler echocardiography method is best suited to sedentary studies where minimal movement interference will occur.

Acetylene Rebreathing

Background

The acetylene rebreathing technique, originally developed by Grollman (1929) is based on the Fick principle applied to physiologically inert soluble gases as described by Borstein (1910) and Krogh and Lindhard (1912). It is assumed that the rate of alveolar-capillary transfer of a soluble gas is proportional to pulmonary capillary blood flow. When a soluble inert gas, such as acetylene, is inhaled, its partial pressure in the blood of the pulmonary capillary bed is proportional to the partial pressure in the alveoli. Thus, the following equation is used to estimate cardiac output ($\dot{Q}$):

$$\Delta V = (F_A)\,(\alpha)\,(\dot{Q}_c)$$

where:

ΔV = the change in the amount of gas in the lungs in the interval before recirculation

F_A = the fractional acetylene concentration at BTPS

α = the solubility in blood

$\dot{Q}_c$ = the amount of blood to which the gas is exposed (pulmonary flow)

The change in the amount of gas in the lungs (ΔV) can be calculated from measured changes in the alveolar volume and gas concentrations during the test. Initially, by use of the Grollman (1929) technique, samples of gas concentrations were taken at the alveolar level, a technique both risky and problematic, especially at high levels of exercise. However, Triebwasser et al. (1977) used a measure of gas concentration at end-expiration using a mass spectrometer, allowing for continuous monitoring of acetylene. It was assumed that the end-expiration concentration of acetylene was equal to the alveolar concentration, i.e. the concentration to which the pulmonary blood was exposed (Triebwasser et al., 1977).

Resting Measurements

Measurement of cardiac output by the acetylene rebreathing method at rest and exercising intensities has correlated well with measurements by the direct Fick method, with reported values as high as 0.95 (Warburton et al., 1999a). A linear relationship and a high degree of correlation between resting cardiac output values obtained simultaneously by the acetylene rebreathing and direct Fick methods has also been reported (Chapman et al., 1950). Hsia et al. (1995) stated that the rebreathing technique provided accurate non-invasive estimates of cardiac output at rest at spontaneously chosen respiratory frequencies when compared with the direct Fick method. Hoeper et al. (1999) concluded that acetylene rebreathing showed an acceptable overall agreement with the Fick method when used in patients with pulmonary hypertension, though the acetylene technique under-predicted the Fick method by 0.23 $l \cdot min^{-1}$. Generally, it has been found that acetylene rebreathing tends to be less accurate (5-15% variation) at

predicting cardiac output at rest than at exercising levels, but the difference is not statistically significant. Liu et al. (1997) found that acetylene rebreathing tended to slightly over-predict cardiac output by the Fick method at rest, but the difference did not approach significance at the 0.05 level.

Exercising Measurements

High agreement has been demonstrated when the acetylene rebreathing technique has been compared with the direct Fick method during exercise. Liu et al. (1997) demonstrated no significant differences between the two methods at 25%, 50%, 75%, and 90% $\dot{V}O_2$ max. The authors concluded that the acetylene rebreathing method was valid in determining cardiac output at high work rates. Concurring with the findings by Liu et al. (1997), Hsia et al. (1995) found that the acetylene rebreathing technique was in good agreement with data from direct Fick methods. Correlations between the C_2H_2 rebreathing method and direct methods have ranged from $r = 0.78$ to $r = 0.95$ (Cournand et al., 1945; Smyth et al., 1984; Nystrom et al., 1986; Hsia et al., 1995), and several studies have shown that C_2H_2 rebreathing technique gives accurate measurements during maximal exercise (Asmussen et al., 1952; Triebwasser et al., 1977; Smyth et al., 1984).

Reproducibility

The acetylene rebreathing technique has been found to reproducible on a day-to-day basis, and has a relatively low methodological error. In submaximal cardiac output measurements on four separate days, the test-retest reliability was found to be high, with an average coefficient of variation of approximately 4.8% between duplicate

measurements (Warburton et al., 1998). Hunt et al. (1997) also found a high correlation ($r = .98$, $p < 0.001$) with cardiac output measurements over two days. The same reproducibility of the technique has been shown for individuals of varying age and gender. It has been reported that there is a high correlation between tests done on two different days in both males and females ($r = 0.93$), and in individuals as old as 71 years of age (Hunt et al., 1997).

Conclusions

The C_2H_2 rebreathing technique is the most extensively used measure of cardiac output in exercise physiology labs (Warburton et al., 1999a), due to its ease of use and ability to measure maximal cardiac outputs. The validity and reliability of the technique has been well established from rest to maximal exercise. However, since rebreathing techniques can result in increases in arterial P_{CO_2} (Pa_{CO_2}) and changes in arterial P_{O_2} (Pa_{O_2}), this may lead to fluctuations in cardiac output (Barker et al., 1999). As well, during high intensities of exercise, the change in Pa_{CO_2} and Pa_{O_2} can lead to subject discomfort and dyspnea. Thus, the use of rebreathing techniques during exercise, particularly at near-maximal levels, can be problematic. This has lead to the development of non-rebreathing acetylene techniques for the determination of cardiac output.

Non-Rebreathing Techniques

Background

The development of non-rebreathing acetylene uptake has increased the possibility of obtaining measures of cardiac output at maximal levels in a truly non-intrusive manner. The non-rebreathing measures do not require the attainment of steady-state, a benefit at near-maximal levels, such that simultaneous readings of cardiac output and $\dot{V}O_2$ can be obtained during a test, leading to a more concise picture of how an athlete or patient is functioning during exercise. This new technique examines the rate of uptake of acetylene by the lungs into the blood stream. The rate of uptake can provide an estimate of pulmonary blood flow, which is assumed to be equal to the volume of blood ejected by the left ventricle during the same unit of time.

There are two non-rebreathing techniques currently being used. The first (open-circuit acetylene uptake) involves subjects breathing a mixture of known gases and the rate of uptake of acetylene is measured with a mass spectrometer. In the second technique (single-breath constant exhalation acetylene uptake) subjects inhale a known concentration of gases, hold their breath for 2 seconds, then exhale at a constant rate, and the rate of acetylene uptake is measured.

Open Circuit Acetylene Uptake

Recent work by Barker et al. (1999) and Johnson et al. (2000) investigated the validity of the open-circuit acetylene uptake method. Based on the technique developed by Gan et al. (1993), the procedure involves breathing a gas mixture of two inert gases: acetylene and an insoluble gas, usually helium. Mathematical analysis is then performed to

determine the rate of uptake of acetylene, based on the mass balance of the two inert gases. This avoids unpleasant rebreathing and resultant changes in Pa_{O_2} or Pa_{CO_2} brought about by rebreathing.

Barker et al. (1999) used a novel technique by assuming alveolar and arterial pressures of acetylene were the same. They also accounted for acetylene recirculation by extrapolating end-tidal acetylene concentrations back to *breath 1* (Figure 8).

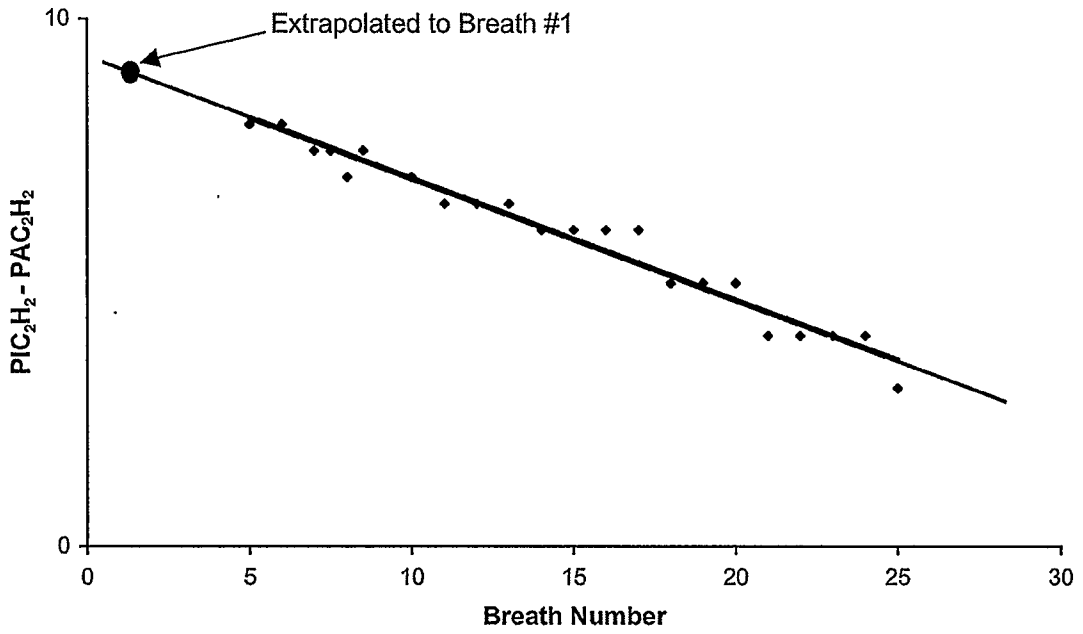

Figure 8. Inspired end-tidal differences for acetylene after correction by corresponding helium differences during same 25-breath acetylene-helium wash in. Value back extrapolated to *breath 1* of wash in, used for cardiac output calculation. PIC_2H_2 = inspired C_2H_2 partial pressure; PAC_2H_2 = end-tidal (alveolar) C_2H_2 partial pressure (adapted from Barker et al., 1999).

Using this technique, they found a linear relationship between the acetylene uptake method and direct Fick measurements (r = 0.93). There was no statistically significant difference between the two measures. As well, they reported that at maximal intensities, cardiac output measured by acetylene uptake differed from Fick measurements by 3%.

Johnson et al. (2000) also found high correlations between direct Fick measurements and two methods of open circuit acetylene uptake (r = 0.94, 0.93, respectively). The two methods involved the same gas sampling, but incorporated two different methods of calculation. The first method (OpCirc1) used the relatively rapid calculation technique described by Gan et al. (1993) and Stout et al. (1975). The second method (OpCirc2) used a post-session finite difference modeling method. Utilizing these two methods to calculate the acetylene uptake, Johnson et al. (2000) reported that the open circuit technique tended to underestimate $\dot{Q}$ at higher intensities, but these differences were only significant in one of the methods (OpCirc1). The conclusion was that open circuit acetylene uptake is a valid, reliable measure of cardiac output at rest and moderate intensities. However, Johnson et al. (2000) suggested there may be some difficulties with the method at higher work intensities due to possible ventilation:perfusion mismatch. Card et al. (1996) reported that the non-rebreathe technique was easily tolerated by all subjects; it imposed no alteration in the physiological condition (unlike the rebreathe technique) and represented a major advancement for exercise physiology laboratories.

Single-Breath Constant Exhalation Acetylene Uptake

Several research groups have investigated the validity of the single-breath constant exhalation method (Zenger et al., 1993; Thomas et al., 1997; Elkayam et al., 1984). Zenger et al. (1993) reported high correlations between single-breath constant exhalation acetylene uptake and both direct Fick and thermodilution (r = 0.90 and 0.92, respectively). However, it was found that this new method tended to underestimate cardiac output at rest, and some subjects were unable to perform the constant flow

exhalation at higher intensities. Thomas et al. (1997) reported similar values obtained by uptake as those obtained by acetylene rebreathing. They concluded that the single-breath technique reliably measured cardiac output across moderate to heavy intensities. Elkayam et al. (1984) compared the single-breath technique with thermodilution and reported a close relationship between the two measures, with mean differences in estimations between the two measures of $\dot{Q}$ reported to be 0.03 ± 0.76 l·min^{-1}. They also reported mean coefficients of variation for the single breath technique at rest of 9%.

After considering this review of literature, it is evident that the new techniques of open-circuit acetylene uptake and single-breath constant exhalation acetylene uptake hold much promise for use in both clinical and research settings, particularly under moderate to strenuous exercise conditions. However, the work is still preliminary, and the reliability of the measures needs further investigation. It is also evident that further comparison is required, and the reliability of the measures needs to be accurately assessed.

CHAPTER 3: METHODOLOGY

Subjects

Thirteen active male cyclists (age 24-39) were recruited from the University of Calgary and local cycling clubs. Athletic inclusion criteria consisted of an ability to achieve a maximal aerobic power output greater than 335 W. Subjects were excluded if they smoked and/or had a history of cardiac, respiratory, or chronic obstructive pulmonary disorders. The subjects gave written informed consent, and all had negative medical histories. The study was approved by the University of Calgary Ethics Review Board (Appendix A). See Table 1 for a summary of subject information.

Table 1. *Subject descriptive data (n = 13)*

	Mean ± SD	Range
Age (years)	30.8 ± 5.5	24-39
Height (cm)	179.1 ± 8.4	169-197
Weight (kg)	81.8 ± 11.1	70.5-110.0
$\dot{V}O_2$max ($l \cdot min^{-1}$)	4.37 ± 0.59	3.46-5.89
$\dot{V}O_2$max ($ml \cdot kg^{-1} \cdot min^{-1}$)	53.7 ± 4.2	45.1-59.6
MAP (W)	410 ± 55	345-555
Peak HR ($b \cdot min^{-1}$)	182 ± 9	161-195

Laboratory Setting

Testing was conducted at three locations: The University of Calgary Human Performance Lab, Calgary, AB; Rockyview General Hospital Pulmonary Diagnostics Laboratory, Calgary, AB and; Foothills Hospital Cardiology Unit, Calgary, AB.

Schedule of Testing

Testing was scheduled to take place over a 6-week time period. However, circumstance dictated that the original schedule could not be maintained. Four subjects completed the testing within the 6-week time period. The remaining nine subjects completed the single-breath technique, CO_2 rebreathing, and echocardiography in a 6-week block. They were then brought back after a two-month break and re-tested on the single breath technique. When it was determined that the re-tested values for the single breath test did not differ significantly from previous values, the subjects then completed the remaining procedures in under 6-weeks. All testing done for reliability was performed within several days of each other. Attempts to randomize the order of testing were performed for the single breath, CO_2 rebreathing, and echocardiography, though most subjects completed the open circuit testing as the final measure.

Maximal Oxygen Consumption ($\dot{V}O_2max$) measurement

Subjects performed a standard, incremental $\dot{V}O_2max$ protocol (initial power output of 150 W, with increases of 30 W every 2 minutes until ventilatory threshold II (Wasserman et al., 1973), then 15 W increases in 1 minute stages from threshold to max) to determine $\dot{V}O_2max$ and maximal aerobic power output (MAP). $\dot{V}O_2max$ ($l \cdot min^{-1}$) was defined as the peak $\dot{V}O_2$ obtained over a 30-second average during the test. MAP (Watts, W) was defined as the peak workload obtained and subsequently maintained for 1 minute (Hawley & Noakes, 1992).

Reliability Protocol

The single-breath constant exhalation acetylene uptake (SB) technique was assessed for both intra-test and test-retest reliability. Six randomly selected subjects agreed to participate in the reliability testing for the SB technique. Each test consisted of three 8-minute recording stages (rest, 100 W, and 200 W), separated by 4-minute recovery stages of 50 W. During each 8-minute recording stage, the subjects performed the SB technique at the 3-minute, 5-minute, and 7-minute marks. Thus, for each testing session, the subjects would have nine total cardiac output measurements taken, three at rest, three at 100 W, and three at 200 W. This procedure was repeated on separate days to assess test-retest reliability.

Reliability measurements for the open-circuit acetylene uptake (OpCirc) technique consisted of the subjects performing identical incremental tests from rest to 300 W with increments of 50 W on subsequent days. Due to the length of OpCirc sampling times (often in excess of 2-minutes), only test-retest reliability was determined.

Comparative Protocol

Four measures of cardiac output were performed: (1) carbon dioxide (CO_2) rebreathing; (2) open-circuit acetylene uptake (OpCirc); (3) single-breath constant exhalation acetylene uptake (SB) and; (4) echocardiography. Subjects performed two incremental trials of each measure of cardiac output (except echocardiography, performed at rest only), and the second trial was used for comparative purposes. A detailed description of each technique follows later in this section. During CO_2 rebreathing, values for cardiac output were taken during four-minute intervals from rest

to 200 W with increments of 50 W. There were no reports of difficulty performing the rebreathing procedure while exercising at this workload, and in each case, steady-state conditions were achieved by the third minute of the stage. During both the single-breath constant exhalation acetylene uptake and open-circuit acetylene uptake, values for cardiac output were taken during four-minute intervals from rest to 300 W with increments of 50 W. The testing schedule is presented in Table 2.

Table 2. *Experimental measures matrix. T1 = testing session 1; T2 = testing session 2; Echo = Echocardiography; CO_2 RB = CO_2 rebreathing; OpCirc = Open circuit acetylene uptake; SB = Single breath constant exhalation acetylene uptake.*

	Power Output (W)													
	Resting		50		100		150		200		250		300	
	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2
Echo	x	x	-	-	-	-	-	-	-	-	-	-	-	-
CO_2RB	x	x	x	x	x	x	x	x	x	x	-	-	-	-
OpCirc	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SB	x	x	x	x	x	x	x	x	x	x	x	x	x	x

CO_2 Rebreathing

Subjects performed the CO_2 rebreathing exercise protocol connected to a three-way breathing assembly, consisting of a room air intake, rebreathing bag, and expired gas line. All expired gases were measured by a ParvoMedics True Max metabolic measurement cart (Salt Lake City, Utah), and heart rate was recorded using a Polar Vantage XL heart rate monitor.

At the 3-minute mark of each interval stage, the cardiac output procedure was initiated. The procedure consisted of two components: the end-tidal measurement phase, and the equilibration measurement phase. For the end-tidal measurement phase, the gas-sampling catheter was removed from the mixing chamber and placed on a small-bore port on the mouthpiece. Once the sampling line was secure, end-tidal concentrations of CO_2 were measured for 4-6 breaths. When a sufficient number of breaths had been recorded for end-tidal calculation, the three-way valve assembly was switched at the end of expiration so that the subjects breathed in a full tidal volume from the rebreathing bag, which corresponded to the beginning of the equilibration measurement phase. The subjects rebreathed from a 5-litre rebreathing bag filled with 9.5-14% CO_2 (Table 3), and balance O_2 until CO_2 equilibrium was been established, or a maximum of 15 seconds. If an equilibration "plateau" was not obtained, the analysis software estimated the value by extrapolation of a line joining the points for expired PCO_2 at 8-12 seconds of rebreathing to that at 20 seconds. This value has been shown to be within ± 2 mm Hg of the equilibrium value (Jones, 1988). At the attainment of a plateau, or end of the 15 seconds, the valve was switched so that the subject again breathed room air, and the power output was then increased to the next stage (until the conclusion of exercise), and the sampling catheter returned to the mixing chamber.

Table 3. *Initial rebreathing bag CO_2 concentrations to obtain rebreathing CO_2 equilibrium.*

Workload (W)	End-Tidal PCO_2	Bag CO_2 Concentration
0	30	9.5
	40	10
50	30	10.5
	40	11.5
100	30	11
	40	12
150	30	12
	40	13
200	30	13
	40	14

Variables recorded during the sampling time were: power output (W); pulmonary minute ventilation ($\dot{V}_E$); oxygen consumption ($\dot{V}O_2$); heart rate (HR); volume of carbon dioxide produced ($\dot{V}CO_2$); and respiratory exchange ratio (RER). Variables recorded during rebreathing were: heart rate (HR); equilibrium partial pressure of CO_2 ($P_{EQ_{CO_2}}$) and; end-tidal partial pressure of CO_2 ($P_{ET_{CO_2}}$). Computer software, utilizing equations based on the dissociation curve of CO_2, then derived Cv_{CO_2} (milliliters of CO_2 per liter of mixed venous blood) and $C_{A_{CO_2}}$ (milliliters of CO_2 per liter of arterial blood). Cardiac output was calculated for each stage utilizing a variant of the Fick equation (Jones, 1988):

$$\dot{Q} = \frac{\dot{V}CO_2}{(Cv_{CO_2} - C_{A_{CO_2}})}$$

Open-Circuit Acetylene Uptake

The open-circuit acetylene (C_2H_2) uptake procedure used in this study followed the methods outlined by Barker et al. (1999). The subjects were connected to a one-way valve assembly with a dual input valve assembly on the upstream side. One input was room air, and the other being a gas mixture containing known concentrations of acetylene (C_2H_2) (0.7%), helium (He) (5%), oxygen (O_2) (20.9%), and nitrogen (N_2) (73%). A 120-litre Hans Rudolph Douglas bag assembly was connected to high-pressure k-sized gas tanks containing the primary medical grade gas mixtures. The Douglas bag was vacuum-emptied prior to each testing session to prevent contamination of inspired gas concentrations and gas dissociation due to density. Heart rate was recorded using a Polar Vantage XL heart rate monitor.

A mass spectrometer (MGA-1100, Perkin-Elmer) sampled C_2H_2, He, and CO_2 gas concentrations at 1 cc·sec^{-1} via small-bore mouth port. Gas concentrations were logged at 50 Hz by use of a 12-bit analog-to-digital converter, and digitized signals interpreted by a commercially available software program (WBreath, Spiroson™ Germany). Pulmonary minute ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}O_2$), and mixed expired PCO_2 ($P_{E_{CO_2}}$) were measured by a metabolic measurement cart (ParvoMedics True Max, Salt Lake City, Utah). End-tidal PCO_2 ($P_{A_{CO_2}}$), inspired C_2H_2 partial pressure ($P_{I_{C_2H_2}}$), and He-corrected end-tidal C_2H_2 partial pressure ($P_{ET_{C_2H_2}}$) were measured by the mass spectrometer. The setup for this technique is presented in Figure 9.

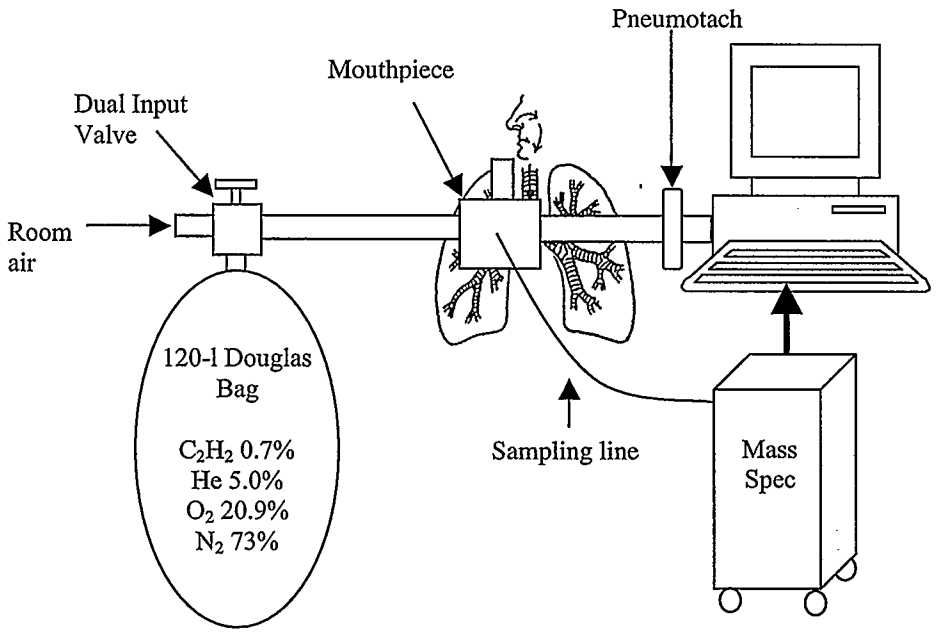

Figure 9. Setup for open-circuit acetylene uptake.

At the 3-minute point of each interval stage the input valve was turned so that the subjects began breathing the known gas mixture. C_2H_2 and He concentrations were monitored until inspired and expired He concentrations reached equilibrium (indicative of adequate alveolar mixing, Figure 10, Figure 11), then the gases were measured for a further 10 breaths. Throughout the resting and exercise sampling, the subjects were encouraged to maintain a constant respiratory rhythm, avoiding coughing, swallowing, and partial breaths. At the end of the sampling time, the input valve was switched back to room air, and the workload was increased until the conclusion of exercise. $P_{ET_{C_2H_2}}$ concentration was monitored via LED display on the mass spectrometer to ensure complete washout of C_2H_2 before the next sampling trial was initiated.

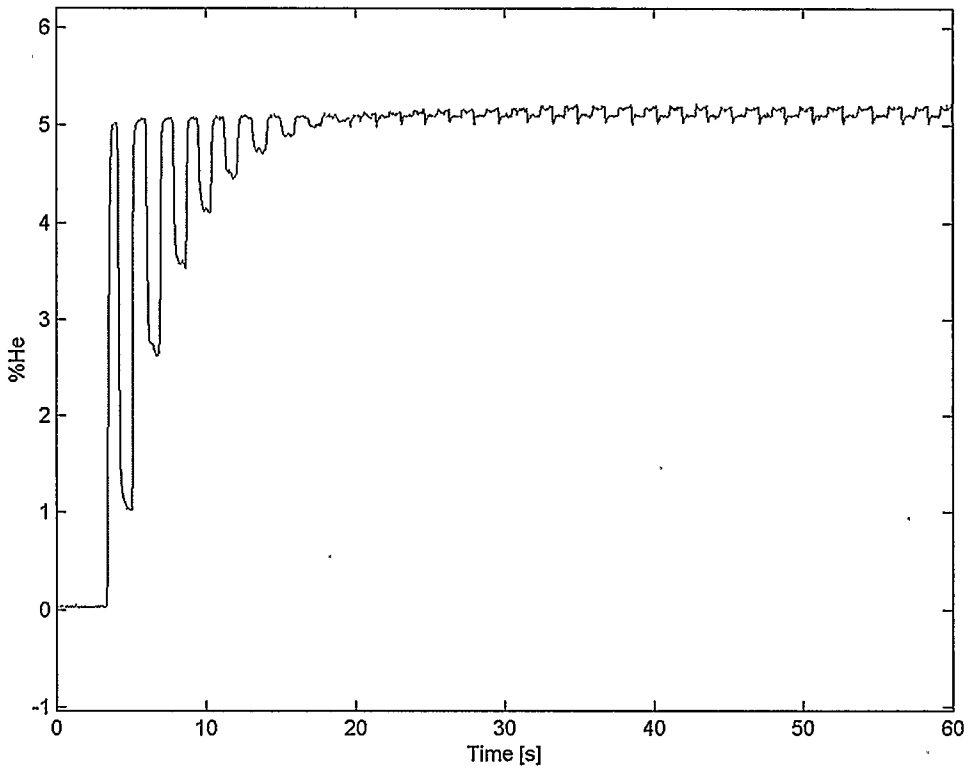

Figure 10. Plot of helium concentration versus time showing breath-by-breath variation and equilibration. In this particular case, equilibration occurred by *breath 9*.

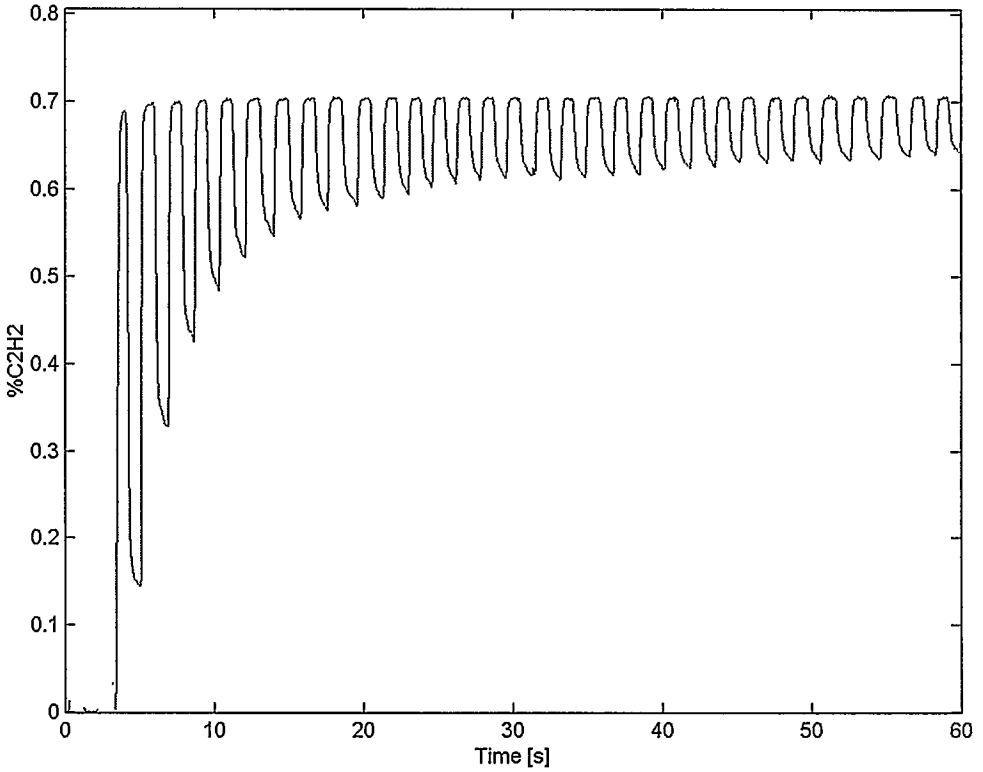

Figure 11. Plot of acetylene concentration versus time showing breath-by-breath variation. Evidence of recirculation is shown by the gradual increase in end tidal C_2H_2 concentration after He equilibration occurred (*breath 9*).

$P_{ET_{C_2H_2}}$ concentrations were corrected for mixing with the ratio of inspired He ($P_{I_{He}}$) to end-tidal He ($P_{ET_{He}}$). The difference between the inspired C_2H_2 partial pressure and this corrected $P_{ET_{C_2H_2}}$ concentration was then extrapolated back to *breath 1* to account for C_2H_2 recirculation (Figure 12).

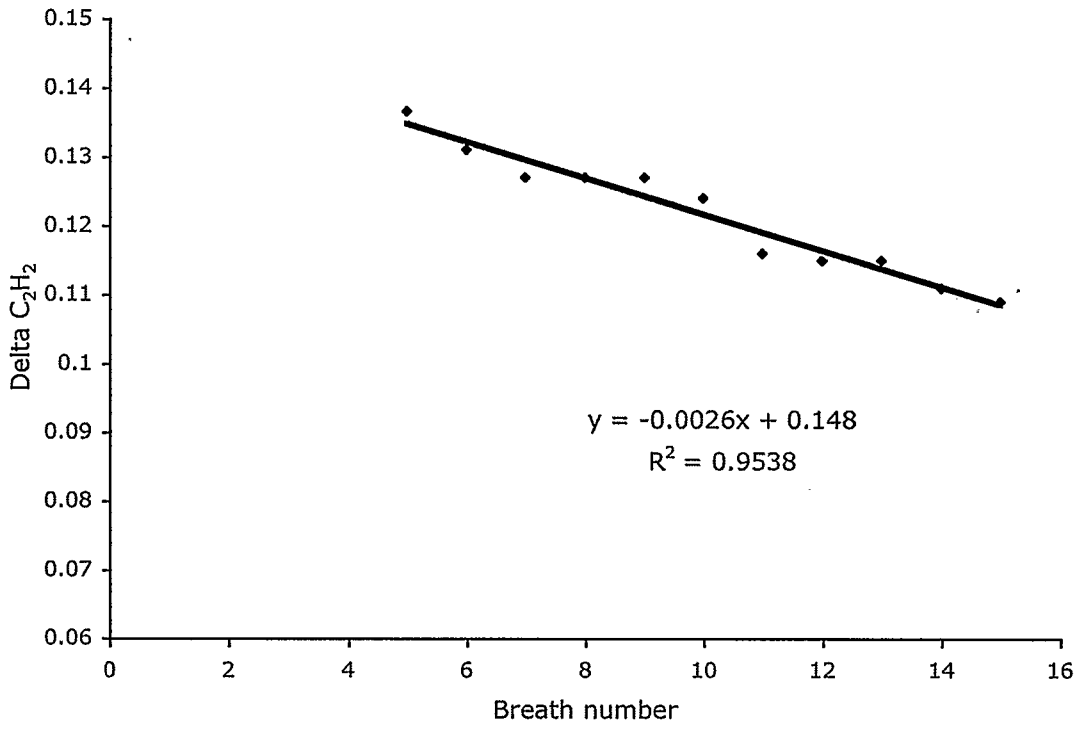

Figure 12. Regression of C_2H_2 differences (inspired – expired). Regression is taken from point of He equilibration (*breath 5*), and equation is used to derive a difference value for *breath 1*.

Cardiac output was then calculated utilizing the mass conservation equation (Barker et al., 1999):

$$\dot{Q} = \frac{[\dot{V}_E \times P_{E_{CO_2}} \times (P_{I_{C_2H_2}} - P_{ET_{C_2H_2}})]}{[\lambda \times P_{A_{CO_2}} \times P_{ET_{C_2H_2}}]}$$

where:

$\dot{V}_E$ = Pulmonary minute ventilation ($l \cdot min^{-1}$)

$P_{E_{CO_2}}$ = Mixed expired PCO_2

$P_{A_{CO_2}}$ = End-tidal PCO_2

$P_{I_{C_2H_2}}$ = Inspired C_2H_2 partial pressure

$P_{ET_{C_2H_2}}$ = He-corrected end-tidal C_2H_2 partial pressure extrapolated back to *breath 1*

λ = C_2H_2 blood-gas partition coefficient

For the present study, a constant value of λ (0.80 ml·ml·tissue^{-1}·atm^{-1}) was used for all subjects, based on the median value presented from the subject pool in Barker et al. (1999).

Single-Breath Constant Exhalation Acetylene Uptake

The single-breath constant exhalation technique used a rapid response infrared C_2H_2 analyzer integrated into a metabolic cart (Sensormedics V_{max}, California, USA). Heart rate was recorded using a Polar Vantage XL heart rate monitor. The subjects were connected to the metabolic cart via the Sensormedics breathing apparatus, which consisted of a gold-filament mass flow sensor that measured inspiratory and expiratory flows directly, perma-pure sampling line at a small-bore mouth port, and the Sensormedics diffusion capacity (DLCO) pneumatically controlled valve assembly. A gas supply line was connected to the valve assembly, providing a gas mixture containing acetylene (C_2H_2) (0.3%), methane (CH_4) (0.3%), oxygen (O_2) (21%), carbon monoxide (CO) (0.3%), and nitrogen (N_2) (78.1%) on demand. At the 3-minute mark of each stage, the subjects were instructed to fully exhale, and then maximally inhale the C_2H_2 gas mixture to total lung volume. The subjects then performed a quick 1-sec breath-hold to allow for tissue absorption and gas distribution equilibration. This was followed by an exhalation at a constant rate of 500 ml·s^{-1} to 2.0 L·s^{-1} (Figure 13). The entire process of valve control and gas supply was automated by the metabolic cart software. The

analyzing software then calculated cardiac output by estimating alveolar C_2H_2 from information obtained from C_2H_2 blood flow. The power output was then increased to the next stage until conclusion of exercise.

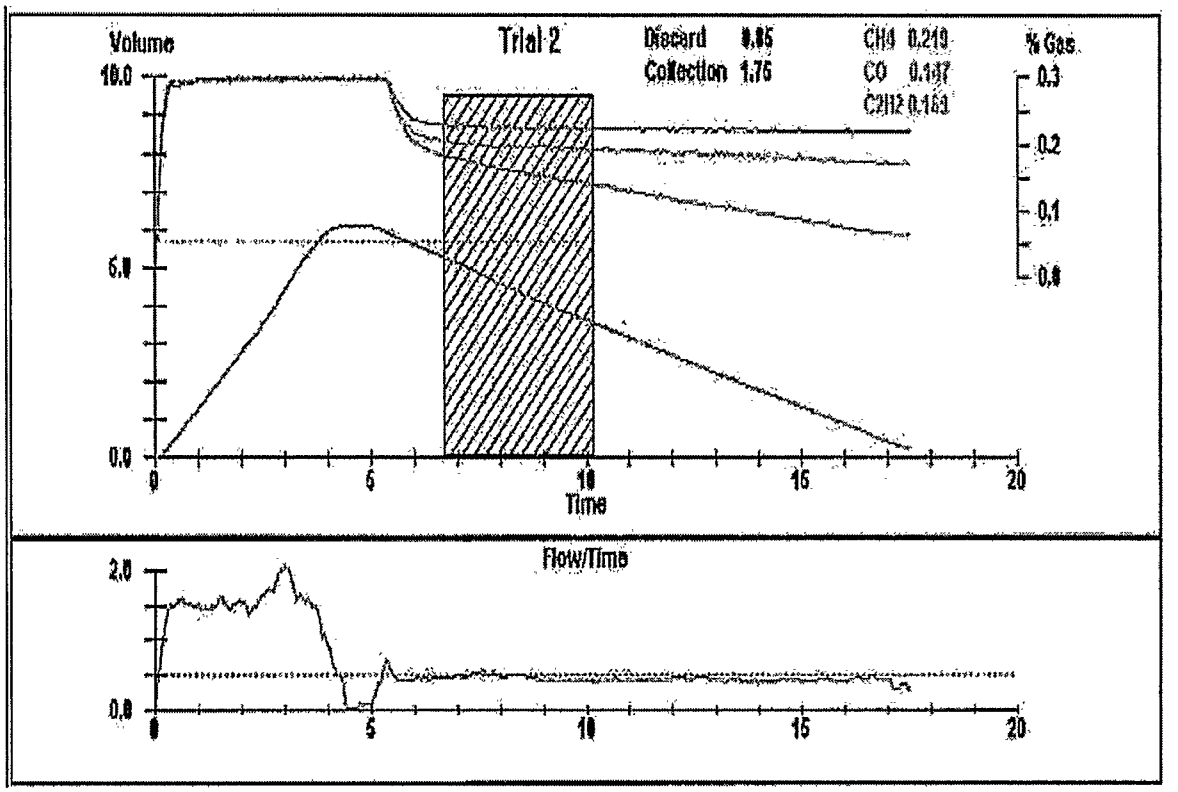

Figure 13. Raw data from single-breath constant exhalation technique. The decay rates for the exhaled gases are shown in the top graph, while the slow, constant exhalation is shown in the bottom graph.

Before each testing session, the subjects were instructed or reminded as to how to perform the constant exhalation procedure. They were then given several opportunities to practice and learn the proper technique, which was repeated until satisfactory flow rates were achieved.

Echocardiography

Echocardiography was performed only at rest, and was used as a standard of comparison for the other measures. The subjects had recordings taken in both the supine and upright positions. A Doppler transducer was placed in the suprasternal notch, where the ultrasound signal passed parallel to the blood flow through the ascending aorta. The movement of erythrocytes caused a shift in the frequency of the ultrasonic transmission. This shift (referred to as the Doppler frequency shift) is proportional to the flow of blood, and can be calculated by using the Doppler formula:

$$V = \frac{(\Delta f)(c)}{(2f)(\cos\theta)}$$

where:

V = blood flow velocity ($cm \cdot sec^{-1}$)

Δf = the Doppler frequency shift (Hz)

f = the known frequency of the discharged ultrasound (Hz)

c = the velocity of sound in tissue (1540 $m \cdot sec^{-1}$)

θ = the angle between the direction of blood flow and the direction of the signal

A second transducer was placed at the level of the 5^{th} intercostal space and recorded aortic dimension (M-Mode echocardiography). Aortic dimension was measured at the aortic semi-lunar valve (ASV), and also at the position of the left ventricular outflow (LVOT). Stroke volume was then calculated by averaging the blood flow velocity and multiplying it by the cross-sectional area of the vessel where the measurement was taken.

The product of stroke volume and heart rate was then used to calculate cardiac output. Two separate measurements were taken to ensure accuracy.

Statistical Analysis

Paired parameters ($\dot{V}O_2$ and $\dot{Q}$) were compared by linear regression analysis, with Pearson product moment correlations calculated for each regression. Multiple linear regression incorporating two-way least significant difference analysis of variance with repeated measures was utilized to compare the different techniques. Statistical analysis of resting values was made using a comparison of groups in a one-way ANOVA – Bonferroni Multiple Comparisons procedure, with $p < 0.05$ (2-tailed) considered significant. The standard error of a single observation (SE), expressed as an absolute and percentage of the mean cardiac output, was used to assess reproducibility. The Student's *t*-test for paired observations was employed to test the significance of differences between duplicate measurements of the same technique. Coefficients of variation were calculated for each workload, linear regression analysis was made between test1 and test2, and a Bland-Altman plot for differences assembled (Bland & Altman, 1986). To assess intra-reliability of the SB technique, the intraclass correlation coefficient (ICC) was computed. Results are presented as means ± SD.

Sample Size

The minimal sample size required for this study was based on measurement effect size, significance level, and power. The significance level (α) was set at 0.05. Therefore, the probability of a Type 1 error (false positive) was 5%. The sample size calculation was

based upon the Pearson-Hartley charts (Keppel, 1991) assuming a population mean cardiac output at 200 W of 15.0 $l \cdot min^{-1}$ with standard deviation of 3.0 $l \cdot min^{-1}$. The minimum sample size calculated to detect a 10% difference (1.5 $l \cdot min^{-1}$) in cardiac output measured at 200 W using a two-sided $\alpha = 0.05$ and a power of 0.80 was 12.

13 subjects completed all aspects of the exercise testing. Nine subjects competed the echocardiography testing. Based on the mean ± SD for each workload, the power of the study to detect a 15% difference in cardiac output (a value great enough to not be the result of daily variation) ranged from 0.60 at rest to 0.95 at 200 W (see Table 4). In general, power increased concomitantly with intensity, more than likely due to decreases in standard deviation relative to mean values.

Table 4. *Calculated statistical power for comparative purposes.*

	Rest	50 W	100 W	150 W	200 W	250 W	300 W
Statistical Power	0.60	0.65	0.78	0.90	0.95	0.93	0.93

CHAPTER 4: RESULTS

Reliability of Open-Circuit Acetylene Uptake

Repeated measurements of cardiac output were made using the OpCirc technique at rest, 100W, 200W, and 300W. There were no statistical differences between repeated measures at any workload. The standard error of measurement for the open-circuit technique decreased (i.e. improved) with increasing intensity (Table 5).

Standard error expressed as a percentage of the mean was 8.6% at rest and 2.4% at 300 W. Standard error (absolute) was similar at all levels of intensity, raging from 0.42 to 0.67 (Table 5). Coefficients of variation (CV) followed similar trends as the standard error (Table 5). The CV decreased with increasing intensity, ranging from 14.1% at rest to 3.4% at 300 W. Individual coefficients of variation are presented in Figure 14.

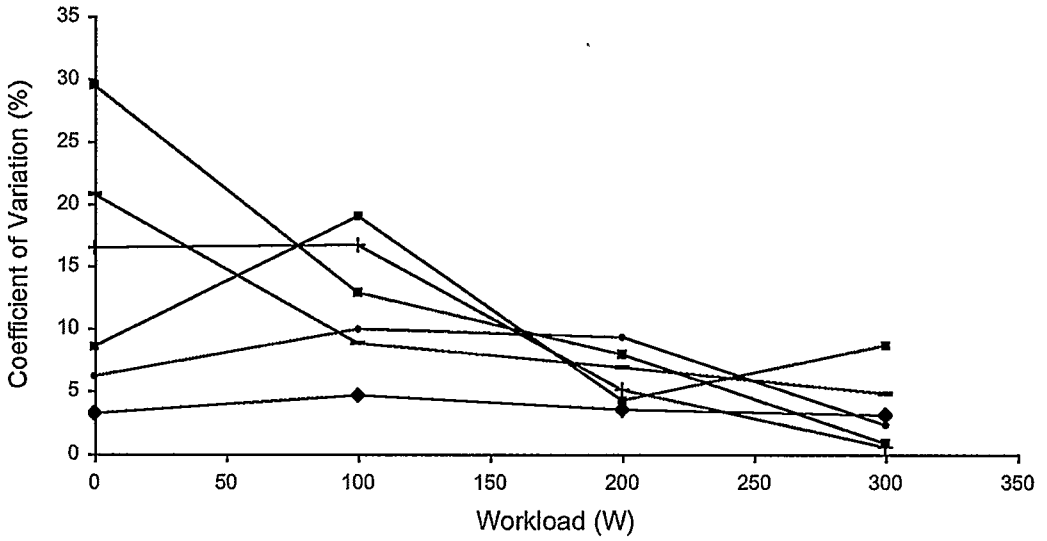

Figure 14. Individual subject coefficients of variation by workload for the open-circuit technique.

Linear regression analysis between test1 and test2 were non-significant for both slope and intercept. Bland-Altman analysis (Figure 15) indicated there were no systematic differences between the replications, although the Bland-Altman plot does show evidence of two outliers for this data set.

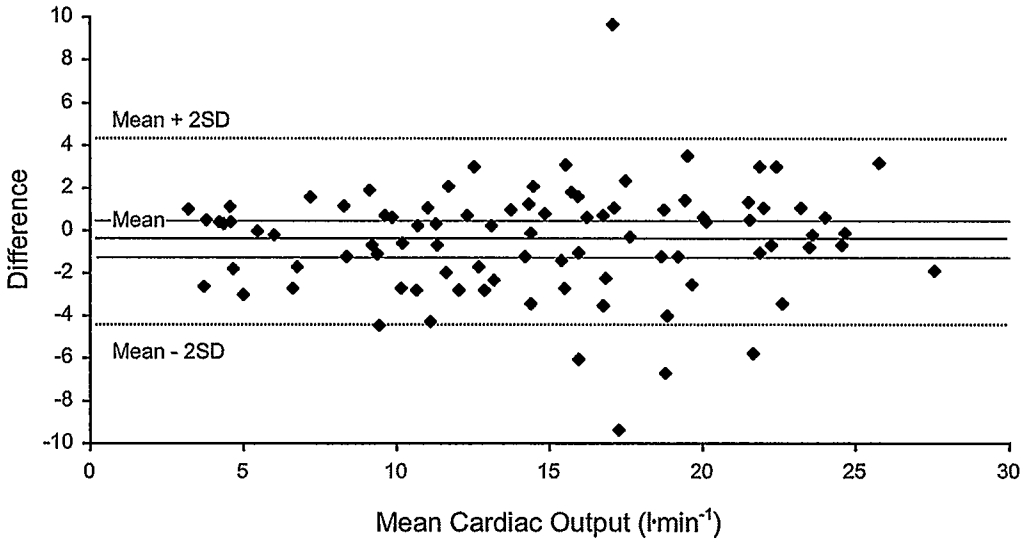

Figure 15. Bland-Altman plot for open-circuit reliability (Time1 - Time2), with 95% CI for mean displayed. Amount of disagreement was 0.354.

Reliability of Single-Breath Acetylene Uptake

Repeated measurements of cardiac output were made using the SB technique at rest, 100 W, and 200 W. As with the open-circuit technique, there were no significant differences between repeated measures of this technique at any workload. The standard error of measurement for the single-breath technique decreased with increasing intensity (Table 5). Standard error expressed as a percentage of the mean was 8.5% at rest and 3.2% at 200 W. Standard error (absolute) was similar at all levels of intensity, raging from 0.47 to 0.56 (Table 5). Coefficients of variation (CV) followed similar trends as the

standard error (Table 5). The CV decreased with increasing intensity, ranging from 17.5% at rest to 7.6% at 200 W. However, the CV for the SB technique was greater at each workload than OpCirc. Individual coefficients of variation are presented in Figure 16.

Table 5. *Comparative and reliability measures for open-circuit and single-breath techniques.*

		Rest	100	200	300
Open-Circuit	Cardiac Output ($l \cdot min^{-1}$)	5.1 ±1.35	12.9* ±1.91	19.2* ±2.47	26.2* ±2.55
	Standard Error (absolute)	0.42	0.61	0.67	0.54
	Standard Error (% of mean)	8.6	5.2	3.8	2.4
	Coefficient of Variation (%)	14.1	12.0	6.1	3.4
Single-Breath	Cardiac Output ($l \cdot min^{-1}$)	5.4 ±1.30	11.9* ±2.33	17.6* ±2.63	22.6* ±3.93
	Standard Error (absolute)	0.47	0.56	0.53	--
	Standard Error (% of mean)	8.5	5.0	3.2	--
	Coefficient of Variation (%)	17.5	14.2	7.6	--

* indicates significant difference, $p < 0.05$, from previous workload

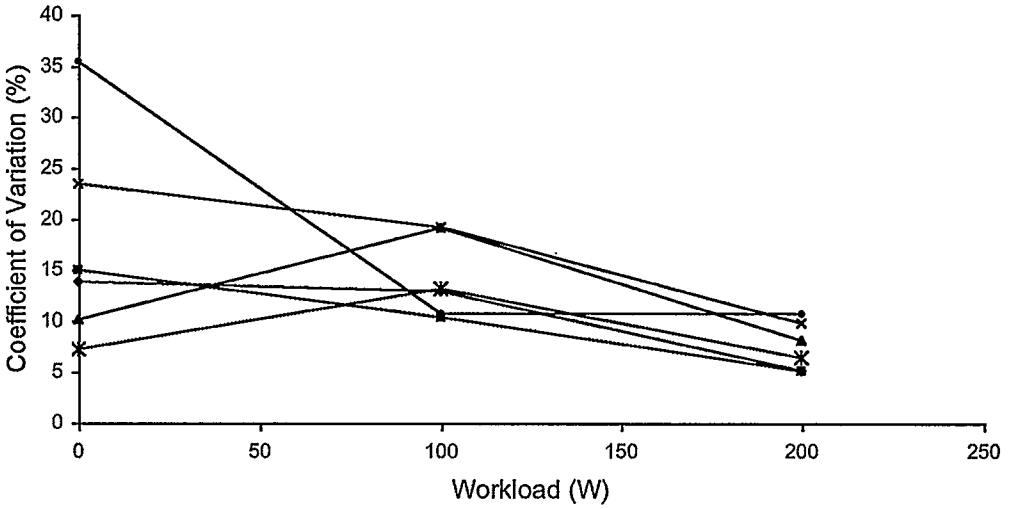

Figure 16. Individual subject coefficients of variation by workload for the single-breath technique.

Linear regression analysis between test1 and test2 were non-significant for both slope and intercept in the single-breath technique. Bland-Altman analysis (Figure 17) indicated there were no systematic differences between the replications. The intra-class correlation coefficient for the single-breath technique was 0.90.

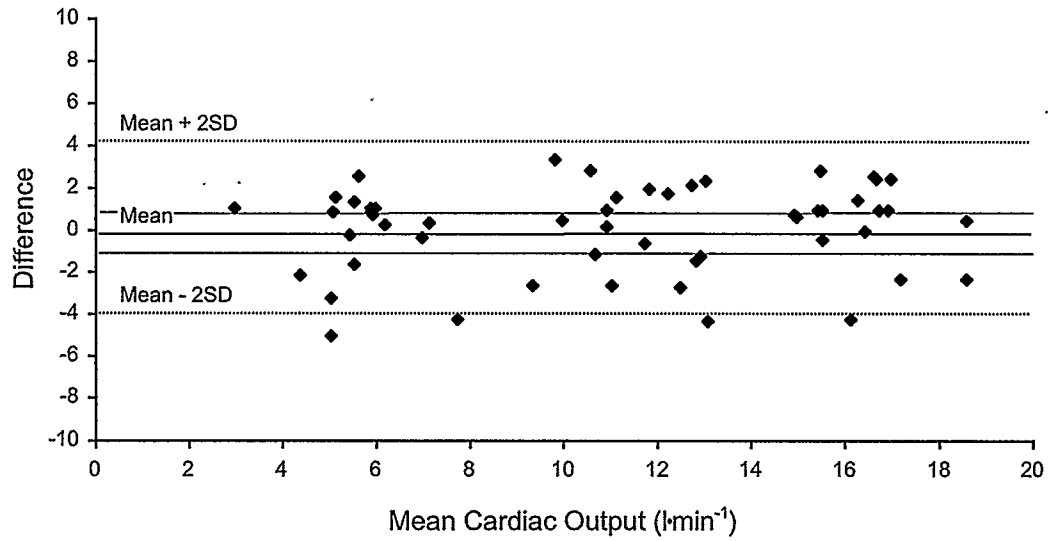

Figure 17. Bland-Altman plot for single-breath reliability (Time1 - Time2), with 95% CI for mean displayed. Amount of disagreement was 0.376.

Cardiac Output Comparisons

Resting values for the four techniques are presented in Table 6. The multiple comparisons procedure revealed $\dot{Q}$ measured by echocardiography at the aortic semi-lunar valve (ASV) to be significantly higher compared to all other techniques. There were no statistical differences between any of the other techniques, including echocardiography measured by the left ventricular outflow (LVOT) technique.

Table 6. *Comparison of resting values for open-circuit acetylene uptake (OpCirc), single-breath acetylene uptake (SB), CO_2 rebreathing (CO_2 RB), aortic semi-lunar valve echocardiography (Echo-ASV), and left ventricular outflow echocardiography (Echo-LVOT). n = 9 for each method.*

	Open Circuit	Single Breath	CO_2 Rebreathing	Doppler Echo (ASV - Supine)	Doppler Echo (ASV - Upright)	Doppler Echo (LVOT)
Mean ($l \cdot min^{-1}$)	4.67	5.49	4.64	8.34*	7.31*	5.31
St. Dev.	0.90	1.26	1.25	1.38	0.94	1.02

* indicates statistical difference from all other techniques except ASV Echo ($p < 0.05$).

Mean cardiac output increased significantly ($p < 0.01$) with each successive increase in power output for all three measures of $\dot{Q}$. Linear regression of the $\dot{Q}$-$\dot{V}O_2$ relationships were:

CO_2RB: $y = 6.18 \times \dot{V}O_2 + 2.59$ ($r = 0.954$, $p < 0.001$)

OpCirc: $y = 6.12 \times \dot{V}O_2 + 2.98$ ($r = 0.949$, $p < 0.001$)

SB: $y = 5.05 \times \dot{V}O_2 + 3.76$ ($r = 0.922$, $p < 0.001$)

Comparison of the regressions of the three techniques is presented in Figure 18. Linear regression of the $\dot{Q}$-$\dot{V}O_2$ relationship for CO_2 rebreathing, Opcirc, and SB are presented in Figure 19, Figure 20, and Figure 21, respectively. Two-way least significant difference analysis of variance with repeated measures revealed the single-breath technique to be significantly lower than both CO_2 rebreathing and open-circuit measurements at power outputs greater than 200 W.

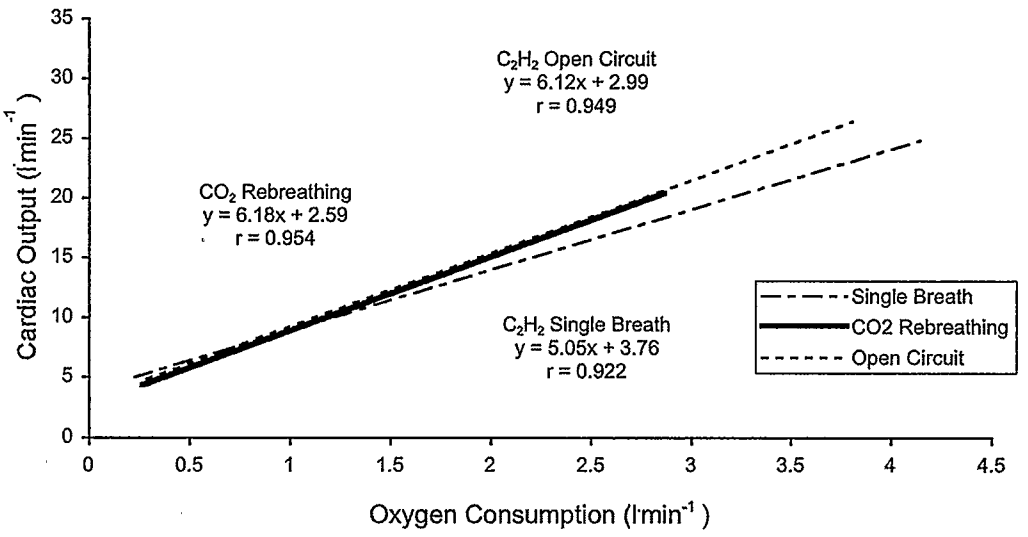

Figure 18. Linear regression and comparison of the three cardiac output techniques (CO_2 rebreathing, open-circuit acetylene uptake, and single-breath acetylene uptake).

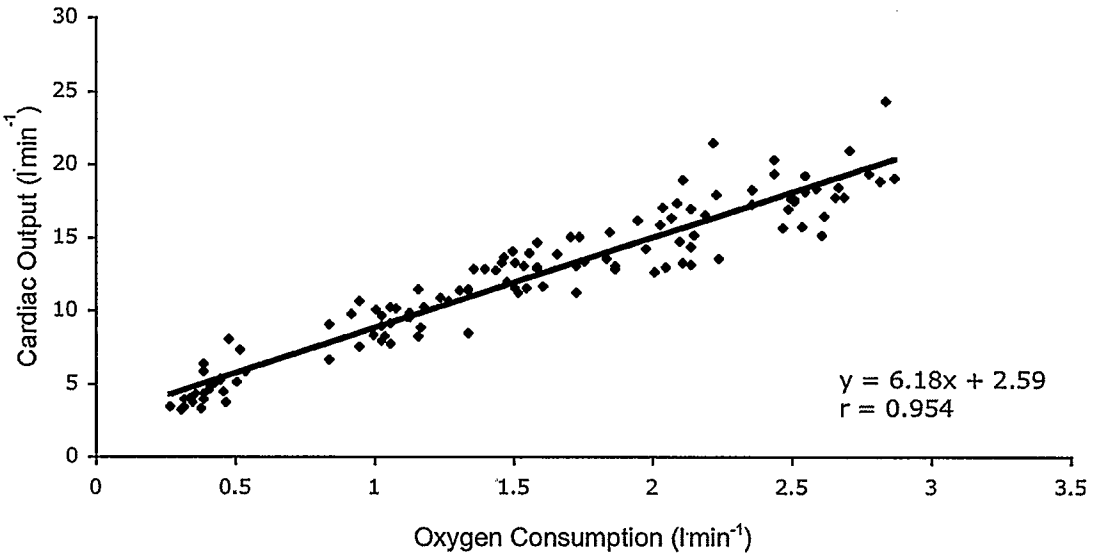

Figure 19. Cardiac output as measured by CO_2 rebreathing plotted versus oxygen consumption for all subjects.

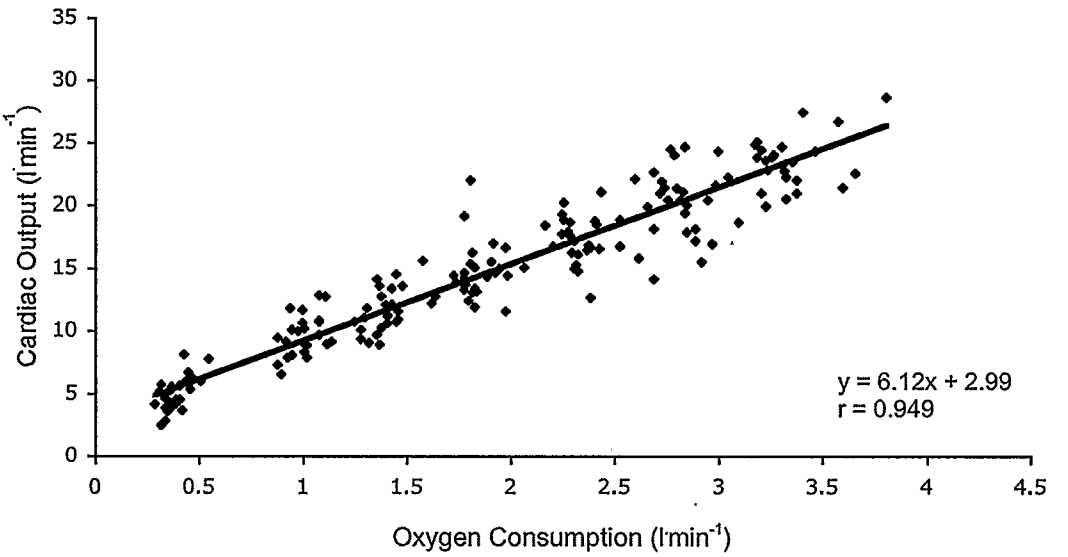

Figure 20. Cardiac output as measured by open-circuit acetylene uptake plotted versus oxygen consumption for all subjects.

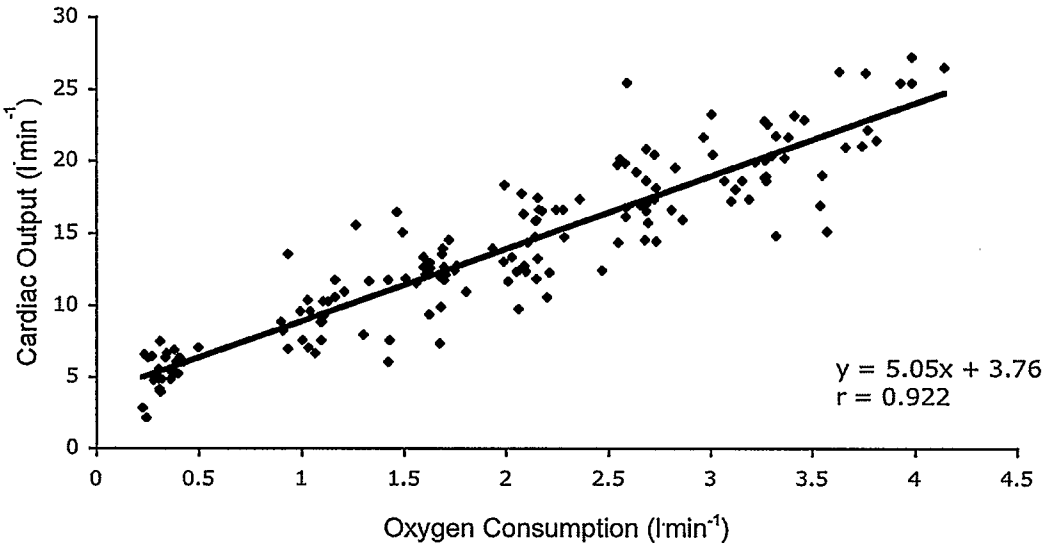

Figure 21. Cardiac output as measured by single-breath acetylene uptake plotted versus oxygen consumption for all subjects.

CHAPTER 5: Discussion

The purpose of the present study was to assess the reliability of the open-circuit acetylene uptake technique and the single-breath constant exhalation acetylene uptake technique to measure cardiac output, and to compare the values measured by these techniques with those of CO_2 rebreathing. Comparisons of resting cardiac output values were also made with echocardiography measures.

The acetylene uptake principle is based upon several key assumptions. First, the C_2H_2 uptake principle involves the conceptual model of a single alveolar gas compartment attached to the inhaled gas reservoir by an anatomical dead space, and therefore acetylene uptake occurs in proportion to the pulmonary blood flow (Bell et al., 2003). This assumption is the underlying principle of acetylene rebreathing as well, though the mathematics and methods are different (Johnson et al., 2000). Second is the assumption that alveolar and arterial C_2H_2 partial pressures are equal during the measurement of cardiac output (Barker et al., 1999). Mismatch of the alveolar-arterial difference for a soluble gas such as acetylene has been shown to be minimal in a normal lung with minor degrees of ventilation-perfusion ($V_A/\dot{Q}$) mismatch (Hlastala & Robertson, 1978). As well, inert gases such as C_2H_2 are theoretically not diffusion limited (Barker et al., 1999). Thus, in subjects with normal pulmonary function, this assumption is valid.

Reliability of the Acetylene Uptake Techniques

This study demonstrated that duplicate measurements of cardiac output were highly correlated, and were not significantly different ($p > 0.05$) in both the open-circuit

and single-breath techniques. Standard error, expressed as a percentage of the mean, was largest at rest in both techniques (8.6% and 8.5% in the OpCirc and SB techniques, respectively), indicating greater variability in the measurements at rest compared to exercising values. However, standard error expressed as an absolute was consistent from rest to 300 W (Table 5). The day-to-day variation in cardiac output in the present study as measured by the acetylene uptake techniques was no greater than reported variations of heart rate, minute ventilation, or oxygen consumption (Zeidfard et al., 1972). Therefore, variance in measurements at rest may reflect true physiological variability, and be exaggerated when expressed as a percentage due to the low values measured at rest.

The coefficients of variation for both the open-circuit technique and single-breath technique during rest and exercise (Table 5) were similar to values produced for other non-invasive techniques (Table 7). In traditional non-invasive techniques, including C_2H_2 rebreathing and CO_2 rebreathing, measured variability decreases with increasing intensity. Bell et al. (2003) recently reported similar findings with an open-circuit technique based upon the method described by Johnson et al. (2000), where the greatest variability was observed at rest and lower intensity exercise. This was evidenced in the present study, and could be due several factors. The subjects were seated on a bicycle ergometer and about to exercise, and cardiac output variation may have occurred due to non-basal state or pre-exercise anxiety. The open-circuit technique required a rhythmic breathing pattern that was more difficult to maintain accurately at rest, but became more natural as intensity increased. It is also possible that the variation at rest could simply reflect true day-to-day cardiac output variability (Warburton et al., 1998).

Table 7. *Comparison of coefficients of variation reported for non-invasive measurements of cardiac output at rest and submaximal exercise.*

Stage	Study	Method	n	CV of repeated measurements
Rest				
	Present	OpCirc	13	14.10%
		SB	13	17.50%
	Ferguson et al. (1968)	CO_2 RB	13	13.30%
	Wigle et al. (1979)	CO_2 RB	4	19.30%
	Warburton et al. (1998)	C_2H_2 RB	9	10.20%
	Saltin (1964)	C_2H_2 RB	4	10.20%
	Smyth et al. (1984)	C_2H_2 RB	6	26.20%
Submaximal Exercise				
	Present	OpCirc	13	3.6 to 12.0%
		SB	13	7.6 to 14.2%
	Ferguson et al. (1968)	CO_2 RB	13	5.50%
	Wigle et al. (1979)	CO_2 RB	4	10.9 to 20.3%
	Warburton et al. (1998)	C_2H_2 RB	9	2.8 to 4.8%
	Saltin (1964)	C_2H_2 RB	4	5.90%
	Smyth et al. (1984)	C_2H_2 RB	6	8.8%
	Johnson et al. (2000)	OpCirc1	6	3.8 to 1.4%
	Johnson et al. (2000)	OpCirc2	6	3.2 to 1.9%

OpCirc = Open-circuit acetylene uptake; SB = Single-breath acetylene uptake; CO_2 RB = Carbon dioxide rebreathing; C_2H_2 RB = Acetylene rebreathing.

Resting Measurements of Cardiac Output

All resting measurements of $\dot{Q}$ were statistically similar, save for the ASV echocardiographic measurements (Table 6). The ASV measurements were on average 1.82 - 2.67 $l \cdot min^{-1}$ (25-36%) higher than the other techniques. This may be explained by the possibility of suprasternal transducer mismatch with the aortic semi-lunar valves. In

echocardiography, the optimal site for vessel diameter measurement is the narrowest diameter that is most in line with the ultrasound beam being emitted from the transducer in the suprasternal notch (Rowland & Obert, 2002). This generally is either the aortic valve ring at its hinge points or the sinotubular junction. Some debate has surrounded the optimal site for determining aortic cross sectional area. Since the value for the measured diameter is squared in the determination of area, 'small differences in aortic root dimensions can have a profound effect on stroke volume calculations' (Rowland & Obert, 2002). For example, a difference in 2.0mm can cause error as much as 20%. In the present study, it is likely that diameter measurement that occurred at the aortic semi-lunar valves was greater than that of where the suprasternal notch transducer was recording velocity, therefore overestimating flow through that particular region.

Other resting measurements had comparable means and standard deviations. Traditional resting values of cardiac output range from 4-7 $l \cdot min^{-1}$ (Table 8), into which all of the remaining values fell. Heart rate was not significantly different between resting measures for any of the techniques.

Table 8. *Resting values of cardiac output as reported in previous studies using different measures.*

Study	Method	Resting $\dot{Q}$ ($l \cdot min^{-1}$)
Klausen (1965)	CO_2 RB	6.7 ± 1.4
Wigle et al. (1979)	CO_2 RB	5.5 ± 1.3
Ferguson et al. (1968)	CO_2 RB	5.6 ± 1.6
Lewis et al. (1984)	Echo	4.5 ± 1.2
Christie et al. (1987)	Echo	5.2 ± 1.1
Klausen (1965)	C_2H_2 RB	6.6 ± 1.1
Smyth et al. (1984)	C_2H_2 RB	4.8 ± 1.1
Hunt et al. (1997)	C_2H_2 RB	5.9 ± 0.4
Johnson et al. (2000)	Fick	5.4 ± 1.0
Zenger et al. (1993)	Fick	5.6 ± 2.1
Christie et al. (1987)	Thermo	5.7 ± 1.1
Zenger et al. (1993)	Thermo	5.2 ± 2.0
Smyth et al. (1984)	Dye	7.3 ± 1.9
Ferguson et al. (1968)	Dye	6.0 ± 1.6
Barker et al. (1999)	OpCirc	4.5 ± 1.3
Johnson et al. (2000)	OpCirc1	5.3 ± 1.2
Johnson et al. (2000)	OpCirc2	5.5 ± 1.4
Zenger et al. (1993)	SB	4.8 ± 2.2

OpCirc = Open-circuit acetylene uptake; SB = Single-breath acetylene uptake; CO_2 RB = Carbon dioxide rebreathing; C_2H_2 RB = Acetylene rebreathing; Echo = Doppler echocardiography; Fick = Direct Fick; Thermo = Thermodilution; Dye = Dye dilution.

Comparison of Acetylene Uptake Techniques with CO_2 rebreathing

The linear regression of cardiac output and oxygen consumption for CO_2 rebreathing was $\dot{Q} = 6.12 \times \dot{V}O_2 + 2.99\ l \cdot min^{-1}$, which is similar to regressions obtained in previous studies. Wigle et al. (1977) reported a regression for cardiac output and oxygen consumption of $\dot{Q} = 5.91 \times \dot{V}O_2 + 3.62\ l \cdot min^{-1}$, while Zeidfard et al. (1972) reported a regression of $\dot{Q} = 5.82 \times \dot{V}O_2 + 3.04\ l \cdot min^{-1}$. Zeidfard et al. (1972) reported that the cardiac output-oxygen consumption regression in their study was almost identical to the combined data of nine separate studies that was reported by Rowell (1969) in which cardiac output was measured by direct methods. The CO_2 rebreathing technique

provides an accurate method of determining $\dot{Q}$ during submaximal conditions (Warburton et al., 1999a), and in this study, $\dot{Q}$ obtained by CO_2 rebreathing was similar to the open-circuit technique (Figure 19). The regression of the single-breath method diverged from the CO_2 rebreathing regression, such that $\dot{Q}$ at 200W in the single-breath technique was significantly lower ($p < 0.05$) than $\dot{Q}$ in CO_2 rebreathing. There was no difference between measures of $\dot{Q}$ in the CO_2 rebreathing technique and the open-circuit technique at any power output up to the maximum power output that CO_2 rebreathing was measured.

The single-breath technique has previously been shown to underestimate cardiac output when compared with both direct Fick and thermodilution methods in normal subjects at rest (Zenger et al., 1993). This may be due to physiologic, intracardiac, or pulmonary shunts limiting pulmonary capillary blood flow, which may become more pronounced with increases in exercise intensity. Also, this may be due to shortened time for the alveolar gases to mix at higher respiratory rates during exercise. However, the conclusion that the SB technique underestimates $\dot{Q}$ may be unwarranted, as the values generated by that technique were well within physiological ranges reported in previous studies at comparable exercise intensities (Astrand et al., 1964; Johnson et al., 2000).

Calculated stroke volume measurements ($\dot{Q} \div HR$) using all three techniques showed increasing SV from rest to 200 W. At power outputs greater than 200 W, SV measured by the OpCirc and SB techniques evidenced signs of a plateau. Reported values of SV have ranged from 60-95 $ml \cdot beat^{-1}$ at rest and 110-195 $ml \cdot beat^{-1}$ during exercise (Astrand et al., 1964; Ekblom & Hermansen, 1968; Gledhill et al., 1994, Zhou et

al., 2001). The measurements in the present study were within these physiological ranges previously reported. The three techniques did show some variability in the calculated stroke volume values; however, it is difficult to determine from the results of this study whether that variability reflects measurement error, or true physiological variability. The subjects displayed a heterogeneous SV-work rate relationship, and subjects who had low SV measurements with one technique were consistently low with the other techniques as well.

Comparison of Results to Other Studies

Many studies have investigated the relationship between cardiovascular and gas-exchange variables, but there does not appear to be a clear consensus on the relation between $\dot{V}O_2$ and $\dot{Q}$. A summary of regression equations for the direct Fick method and dye-dilution, which have been published in the literature, as well as our regressions for C_2H_2 uptake and CO_2 rebreathing are presented in Table 9.

The findings in the present study indicate that both methods of acetylene uptake compare well with previously published measurements. Studies investigating elite and high performance endurance athletes have shown evidence of a steeper regression for $\dot{V}O_2$ vs. $\dot{Q}$ (Barker et al., 1999; Gledhill et al., 1994), which is similar to the data obtained in this study on active male cyclists. The usefulness of comparing the methods of acetylene uptake with data using other techniques, however, is ultimately limited, at best. The abundance of published literature in this area has generated variation in actual accepted values of cardiac output in similar population pools. This has lead to the conclusion that even the most accepted measure of cardiac output has at least a 10%

variation with repeated measurements in the same subject (Driscol et al., 1989). It therefore stands that it may be inappropriate to conclude that one technique 'overestimates' or 'underestimates' values of another method (Rowland & Obert, 2002). The reliability of the techniques thus becomes much more significant, particularly when wanting to assess change or improvement in an individual's cardiovascular profile.

Table 9. *Regression equations, where $Q = C \times VO_2 + Y_o$, from literature compared with regressions from present study.*

Study	Regression Equation	Method	Subject training status
Johnson et al. (2000)	y = 4.60x + 4.65*	Fick	Active & Untrained
Barker et al. (1999)	y = 4.71x + 5.63	Fick	Active
Ekblom & Hermansen (1968)	y = 5.30x + 7.24*	Dye	Highly Trained
Astrand et al. (1964)	y = 5.10x + 4.15*	Dye	Active
Smyth et al. (1984)	y = 4.82x + 6.70	Dye	Active
Smyth et al. (1984)	y = 5.04x + 4.67	C_2H_2 RB	Active
Gledhill et al. (1994)	y = 5.10x + 6.62	C_2H_2 RB	Untrained
Gledhill et al. (1994)	y = 5.92x + 7.18	C_2H_2 RB	Highly Trained
Zeidfard et al. (1972)	y = 5.82x + 3.04	CO_2 RB	Untrained
Wigle et al. (1979)	y = 5.91x + 3.62	CO_2 RB	Untrained
Barker et al. (1999)	y = 6.67x + 2.38	Open-Circuit	Highly Trained
Present Study	y = 6.18x + 2.59	CO_2 RB	Active & Trained
Present Study	y = 6.12x + 3.00	Open-Circuit	Active & Trained
Present Study	y = 5.05x + 3.76	Single-Breath	Active & Trained

RB, rebreathing. * Regression equations calculated on the basis of raw data provided.

Blood:Gas Partition Coefficient

The solubility of a gas in liquid is given by its Ostwald solubility coefficient. This represents the ratio of the concentration in blood to the concentration in the gas phase, and is independent of pressure, obeying Henry's law. The alveolar membrane poses no barrier to the transfer of C_2H_2 in either direction. The major determinants of

solubility are thought to be serum proteins and red blood cells (RBC's) (Barker et al. 1999). Lower blood:gas coefficients have been seen with hemodilution, obesity, hypoalbuminaemia, and starvation, while higher coefficients have been seen in adults versus children, hypothermia, and postprandially (following a meal) (Jibelian et al., 1981).

Traditionally in acetylene rebreathing, the blood:gas partition coefficient is assumed and held constant for each subject. Reported values for C_2H_2 solubility range from 0.740 to 0.843 $mlC_2H_2 \cdot 100ml\ blood^{-1}$ (Barker et al., 1999; Wagner et al., 1974), though most commonly a value of 0.740 is used. However, as the blood:gas solubility is affected by several factors, the value of measuring this value individually holds some merit. Barker et al. (1999) showed very weak correlation between solubility and hemoglobin (Hb; $r^2 = 0.10$) and hematocrit (Hct; $r^2 = 0.05$), and thus correcting C_2H_2 solubility for the Hb level is not a good substitution for measuring the actual value. In the present study, we used a constant value of 0.80 $ml \cdot ml \cdot tissue^{-1} \cdot atm^{-1}$, based on the median value presented from the subject pool in Barker et al. (1999).

Limitations – Open-Circuit

This technique is limited in use to laboratories with access to a mass spectrometer or infrared acetylene analyzer, and requires large amounts of acetylene mixed gas to be consumed during the sampling period. Due to the length of the wash-in period, the amount of gas consumed was sometimes as high as 350 litres. The length of sampling time is in itself a limitation, as repeated measures of the open-circuit technique are difficult to obtain, particularly at lower intensities. Sampling times at rest were as long as

3-minutes, and the subsequent washout time of acetylene was correspondingly high. To obtain multiple measurements at rest or submaximal intensities, the subjects are required to maintain a given workload for up to 10-minutes for two readings.

A limitation specific to this study was in the assumption of the blood-gas partition coefficient. Barker et al. (1999) measured this factor using gas chromatography and found it to be quite variable (0.596-0.910 $mlC_2H_2 \cdot 100ml\ blood^{-1}$). It is acceptable to use an assumed constant value for reliability purposes and measuring change provided there is no significant intra-individual variation from day to day, though it limits the use of the technique in measuring individual absolute cardiac output. This contention is in agreement with the conclusions of Barker et al. (1999) that where possible this variable should be measured.

Limitations – Single-Breath

The single-breath technique was shown to be a reliable measure of cardiac output during rest and submaximal exercise. However, the procedure was difficult to perform at intensities nearing the second ventilatory threshold and during initial pilot work it was determined that the SB technique was difficult or impossible to perform at near maximal intensities. A fundamental procedural issue is the necessity of a constant-flow exhalation. Initial testing in this study found that a constant-flow exhalation is imperative to obtain repeatable data, and this is not feasible at intensities above threshold. This also means that by necessity there is a learning effect for subjects to be able to perform the technique. In this study it was found that 10-minutes of pre-testing practice by the subject was sufficient to learn the technique.

At higher workloads the single-breath method was particularly sensitive to improper subject technique. The method required a maximal, vital capacity inhalation, a constant-flow exhalation between 0.5 $l \cdot min^{-1}$ to 2.0 $l \cdot min^{-1}$, and at least 2-seconds of constant-flow for analysis. If any or all of these factors were missing, the technique would fail. At intensities above threshold, these conditions were very difficult to achieve. For several of the subjects in this study, ventilatory threshold II occurred below or near 300 W, and they were unable to perform the SB procedure with any success at that intensity. It was also observed that there was a significant, but acute, increase in heart rate immediately post-procedure, and the acetylene adapter restricted the airway for breathing. The specialized mouthpiece was particularly prone to difficulties when exposed to salivary or expiratory moisture. During longer testing periods, the mouthpiece screen became partially obstructed, decreasing V_E measurements and increasing the difficulty of breathing.

Conclusions

The OpCirc and SB techniques were both shown to be reliable techniques for measuring cardiac output up to 300 W with OpCirc and 200 W with SB. In the present investigation, the cardiac output measured for the OpCirc technique was similar to cardiac output measurements made with CO_2 rebreathing, though both OpCirc and SB yielded cardiac output values that were comparable to previously reported studies. Both the OpCirc and SB techniques are advantageous for use in cardiac output determination over traditional non-invasive, rebreathing techniques in that there is increased comfort to the subject (increasing or initially high levels of CO_2 do not become a factor) and both

procedures are simple to perform, both for the subject and the tester (Bell et al., 2003). Both methodologies seem suitable for use during exercise testing with some specific limitations. The OpCirc technique did not impose any physical procedural limitations on the subjects, and should be suitable for use at maximum power outputs. However, the SB technique, which required a constant, slow exhalation rate, made the procedure difficult to perform at exercise intensities near or above the second ventilatory threshold, and is thus limited in its use to only sub-threshold exercise. In this respect, the SB technique may not pose much advantage over CO_2 rebreathing, other than a decrease in subject discomfort during the test.

These acetylene uptake techniques may be applied to measure cardiac output in endurance athletes and for training studies. Specifically, they can be used for monitoring how different training modalities can influence the different cardiovascular parameters (calculated stroke volume and a - $\bar{v}O_2$diff). Precise investigations into the influence of training on changes in stroke volume at all intensities of exercise are made possible with the knowledge that cardiac output can be reliably measured. The techniques of the present study allow for truly non-invasive, reliable measurement of cardiac output and calculated stroke volume in sedentary and elite athletes, providing further potential to examine the effects of training and detraining. As demonstrated by Barker et al. (1999), the OpCirc technique has the ability to measure cardiac output during maximal exercise, and thus investigations into the effects of training on maximal cardiac output are possible without having to use a rebreathing or invasive technique.

Future investigations should also include assessing the validity and reliability of both the OpCirc and SB techniques in patients with pulmonary vascular or obstructive

diseases, where significant $V_A/\dot{Q}$ inequality may exist. In patients or subjects with significant $V_A/\dot{Q}$ inequality, the assumptions of the acetylene uptake principle may not hold and is an area for further study (Barker et al., 1999; Johnson et al., 2000). As well, there is a need to assess the reliability of the OpCirc technique at maximal exercise intensities. The potential of the OpCirc technique to simultaneously measure cardiac output and oxygen consumption may lead to further research in the area of possible $\dot{Q}$-$\dot{V}O_2$ dissociation at $\dot{V}O_2max$, as well as understanding cardiovascular contributions to $\dot{V}O_2max$ and performance.

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Appendix A: Informed Consent Form & Ethics Approval

Research Project Title: Comparison and reliability of non-invasive acetylene uptake techniques for measuring cardiac output

Investigators: Danny Dibski, D.J. Smith, PhD, S. R. Norris, PhD, R. Jensen, PhD, G.T. Ford, MD.

This consent form, a copy of which has been given to you, is only a part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, you should feel free to ask. Please take the time to read this carefully and to understand any accompanying information.

The purpose of this investigation is to compare two non-invasive acetylene uptake methods to measure the amount of blood pumped by the heart per minute (known as cardiac output) with traditional non-invasive techniques, and also to assess the reliability of the two acetylene techniques.

Initially, you will be asked to perform an incremental exercise test on a bicycle ergometer to maximal levels to determine your maximal oxygen consumption ($\dot{V}O_2$ max).

On a separate day, you will also perform a 20 km time trial on a bicycle ergometer. This will be a maximal effort ride where you will attempt to ride 20 km as fast as you can. This test will serve as a performance assessment.

There will be four methods used to measure your cardiac output: echocardiography, carbon dioxide (CO_2) rebreathing, open-circuit acetylene uptake (OpCirc), and single-breath constant exhalation acetylene uptake (SbCe).

The first test performed will be echocardiography, and will only be done at rest. You will sit on a stationary bicycle while an ultrasound image is taken of your heart and major blood vessels. The test will be performed at the University of Alberta in Edmonton, AB. We will travel up to Edmonton for one day to have the tests done. Your transportation will be provided, and the whole day is required for travel and testing.

The next three tests (CO_2 rebreathing, OpCirc, and SbCe) will be randomized in the order that you perform them. The CO_2 rebreathing will be performed at the University of Calgary HPL. You will be asked to sit on a bicycle ergometer at rest and ride at four submaximal workloads: 50 W, 100 W, 150 W, and 200 W. Each intensity will be 4 minutes in duration, and during the last 30 seconds (approximately) of each stage, you will rebreathe from a sealed bag containing 12-14% carbon dioxide, and 86-88% oxygen for the purposes of determining cardiac output. You will perform this test twice on separate days.

It is possible that during the rebreathing period, you may feel light-headed or nauseous, though the effects should only be short term and alleviated by breathing room air. At least two Professional Fitness and Lifestyle Consultant (PFLC) certified testing personnel will be present at all times during the test, and will be continually monitoring your condition. If at any time during the test you feel uneasy or uncomfortable, the test will be terminated. Oxygen will be available if required.

The SbCe acetylene uptake test will be performed at the Rockyview Hospital, Calgary, AB. You will be asked to sit on a bicycle ergometer at rest and ride at six submaximal workloads: 50 W, 100 W, 150 W, 200 W, 250 W and 300 W. Each intensity will be 4 minutes in duration, and during the last 30 seconds (approximately) of each stage, you will be instructed to inhale a gas mixture of acetylene (0.3%), methane (0.3%), oxygen (21%), carbon monoxide (0.3%), and nitrogen (78.1%) to maximal lung volume. You will then hold your breath for approximately 2 seconds, followed by an exhalation at a slow, constant rate. You will perform this test twice on separate days. There is very little hazard involved with inhaling the gas mixtures, and the concentrations are such as to pose little risk to your health.

The OpCirc test will be performed at the University of Calgary HPL. During the OpCirc test, you will be asked to sit on a bicycle ergometer at rest and ride at six submaximal workloads: 50 W, 100 W, 150 W, 200 W, 250 W, and 300 W. Each intensity will be 4 minutes in duration, and during the last 30 seconds (approximately) of each stage, a valve will be turned so that you begin to inhale a gas mixture of acetylene (0.7%), helium (5%), oxygen (21%), and nitrogen (73%) for 20-25 breaths. The change in inspired gas will not be noticeable, and you will continue to breath normally. You will perform this test twice on separate days.

Five subjects will be randomly selected to assess the reliability of the two acetylene uptake methods. If you are selected, you will be required to perform the reliability procedure, which will be performed on the OpCirc method and SbCe method. For the reliability procedure, you will sit on a bicycle ergometer at rest for eight minutes. Cardiac output measurements (as described above) will be taken at the 4, 6, and 8 minute marks. At the end of the eight minutes, you will immediately begin to cycle at 50 W for 5 minutes. At the end of that 5 minutes, the load will be increased to 100 W. You will ride at that intensity (100 W) for eight minutes. Cardiac output measurements (as described above) will be taken at the 4, 6, and 8 minute marks. At the end of that eight minute period, the load will be decreased to 50 W, and you will ride at that intensity for 5 minutes. At the end of the 5 minutes, the load will be increased to 200 W, and you will ride at that intensity for eight minutes. Cardiac output measurements (as described above) will be taken at the 4, 6, and 8 minute marks. The test is finished after the eighth minute at 200 W.

The time commitment for the study is approximately six weeks. The time commitment for each testing session will take approximately one hour. It is asked that you refrain

from any strenuous activity for at least 24 hours before testing, and attempt to follow the same eating pattern before each testing session.

The benefit to you from participating in this study is a knowledge of what your cardiac output is at a given workload. The researchers will be available to answer particular questions you may have to help you target specific training adaptations to improve both health and performance. You are also contributing to an advancement of knowledge in this area of research.

All information gathered during this investigation will be kept in strict confidence, and your name will be replaced with an identifying code on all project documents. Any publications resulting from this research will report results as group mean values. Therefore, your individual results will not be highlighted. Participation in this project is voluntary and you reserve the right to withdraw at any time without prejudice. Data will be kept in locked storage for a period of 5 years and then destroyed. During storage only the investigators and laboratory staff will have access to the data.

In the event that you are injured as a result of participating in this research, the University of Calgary, and the researchers involved in this study will provide no compensation for your treatment. You will be responsible for paying for any treatment your doctor recommends that is not covered by health care insurance. You still have your legal rights. Nothing said here about treatment or compensation in any way alters your right to recover damages.

Your signature on this form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time. Your continued participation should be as informed as your initial consent, so you should feel free to ask for clarification or new information throughout your participation. If you have further questions concerning matters related to this research, please contact: Danny Dibski (220-2221), or David Smith, Ph.D. (220-3440).

If you have any questions concerning your rights as a possible participant in this research, please contact Patricia Evans at the Office of Research Services, University of Calgary, at 220-3782.

_____ _____

Participants Signature Date

Investigator and/or Delegate's Signature	Date
Witness Signature	Date

A copy of this consent form has been given to you to keep for your records and reference.

UNIVERSITY OF CALGARY

FACULTY OF MEDICINE

Office of Medical Bioethics
Heritage Medical Research Building/Rm 93
Telephone: (403) 220-7990
Fax: (403) 283-8524

2001-05-14

Dr. D.J. Smith
Faculty of Kinesiology
University of Calgary
KN B2228
Calgary, Alberta.

Dear Dr. Smith:

Re: Comparison and Reliability of Non-Invasive Acetylene Uptake Techniques for Measuring Cardiac Output
Student: Mr. Daniel Dibski **Degree: MSc**

The above-noted thesis proposal has been submitted for Committee review and found to be ethically acceptable. Please note that this approval is subject to the following conditions:

(1) a copy of the informed consent form must have been given to each research subject, if required for this study;
(2) a Progress Report must be submitted by 2002-05-14, containing the following information:
    (i) the number of subjects recruited;
    (ii) a description of any protocol modification;
    (iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
    (iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
    (v) a copy of the current informed consent form;
    (vi) the expected date of termination of this project;
(3) a Final Report must be submitted at the termination of the project.

Please note that you have been named as a principal collaborator on this study because students are not permitted to serve as principal investigators. Please accept the Board's best wishes for success in your research.

Yours sincerely,

Christopher J. Doig, MD, MSc, FRCPC
Chair, Conjoint Health Research Ethics Board

cc: Adult Research Committee
Dr. W. Herzog (information)
Mr. Daniel Dibski

Appendix B: Subject Physical and Performance Characteristics

Table 10. Individual physical characteristics

Subject	Age (years)	Height (cm)	Weight (kg)	HR max ($b \cdot min^{-1}$)
1	27	184	77.8	179
2	31	181	92.4	161
3	33	169	76.6	192
4	27	190	92.6	193
5	36	186	84.0	180
6	28	174	72.7	176
7	26	184	84.1	187
8	27	188	79.8	187
9	28	174	70.8	195
10	28	178	74.8	188
11	36	177	77.3	181
12	36	199	110.0	180
13	39	170	70.5	173

Table 11. Individual performance characteristics

Subject	VO_2 max ($l \cdot min^{-1}$)	VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$)	MAP (Watts)	VO_2 at VTII ($l \cdot min^{-1}$)	P.O. at VTII (Watts)
1	4.12	53.0	390	3.48	330
2	4.58	49.6	450	3.57	345
3	3.46	45.1	345	2.68	260
4	4.39	47.4	420	3.37	310
5	4.55	54.1	410	3.75	330
6	4.11	56.5	405	3.29	300
7	4.85	57.7	400	3.44	290
8	4.75	59.6	435	4.10	350
9	4.01	57.5	345	2.84	245
10	4.07	54.4	390	3.14	280
11	4.18	54.1	420	3.33	320
12	5.89	53.5	555	4.99	480
13	3.92	55.6	365	2.74	275

Appendix C: Individual Cardiac Output Measurements

SUBJECT 1

Open Circuit

	Power Output (W)	VO_2 (l·min^{-1})	Q (l·min^{-1})	HR (b·min^{-1})	SV (ml·beat^{-1})	a-vO_2diff (ml·100ml^{-1})
Test 1	0	0.44	5.9	61	97	7.4
	50	0.88	7.2	72	100	12.2
	100	1.30	11.0	88	125	11.8
	150	1.82	13.0	104	125	14.1
	200	2.25	19.2	121	159	11.7
	250	2.72	20.9	136	154	13.0
	300	3.26	23.8	157	151	13.7
Test 2	0	0.47	6.2	67	93	7.6
	50	0.94	11.7	78	151	8.0
	100	1.31	11.7	93	126	11.2
	150	1.78	19.1	108	176	9.3
	200	2.17	18.3	125	147	11.8
	250	2.77	24.4	144	170	11.3
	300	3.24	22.8	160	142	14.2
Single Breath						
Test 1	0	0.40	5.2	67	78	7.8
	50	1.10	7.5	79	95	14.7
	100	1.68	11.9	92	129	14.1
	150	2.09	16.3	109	150	12.8
	200	2.36	17.3	126	137	13.7
	250	3.01	23.2	150	155	13.0
	300	3.64	26.2	168	156	13.9
Test 2	0	0.39	5.2	61	85	7.5
	50					
	100	1.70	11.7	90	130	14.5
	150	1.99	13.0	105	124	15.3
	200	2.55	19.7	123	160	12.9
	250	3.27	20.0	146	137	16.4
	300	3.77	26.1	166	157	14.4
CO_2 Rebreathing						
Test 1	0	0.46	4.4	68	65	10.5
	50	0.84	9.0	75	120	9.3
	100	1.44	12.7	89	143	11.3
	150	2.11	18.9	109	173	11.2
	200	2.44	20.3	127	160	12.0
Test 2	0	0.45	5.3	66	80	8.5
	50	0.95	10.6	78	136	9.0
	100	1.47	13.6	97	140	10.8
	150			108		
	200	2.44	19.3	128	151	12.6

Echo (l·min^{-1})	Supine ASV	Upright ASV	LVOT
	5.9	6.2	4.4

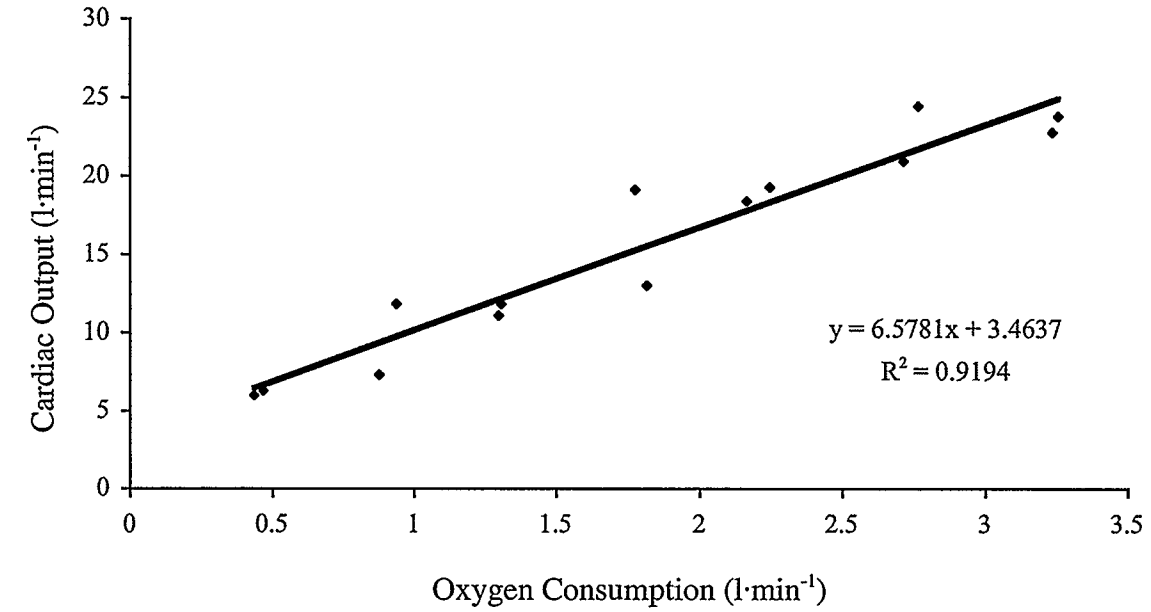

Figure 22. Cardiac output vs. oxygen consumption for the OpCirc technique (Subject 1).

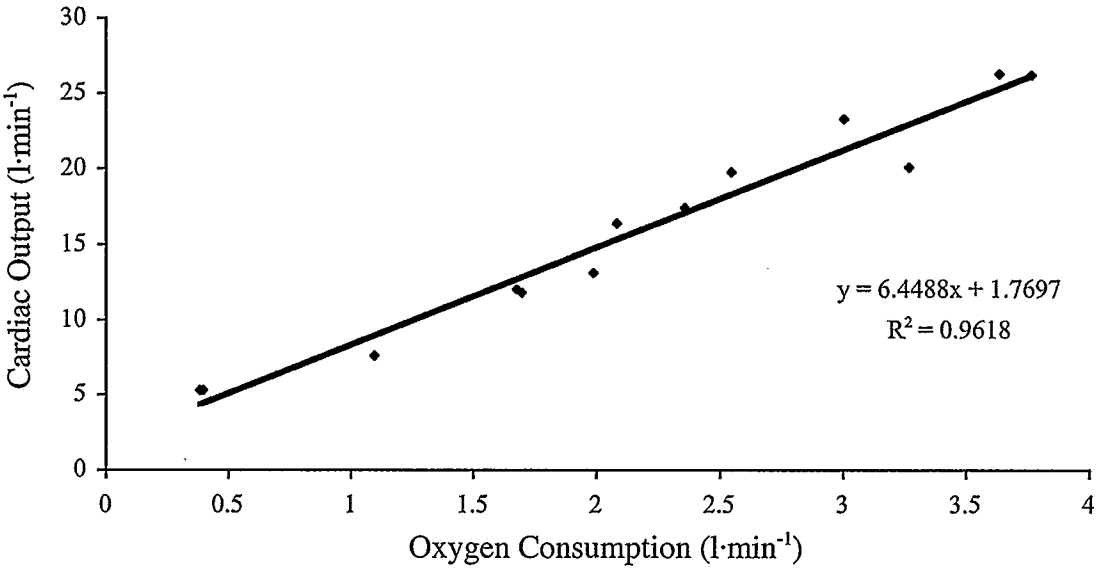

Figure 23. Cardiac output vs. oxygen consumption for the SB technique (Subject 1).

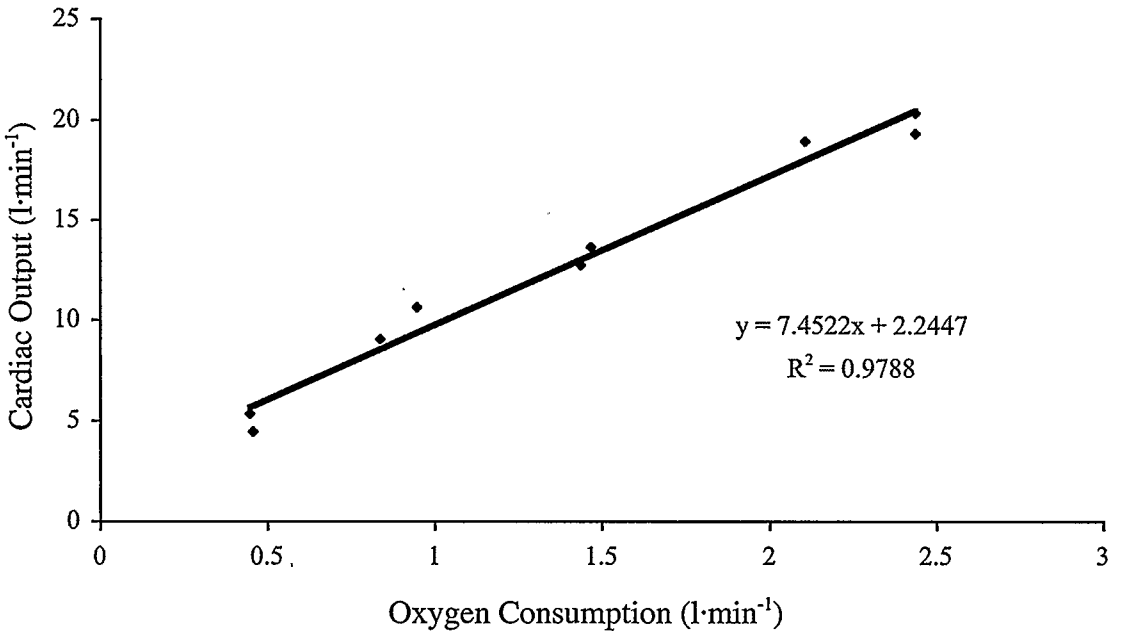

Figure 24. Cardiac output vs. oxygen consumption for the CO_2 rebreathing technique (Subject 1).

SUBJECT 2

Open Circuit

	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Test 1	0	0.46	5.3	70	75	8.7
	50	1.08	10.6	84	127	10.2
	100	1.43	12.0	92	131	11.9
	150	1.78	14.2	99	143	12.6
	200	2.21	16.7	111	150	13.3
	250	2.76	20.4	123	165	13.6
	300	3.23	23.5	135	174	13.7
Test 2	0	0.43	8.0	73	110	5.3
	50	1.11	12.7	81	156	8.8
	100	1.45	14.4	92	157	10.0
	150	1.92	16.9	101	168	11.3
	200	2.31	14.9	110	135	15.5
	250	2.84		124		
	300	3.19	23.8	135	176	13.4
Single Breath						
Test 1	0	0.37	4.8	62	77	7.6
	50	1.00	9.5	77	123	10.5
	100	1.69	13.5	96	141	12.5
	150	2.03	13.3	104	128	15.3
	200	2.59	16.7	117	143	15.5
Test 2	0	0.32	3.9	60	65	8.1
	50	1.01	7.5	75	100	13.5
	100	1.63	9.3	88	106	17.5
	150	2.21	10.5	101	104	21.0
	200	2.68	14.5	115	126	18.5
	250	3.27	22.7	131	173	14.4
CO_2 Rebreathing						
Test 1	0	0.32	3.9	63	62	8.2
	50	0.84	6.6	68	97	12.7
	100	1.34	8.4	76	111	16.0
	150	1.73	11.2	87	129	15.4
	200	2.01	12.6	96	131	16.0
Test 2	0	0.47	3.7	63	59	12.7
	50	1.00	8.3	74	112	12.0
	100	1.34	11.3	84	135	11.9
	150	1.87	13.0	82	159	14.4

Echo ($l \cdot min^{-1}$)	**Supine ASV**	**Upright ASV**	**LVOT**
	Echo not performed		

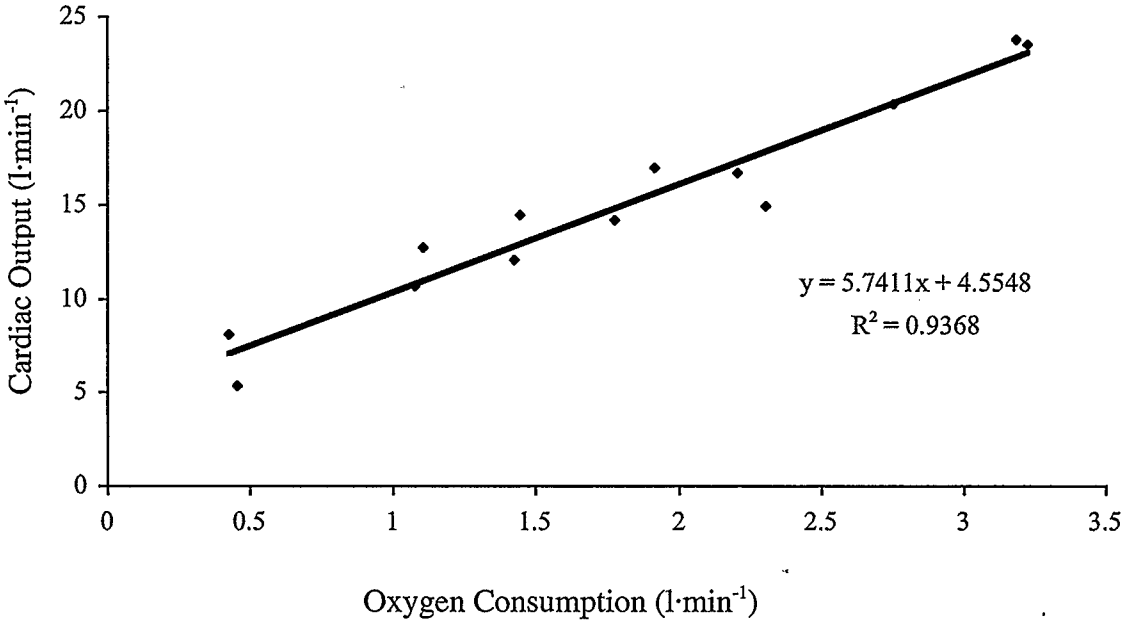

Figure 25. Cardiac output vs. oxygen consumption for the OpCirc technique (Subject 2).

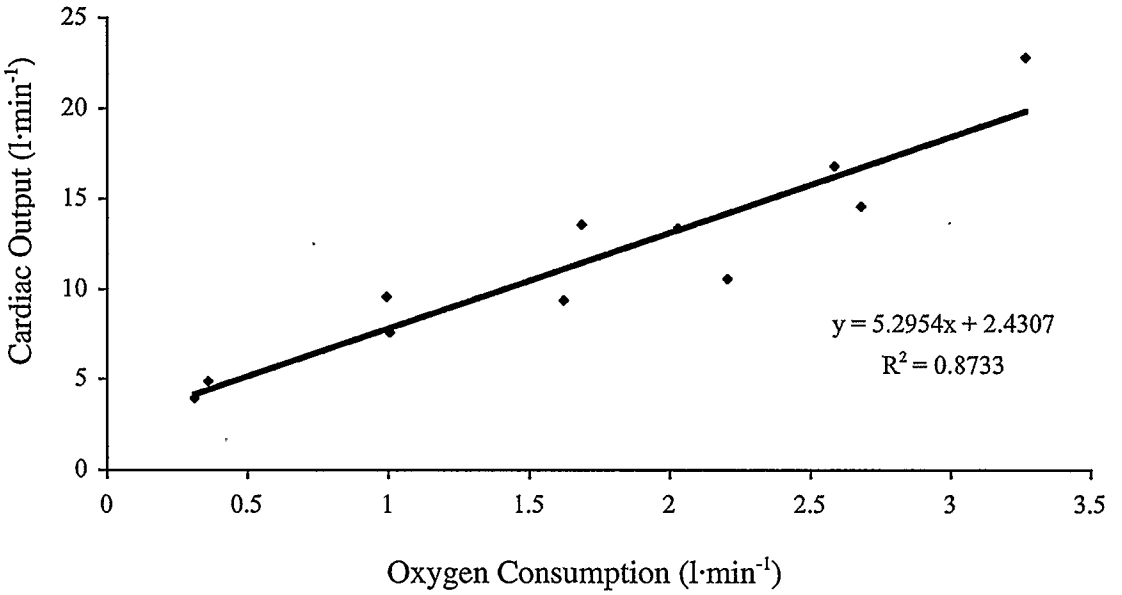

Figure 26. Cardiac output vs. oxygen consumption for the SB technique (Subject 2).

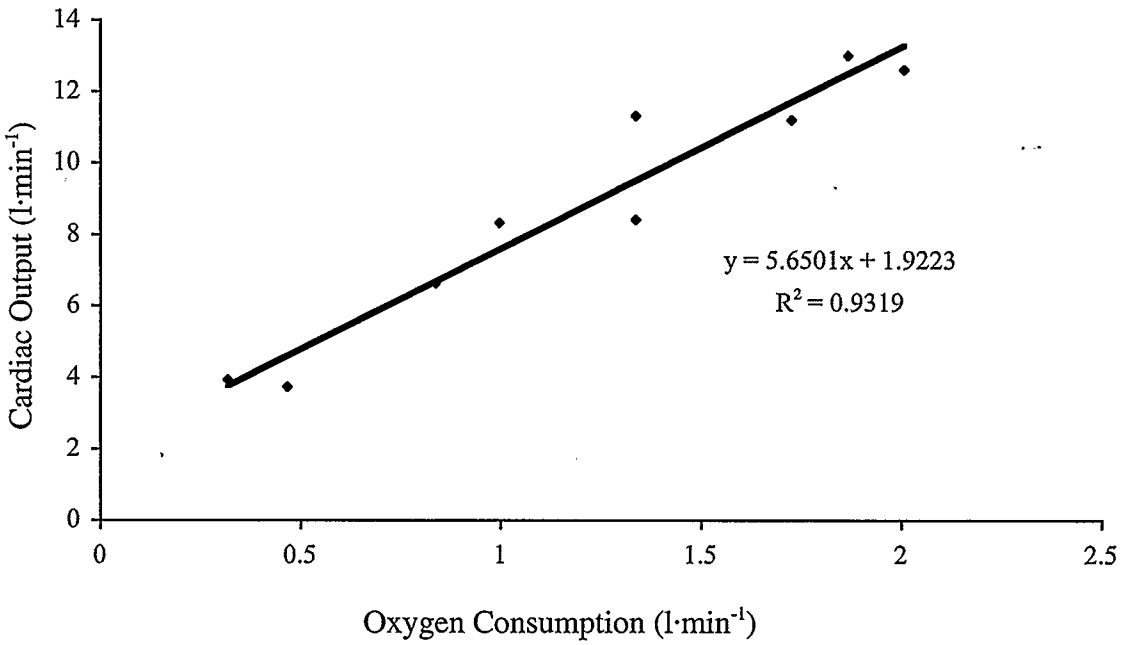

Figure 27. Cardiac output vs. oxygen consumption for the CO_2 rebreathing technique (Subject 2).

SUBJECT 3

Open Circuit

	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Test 1	0	0.33	4.8	84	57	6.9
	50	1.01	8.9	109	81	11.4
	100	1.40	11.6	122	95	12.1
	150	1.78	13.6	136	100	13.1
	200	2.31	17.1	154	111	13.5
	250	2.62	15.7	168	94	16.7
	300	2.97	16.8	178	95	17.6
Test 2	0	0.39	4.4	87	51	8.8
	50	1.08	9.6	110	87	11.2
	100	1.41	10.5	122	86	13.4
	150	1.95	14.9	137	109	13.1
	200	2.43	16.5	152	108	14.8
	250	2.69	18.0	165	109	14.9
	300	3.21	20.9	180	116	15.4
Single Breath						
Test 1	0	0.36	5.4	91	59	6.7
	50	1.10	8.8	117	75	12.5
	100	1.60	12.6	138	91	12.7
	150	2.07	12.4	147	84	16.7
	200	2.59	19.8	166	119	13.1
Test 2	0	0.31	4.1	73	56	7.6
	50	1.06		105		
	100	1.68	7.3	124	59	23.0
	150	2.09	12.7	140	91	16.5
	200	2.69	17.0	159	107	15.8
	250	3.16	18.6	177	105	17.0
CO_2 Rebreathing						
Test 1	0	0.32	3.4	65	52	9.4
	50	0.92	9.7	107	91	9.5
	100	1.48	11.9	119	100	12.4
	150			134		
	200	2.24	13.5	147	92	16.6
Test 2	0	0.39	4.3	73	59	9.1
	50	1.06	9.1	104	88	11.6
	100	1.51	11.5	117	98	13.1
	150	2.11	13.2	134	99	16.0
	200	2.47	15.6	147	106	15.8

Echo ($l \cdot min^{-1}$)	**Supine ASV**	**Upright ASV**	**LVOT**
	Echo not performed		

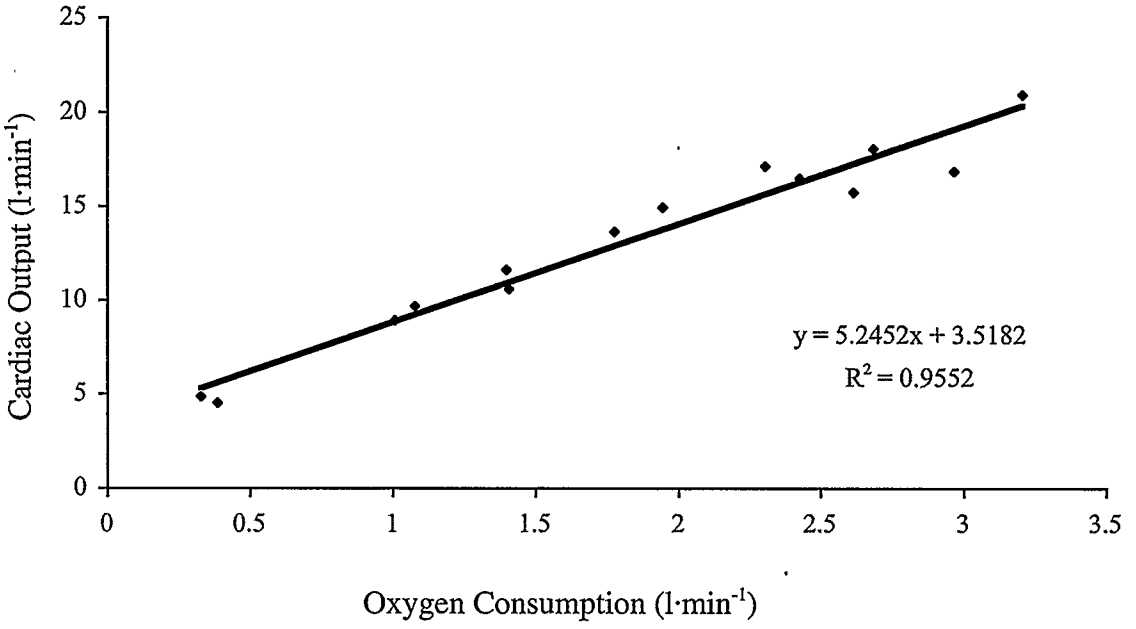

Figure 28. Cardiac output vs. oxygen consumption for the OpCirc technique (Subject 3).

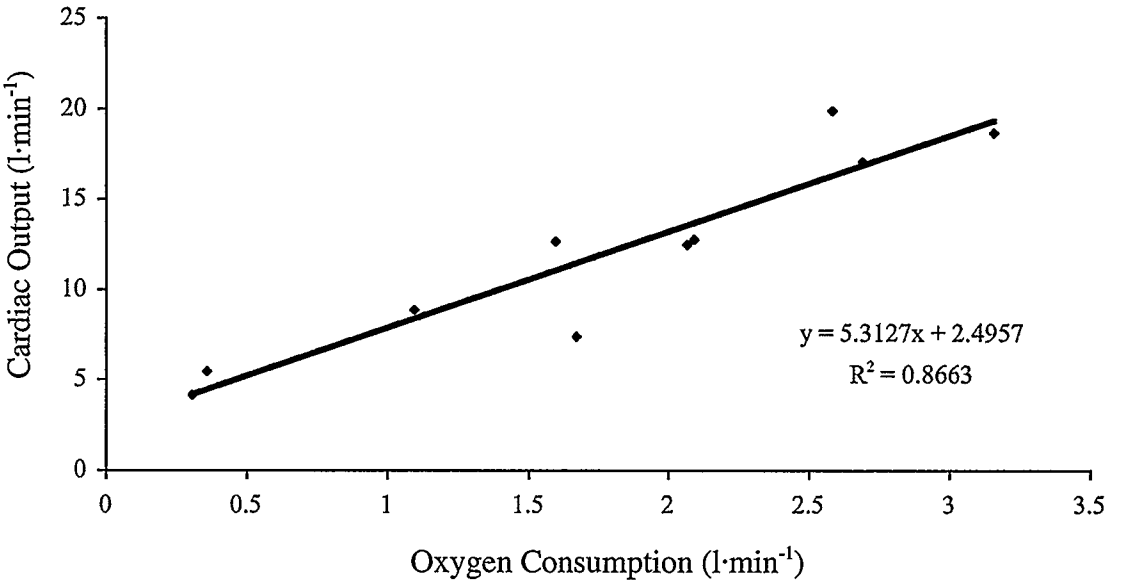

Figure 29. Cardiac output vs. oxygen consumption for the SB technique (Subject 3).

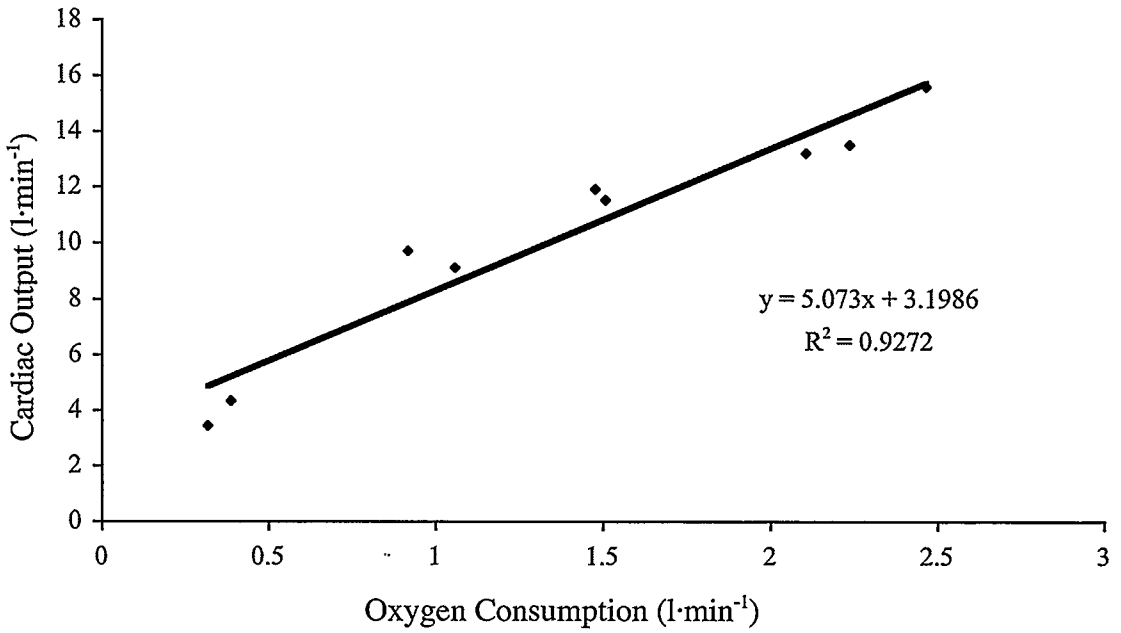

Figure 30. Cardiac output vs. oxygen consumption for the CO_2 rebreathing technique (Subject 3).

SUBJECT 4

Open Circuit

	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Test 1	0	0.35	3.5	84	42	10.0
	50	0.92	9.1	101	90	10.1
	100	1.32	9.0	115	78	14.7
	150	1.83	15.0	130	115	12.2
	200	2.33	14.7	150	98	15.8
	250	2.89	18.0	168	107	16.0
	300	3.36	23.4	179	131	14.4
Test 2	0	0.45	6.6	89	74	6.8
	50					
	100	1.43	13.3	119	112	10.7
	150	1.74	13.8	130	106	12.6
	200	2.30	16.2	151	107	14.2
	250	2.84	19.3	167	116	14.7
	300	3.33	20.4	180	114	16.3
Single Breath						
Test 1	0	0.42		84		
	50	1.33	11.6	101	115	11.5
	100	1.70	12.6	115	110	13.5
	150	2.17	16.6	130	128	13.0
	200	2.69	18.6	150	124	14.5
	250	3.28	18.6	168	111	17.6
	300	3.82	21.4	179	120	17.9
Test 2	0	0.41	6.3	83	76	6.5
	50	1.24		101		
	100	1.63	12.9	116	111	12.6
	150	2.15	15.8	131	121	13.6
	200	2.69	16.5	148	111	16.3
	250	3.31	20.3	165	123	16.3
	300	3.78	22.1	178	124	17.1
CO_2 Rebreathing						
Test 1	0	0.52	7.3	88	83	7.1
	50	1.18	10.2	106	96	11.6
	100	1.40	12.8	122	105	10.9
	150	1.84	13.5	136	99	13.6
	200	2.78	19.3	159	121	14.4
Test 2	0	0.39	5.8	89	65	6.7
	50	1.13	9.5	108	88	11.9
	100	1.51	13.2	122	108	11.4
	150	1.85	15.3	141	109	12.1
	200	2.49	16.9	165	102	14.7

Echo ($l \cdot min^{-1}$)	**Supine ASV**	**Upright ASV**	**LVOT**
	8.4	7.2	4.7

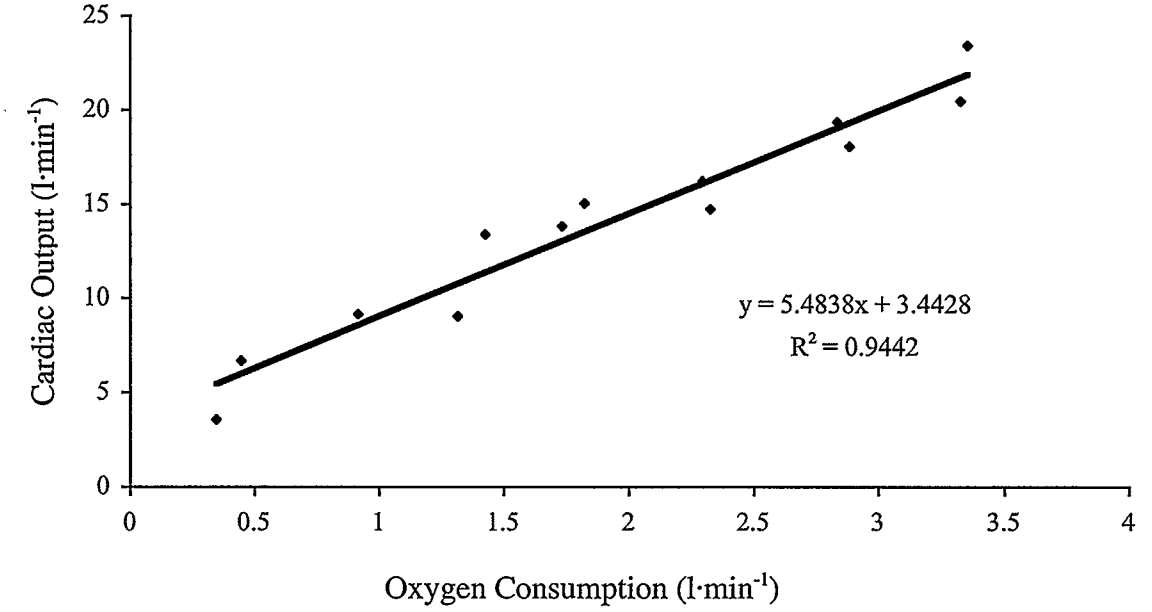

Figure 31. Cardiac output vs. oxygen consumption for the OpCirc technique (Subject 4).

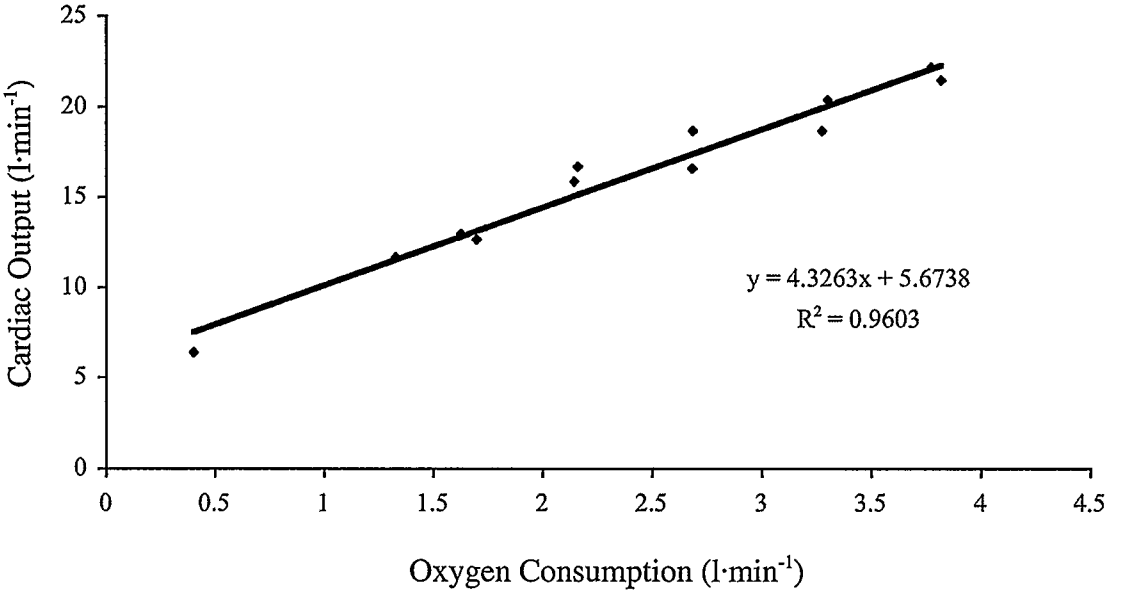

Figure 32. Cardiac output vs. oxygen consumption for the SB technique (Subject 4).

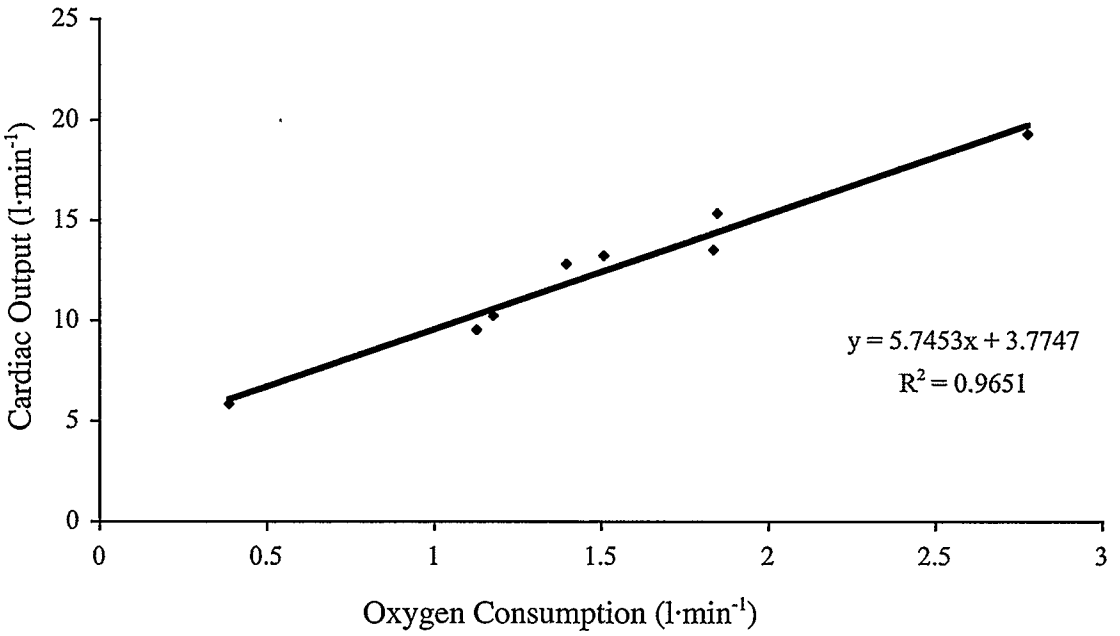

Figure 33. Cardiac output vs. oxygen consumption for the CO_2 rebreathing technique (Subject 4).

SUBJECT 5

Open Circuit

	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Test 1	0	0.29	4.1	56	73	7.1
	50	0.93	7.8	71	109	12.0
	100	1.28	9.3	82	113	13.8
	150	1.73	14.3	101	142	12.1
	200	2.25	17.7	119	148	12.7
	250	2.69	22.6	139	162	11.9
	300	3.41	27.4	158	173	12.5
Test 2	0	0.42	3.6	53	68	11.6
	50	1.14	9.1	79	115	12.6
	100	1.62	12.1	94	129	13.4
	150	1.93	14.5	107	136	13.3
	200	2.53	16.7	124	134	15.2
	250	2.99	21.6	138	156	13.9
	300	3.47	24.2	160	151	14.3
Single Breath						
Test 1	0	0.28	4.7	56	84	6.0
	50	0.90	8.8	68	129	10.3
	100	1.43	11.7	90	130	12.2
	150	2.08	17.7	117	151	11.8
	200	2.69	20.8	140	149	12.9
	250	3.28	22.5	158	142	14.6
Test 2	0	0.31	4.0	53	75	7.8
	50	1.03	10.3	74	139	10.0
	100	1.50	15.0	95	158	10.0
	150	2.18	16.5	119	139	13.2
	200	2.83	19.5	141	138	14.5
	250	3.42	23.1	159	145	14.8
	300	4.15	26.5	172	154	15.7
CO_2 Rebreathing						
Test 1	0	0.36	4.3	58	74	8.4
	50	1.03	8.9	77	116	11.6
	100	1.59	14.6	94	155	10.9
	150	1.71	15.0	109	138	11.4
	200	2.55	19.2	126	152	13.3
Test 2	0	0.41	4.6	55	84	8.9
	50	1.01	10.0	78	128	10.1
	100	1.46	13.2	90	147	11.1
	150	1.76	13.3	110	121	13.2
	200	2.51	17.6	121	145	14.3

Echo ($l \cdot min^{-1}$)	**Supine ASV**	**Upright ASV**	**LVOT**
	Echo not performed		

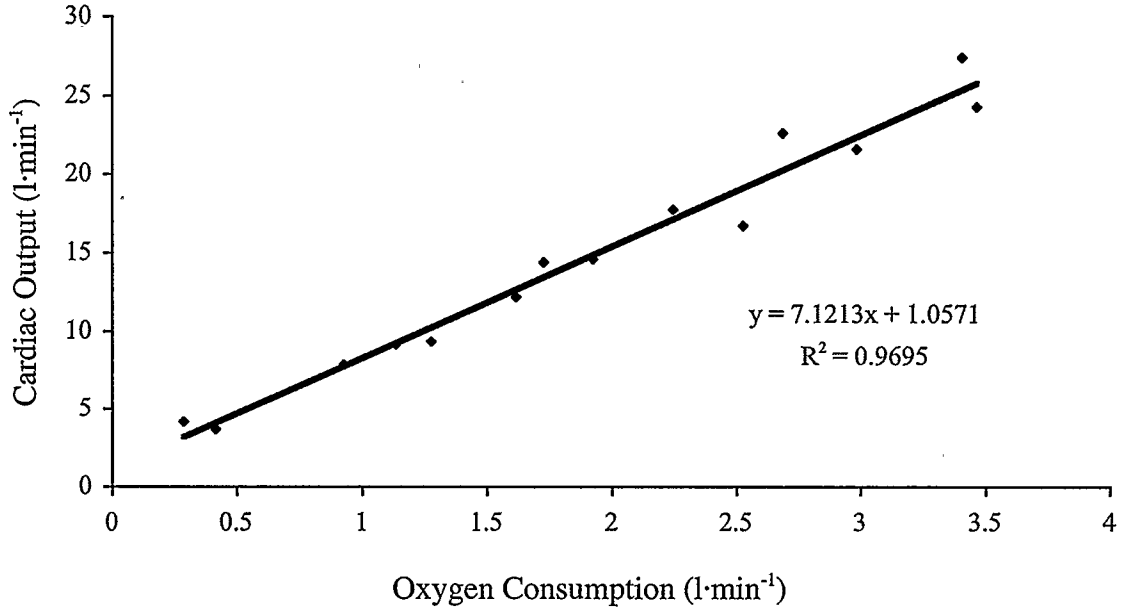

Figure 34. Cardiac output vs. oxygen consumption for the OpCirc technique (Subject 5).

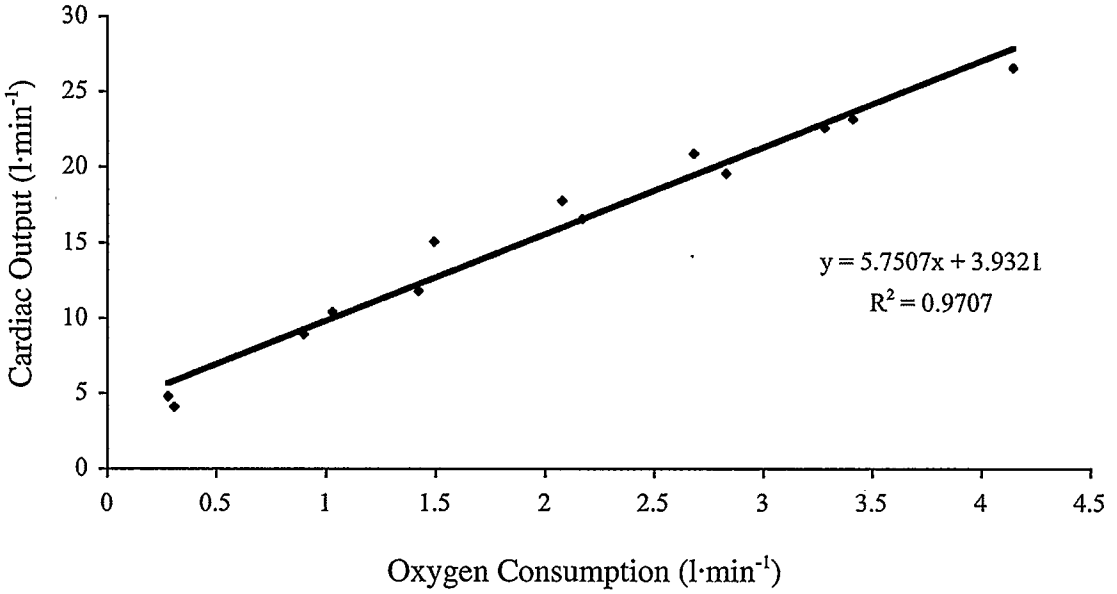

Figure 35. Cardiac output vs. oxygen consumption for the SB technique (Subject 5).

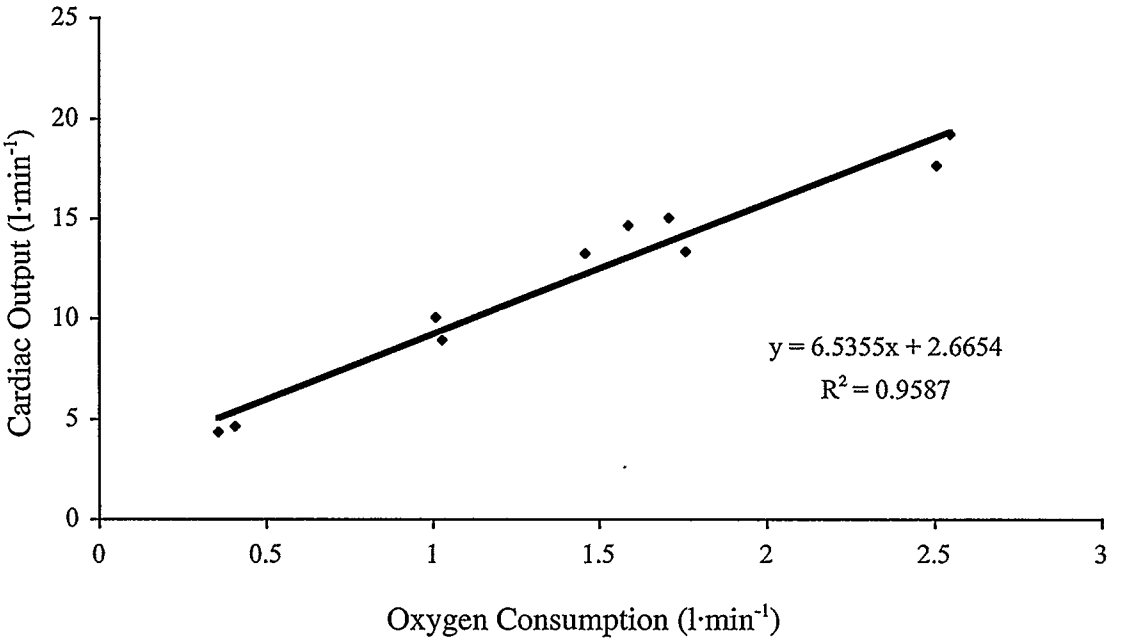

Figure 36. Cardiac output vs. oxygen consumption for the CO_2 rebreathing technique (Subject 5).

SUBJECT 6

Open Circuit

	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Test 1	0	0.41	4.4	57	78	9.2
	50	1.08	12.8	82	156	8.5
	100	1.58	15.5	94	165	10.2
	150	1.91	15.4	111	139	12.4
	200	2.42	18.4	125	147	13.1
	250	2.95	20.4	140	145	14.5
	300	3.38	21.9	157	140	15.4
Test 2	0	0.39	4.1	60	68	9.6
	50	1.08	10.7	87	123	10.1
	100	1.48	13.5	101	134	11.0
	150	1.98	16.6	114	145	12.0
	200	2.44	21.0	129	163	11.6
	250	2.85	20.0	148	135	14.3
	300	3.32	22.7	162	140	14.6
Single Breath						
Test 1	0	0.43	6.0	55	109	7.2
	50	1.11	9.2	85	108	12.1
	100	1.75	12.4	105	118	14.1
	150	2.28	16.6	118	141	13.8
	200	2.81	16.6	132	126	16.9
	250	3.39	21.6	147	147	15.7
Test 2	0	0.35	6.6	48	138	5.3
	50	1.10	8.8	76	116	12.5
	100	1.70	12.1	94	129	14.1
	150	2.16	13.2	111	119	16.4
	200	2.74	18.1	129	140	15.1
	250	3.33	21.7	148	147	15.3
CO_2 Rebreathing						
Test 1	0	0.45	5.2	53	98	8.7
	50	1.17	8.8	77	114	13.3
	100	1.73	13.0	96	135	13.3
	150	2.23	17.9	106	169	12.5
	200	2.67	18.4	124	148	14.5
Test 2	0	0.39	6.3	56	113	6.2
	50	1.27	10.6	89	119	12.0
	100	1.74	15.0	101	149	11.6
	150	2.19	16.5	113	146	13.3
	200	2.87	19.0	131	145	15.1

Echo ($l \cdot min^{-1}$)	**Supine ASV**	**Upright ASV**	**LVOT**
	Echo not performed		

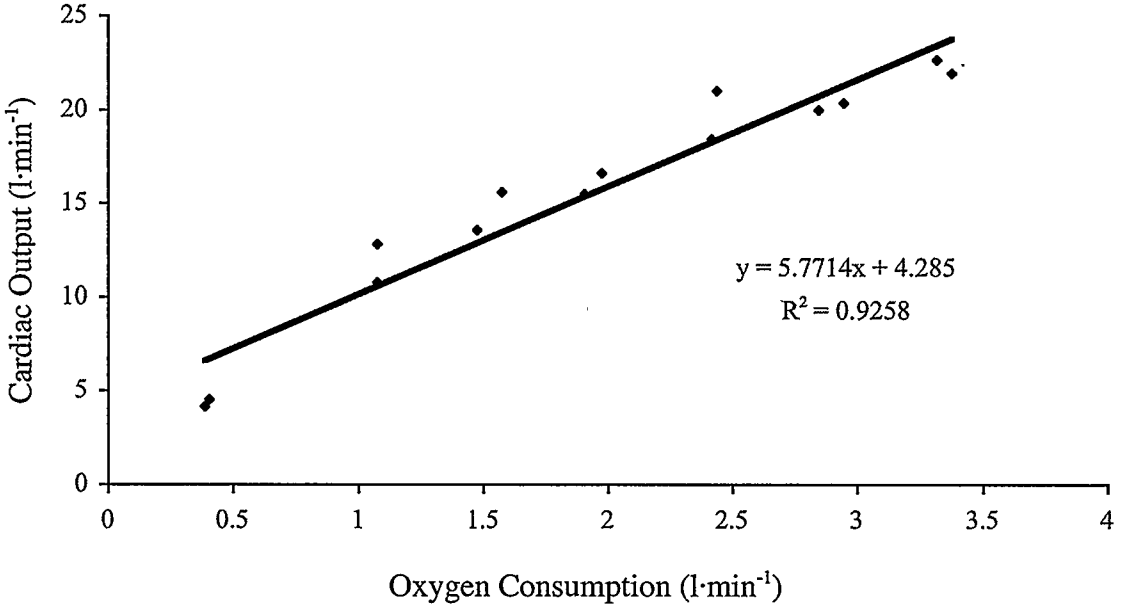

Figure 37. Cardiac output vs. oxygen consumption for the OpCirc technique (Subject 6).

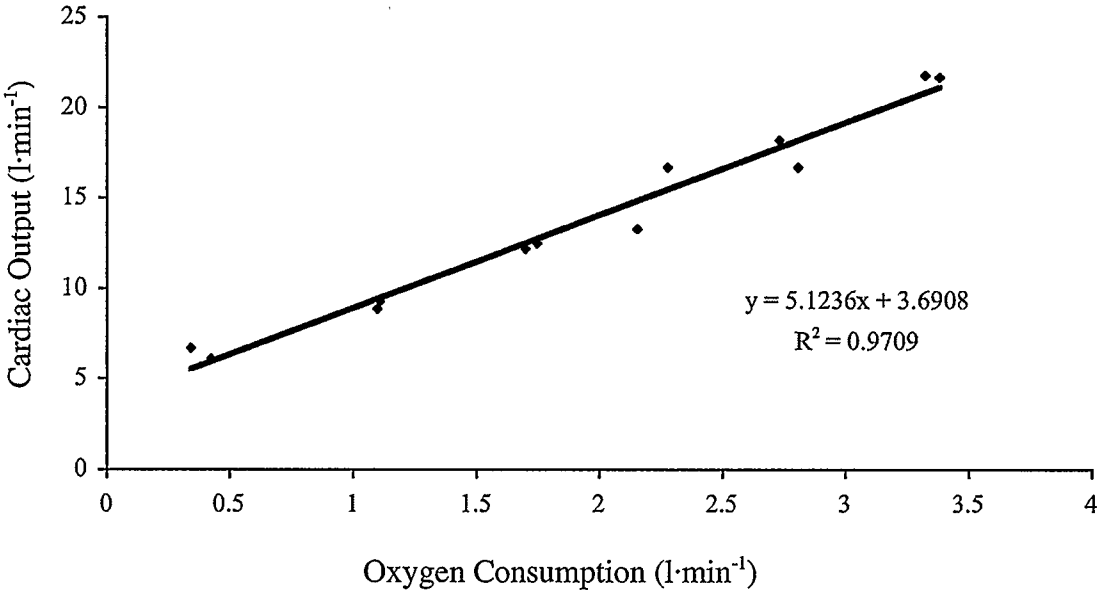

Figure 38. Cardiac output vs. oxygen consumption for the SB technique (Subject 6).

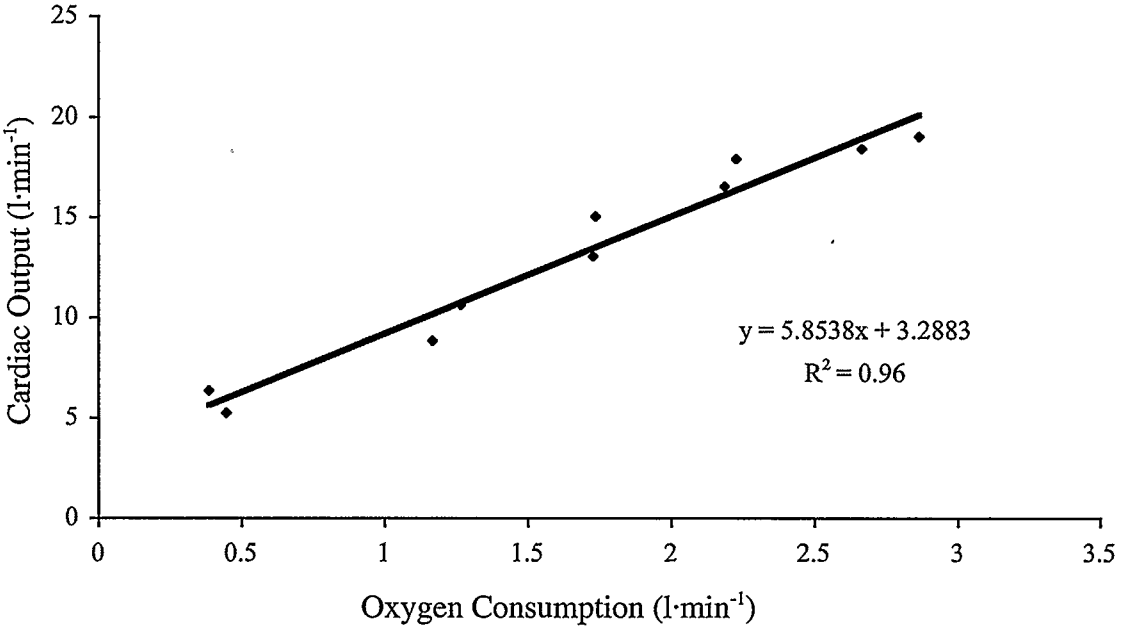

Figure 39. Cardiac output vs. oxygen consumption for the CO_2 rebreathing technique (Subject 6).

SUBJECT 7

Open Circuit

	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Test 1	0	0.36	5.1	62	83	7.0
	50	0.98	9.9	93	106	9.9
	100	1.36	14.1	105	134	9.7
	150	1.81	21.9	116	189	8.3
	200	2.26	20.2	125	161	11.2
	250	2.79	24.0	142	169	11.6
	300	3.31	24.6	158	156	13.5
Test 2	0	0.37	4.1	57	71	9.1
	50	1.00	10.5	89	118	9.5
	100	1.41	11.1	103	108	12.7
	150	1.80	12.3	113	109	14.6
	200	2.26	18.8	122	154	12.0
	250	2.83	21.0	135	156	13.5
	300	3.18	24.8	147	169	12.8
Single Breath						
Test 1	0	0.26	6.3	60	105	4.1
	50	1.17	11.7	96	122	10.0
	100	1.69	13.9	101	138	12.2
	150	2.00	18.3	111	165	10.9
	200	2.56	20.1	126	160	12.7
	250	2.97	21.6	144	150	13.8
Test 2	0	0.31	5.5	66	83	5.6
	50	1.07	6.6	89	74	16.2
	100	1.60	13.3	102	130	12.0
	150	2.16	17.4	116	150	12.4
	200	2.73	20.4	129	158	13.4
	250	3.47	22.8	148	154	15.2
CO_2 Rebreathing						
Test 1	0	0.48	8.0	62	129	6.0
	100	1.31	11.3	105	108	11.6
	200	2.36	18.2	125	146	13.0
Test 2	0	0.43	5.0	57	88	8.6
	50	1.06	10.2	89	115	10.4
	100	1.36	12.8	103	124	10.6
	150	1.95	16.1	113	142	12.1
	200	2.36	17.2	122	141	13.7

Echo ($l \cdot min^{-1}$)	**Supine ASV**	**Upright ASV**	**LVOT**
	8.8	8.65	5.81

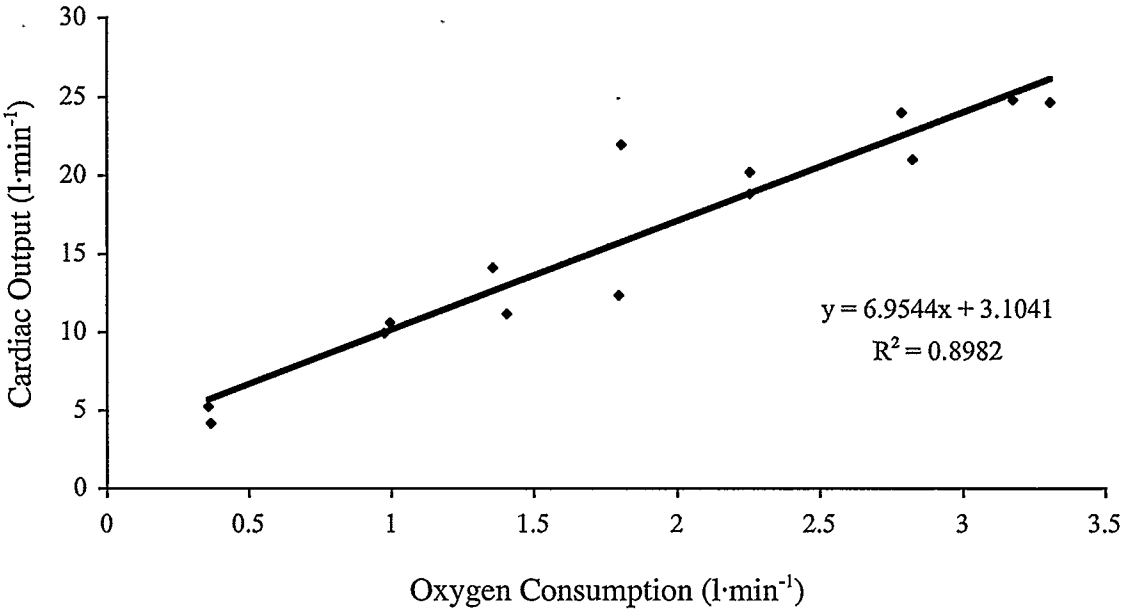

Figure 40. Cardiac output vs. oxygen consumption for the OpCirc technique (Subject 7).

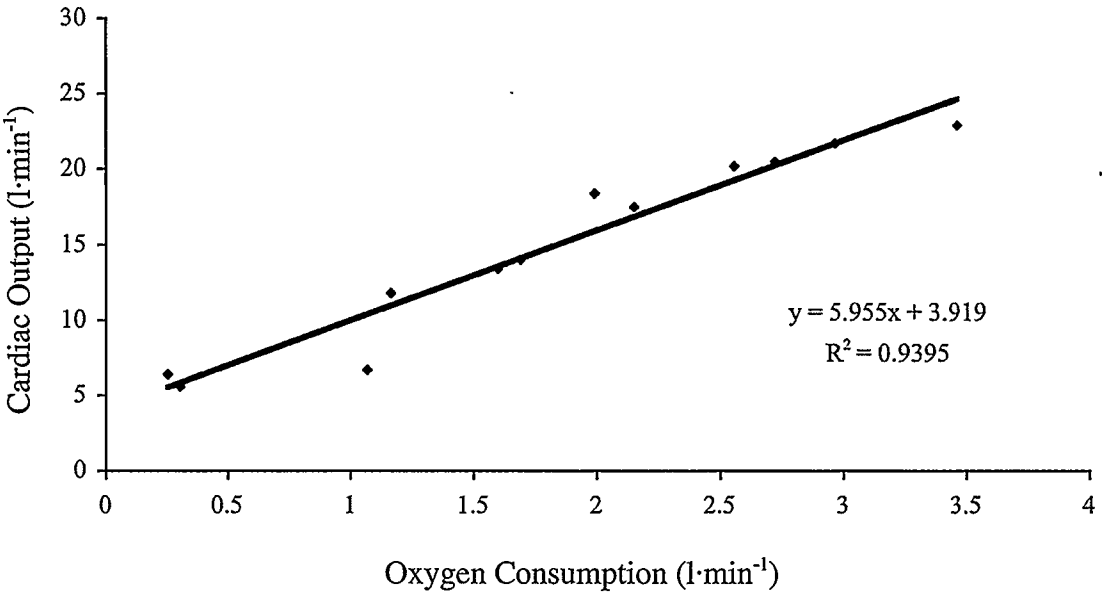

Figure 41. Cardiac output vs. oxygen consumption for the SB technique (Subject 7).

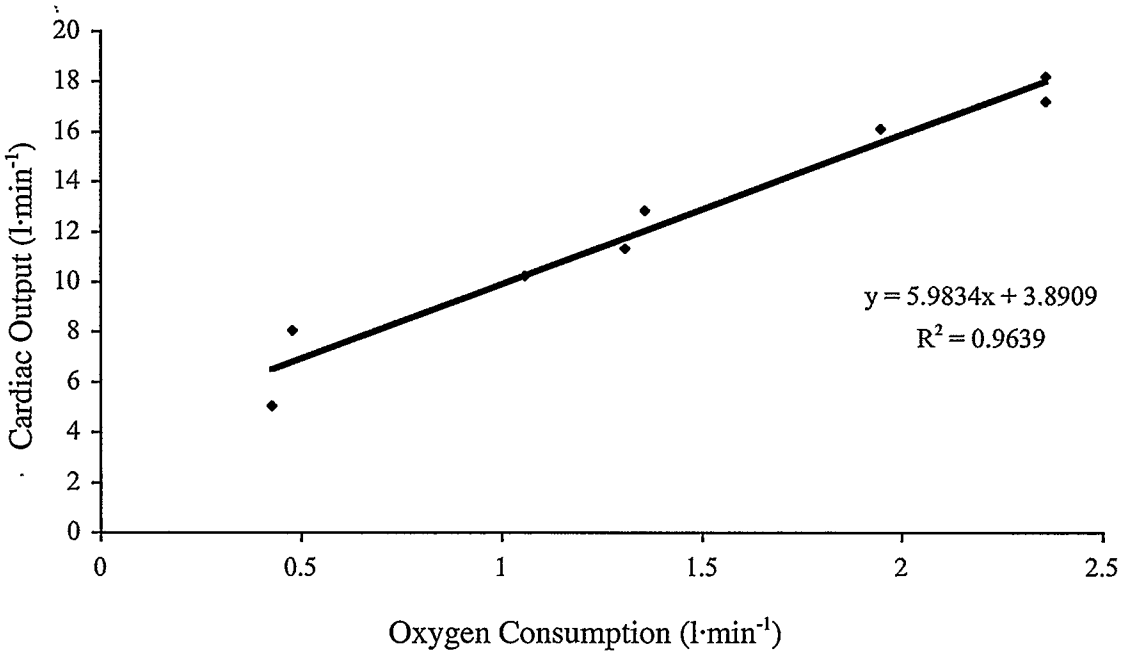

Figure 42. Cardiac output vs. oxygen consumption for the CO_2 rebreathing technique (Subject 7).

SUBJECT 8

Open Circuit

	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Test 1	0	0.34	4.5	73	62	7.5
	50	1.12	8.9	87	102	12.6
	100	1.46	10.8	94	115	13.5
	150	1.98	11.5	104	110	17.3
	200	2.39	12.6	118	107	19.0
	250	2.92	15.4	134	115	18.9
	300	3.60	21.4	155	138	16.8
Test 2	0	0.36	4.3	70	61	8.5
	50	1.02	7.8	82	95	13.1
	100	1.45	10.6	95	112	13.6
	150	1.99	14.3	107	134	13.9
	200	2.60	22.0	125	176	11.8
	250	3.05	22.2	138	161	13.7
	300	3.66	22.5	158	142	16.3
Single Breath						
Test 1	0	0.50	7.0	75	93	7.2
	50	1.17	10.5	81	130	11.1
	100	1.71	12.1	88	138	14.1
	150	2.25	16.6	99	168	13.6
	200	2.87	15.9	115	138	18.0
	250	3.27	18.8	134	140	17.4
	300	3.99	25.4	155	164	15.7
Test 2	0	0.34	6.3	67	94	5.4
	50	1.13	10.2	86	119	11.1
	100	1.57	11.5	97	119	13.6
	150	2.15	11.8	107	110	18.3
	200	2.74	14.4	117	123	19.0
	250	3.07	18.6	137	136	16.5
	300	3.55	19.0	161	118	18.7
CO_2 Rebreathing						
Test 1	0	0.48		66		
	50	1.16	11.4	84	136	10.2
	100	1.56		93		
	150	2.09	17.3	101	171	12.1
	200	2.82	18.8	116	162	15.0
Test 2	0	0.35	3.7	63	59	9.5
	50	1.04	8.2	73	112	12.7
	100	1.54	13.0	88	148	11.8
	150	2.14	14.3	101	142	15.0
	200	2.69	17.7	118	150	15.2

Echo ($l \cdot min^{-1}$)	Supine ASV	Upright ASV	LVOT
	10.2	8.1	6.2

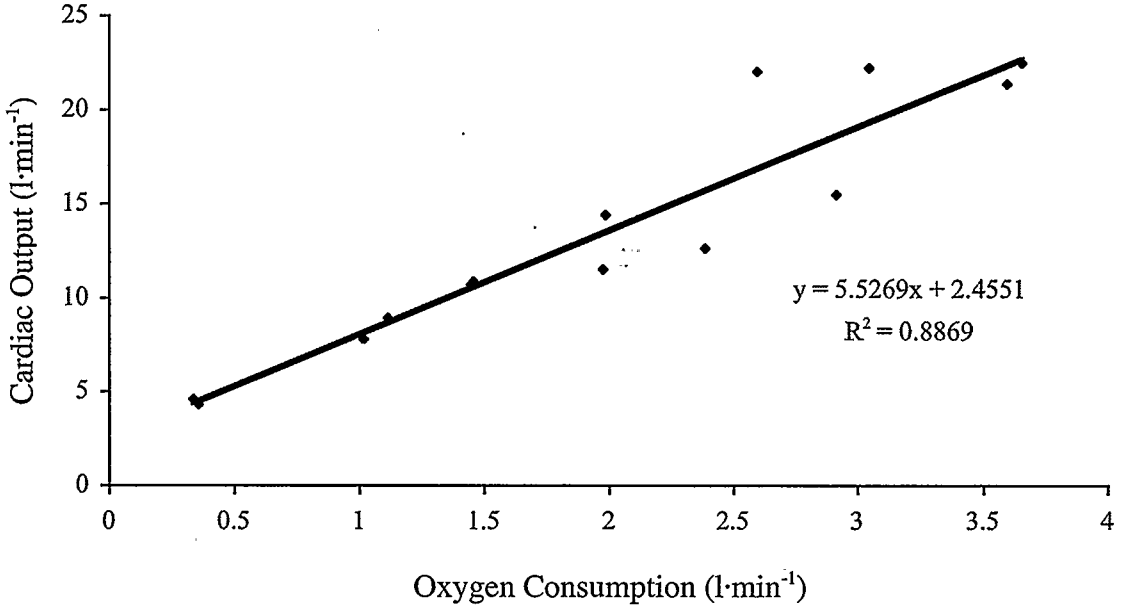

Figure 43. Cardiac output vs. oxygen consumption for the OpCirc technique (Subject 8).

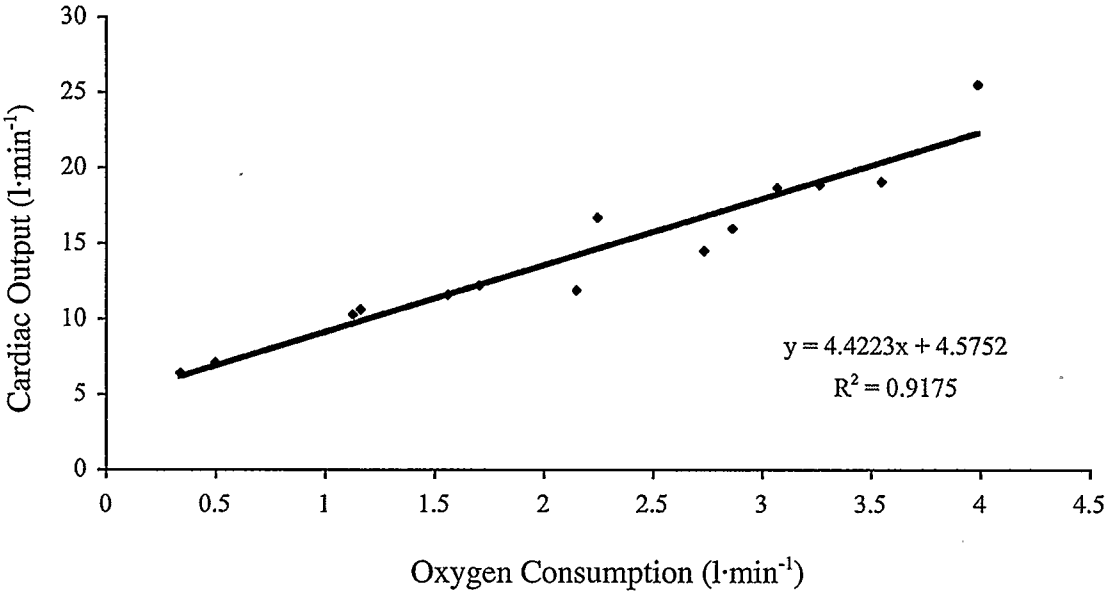

Figure 44. Cardiac output vs. oxygen consumption for the SB technique (Subject 8).

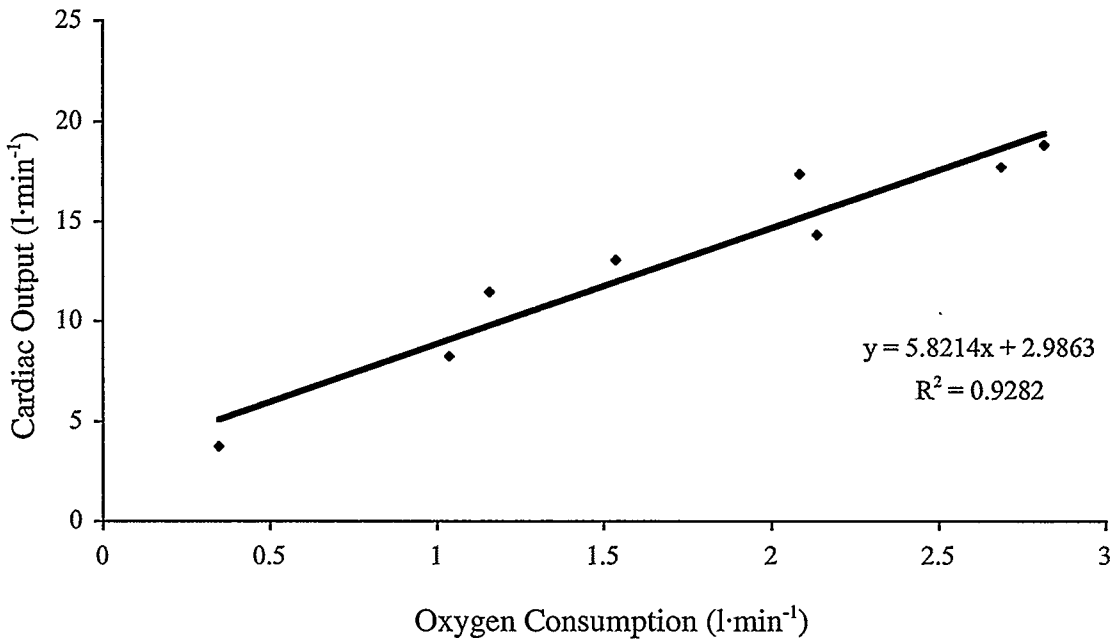

Figure 45. Cardiac output vs. oxygen consumption for the CO_2 rebreathing technique (Subject 8).

SUBJECT 9

Open Circuit

	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Test 1	0	0.36	3.7	76	49	9.7
	50	0.95	8.0	100	80	11.9
	100	1.37	8.8	120	74	15.5
	150	1.83	11.8	142	83	15.5
	200	2.38	16.7	161	104	14.2
	250	2.89	17.1	177	97	16.9
	300	3.10	18.6	182	102	16.7
Test 2	0	0.34	2.8	98	28	12.3
	50	0.90	6.5	112	58	13.9
	100	1.28	10.0	135	74	12.8
	150	1.79	13.6	156	87	13.2
	200	2.32	15.2	174	87	15.3
	250	2.69	14.1	185	76	19.1
	300	3.23	19.9	192	104	16.2
Single Breath						
Test 1	0	0.32	7.4	86	86	4.3
	50	1.14		112		
	100	1.81	10.9	132	83	16.6
	150	2.11	14.3	148	97	14.8
	200	2.69	17.2	172	100	15.6
	250	3.31		182		
	300	3.67	20.9	193	108	17.5
Test 2	0	0.28	6.4	81	79	4.3
	50	1.05	9.5	103	92	11.0
	100	1.61	12.1	131	92	13.3
	150	2.10	12.3	157	78	17.1
	200	2.66	16.9	176	96	15.7
	250	3.33	14.8	189	78	22.5
CO_2 Rebreathing						
Test 1	0	0.33		76		
	50	1.24	10.8	110	98	11.5
	100	1.62		130		
	150	2.07	16.3	152	107	12.7
	200	2.55	18.1	172	105	14.1
Test 2	0	0.35	4.1	82	50	8.5
	50	1.03	7.9	112	71	13.0
	100	1.59	12.8	133	96	12.4
	150	2.04	17.0	156	109	12.0
	200	2.66	17.7	173	102	15.0

Echo ($l \cdot min^{-1}$)	**Supine ASV**	**Upright ASV**	**LVOT**
	9.0	8.2	5.1

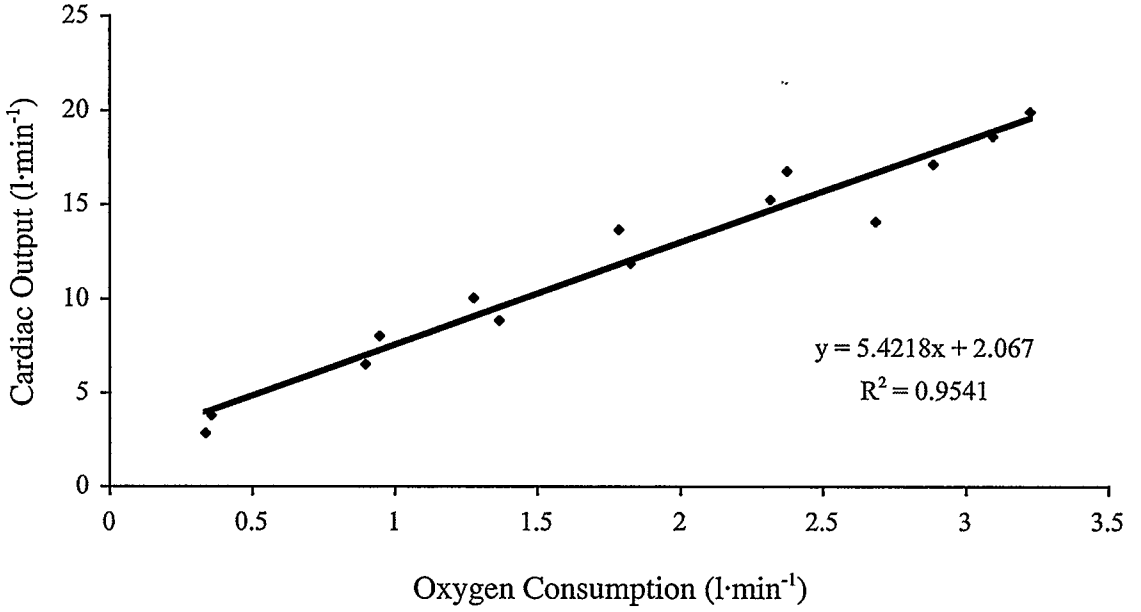

Figure 46. Cardiac output vs. oxygen consumption for the OpCirc technique (Subject 9).

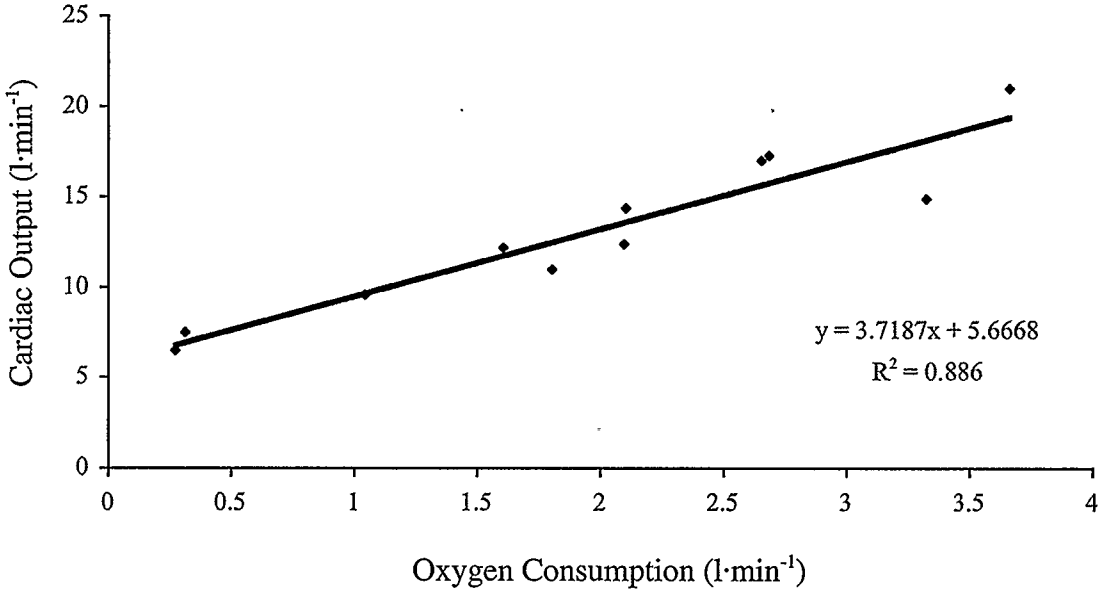

Figure 47. Cardiac output vs. oxygen consumption for the SB technique (Subject 9).

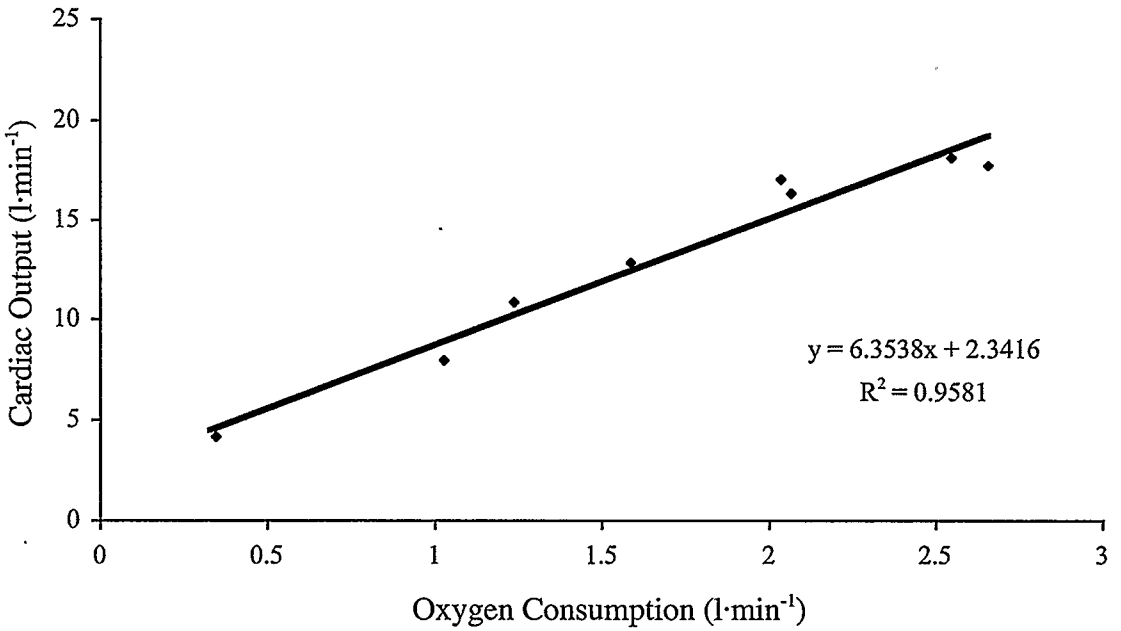

Figure 48. Cardiac output vs. oxygen consumption for the CO_2 rebreathing technique (Subject 9).

SUBJECT 10

Open Circuit

	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Test 1	0	0.32	2.4	54	45	13.3
	50	0.95	10.0	74	135	9.5
	100	1.38	12.7	90	141	10.9
	150	1.81	15.3	110	139	11.9
	200	2.29	17.5	123	142	13.1
	250	2.73	21.8	142	154	12.5
	300	3.21	24.3	157	155	13.2
Test 2	0	0.31	5.1	60	85	6.1
	50	0.88	9.3	79	118	9.4
	100	1.40	12.0	96	125	11.6
	150	1.78	14.5	108	134	12.3
	200	2.28	17.9	127	141	12.8
	250	2.74	21.4	146	146	12.8
	300	3.19	23.8	162	147	13.4
Single Breath						
Test 1	0	0.30	4.8	66	73	6.3
	50	1.11	10.2	82	124	10.9
	100	1.63	12.5	101	124	13.1
	150	1.94	13.9	115	121	13.9
	200	2.64	19.2	134	143	13.8
	250	3.02	20.4	149	137	14.8
Test 2	0	0.24	6.5	60	108	3.7
	50	0.94	13.5	80	169	6.9
	100	1.47	16.4	99	166	9.0
	150	2.06	12.3	118	104	16.7
	200	2.59	25.4	136	187	10.2
CO_2 Rebreathing						
Test 1	0	0.31	3.2	85	38	9.7
	50	1.12	9.5	98	97	11.8
	100	1.55	11.5	108	106	13.5
	150	2.05	12.9	133	97	15.9
	200	2.54	15.7	146	108	16.2
Test 2	0	0.38	3.3	57	58	11.5
	50	1.16	8.2	84	98	14.1
	100	1.61	11.6	98	118	13.9
	150	2.14	13.1	115	114	16.3
	200	2.61	15.1	136	111	17.3

Echo ($l \cdot min^{-1}$)	**Supine ASV**	**Upright ASV**	**LVOT**
	8.1	7.2	6.95

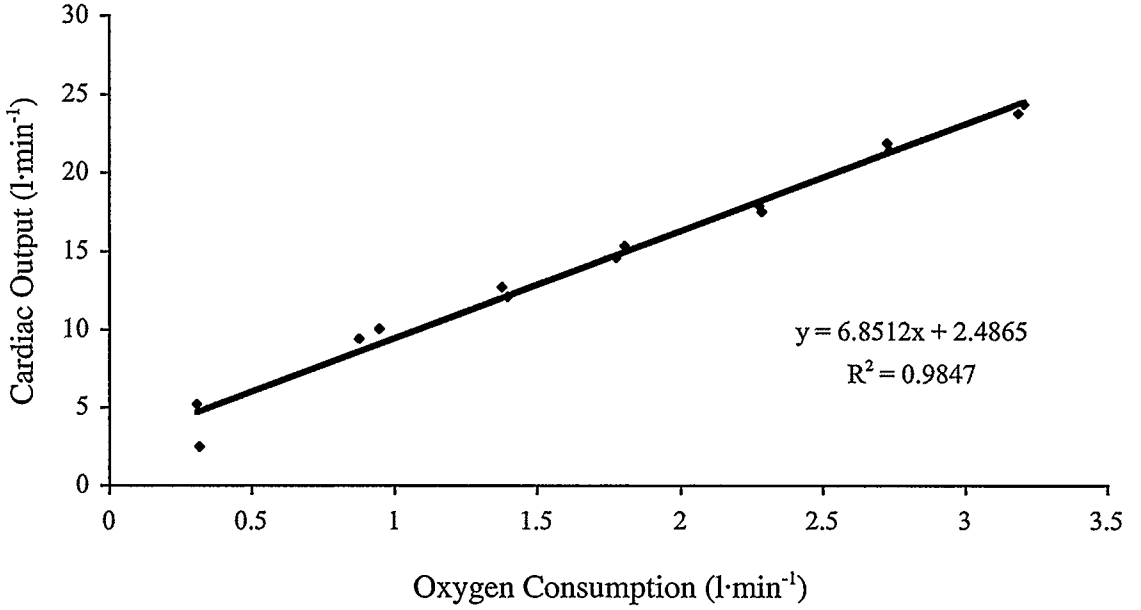

Figure 49. Cardiac output vs. oxygen consumption for the OpCirc technique (Subject 10).

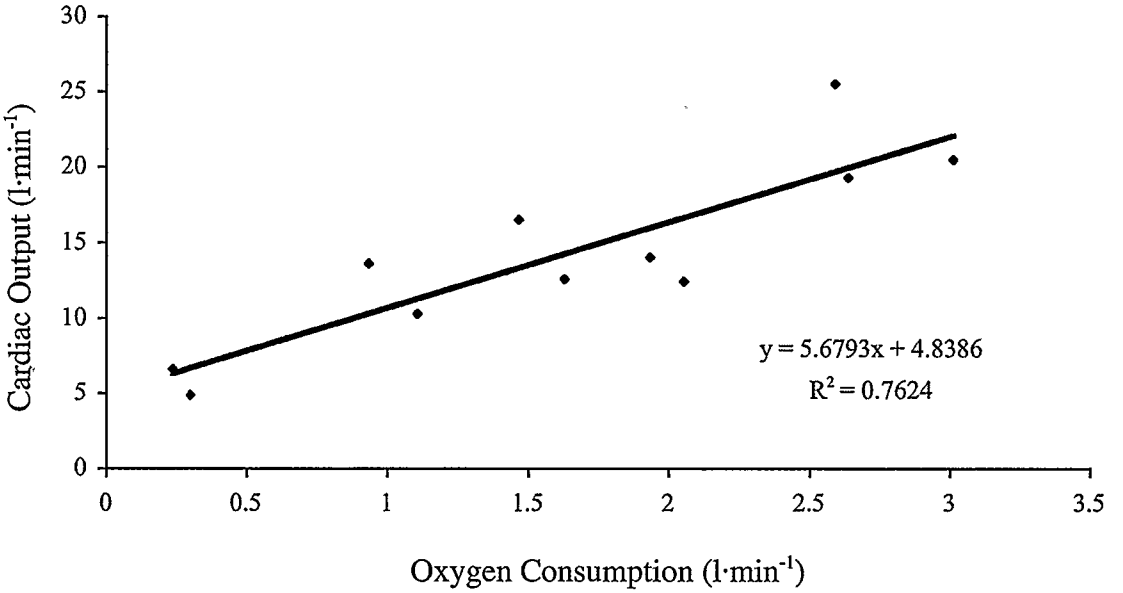

Figure 50. Cardiac output vs. oxygen consumption for the SB technique (Subject 10).

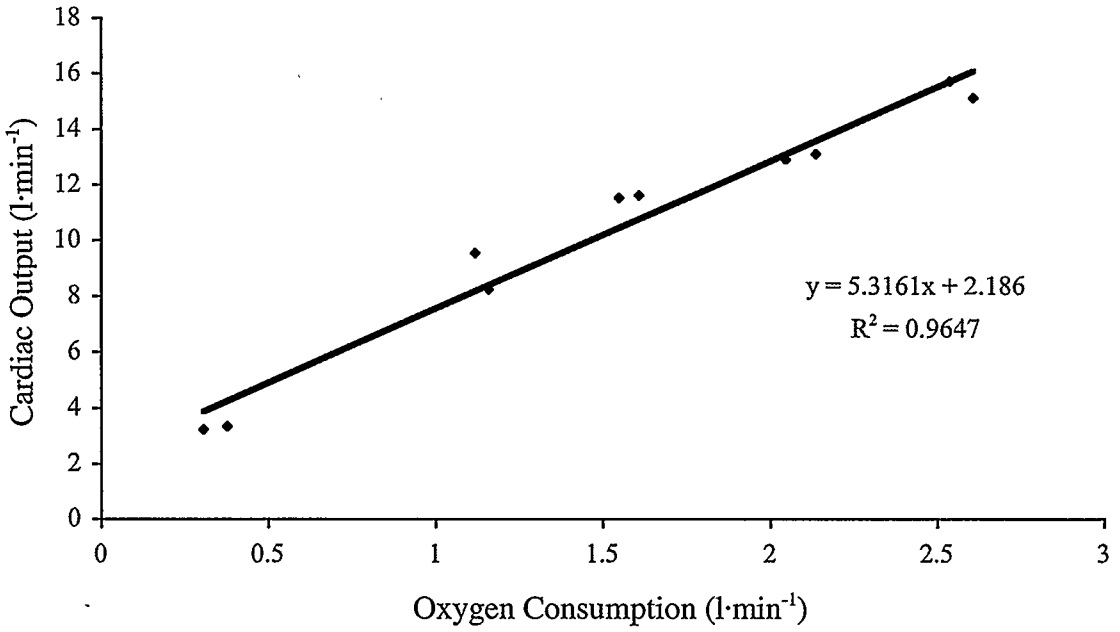

Figure 51. Cardiac output vs. oxygen consumption for the CO_2 rebreathing technique (Subject 10).

SUBJECT 11

Open Circuit

	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Test 1	0	0.34	3.8	54	70	9.0
	50	1.02	8.8	76	116	11.6
	100	1.46	11.5	90	127	12.7
	150	1.89	14.2	103	138	13.3
	200	2.39	16.6	118	140	14.4
	250	2.82	20.4	136	150	13.9
	300	3.31	23.1	155	149	14.3
Test 2	0	0.32	5.6	56	101	5.7
	50	1.00	11.6	76	152	8.6
	100	1.41	11.2	91	123	12.6
	150	1.83	13.3	104	128	13.7
	200	2.33	16.0	121	132	14.6
	250	2.66	19.8	136	146	13.4
	300	3.27	24.0	157	153	13.6
Single Breath						
Test 1	0	0.32	4.8	57	84	6.8
	50	1.04	7.0	82	85	14.8
	100	1.51	11.8	101	117	12.8
	150	2.15	14.7	118	125	14.6
	200	2.59	16.7	131	127	15.5
	250	3.22	19.9	149	134	16.2
	300	3.75	21.0	165	127	17.9
Test 2	0	0.23	2.8	57	49	8.3
	50	0.91	8.2	77	106	11.1
	100	1.43	7.5	91	82	19.1
	150	2.01	11.6	105	110	17.4
	200	2.55	14.3	125	114	17.8
	250	3.13	18.0	148	122	17.4
CO_2 Rebreathing						
Test 1	0	0.27	3.4	47	72	7.9
	50	1.06	7.7	70	110	13.8
	100	1.52	11.2	79	142	13.6
	150	1.98	14.2	96	148	13.9
	200	2.50	17.6	114	154	14.2
Test 2	0	0.51	5.1	53	96	10.0
	50	0.95	7.5	72	104	12.7
	100	1.66	13.8	89	155	12.0
	150	2.10	14.7	103	143	14.3
	200	2.59	18.3	124	148	14.2

Echo ($l \cdot min^{-1}$)	**Supine ASV**	**Upright ASV**	**LVOT**
	6.9	6.8	5.5

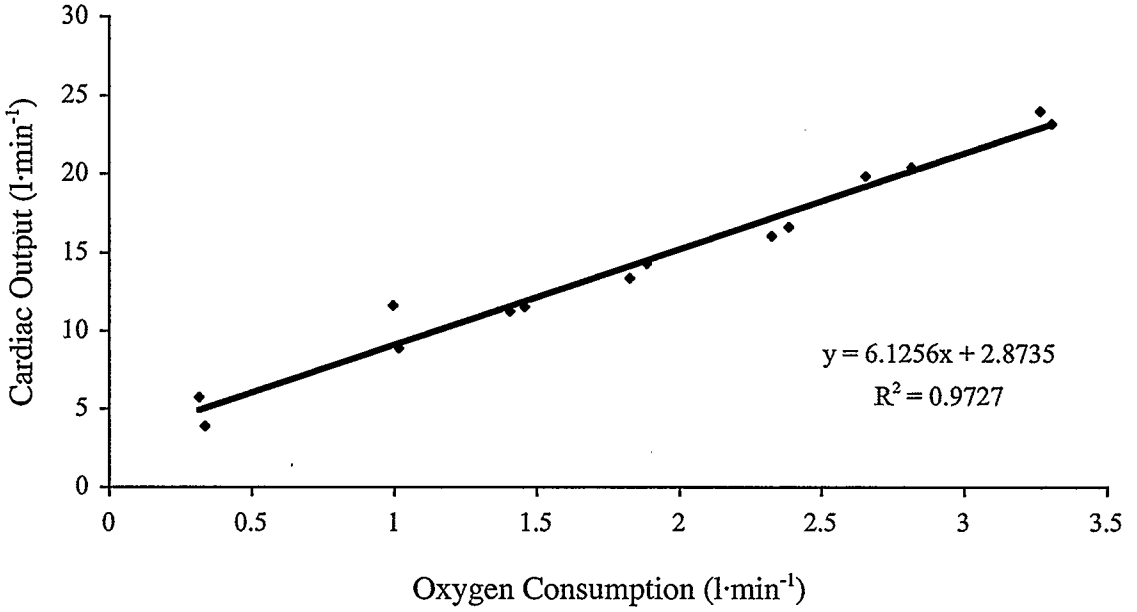

Figure 52. Cardiac output vs. oxygen consumption for the OpCirc technique (Subject 11).

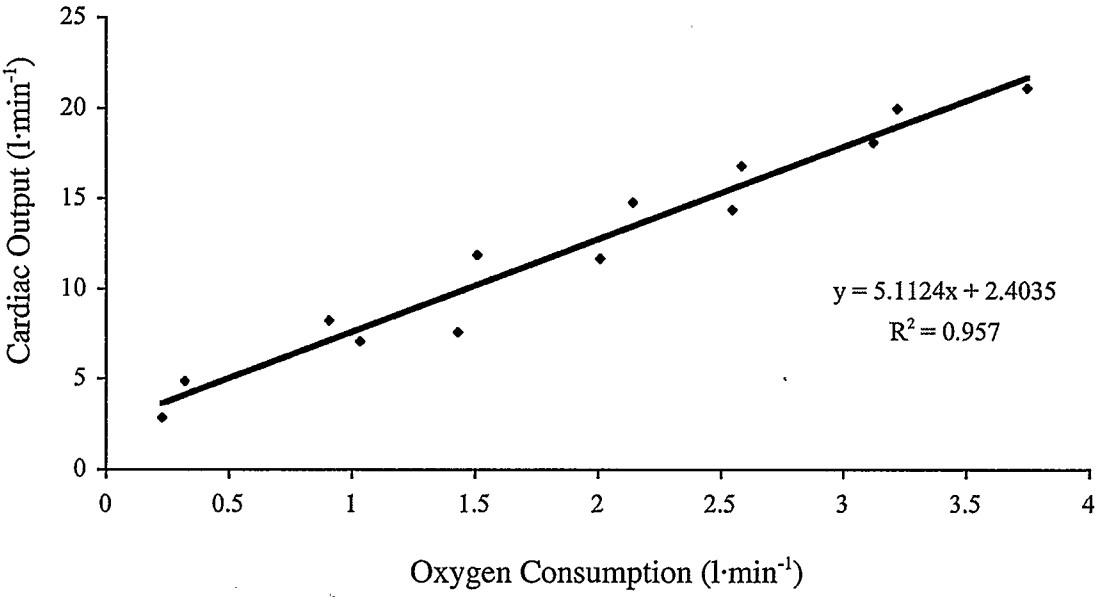

Figure 53. Cardiac output vs. oxygen consumption for the SB technique (Subject 11).

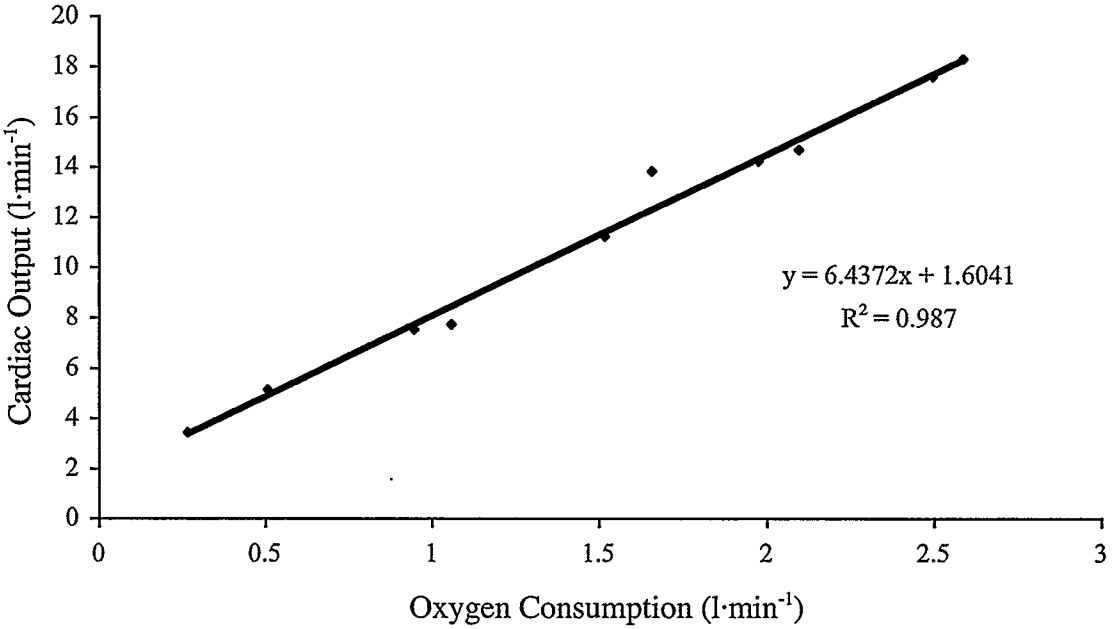

Figure 54. Cardiac output vs. oxygen consumption for the CO_2 rebreathing technique (Subject 11).

SUBJECT 12

Open Circuit

	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Test 1	0	0.51	5.9	58	102	8.6
	50	1.25	10.6	75	142	11.8
	100	1.64	12.7	86	147	12.9
	150	2.07	15.0	96	156	13.8
	200	2.53	18.8	104	181	13.5
	250	3.00	24.2	117	207	12.4
	300	3.58	26.6	138	193	13.4
Test 2	0	0.55	7.7	67	115	7.2
	50	1.37	13.5	78	173	10.1
	100	1.82	16.2	89	182	11.2
	150	2.29	18.6	101	184	12.3
	200	2.84	24.6	111	222	11.5
	250	3.19	25.0	123	203	12.8
	300	3.81	28.6	137	209	13.3
Single Breath						
Test 1	0	0.38	6.8	65	105	5.6
	50	1.21	10.9	77	142	11.1
	100	1.76	12.7	85	149	13.9
	150	2.15	15.9	99	161	13.5
	200	2.70	15.7	113	139	17.2
	250	3.28	18.9	132	143	17.3
	300					
Test 2	0	0.39	6.0	70	86	6.6
	50	1.27	15.5	83	187	8.2
	100	1.73	14.5	94	154	11.9
	150	2.29	14.7	104	141	15.6
	200	2.73	17.3	115	150	15.8
	250	3.37	20.2	130	155	16.7
	300	3.94	25.4	145	175	15.5
CO_2 Rebreathing						
Test 1	0	0.41	4.9	63	78	8.4
	50	1.13	9.8	71	138	11.5
	100	1.50	14.0	80	175	10.7
	150	2.03	15.8	90	176	12.8
	200	2.51	17.4	103	169	14.4
Test 2	0	0.54	5.8	73	79	9.3
	50	1.34	11.4	78	146	11.8
	100	1.87	12.8	86	149	14.6
	150	2.15	15.1	96	157	14.2
	200	2.62	16.4	103	159	16.0

Echo ($l \cdot min^{-1}$)	**Supine ASV**	**Upright ASV**	**LVOT**
	Echo not performed		

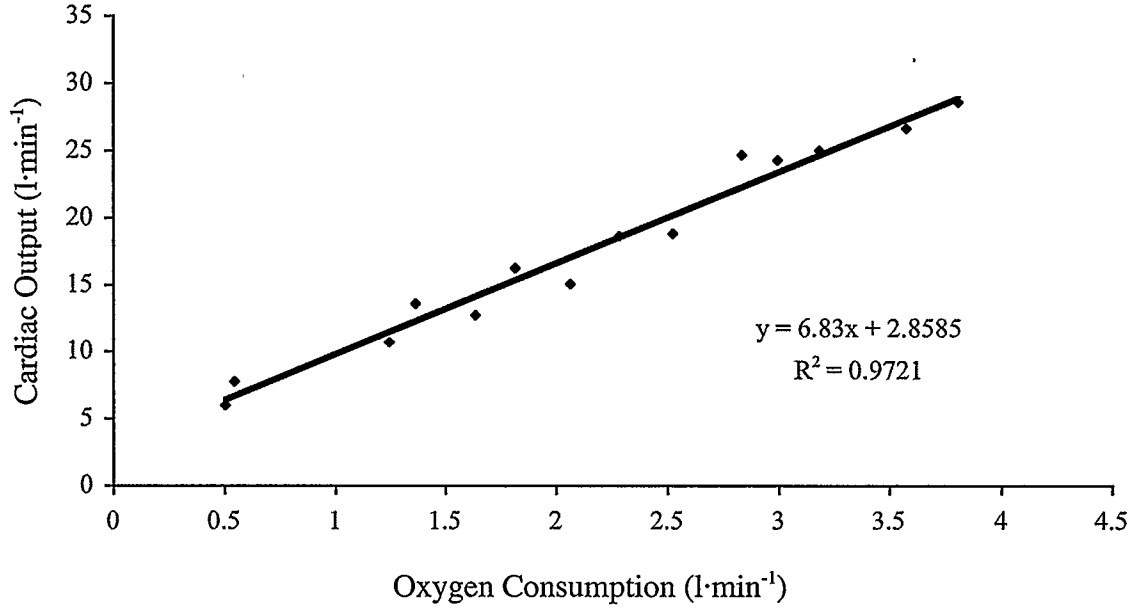

Figure 55. Cardiac output vs. oxygen consumption for the OpCirc technique (Subject 12).

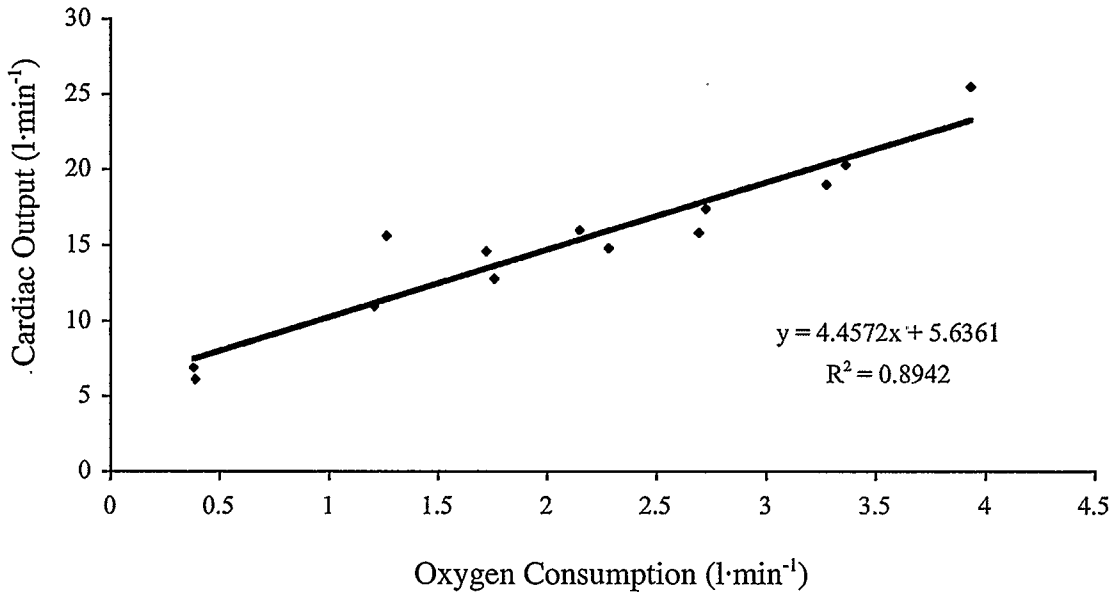

Figure 56. Cardiac output vs. oxygen consumption for the SB technique (Subject 12).

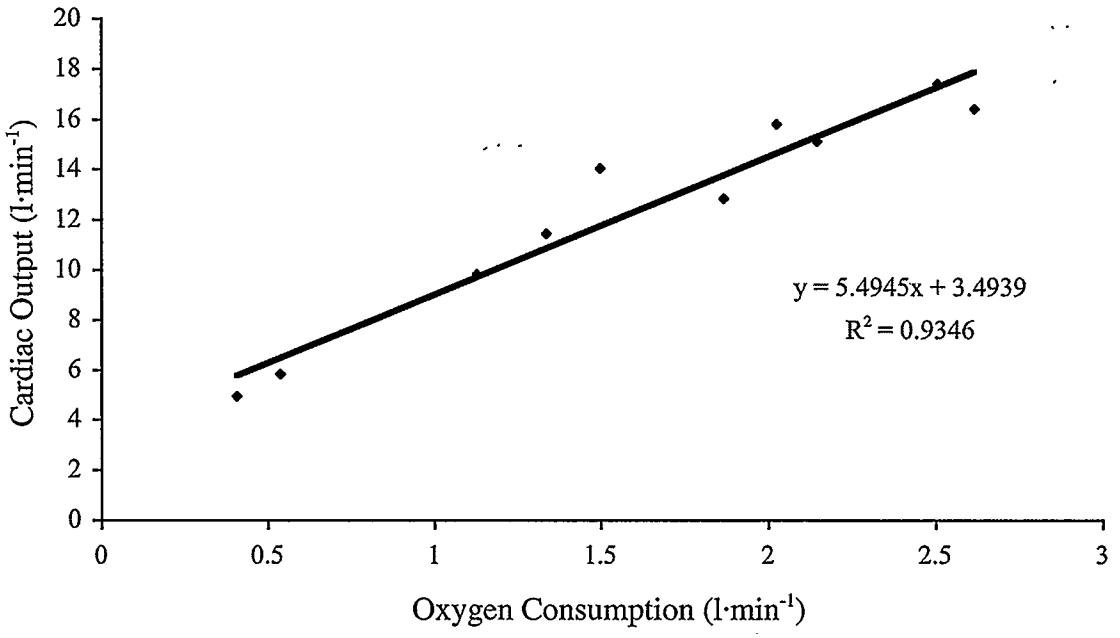

Figure 57. Cardiac output vs. oxygen consumption for the CO_2 rebreathing technique (Subject 12).

SUBJECT 13

Open Circuit

	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Test 1	0	0.37	5.5	57	96	6.8
	50	1.01	10.1	77	131	10.0
	100	1.38	10.2	88	116	13.6
	150	1.78	13.2	102	130	13.5
	200	2.41	18.7	116	161	12.9
	250	2.80	21.3	135	158	13.2
	300	3.33	22.2	153	145	15.0
Test 2	0	0.41	5.6	61	91	7.4
	50	1.01	8.2	74	111	12.3
	100	1.36	9.6	89	108	14.1
	150	1.84	13.0	103	127	14.1
	200	2.37	16.4	117	140	14.5
	250	2.85	17.8	136	131	16.0
	300	3.38	20.9	157	133	16.2
Single Breath						
Test 1	0	0.25	2.1	60	35	11.8
	50	1.31	7.9	77	103	16.5
	100	1.69	9.8	95	103	17.2
	150	2.22	12.2	108	113	18.2
	200	2.59	16.1	122	132	16.1
	250	3.19	17.3	147	118	18.5
	300	3.58	15.1	166	91	23.7
Test 2	0	0.31	4.9	50	98	6.4
	50	0.94	6.9	68	101	13.6
	100	1.43	6.0	88	68	23.8
	150	2.07	9.7	101	96	21.3
	200	2.47	12.4	119	104	20.0
	250	3.11	17.2	142	121	18.1
	300	3.54	16.9	161	105	21.0
CO_2 Rebreathing						
Test 1	0	0.34	4.0	64	63	8.5
	50	1.08	10.1	79	128	10.7
	100	1.56	13.9	91	153	11.2
	150	2.22	21.4	108	198	10.4
	200	2.84	24.3	127	191	11.7
Test 2	0	0.39	3.9	66	59	10.0
	50	1.03	9.6	76	126	10.7
	100	1.59	12.9	98	132	12.3
	150	2.14	16.9	111	152	12.7
	200	2.71	20.9	128	163	13.0

Echo ($l \cdot min^{-1}$)	**Supine ASV**	**Upright ASV**	**LVOT**
	9.4	6.1	3.8

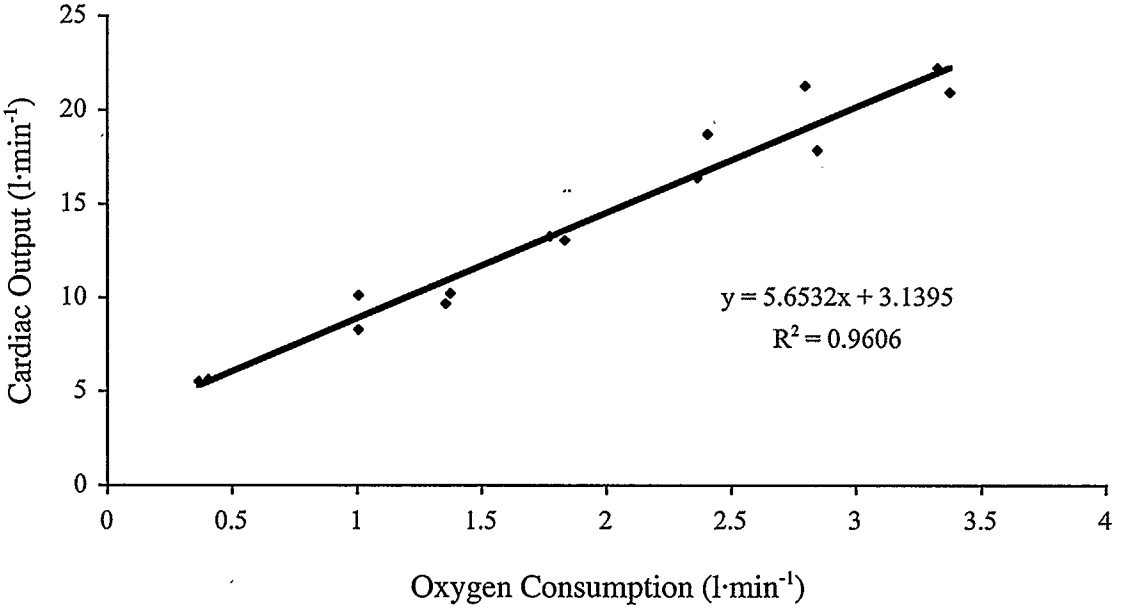

Figure 58. Cardiac output vs. oxygen consumption for the OpCirc technique (Subject 13).

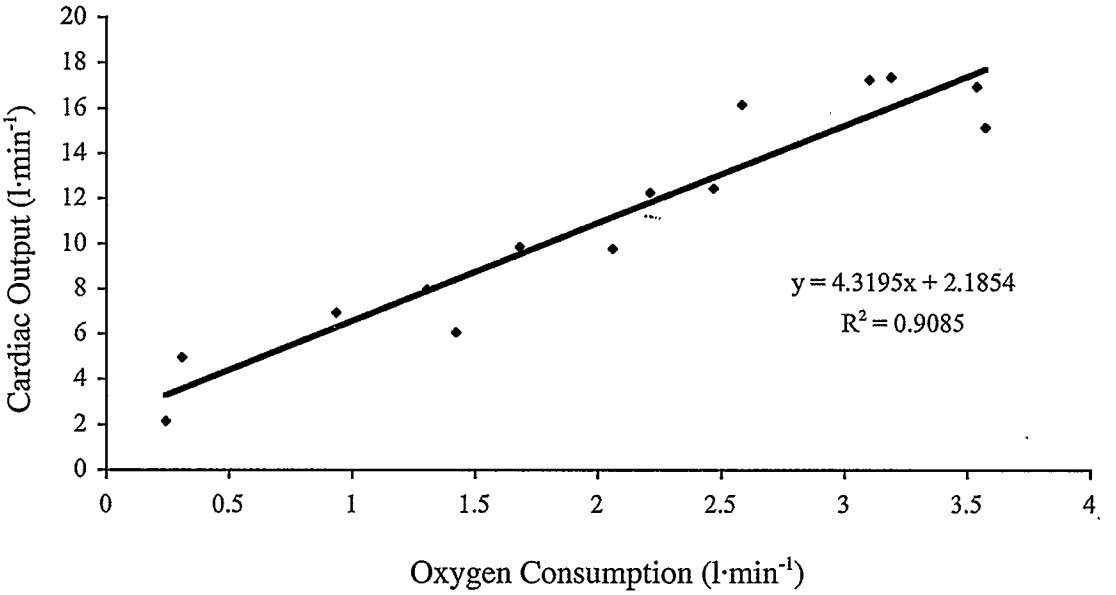

Figure 59. Cardiac output vs. oxygen consumption for the SB technique (Subject 13).

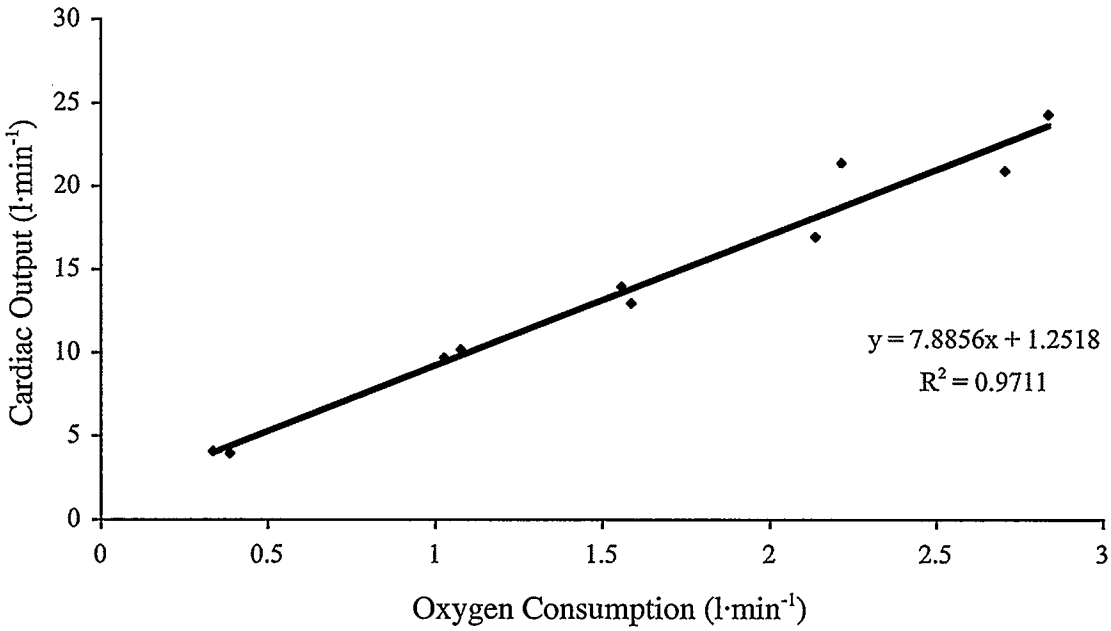

Figure 60. Cardiac output vs. oxygen consumption for the CO_2 rebreathing technique (Subject 13).

Appendix D: Individual Cardiac Output Reliability Measurements

SUBJECT 1

OpCirc Reliability	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Time 1	0	0.5	5.3	58	91	8.7
	50	1.1	10.6	84	127	10.2
	100	1.4	12.0	90	134	11.9
	150	1.8	14.2	99	143	12.6
	200	2.2	16.7	111	150	13.3
	250	2.8	20.4	123	165	13.6
	300	3.2	23.5	135	174	13.7
	0	0.4	8.0	73	110	5.3
	50	1.1	12.7	81	156	8.8
	100	1.5	14.4	92	157	10.0
	150	1.9	16.9	101	168	11.3
	200	2.3	14.9	110	135	15.5
	250	2.8				
	300	3.2	23.8	135	176	13.4
SB						
Reliability	0	0.38	5.9	59	100	6.5
Time 1	0	0.49	6.5	60	108	7.5
	100	1.49	11.4	90	127	13.1
	100	1.69	11.4	91	125	14.8
	100	1.61	11.5	91	126	14.0
	200	2.76	16.4	118	139	16.8
	200	2.78	17.9	119	150	15.6
Time 2	0	0.39	4.4	67	66	8.9
	0	0.36	5.5	66	83	6.5
	100	1.53	12.1	88	138	12.7
	100	1.60	10.5	88	119	15.2
	100	1.53	8.2	88	93	18.6
	200	2.60	16.5	112	147	15.8
	200	2.66	15.4	114	135	17.3
	200	2.65	16.3	117	139	16.2

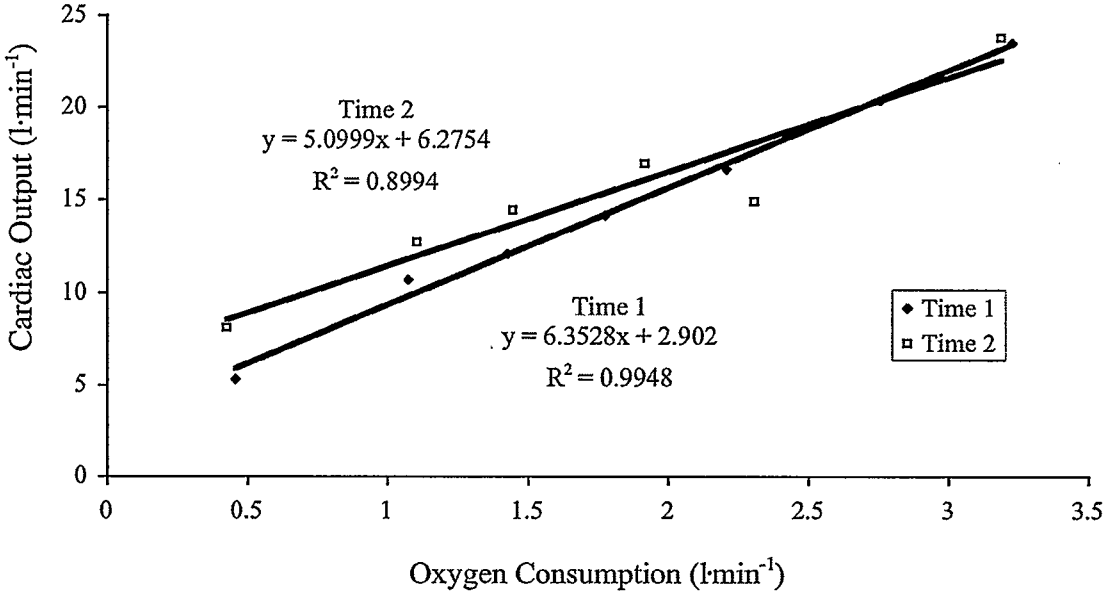

Figure 61. Cardiac output vs. oxygen consumption for the OpCirc technique Time 1 and Time 2 (Subject 1).

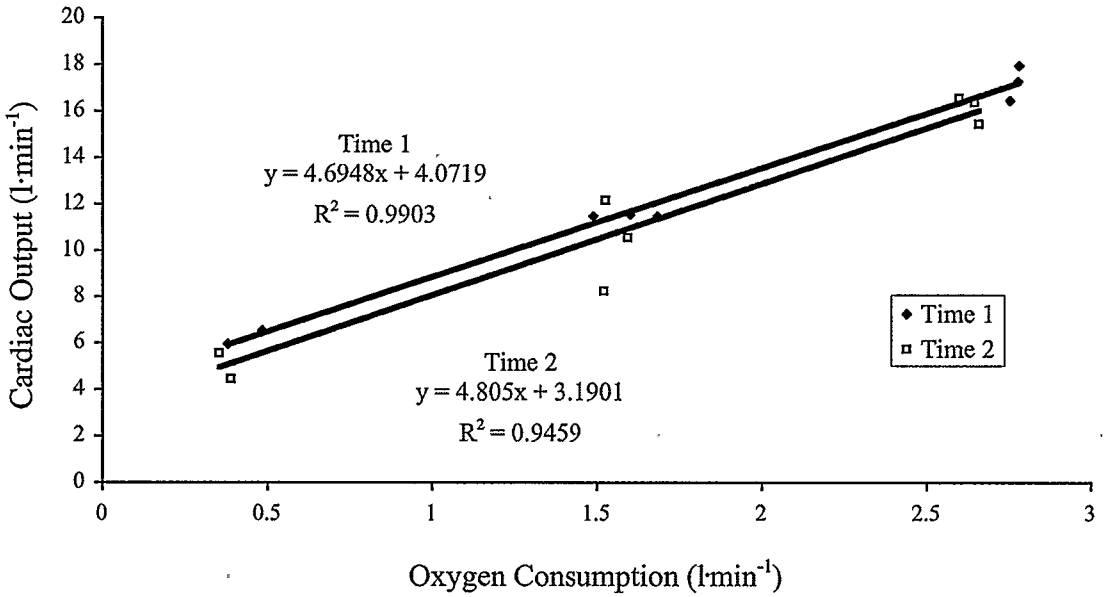

Figure 62. Cardiac output vs. oxygen consumption for the SB technique Time 1 and Time 2 (Subject 1).

SUBJECT 2

OpCirc Reliability	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Time 1	0	0.36	5.1	70	73	7.0
	50	0.98	9.9	101	98	9.9
	100	1.36	14.1	115	122	9.7
	150	1.81	21.9	130	169	8.3
	200	2.26	20.2	150	134	11.2
	250	2.79	24.0	168	143	11.6
	300	3.31	24.6	179	137	13.5
	0	0.37	4.1	75	54	9.1
	50	1.00	10.5	101	104	9.5
	100	1.41	11.1	115	97	12.7
	150	1.80	12.3	132	93	14.6
	200	2.26	18.8	150	125	12.0
	250	2.83	21.0	169	124	13.5
	300	3.18	24.8	178	139	12.8
SB						
Reliability	0	0.377	5.5	65	85	6.9
Time 1	0	0.326	4.4	65	68	7.4
	0	0.396	5.6	65	86	7.1
	100	1.479	11.7	110	106	12.6
	100	1.488	13.6	113	120	10.9
	100	1.47	10.9	115	95	13.5
	200	2.497	15.6	146	107	16.0
	200	2.584	16.5	150	110	15.7
	200	2.543	15.8	155	102	16.1
Time 2	0	0.416	6.3	67	94	6.6
	0	0.391	6.9	67	103	5.7
	0	0.479	6.3	66	95	7.6
	100	1.78	13.8	111	124	12.9
	100	1.751	12.1	115	105	14.5
	100	1.581	11	114	96	14.4
	200	3.044	17	145	117	17.9
	200	3.023	17.4	147	118	17.4
	200	3.046	15.3	147	104	19.9

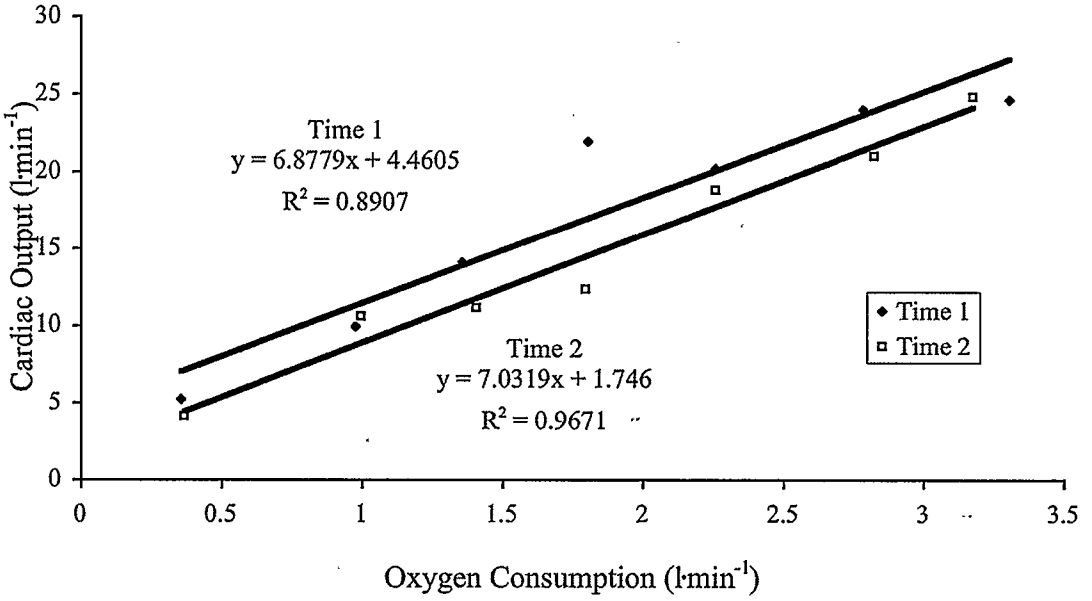

Figure 63. Cardiac output vs. oxygen consumption for the OpCirc technique Time 1 and Time 2 (Subject 2).

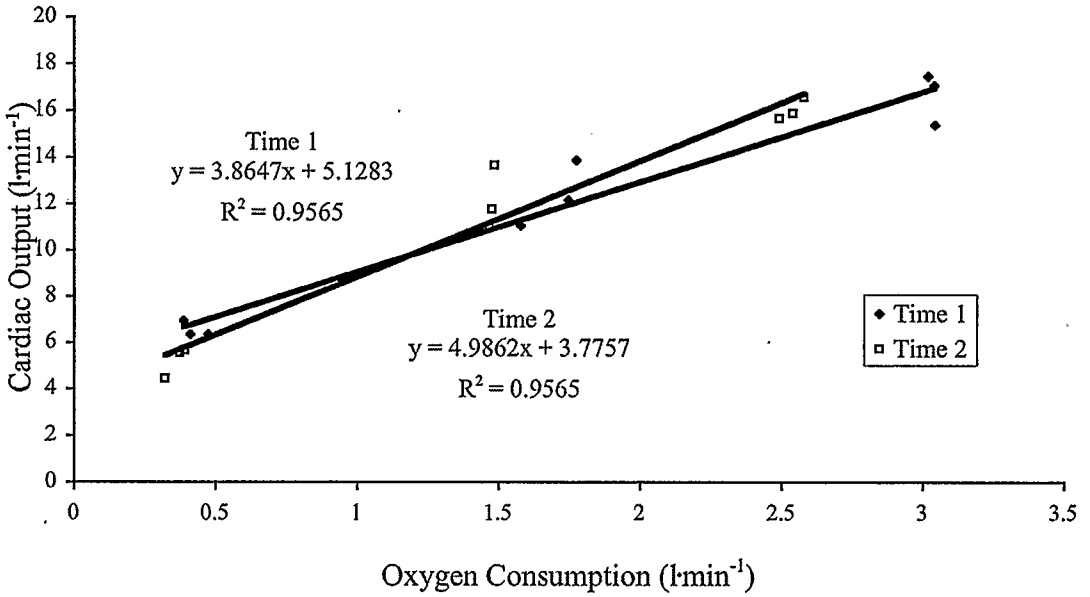

Figure 64. Cardiac output vs. oxygen consumption for the SB technique Time 1 and Time 2 (Subject 2).

SUBJECT 3

OpCirc Reliability	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Time 1	0	0.29	4.1	56	73	7.1
	50	0.93	7.8	71	109	12.0
	100	1.28	9.3	82	113	13.8
	150	1.73	14.3	101	142	12.1
	200	2.25	17.7	119	148	12.7
	250	2.69	22.6	139	162	11.9
	300	3.41	27.4	158	173	12.5
	0	0.42	3.6	58	62	11.6
	50	1.14	9.1	79	115	12.6
	100	1.62	12.1	94	129	13.4
	150	1.93	14.5	107	136	13.3
	200	2.53	16.7	124	134	15.2
	250	2.99	21.6	138	156	13.9
	300	3.47	24.2	160	151	14.3
SB						
Reliability	0	0.23	5.3	60	88	4.4
Time 1	0	0.27	6.2	63	98	4.4
	0	0.23	6.4	61	105	3.5
	100	1.37	11.9	91	131	11.5
	100	1.49	10.9	90	121	13.7
	100	1.46	12.8	93	138	11.4
	200	2.62	17.9	128	140	14.6
	200	2.62	18.8	131	144	13.9
	200	2.75	17.4	134	130	15.8
Time 2	0	0.27	5.6	67	84	4.8
	0	0.24	4.9	64	77	4.9
	0	0.21	5.4	67	81	3.9
	100	1.37	10.4	94	111	13.2
	100	1.57	15.3	100	153	10.3
	100	1.56	8.8	100	88	17.8
	100	1.53	10.9	100	109	14.0
	200	2.69	15.5	135	115	17.3
	200	2.67	18.4	133	138	14.5
	200	2.69	19.8	137	145	13.6

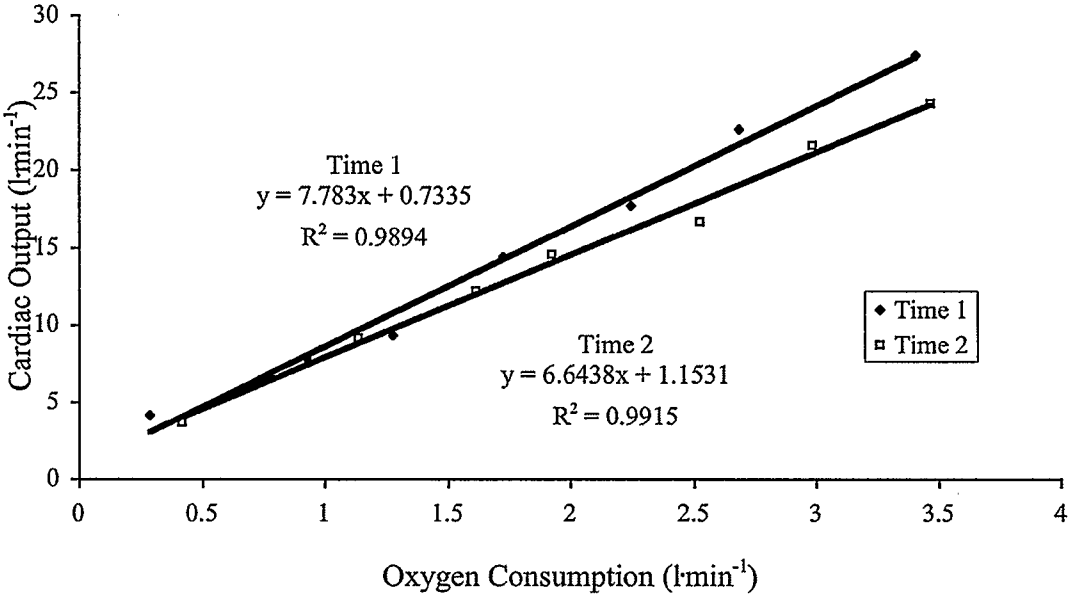

Figure 65. Cardiac output vs. oxygen consumption for the OpCirc technique Time 1 and Time 2 (Subject 3).

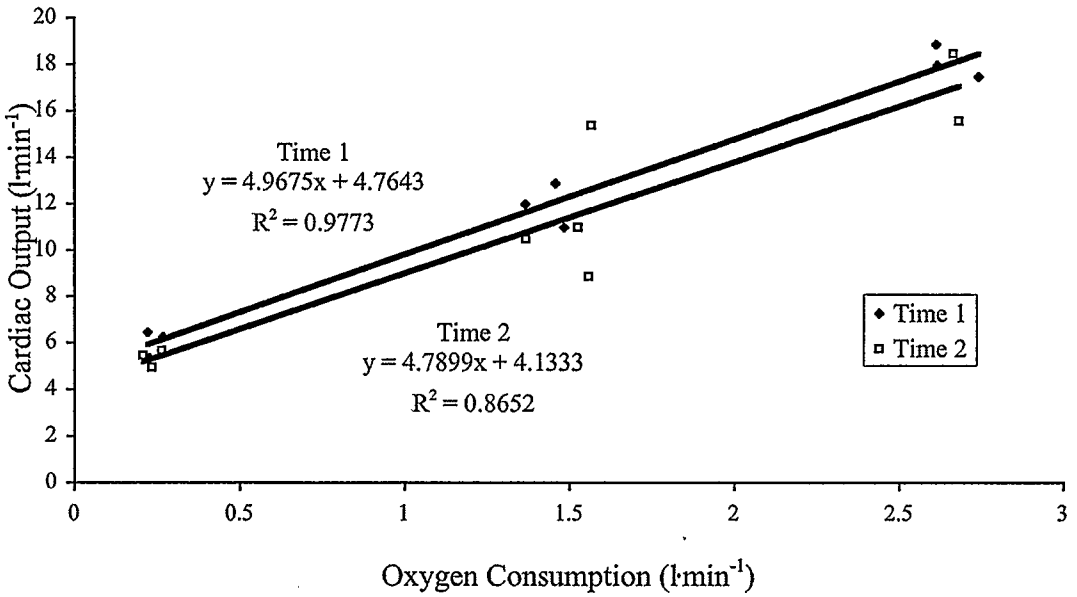

Figure 66. Cardiac output vs. oxygen consumption for the SB technique Time 1 and Time 2 (Subject 3).

SUBJECT 4

OpCirc Reliability	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Time 1	0	0.41	4.4	73	61	9.2
	50	1.08	12.8	87	147	8.5
	100	1.58	15.5	94	165	10.2
	150	1.91	15.4	104	149	12.4
	200	2.42	18.4	118	156	13.1
	250	2.95	20.4	134	152	14.5
	300	3.38	21.9	155	141	15.4
	0	0.39	4.1	70	58	9.6
	50	1.08	10.7	82	131	10.1
	100	1.48	13.5	95	142	11.0
	150	1.98	16.6	107	155	12.0
	200	2.44	21.0	125	168	11.6
	250	2.85	20.0	138	145	14.3
	300	3.32	22.7	158	143	14.6
SB						
Reliability	0	0.40	5.5	63	87	7.2
Time 1	0	0.39	3.4	65	52	11.4
	0	0.32	4.7	72	65	6.8
	100	1.72	11.1	92	121	15.5
	100	1.59	8.0	91	88	19.9
	200	2.63	16.0	121	132	16.4
	200	2.79	15.3	122	125	18.2
	200	2.30	14.2	121	117	16.2
Time 2	0	0.34	4.7	63	75	7.2
	0	0.34	6.7	63	106	5.0
	0	0.46	6.4	62	103	7.2
	100	1.53	13.9	93	149	11.0
	100	1.47	10.7	92	116	13.8
	200	1.50	9.2	122	75	16.3
	200	2.52	15.1	122	124	16.7
	200	2.51	14.6	121	121	17.2

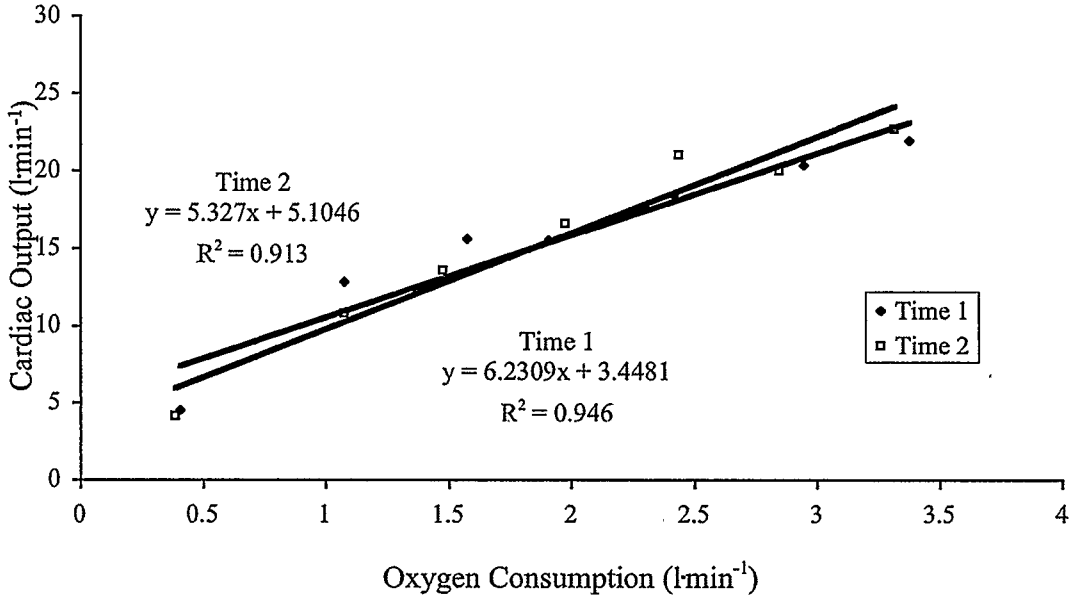

Figure 67. Cardiac output vs. oxygen consumption for the OpCirc technique Time 1 and Time 2 (Subject 4).

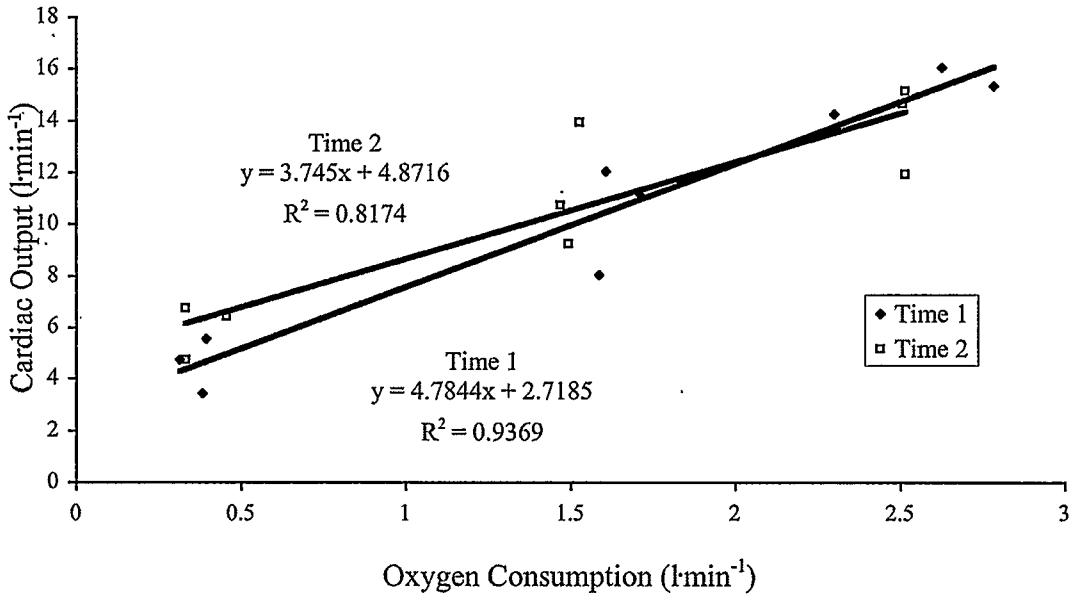

Figure 68. Cardiac output vs. oxygen consumption for the SB technique Time 1 and Time 2 (Subject 4).

SUBJECT 5

OpCirc Reliability	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Time 1	0	0.36	3.7	76	49	9.7
	50	0.95	8.0	100	80	11.9
	100	1.37	8.8	120	74	15.5
	150	1.83	11.8	142	83	15.5
	200	2.38	16.7	161	104	14.2
	250	2.89	17.1	177	97	16.9
	300	3.10	18.6	182	102	16.7
	0	0.34	2.8	98	28	12.3
	50	0.90	6.5	112	58	13.9
	100	1.28	10.0	135	74	12.8
	150	1.79	13.6	156	87	13.2
	200	2.32	15.2	174	87	15.3
	250	2.69	14.1	185	76	19.1
	300	3.23	19.9	192	104	16.2
SB						
Reliability	0	0.32	6.3	88	72	5.1
Time 1	0	0.39	7.3	88	83	5.3
	0	0.35	6.8	88	77	5.1
	100	1.52	10.2	138	74	14.9
	100	1.63	13.1	142	92	12.4
	100	1.59	12.3	141	87	12.9
	200	2.47	15.3	170	90	16.2
	200	2.66	16.9	177	95	15.7
Time 2	0	0.27	6.1	102	60	4.5
	0	0.32	7.0	95	74	4.6
	0	0.40	7.2	97	74	5.6
	100	1.49	9.8	140	70	15.2
	100	1.32	11.4	141	81	11.6
	100	1.39	13.6	142	96	10.2
	200	2.44	14.7	171	86	16.6
	200	2.42	15.0	174	86	16.1
	200	2.40	14.1	177	80	17.0

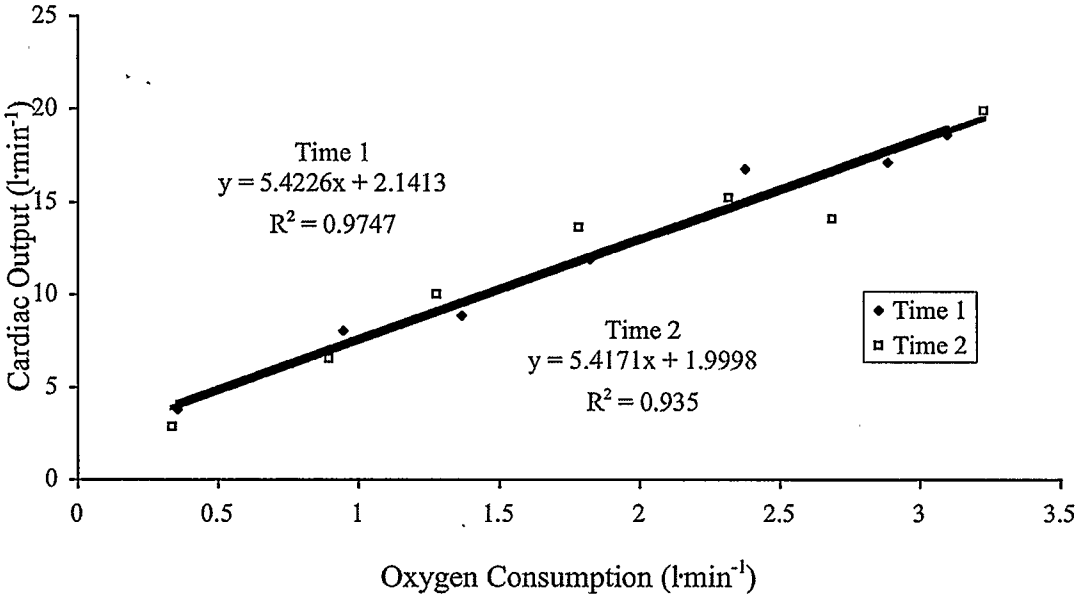

Figure 69. Cardiac output vs. oxygen consumption for the OpCirc technique Time 1 and Time 2 (Subject 5).

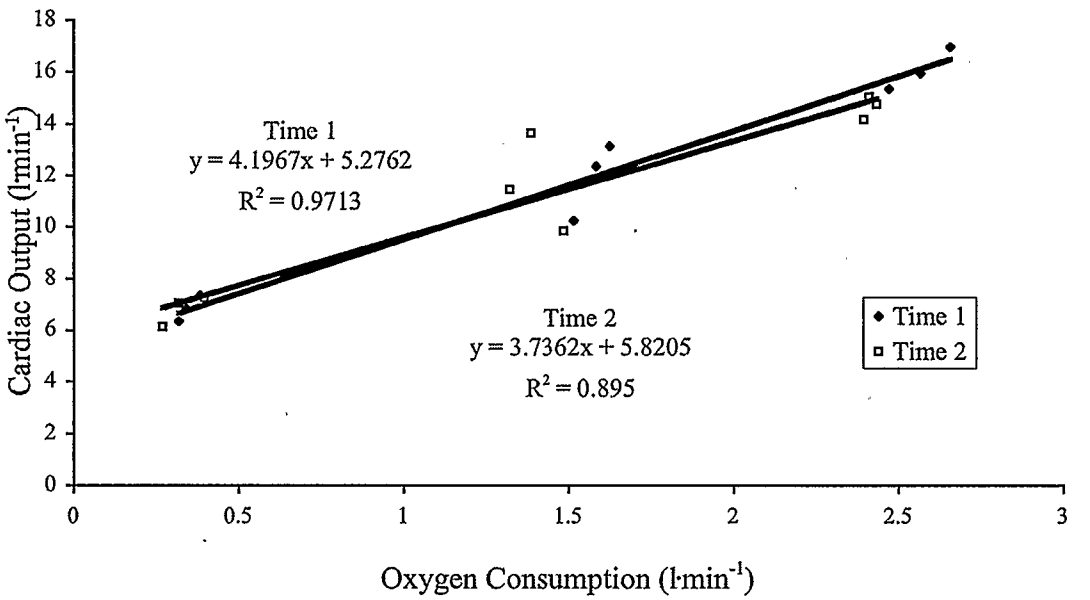

Figure 70. Cardiac output vs. oxygen consumption for the SB technique Time 1 and Time 2 (Subject 5).

SUBJECT 6

OpCirc Reliability	Power Output (W)	VO_2 ($l \cdot min^{-1}$)	Q ($l \cdot min^{-1}$)	HR ($b \cdot min^{-1}$)	SV ($ml \cdot beat^{-1}$)	a-vO_2diff ($ml \cdot 100ml^{-1}$)
Time 1	0	0.44	5.9	54	110	7.4
	50	0.88	7.2	76	95	12.2
	100	1.30	11.0	90	122	11.8
	150	1.82	13.0	103	126	14.1
	200	2.25	19.2	118	163	11.7
	250	2.72	20.9	136	154	13.0
	300	3.26	23.8	155	153	13.7
	0	0.47	6.2	56	111	7.6
	50	0.94	11.7	76	155	8.0
	100	1.31	11.7	91	129	11.2
	150	1.78	19.1	104	183	9.3
	200	2.17	18.3	121	151	11.8
	250	2.77	24.4	136	180	11.3
	300	3.24	22.8	157	145	14.2
SB						
Reliability	0	0.30	3.5	69	51	8.7
Time 1	0	0.35	3.3	67	49	10.6
	0	0.33	2.5	68	37	13.2
	100	1.38	10.1	95	106	13.7
	100	1.55	9.7	97	100	16.0
	100	1.47	5.6	95	59	26.3
	200	2.34	16	127	126	14.6
	200	2.44	14	134	104	17.4
	200	2.60	18.2	134	136	14.3
Time 2	0	0.35	2.5	71	35	13.8
	0	0.37	5.5	68	81	6.7
	0	0.38	7.6	71	107	4.9
	100	1.53	11.3	100	113	13.6
	100	1.56	12.4	101	123	12.6
	100	1.77	9.9	101	98	17.9
	200	2.48	18.4	136	135	13.5
	200	2.53	18.3	135	136	13.8
	200	2.57	15.8	136	116	16.3

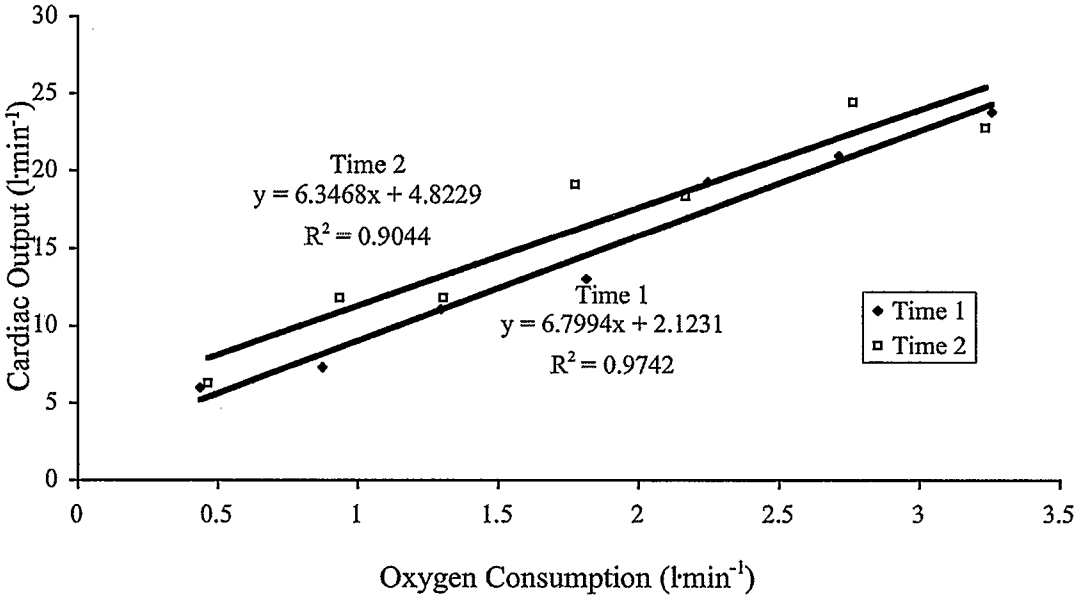

Figure 71. Cardiac output vs. oxygen consumption for the OpCirc technique Time 1 and Time 2 (Subject 6).

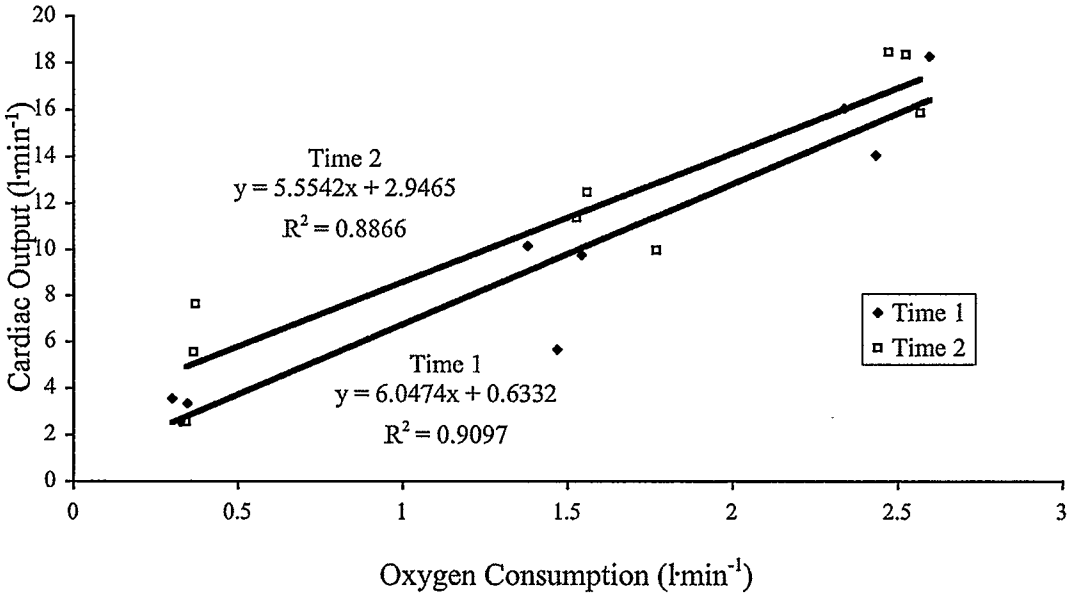

Figure 72. Cardiac output vs. oxygen consumption for the SB technique Time 1 and Time 2 (Subject 6).

Appendix E: Statistical Analysis

Linear Regression Analysis

Open Circuit

. regress Q VO_2 testtime

Source	SS	df	MS	Number of obs = 180
				F(2, 177) = 808.91
Model	6283.27629	2	3141.63815	Prob > F = 0.0000
Residual	687.433803	177	3.88380679	R-squared = 0.9014
				Adj R-squared = 0.9003
Total	6970.71009	179	38.9425145	Root MSE = 1.9707

Q	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
VO_2	6.122181	.1523438	40.19	0.000	5.821537	6.422825
testtime	0.271971	.2938512	0.93	**0.356**	-.3079317	.851874

Single Breath

. regress Q VO_2 testtime

Source	SS	df	MS	Number of obs = 107
				F(2, 104) = 417.03
Model	2052.56643	2	1026.28321	Prob > F = 0.0000
Residual	255.935767	104	2.46092084	R-squared = 0.8891
				Adj R-squared = 0.8870
Total	2308.50219	106	21.7783226	Root MSE = 1.5687

Q	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
VO_2	4.702389	.1628382	28.88	0.000	4.379475	5.025304
testtime	.3060175	.3036737	1.01	**0.316**	-.2961788	.9082139

Resting Comparisons

. oneway Q Test, tabulate

Test	Summary of LVOT Mean	Std. Dev.	Freq.
1	4.6670001	.84560776	9
2	5.4877778	1.1770597	9
3	4.6433333	1.1665762	9
4	8.3377778	1.2902884	9
5	7.3066666	.87978689	9
6	5.3077777	.95473522	9
Total	5.9583889	1.7276061	54

Analysis of Variance

Source	SS	df	MS	F	Prob > F
Between groups	103.690531	5	20.7381062	18.27	0.0000
Within groups	54.4944851	48	1.13530177		
Total	158.185016	53	2.98462295		

Bartlett's test for equal variances: chi2(5) = 2.3015 Prob>chi2 = 0.806

. oneway Q Test, bonferroni

Analysis of Variance

Source	SS	df	MS	F	Prob > F
Between groups	103.690531	5	20.7381062	18.27	0.0000
Within groups	54.4944851	48	1.13530177		
Total	158.185016	53	2.98462295		

Bartlett's test for equal variances: chi2(5) = 2.3015 Prob>chi2 = 0.806

Resting Comparisons (cont.)

Comparison of LVOT by Test
(Bonferroni)

Row Mean-| Col Mean |	1	2	3	4	5
2 |	.820778				
	1.000				
3 |	-.023667	-.844444			
	1.000	1.000			
4 |	3.67078	2.85	3.69444		
	0.000	0.000	0.000		
5 |	2.63967	1.81889	2.66333	-1.03111	
	0.000	0.011	0.000	0.683	
6 |	.640778	-.18	.664444	-3.03	-1.99889
	1.000	1.000	1.000	0.000	0.003

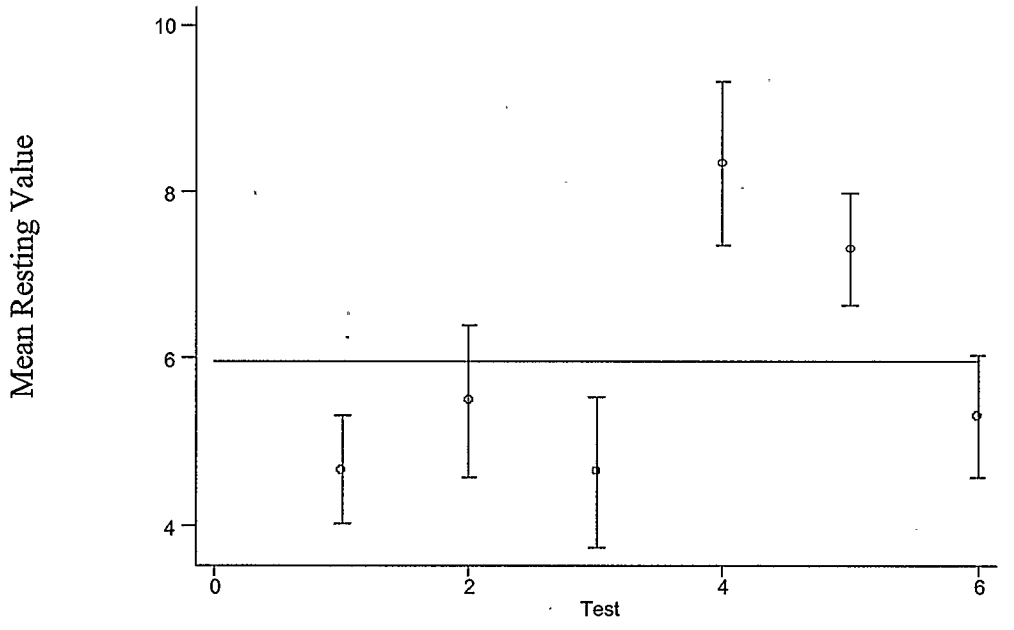

Figure 72. Mean and SD of resting values for different techniques. Test 1 = OpCirc; Test 2 = SB; Test 3 = CO_2 RB; Test 4 = ASV Echo Supine; Test 5 = ASV Echo Upright; Test 6 = LVOT.

Test-Retest Analysis

. ttest Q_OpCirc1 = Q_OpCirc2

Paired t test

Variable	Obs	Mean	Std. Err.	Std. Dev	[95% Conf. Interval]
Q_OpCi~1	6	23.89429	.8169043	2.000999	21.79 - 25.99
Q_OpCi~2	6	23.27917	.6477938	1.586764	21.61 - 24.94
diff	6	.615125	.7836293	1.919492	-1.399 - 2.629

Ho: mean(Q_OpCirc1 - Q_OpCirc2) = mean(diff) = 0

Ha: mean(diff) < 0	Ha: mean(diff) ~= 0	Ha: mean(diff) > 0
t = 0.7850	t = 0.7850	t = 0.7850
P < t = 0.7660	P > |t| = 0.4680	P > t = 0.2340

. ttest Q_SB1 = Q_SB2

Paired t test

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
Q_SB1	6	21.66667	1.619808	3.967703	17.50282	25.83052
Q_SB2	6	22.58333	1.649933	4.041494	18.34205	26.82462
diff	6	-.916667	.7254501	1.776983	-2.781496	.9481619

Ho: mean(Q_SB1 - Q_SB2) = mean(diff) = 0

Ha: mean(diff) < 0	Ha: mean(diff) ~= 0	Ha: mean(diff) > 0
t = -1.2636	t = -1.2636	t = -1.2636
P < t = 0.1310	P > |t| = 0.2621	P > t = 0.8690