EFFECTS OF SUPINE AND -6° HEAD-DOWN TILT POSTURE ON CARDIOVASCULAR
AND EXERCISE PERFORMANCE

by

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Abstract

Background and Aim: Long-term microgravity exposure, via spaceflight or -6° head-down tilt bedrest, has been shown to produce significant cardiovascular deconditioning and decreases in exercise performance. However, there is little known about how acute microgravity exposure influences the cardiovascular system's ability to adjust to increases in physical work. Therefore, the aim of this study was to compare cardiovascular and exercise performance during acute upright, supine and -6° head-down tilt positions.

Methods: Seven healthy inactive men performed maximal cycle exercise (VO_{2peak}) tests in the upright, supine, and -6° head-down tilt on separate days. Oxygen consumption and heart rate were measured continuously throughout the testing procedures. Cardiac output (acetylene exhalation technique) was measured periodically and interpolated to the 100-watt work rate. Stroke volume was calculated from cardiac output and heart rate data.

Results: Peak oxygen uptake and heart rate were significantly decreased in the supine and -6° head-down tilt positions compared to the upright (VO_{2peak} 2.01±0.46, 2.01±0.51 versus 2.32±0.61 L/min respectively; peak heart rate 161±13, 160±14 versus 172±11 bmp). However, cardiac output at 100-watts was similar in all three-exercise positions. Calculated stroke volume at 100-watts was significantly higher in the -6° head-down tilt position compared to the upright position (76.6±4.7 versus 71.2±4.5, ml).

Conclusion: These results suggest that exercise capacity is immediately decreased upon exposure to a microgravity environment, prior to any cardiovascular deconditioning. Therefore, an astronaut's exercise performance should be evaluated with exercise tests in the -6° head-down tilt position prior to space flight in order to establish a baseline response.

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CHAPTER 1 - Introduction

The ability to tolerate an increase in physical work depends on the rate at which the body can take in, transport and utilize oxygen to meet the metabolic demands of the functioning muscle (Rowell 1993; Tipton and American College of Sports Medicine. 2006). Limitations by one or more of these factors will ultimately decrease the overall work capacity. When exercise is performed in the presence of additional stress, the body's ability to increase oxygen uptake with work intensity becomes compromised (Rowell 1986; Tipton and American College of Sports Medicine. 2006).

Many cardiovascular adjustments and adaptations have been shown to occur during gravitational stress (Blomqvist and Stone 1977; Watenpaugh and Hargens 1977). Microgravity exposure begins with a fluid shift, caused by a decrease in the body's gravitational hydrostatic pressure gradient, that results in redistribution of blood from the lower portions of the body to the thoracic region (Blomqvist and Stone 1977; Fortney, Schneider et al. 1977; Hoffler, Bergman et al. 1977; Thornton, Hoffler et al. 1977; Nixon, Murray et al. 1979; Blomqvist, Nixon et al. 1980; Hargens, Tipton et al. 1983). This shift acutely increases central venous pressure, left ventricular end-diastolic diameter and volume, which can remain elevated for up to 4-6 hrs before returning to normal levels (Fortney, Schneider et al. 1977; Nixon, Murray et al. 1979; Blomqvist, Nixon et al. 1980; Poliner, Dehmer et al. 1980; Gaffney, Nixon et al. 1985). The long term effects of microgravity exposure on the cardiovascular system indicate that significant cardiovascular deconditioning will occur within a relatively short time and may contribute to a decrease in exercise performance and increased orthostatic intolerance upon return to Earth (Fortney, Schneider et al. 1977; Levine, Zuckerman et al. 1997). These variables have all been examined during actual spaceflight or during -6 head down tilt posture, which has been shown to produce the same fluid shift experienced in an actual spaceflight environment (Kakurin, Lobachik et al. 1976; Fortney, Schneider et al. 1977; Trappe, Trappe et al. 2006).

Research comparing changes in gravitational stress during upright and supine exercise suggests that in the supine position peak oxygen uptake decreases and VO_2 kinetics slow and sub-maximal stroke volume increases (Blomqvist and Stone 1977; Poliner, Dehmer et

al. 1980; Ray and Cureton 1991; Koga, Shiojiri et al. 1999). However, despite the vast amount of research involving supine exercise to date, little is known about how exercise performance is influenced acutely in a true microgravity model before the onset of cardiovascular deconditioning. Research has previously shown that at rest in the -6° head-down tilt position the blood filling of the torso and the change in body fluid parameters is greater and occurs at an increased rate compared to that in the supine position (Stegall 1966; Kakurin, Lobachik et al. 1976; Fortney, Schneider et al. 1977). It was, therefore, the purpose of this study to test the hypothesis that acute simulated microgravity exposure created by -6 head down tilt posture would result in 1) decreased peak oxygen uptake, 2) and an increase in sub-maximal exercising stroke volume at 100-watts compared to that measured during supine and upright exercise.

CHAPTER 2 - Literature Review

Cardiovascular Adjustments to Microgravity Settings

In the early days of space exploration, little was known about how the human body would react to the new environment. Fortunately, like the adventurers of our past, this lack of knowledge did not delay scientists from moving forward towards the mysterious and unknown. Since then, the discipline of space science and physiology has grown and allowed for new research areas to arise. This section will review how the human cardiovascular system adjusts to the stresses of space and its simulation.

Gravity

In the 17th century, Sir Isaac Newton described a phenomenon known as Newton's Law of Universal Gravitation. This law states that all objects in the universe are attracted to one another. This force of attraction is directed along a line between each object's center of mass and is directly proportional to their masses and inversely proportional to the square of the distance separating them (Equation 1-1). On earth, this force of attraction between the planet and humans is known as the force of gravity.

$$\text{Force} = \text{Gravitational Constant} \times (\text{mass}_1 \times \text{mass}_2) / \text{distance}^2) \qquad \text{1-1}$$

Like a falling object from a tree, the different components that make up blood within the cardiovascular system have a given mass and are exposed to the same force that constantly pulls objects towards the Earth's surface. This constant influence of gravity creates a pressure gradient within the cardiovascular system between the upper and lower portions of the body, where the lower portions operate at a much higher pressure than the upper sections in the upright position (Watenpaugh and Hargens 1977). This pressure is referred to as hydrostatic

pressure, and is one of the three main components that influence total measured pressure within the cardiovascular system. The other two sources of pressure are the filling pressure of the system, and the dynamic pressure from the relationship between flow and resistance (Blomqvist and Stone 1977). One consequence of gravity and hydrostatic pressure is the redistribution of blood that occurs with terrestrial life. An example is the upright human who has approximately 70% of their total blood volume below the level of the heart (Rowell 1984). If positioned in the upright position for prolonged periods, this percentage will begin to increase and result in significant venous pooling (Gauer and Thron 1965). This concept is reinforced when observing a change in posture from a supine or recumbent position to an upright one. Research has shown that with this type of postural change, approximately 600 to 700 ml of blood is displaced from the thoracic regions to the legs (Gauer and Thron 1965). This data suggests that when gravitational forces are changed, the distribution of blood within cardiovascular system changes accordingly.

Understanding the human cardiovascular system at Earth's surface allows for a better discussion of what occurs when the distance between Earth and the human body are greatly increased. In accordance with the Law of Universal Gravitation, as the distance between two objects increases, the force drawing them together decreases. Applying this to what has previously been mentioned, as the force of gravity decreases, the pressure gradient between the upper and lower portions of the body will narrow as a result of the removal of the hydrostatic pressure. This decrease in gravitational force and subsequent removal of hydrostatic pressure is what is commonly referred to as a microgravity environment.

Models of Altered Gravity

In order to examine a removal or change in hydrostatic pressure, scientists had to invent new ways to study the human cardiovascular system. Obviously, the effect of a reduced gravitational force could be examined during spaceflight, but the high cost and difficult data collection makes this type of research protocol complicated. To combat these problems, researchers began to develop ground-based models of spaceflight. Two widely used models include a supine or slightly head-down tilt posture, both of which result in similar adaptive

responses seen during spaceflight (Fortney, Schneider et al. 1977). As research continued to grow, an increasing amount of data began to show that certain degrees of head-down tilt produced a more accurate analog for spaceflight conditions compared to the supine model (Kakurin, Lobachik et al. 1976; Trappe, Trappe et al. 2006).

Fluid Redistribution

Using the above-mentioned models, one key component was discovered that influenced several central cardiovascular parameters. Astronauts first noticed that within a few hours of spaceflight their legs, particularly in the calf regions began to decrease in size. The Apollo-Soyuz Test Project was one of the first missions to make actual measurements of leg volumes and discovered that within 32 hours of microgravity there was a 5-10% decrease in all crew members (Hoffler, Bergman et al. 1977). This change in leg volume provoked several ground-based studies that found both supine and head-down tilt positions also caused a significant change in resting leg volumes. Within 30 minutes of initiating supine rest, a 1.5% volume loss has been shown to occur, with an additional 1% after 90 minutes (Thornton, Hedge et al. 1992). Data comparing supine leg volumes suggests that a head-down tilt position will either elicit an equal or greater response, while an upright position will bring leg volumes back to pre-tilt values and that all changes occur approximately within a 24 hour period (Robinson, Epstein et al. 1966; Thornton, Hoffler et al. 1977; Hargens, Tipton et al. 1983; Gaffney, Nixon et al. 1985; Thornton, Hedge et al. 1992).

These changes in lower leg volumes were the first indication that a cardiovascular fluid shift was occurring in microgravity settings (Nixon, Murray et al. 1979; Blomqvist, Nixon et al. 1980). The proposed fluid shift was validated when 700-900 ml blood redistribution was measured following a transition from an upright to supine body position (Fortney, Schneider et al. 1977). This fluid redistribution was directed towards the heart and lungs, resulting in an increase in pulmonary blood flow of 20-30% (Fortney, Schneider et al. 1977). Data comparing supine to head-down tilt data also suggests that a tilted position causes an accelerated and greater filling of the torso regions (Kakurin, Lobachik et al. 1976; Fortney, Schneider et al. 1977).

Central Circulation

The above information regarding fluid shifts has allowed for a gross understanding of the cardiovascular adjustments that occur within the first stage of microgravity exposure. The remaining paragraphs of this section will expand this premise and provide greater detail into how the fluid shift influences specific cardiovascular functions.

With 75% of the blood volume being in the distensible veins below the heart, any fluid shift will directly influence the heart. This influence is first seen as an increase in central venous pressure within the first 15 minutes of a head-down tilt posture (Gaffney, Nixon et al. 1985). This pressure continues to increase above upright values after 30 minutes where for some subjects it peaks, while others have reported it elevating for up to 4 hours post tilt (Nixon, Murray et al. 1979; Blomqvist, Nixon et al. 1980; Gaffney, Nixon et al. 1985).

The increase in central venous pressure at the level of the heart can also be viewed as an increase in preload. Basic cardiovascular physiology demonstrates that changes in preload, like that seen during exercise or with blood volume changes, can influence cardiac filling and performance (Fortney, Schneider et al. 1977). The increase in central venous pressure at 90 and 120 minutes of head-down tilt posture also causes an increase in left ventricular diameter of 3.9 and 4.7 cm, respectively (Nixon, Murray et al. 1979). Other investigators have seen similar results through changes in left ventricular volumes that are increased within 90 minutes of exposure and remain elevated for up to 24 hours (Fortney, Schneider et al. 1977; Nixon, Murray et al. 1979; Poliner, Dehmer et al. 1980). However, microgravity had little influence on ventricular contractility or end-systolic volumes (Fortney, Schneider et al. 1977; Poliner, Dehmer et al. 1980). Based on this information, the increase in preload and subsequent increases in end-diastolic volume are the main factors influencing the measured increase in stroke volume (Chapman, Fisher et al. 1960; Fortney, Schneider et al. 1977; Blomqvist, Nixon et al. 1980; Martin, Montgomery et al. 1987).

The high cardiac filling pressure and thoracic blood volume that occurs with a microgravitational fluid shift also influences cardiopulmonary baroreceptors. When stimulated, these receptors cause a decrease in heart rate and peripheral vascular resistance (Fortney, Schneider et al. 1977; Poliner, Dehmer et al. 1980; Hargens, Tipton et al. 1983). This change in heart rate offsets the observed increases in stroke volume resulting in an unchanged cardiac

output following the blood volume redistribution (Fortney, Schneider et al. 1977; Nixon, Murray et al. 1979; Poliner, Dehmer et al. 1980; Martin, Montgomery et al. 1987).

Peripheral Circulation

There are some key vascular responses to acute microgravity exposure. One early adjustment observed with immediate supine posture is a transient vaso-venodilation (Fortney, Schneider et al. 1977). As the blood that is involved with upright venous pooling is removed, there is a decrease in local sympathetic nervous stimulation (Fortney, Schneider et al. 1977). As time in a supine or head-down tilt position is extended the relaxation of the venous smooth muscle and decreasing tone of the leg vasculature continues until approximately 30-60 minutes where it reaches a maximal effect (Fortney, Schneider et al. 1977).

Cardiovascular Adjustments to Upright and Supine Exercise

When the human body is placed under stress, like that seen during exercise, certain adjustments must take place for work to continue. These adjustments can be observed through measurements of oxygen consumption, which is the rate at which the body can take in, transport and utilize oxygen. According to Adolfus Fick, oxygen consumption can be expressed as:

$$VO_2 = \text{Heart Rate} \times \text{Stroke Volume} \times \text{arterial-venous Oxygen Difference} \qquad 2\text{-}1$$

The relationship among these variables determines the rate and amount of oxygen consumed at rest and during exercise. This section will focus on the central cardiovascular adjustments that influence this relationship and describe how external factors may play a role in oxygen consumption.

The linear relationship between work rate and oxygen consumption has been recognized for many years. At rest, oxygen consumption is generally around .25 L/min for healthy individuals in either a seated or supine position (Egana, Green et al. 2006), and once

exercise begins and workload increases, oxygen consumption also increases. This relationship continues until oxygen consumption no longer increases with increasing exercise intensity. It is at this point that maximal oxygen consumption has been reached and the body can no longer meet the demands of the working muscle. What becomes interesting is that in two studies examining maximal oxygen consumption in both an upright and supine position, a significant decrease was observed with the supine posture (Ray and Cureton 1991; Koga, Shiojiri et al. 1999). Others have also found that subjects performing supine exercise became tired and experienced more pain in the working muscles (Folkow, Haglund et al. 1971).

Cardiac Output

Cardiac output is the product of heart rate and stroke volume and is measured as the output of the ventricles per minute (Scher 1974). During exercise, cardiac output increases linearly with oxygen consumption at rate of 5-6 L/min of cardiac output for every 1 L/min of oxygen consumption (Rowell 1993), but this relationship may decrease as maximal values of oxygen consumption (above 3 L/min) are approached (Astrand, Cuddy et al. 1964). Unlike the above-mentioned differences between upright and supine maximal oxygen consumption, cardiac output has been shown to have no differences in the linear relationship or maximal values when comparing the two positions (Blomqvist and Stone 1977; Poliner, Dehmer et al. 1980). It is important to mention that these measurements of cardiac output were made at the heart and do not necessarily reflect blood flow that is occurring at the working muscle. For example, calf blood flow measurements made during exercise when exercise position was rapidly changed from a supine to leg down position measured a 60% increase in calf muscle blood flow in the leg down position (Folkow, Haglund et al. 1971; Blomqvist and Stone 1977). This difference in muscle blood flow may be one of the contributing factors for the differences seen in maximal oxygen consumption.

Heart Rate

The linear relationship between heart rate and oxygen consumption becomes important when discussing changes in blood flow. The range over which a specific individual can change his/her heart rate is dependent on resting and maximal heart rates. Resting heart rate can be

influenced by a number of conditions ranging from pharmaceutical influences to changes in blood volume, while maximal heart rate is generally only negatively influenced by increasing age. It is therefore the rate at which heart rate increases with oxygen consumption that becomes important during exercise.

The mechanism by which heart rate increases during exercise is important. At rest a major controller of heart rate is the barorecptors of the carotid sinus and aortic arch (Scher 1974). In addition, changes in filling pressure of the heart are easily detected and result in an adjusted heart rate. One example of this is in the supine position when there is a increase in ventricular preload, which causes heart rate to be lower than that measured during upright sitting (Stegall 1966; Egana, Green et al. 2006). In this state, the small changes in heart rate occur primarily through vagal or parasympathetic modulation. However, as exercise begins the inhibitory influence of the vagal nerve begins to rapidly withdraw, which allows for an increase in heart rate. With continued exercise and the need for higher heart rates the removal of parasympathetic inhibition becomes complete and sympathetic activation takes place.

The discovery of the relationship between parasympathetic and sympathetic stimulation of the heart is key in understanding basic exercise physiology. Early researchers found that the initial increase in heart rate was uninfluenced by sympathetic blockade, but that heart rates above 90-100 bpm could not be obtained with further increases in work load (Robinson, Epstein et al. 1966). It was also found that at the same heart rate in which a potential sympathetic drive took place, other organ systems were demonstrating decreases in blood flow, that were caused by rising plasma norepinephrine and plasma renin concentrations from increased sympathetic stimulation, and an increased sympathetic vasoconstrictor outflow (Rowell 1984).

The information regarding exercising heart rate and the method by which it is achieved becomes even more interesting when examining exercising data in the upright compared to supine positions. Data suggests that for any given sub-maximal work load heart rate is higher in an upright position vs. supine (Thadani and Parker 1978; Egana, Green et al. 2006; Egana, Smith et al. 2007) and this trend in heart rate differences continues to maximal workloads (Poliner, Dehmer et al. 1980).

Stroke Volume

The other key determinant of cardiac output is stroke volume, which is defined as the volume of blood ejected from the ventricle during a single heart beat, and is calculated as the difference between end-diastolic and end-systolic volumes. Unlike heart rate, stroke volume does not have a linear response to increases in oxygen consumption (Chapman, Fisher et al. 1960). Early investigators found that at an oxygen consumption of approximately 40% of the maximum or a heart rate of about 110 beats per minute (bpm) a maximal stroke volume was observed (Astrand, Cuddy et al. 1964), because as heart rate increases the time allowed for the filling of the ventricles becomes drastically shortened (Katz 1977; Cheng, Igarashi et al. 1992). However others have more recently shown that endurance athletes do not reach a stroke volume plateau due to a increased diastolic filling time and enhanced ventricular emptying (Gledhill, Cox et al. 1994). Stroke volume contributes to about 50% of the increase in cardiac output that is observed during maximal exercise (Chapman, Fisher et al. 1960).

When comparing supine to upright responses, stroke volume is higher in recumbent positions (Poliner, Dehmer et al. 1980). This increased stroke volume during supine exercise is likely the result of the fluid shifts mentioned in the previous section and the reason for the decreased exercising heart rates mentioned above.

Stroke volume is influenced by several extrinsic and intrinsic factors (Scher 1974; Rowell 1993). Extrinsic factors include changes in preload, also referred to as filling pressure, and which are often described in terms of the atria-ventricle pressure gradient and the Frank-Starling mechanism. Basic fluid mechanics states that fluids will move down a pressure gradient, and in the heart it is no different. With regard to preload there are two ways of influencing this gradient. One is by changing left atrial pressure, which can be done by changing blood volume, activating/deactivating the muscle pump, or through fluid redistribution (Stegall 1966; Scher 1974; Katz 1977; Thadani and Parker 1978; Laughlin 1987; Rowell 1993). During exercise, however, there is generally no change in left atrial pressure when compared to resting conditions (Cheng, Igarashi et al. 1992). Left ventricular pressure, however, decreases during exercise resulting in an increased pressure gradient and ventricular filling (Cheng, Igarashi et al. 1992).

The increased filling at the end of diastole during exercise is measured as an increased end-diastolic volume, which in turn forces the cardiac muscle to elongate allowing for increased

force production via the Frank-Starling mechanism (Feigl 1974). The Frank-Starling mechanism states that as the volume or length of cardiac muscle increases the amount of force that can be produced also increases, allowing for adequate emptying (Feigl 1974; Katz 1977). This information is based on the finding that muscle fibers contract optimally when there is maximal actin and myosin interaction, approximately at a sarcomere length of 2.2 μm (Scher 1974).

The other extrinsic factor that influences stroke volume is afterload, which is defined as the load the ventricle must overcome during systole (Rowell 1993). Situations such as hypertension where arterial blood pressure is very high force the left ventricle to work harder to accomplish the necessary stroke volume.

Increases in stroke volume can also occur through several intrinsic factors that are often referred to as changes in contractility (Katz 1977; Rowell 1993). Contractility changes when the ventricular work is influenced without any change in muscle fiber length (Katz 1977). One mechanism by which contractility is modulated is through changes in circulating norepinephrine and acetylcholine via the autonomic nervous system (Feigl 1974). It is no coincidence that sympathetic activation increases both heart rate and contractility during exercise. Higher cytosolic calcium will also increase ventricular contractility. During exercise, this occurs when heart rate increases to a point where calcium reuptake into the sarcoplasmic reticulum is slower than the repeated action potentials (Rowell 1993).

Section 3: Cardiovascular Adaptations to Exercise Training

The goal of any exercise-training program is to increase the contracting muscles' ability to sustain power or work. As previously mentioned, the measurement of oxygen consumption during maximal exercise permits evaluation of the improvement in aerobic capacity. Several longitudinal training programs have shown significant increases in peak oxygen consumption in normal healthy subjects (Ehsani, Hagberg et al. 1978; Shapiro and Smith 1983; Martin, Montgomery et al. 1987; Ray and Cureton 1991; Goodman, Liu et al. 2005). All training programs are influenced by several factors, including mode of exercise as well as frequency, intensity, and duration of training sessions. The potential variability between different study protocols creates problems when determining specifically what adaptations occur within the cardiovascular system. Therefore, this section will attempt to give a general description

describing the central cardiovascular adaptations that occur with moderate to vigorous intensity endurance exercise training.

Cardiac Output and Heart Rate

Adapting equation 1-1 to represent maximal exercising conditions gives insight to what variables must change to influence oxygen consumption following exercise training.

$$VO_{2max} = Heart\ Rate_{max} \times Stroke\ Volume_{max} \times arterial\text{-}venous\ Oxygen\ Difference_{max} \qquad 2\text{-}1$$

Any increase in maximal stroke volume will ultimately be seen as a higher maximal cardiac output, which has been shown to occur with exercise training (Rerych, Scholz et al. 1980; Ray, Cureton et al. 1990). However, the increase in maximal cardiac output does not change the relationship between oxygen consumption and cardiac output (Martin, Montgomery et al. 1987).

Depending on the training protocol exercise training may cause a decrease in resting and/or sub-maximal heart rates (Rerych, Scholz et al. 1980; Goodman, Liu et al. 2005). Maximal heart rate, however, is not influenced by training and is only influenced by an increase in age (Rerych, Scholz et al. 1980; Rowell 1986).

Stroke Volume

The increase in maximal cardiac output with training despite an unchanged peak or maximal heart rate means that stroke volume must increase with exercise training. Resting measurements of stroke volume show that within 1 week of intense training stroke volume will be higher than pre-training values (Ehsani, Hagberg et al. 1978), while other research suggests the increase in resting stroke volume occurs much later (Martin, Montgomery et al. 1987). The different time course of these two studies may be attributed to the different training protocols used. Both studies, however, attribute the increase in stroke volume to the directly measured increase in left ventricular internal dimension, diastolic index, and diastolic volume (Ehsani, Hagberg et al. 1978; Martin, Montgomery et al. 1987).

Measurements of exercising stroke volume also show elevated volumes at both sub-maximal and peak work rates (Martin, Montgomery et al. 1987; Goodman, Liu et al. 2005). As with rest, the exercising stroke volume is paralleled by increases in ventricular end-diastolic diameter and end-diastolic volume (Rerych, Scholz et al. 1980; Bar-Shlomo, Druck et al. 1982; Blomqvist and Saltin 1983; Martin, Montgomery et al. 1987; Ray, Cureton et al. 1990; Goodman, Liu et al. 2005). Other studies using both human and animal models show that there is a potential for ventricular contractility to increase or remain unchanged (Blomqvist and Saltin 1983)

It is generally accepted that the observed increase in end-diastolic volume is the major determinant of the increase in stroke volume following exercise training. Describing the mechanism by which end-diastolic volume increases is, however, not an easy task. As mentioned previously any increase in the atria-ventricle pressure gradient will subsequently increase ventricular end-diastolic volume. Exercise training may influence this gradient by two methods. The first is through increases in atrial pressure. Several researchers have found significant increases in blood and plasma volumes following training, which result in an increase in atrial filling pressure (Rerych, Scholz et al. 1980; Blomqvist and Saltin 1983; Rowell 1986; Ray, Cureton et al. 1990; Goodman, Liu et al. 2005).

The concept that blood volume is the sole major contributor to increased stroke volumes was weakened when researchers expanded the blood volume of sedentary subjects equal to that of athletes and found that athletes still had a 15% higher stroke volume (Hopper, Coggan et al. 1988). This study suggests that something other or in additional to the change in filling pressure via increased blood volume is responsible for the increased stroke volume. The authors suggest that a key component to increasing end-diastolic volume is through longitudinal myocardial hypertrophy that is observed through increases in left ventricular dimensions (Tipton and American College of Sports Medicine. 2006). As individual myocytes increase in length the overall chamber size will be forced to increase (Tipton and American College of Sports Medicine. 2006). This idea is further supported by the research showing increased ventricular mass and wall thickness following endurance training (Ehsani, Hagberg et al. 1978; Shapiro and Smith 1983; Rowell 1986; Martin, Montgomery et al. 1987; Tipton and American College of Sports Medicine. 2006).

Additional theories suggest that a trained state, like that of athletes, results in a more compliant and distensible ventricle than that seen in untrained individuals (Levine, Lane et al. 1991). Greater compliance would allow for greater ventricular volumes with the same filling pressure or myocyte size. Some authors also suggest that the chronic volume loading experienced with exercise training causes increased compliance through adaptations of the pericardium rather than the myocardium (Blomqvist and Saltin 1983). This was further supported by the work of Stray-Gunderson et. al. (Stray-Gundersen, Musch et al. 1986) who observed increases in maximal stroke volume and cardiac output in exercising dogs following pericardiectomy. They concluded that the removal of the pericardium allowed for an increase in ventricular compliance that led to the measured increase in ventricular performance.

Summary

Despite the vast amount of research involving the cardiovascular adjustments to upright and supine exercise, little is known about how exercise and cardiovascular performance is influenced acutely in a true microgravity model. As previously mentioned the -6° head-down tilt position produces a central fluid shift at rest and that this rate and degree of that shift is greater than that during resting supine posture.

It was, therefore, the purpose of this study to test the hypothesis that acute simulated microgravity exposure created by -6° head-down tilt posture would result in 1) decreased peak oxygen uptake, 2) and an increase in sub-maximal exercising stroke volume compared to that measured during supine and upright exercise.

CHAPTER 3 - Methods

Subjects

The subjects of this investigation were seven college aged (18-24 years) male volunteers, who had not participated in systematic endurance training for at least two months prior to the study. Each subject was given a detailed explanation of the experimental protocol and provided written and verbal consent. Each subject completed a medical history questionaire to determine the presence of cardiovascular disease and smoking status. Individuals with known cardiovascular disease or currently smoking were excluded. The experimental protocol was approved by the Institutional Review Board for Reseach Involving Human Subjects at Kansas State University.

Experimental Design

Each subject performed three maximal exercise tests (VO_{2peak}), described below, with at least 48 hours of rest between testing sessions. VO_2, VCO_2, VE, estimated lactate threshold (LT), cardiac output (CO), and heart rate (HR) were assessed during incremental cycling in the upright, supine and -6° head-down tilt positions. The following protocol was used for each test. Subjects rested on the cycle ergometer for 5 minutes, then began cycling at 60 rotations per minute (rpm) at 20-watts for an additional 5 minutes. Following the resting and warm-up periods the test began at 25-watts with the work rate progressively increased 25-watts every minute until the subject could no longer maintain the required pedal rate for at least 5 revolutions despite verbal encouragement. Pedal rate was continuously monitored by digital readout.

Upright cycle tests were peformed on a electronically braked cycle ergometer (800 Ergometer, SensorMedics, USA). Supine and -6° head-down tilt cycle tests were performed on a mechanically braked Monarch 818E cycle ergometer that was mounted to a custom made

apparatus designed for -6° head-down tilt exercise (Figure 3-1) that could be modified to accommodate a supine exercising posture. All cycle ergometers elicited similar exercise responses based on the non-signifiantly different oxygen consumptions and heart rates recorded at 100W (Table 4-3 and Figure 4-1).

Experiemental Methods

Breath-by-breath metabolic and ventilatory data were obtained continuously throughout the testing procedures and converted to fifteen second averages (SensorMedics 229 Metabolic Cart, SensorMedics Corp.,Yorba Linda, CA). Heart rate was collected continuously by a four lead ECG interfaced to the metabolic cart. The maximum VO_2, VCO_2, HR, and VE obtained during the incremental test was considered peak values for a given position. The VO_2 corresponding to the lactate threshold was estimated as the change in slope in the plot of VCO_2 against VO_2 (V-slope method).

Pulmonary capillary blood fow was measured and used as an index of cardiac output at rest and during exercise via a single-breath exhalation technique. Subjects were instructed to take a full inhalation of a test gas mixture of 0.3% methane, 0.3% acetylene, 0.3% carbon monoxide, 21% oxygen, with the remainder nitrogen. Following the inhilation, subjects were told to hold their breath for a period of 3-5 seconds before they exhaled at a constant rate of 200-800 ml/s. Since acetylene and carbon monoxide are both soluble in blood, during the constant exhalation the concentrations of acetylene and carbon monoxide decline at a rate that is proportional to pulmonary capillary blood flow (Wilson, Savariryan et al. 1996). In healthy humans, cardiac output can be estimated nonivasively from the resulting pulmonary capillary blood flow (Liu, Menold et al. 1997; Downey, Chenoweth et al. 2007). However, pulmonary capillary blood flow underestimates cardiac output and therefore values reported in the current study should not be directly compared with values measured via thermodilution or echocardiography (Sadeh, Miller et al. 1997). This technique has previously been used to estimate cardiac output at rest and during exercise (Liu, Menold et al. 1997; Downey, Chenoweth et al. 2007).
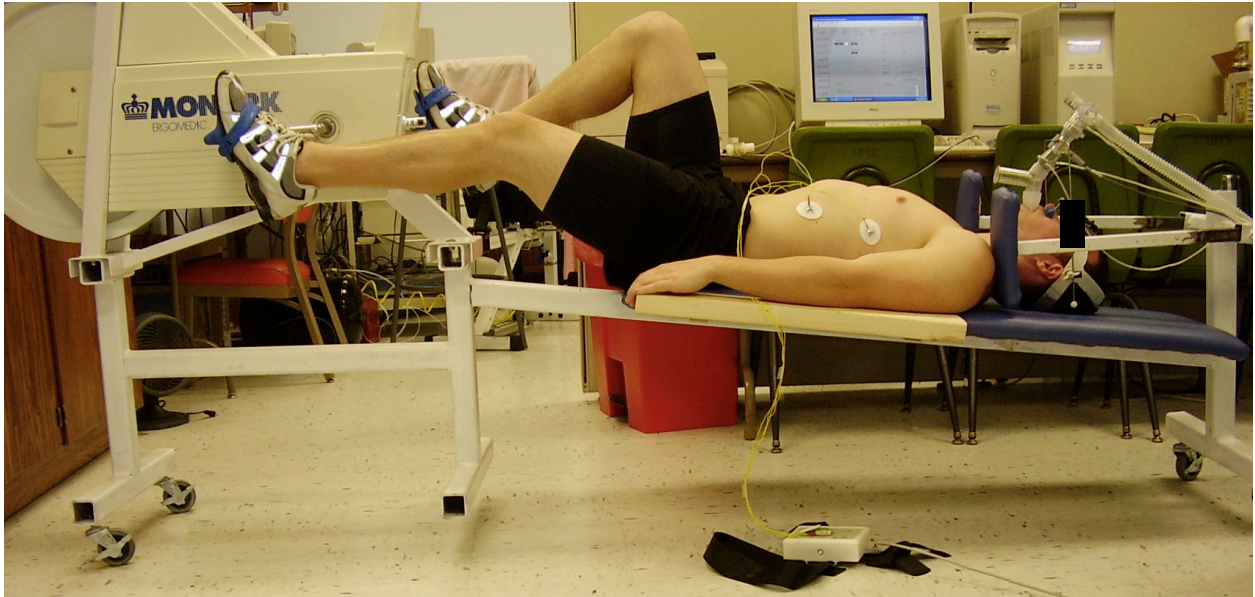
During all incremental exercise tests in all three positions, cardiac output was measured at rest, and 30 seconds into the 50W, 100W and 150W workrate stages for each individual. A

regression line was created using these data to predict each subject's cardiac output at the end of the 100-watt stage. The collected values were deemed acceptable if the subject performed the proceedure correctly and data output was sufficient to make needed calcuations. The estimated cardiac output was then divided by the measured heart rate taken at 100W to calculated exercising stroke volume. The above estimate of a subject's cardiac ouput at 100-watts minimized the potential error of a single measure at 100-watts.

Statistical Analysis

A one-way within-subject analysis of variance was used to determine the effects of posture on the above described dependent variables. A Fishers posthoc test for repeated measures was used to follow up on significant main effects. Associations between subject characteristics and metabolic variables were analysed using a Pearson Product Moment correlation coefficient. All data were expressed as mean ± standard deviaton. Statistical significance was declared when $P < 0.05$.

Figure 3-1

Representative subject in the -6 degree head-down tilt position.

CHAPTER 4 - Results

Subject Characteristics

Mean values for age, height, body weight, and body mass index are presented in Table 4-1. All seven subjects were able to complete each test with no problems.

Maximal Responses

Oxygen uptake during the three incremental exercise tests is shown for one subject in Figure 4-1. Mean peak physiological responses for each of the three positions are shown in Table 4-2. Peak VO_2, peak VCO_2, and peak heart rate were significantly lower during supine and -6° head down tilt exercise compared to those during the upright exercise ($P < 0.05$). However, there was no significant difference for peak VO_2, peak VCO_2, and peak heart rate between the supine and -6° head down tilt positions. The estimated lactate threshold was significantly lower during supine (1.10 ± 0.14 l/min) exercise but not -6° head down tilt (1.25 ± 0.15 l/min) compared to upright exercise (1.32 ± 0.20 l/min, $P<0.05$). Measurements of peak ventilation and peak RER were not significantly different between any of the three positions.

Sub-maximal Responses

The sub-maximal responses to exercise at 100W are presented in Table 4-3. The measured oxygen uptake at 100 W was not significantly different between upright, supine and -6° head down tilt exercise. Calculated stroke volume at 100W was significantly higher in the -6° head down tilt position (76.6 ± 4.7 ml) but not the supine (75.6 ± 16.7 ml) compared to the upright position (71.2 ± 4.5 ml, $P < 0.05$). There was no significant difference between the 100W stroke volumes measured in the upright and supine exercise postures. Cardiac output during the three incremental exercise tests are shown for one subject in Figure 2. Mean heart rate

and cardiac output were not significantly different between any of the exercising postures at 100W.

Table 4-1 Subject Characteristics

	Subject Data		
Age (yr)	21.3	±	2.1
Height (cm)	175.4	±	7.0
Weight (kg)	68.1	±	11.9
BMI (kg/m2)	21.7	±	3.7

Values are mean ± standard deviation

Table 4-2 Peak Exercise Responses

	VO_2 (l/min)			VCO_2 (l/min)			VE (l/min)			HR (bpm)			RER		
Upright	2.32	±	0.61	2.64	±	0.62	78.9	±	23.1	172	±	12	1.14	±	0.04
Supine	2.01	±	0.46*	2.37	±	0.35*	76.1	±	10.5	160	±	15*	1.16	±	0.11
-6° HDT	2.01	±	0.51*	2.27	±	0.48*	72.6	±	17.3	161	±	14*	1.14	±	0.06

Values are mean ± standard deviation

* Significantly different from Upright (P<0.05)

Table 4-3 Cardiorespiratory Responses at 100W

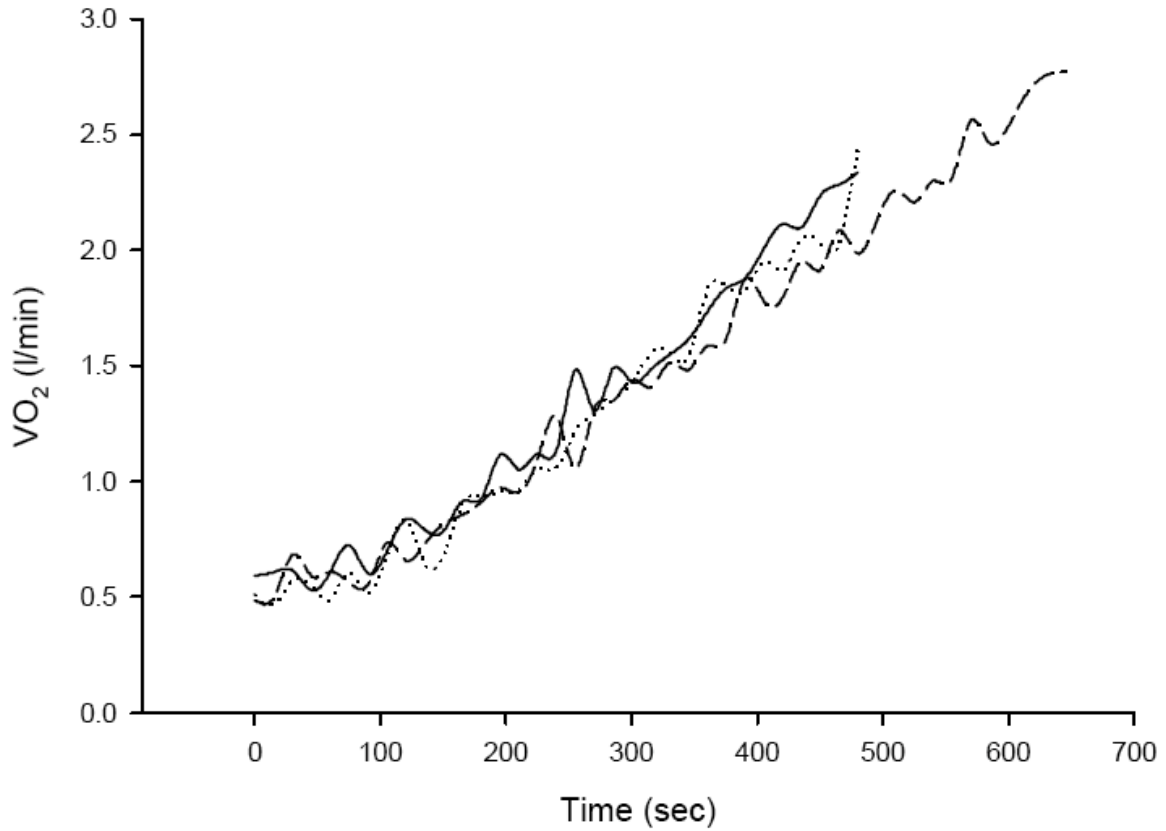|	VO_2 (l/min)			HR (bpm)			SV (ml)			Q (l/min)			Slope[a]			Y - Intercept[a]		
Upright	1.12	±	0.08	122	±	19	71.2	±	4.5	8.61	±	0.47	5.57	±	0.23	2.40	±	0.31
Supine	1.17	±	0.14	120	±	15	75.6	±	16.7	9.46	±	2.4	5.32	±	0.19*	2.64	±	0.12*
-6° HDT	1.19	±	0.13	121	±	15	76.6	±	4.7*	9.17	±	0.84	5.61	±	0.19**	2.49	±	0.17

Values are mean ± standard deviation

[a] Slope and Y-Intercept of Q:VO_2 relationship
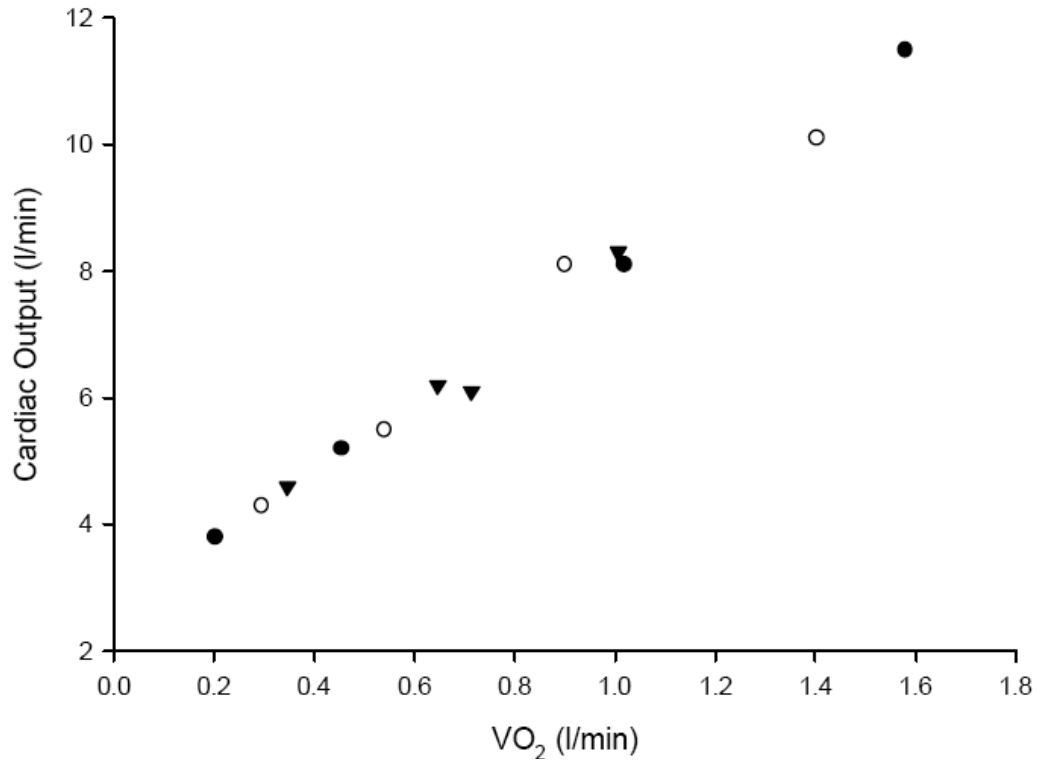
* Significantly different from Upright (P<0.05)

** Significantly different from Supine (P<0.05)

Figure 4-1 Oxygen Uptake

Response of VO$_2$ during incremental cycling in a representative subject under conditions of upright (dashed line), supine (solid line), and -6° head-down tilt (dotted line) position. Data averaged over 15 second intervals.
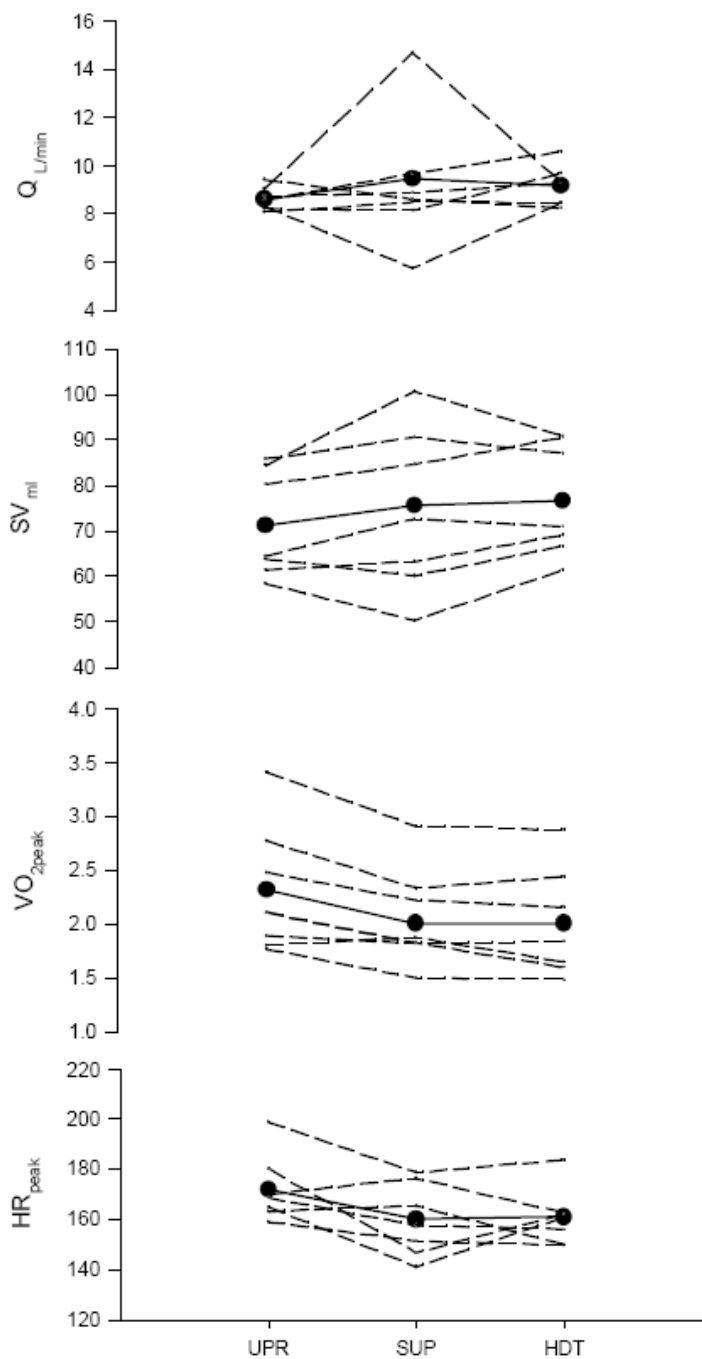
Figure 4-2 Cardiac Output

Values of cardiac output in relation to VO₂ in a representative subject during upright (closed circle), supine (open circle), and -6° head-down tilt (closed triangle) incremental exercise tests, measured via single-breath exhalation.

Figure 4-3 Individual and Group Responses

Individual and mean values of cardiac output and stroke volume at 100-watts and peak oxygen uptake and heart rate in the upright (UPR), supine (SUP) and -6° head-down tilt (HDT) positions.

CHAPTER 5 - Discussion

The key findings of this study were as follows. Consistent with our first hypothesis peak oxygen uptake was decreased during supine and -6° head-down tilt exercise when compared to that obtained in the upright, but in contrast to hypothesis one, there was no difference between peak oxygen uptake in the supine and -6° head-down tilt positions. Consistent with our second hypothesis, sub-maximal exercising stroke volume at 100-watts was increased during -6° head-down tilt exercise compared to that measured in the upright.

Peak Oxygen Uptake Response

In this study mean peak oxygen uptake was decreased by ~10% and ~13% in the supine and -6° head-down tilt positions, respectively, compared to the upright position. This data is consistent with that of Ray and Cureton (Ray and Cureton 1991) who found that maximal oxygen consumption measured during supine exercise was only 86.3% of that measured during upright exercise. Koga et al. (Koga, Shiojiri et al. 1999) not only found reductions in peak oxygen consumption during supine exercise but also in peak work rate and estimated lactate threshold. Several other studies, using small muscle groups, have found that when an exercising limb is at or elevated above the level of the heart, exercise performance (Fitzpatrick, Taylor et al. 1996; Rowell 1997; Wright, McCloskey et al. 1999; Goodman, Liu et al. 2005) and limb blood flow (Folkow, Gaskell et al. 1970; Folkow, Haglund et al. 1971) are significantly reduced compared to exercise below heart level. These data and the observed decrease in exercise performance observed in this study are likely due to a decrease in muscle blood flow caused by a reduction in muscle perfusion pressure, inadequate autoregulation of vascular conductance, and a possible decrease in muscle pump effectiveness.

During upright exercise lower limb arterial pressure is the sum of mean arterial pressure at the heart and the hydrostatic pressure created by the arterial column (Rowell 1974). However, during supine exercise the hydrostatic column is reduced, or slightly reversed in the case of a -6°

head-down tilt position, both of which cause a drastic reduction in lower limb arterial pressure (Watenpaugh and Hargens 1977; Nielsen 1983).

Sub-maximal Stroke Volume Response

The current study also showed that despite a decrease in peak oxygen uptake, sub-maximal exercising stroke volume is maintained during supine exercise and is increased during -6° head-down tilt exercise. Poliner et al. (Poliner, Dehmer et al. 1980) also observed a slightly higher stroke volume and lower heart rate during low level exercise in the supine position compared to the upright.

The increased sub-maximal stroke volume measured in this study is likely due to a central fluid shift and increase in central venous pressure. The transition from an upright position to a supine or head-down tilt position results in an immediate redistribution of blood towards the thoracic region of the body (Fortney, Schneider et al. 1977; Thornton, Hedge et al. 1992). However, the head-down tilt position results in a faster rate of change in fluid shifts than that measured in the supine position (Robinson, Epstein et al. 1966; Fortney, Schneider et al. 1977). Several researchers have also observed that a transition from the supine to the -6° head-down tilt position results in a significant increase in central venous pressure (Nixon, Murray et al. 1979; Blomqvist, Nixon et al. 1980; Gaffney, Nixon et al. 1985). During exercise the action of the muscle pump works to propel blood back to the heart independent of the exercising position (Robinson, Epstein et al. 1966; Scher 1974; Laughlin 1987), allowing for an increase in central venous pressure. The combination of an accelerated fluid shift and a working muscle pump during -6° head-down tilt exercise in this study presumably increased preloading conditions of the heart allowing for the observed increase in sub-maximal stroke volume. As a result, the slope of cardiac output versus oxygen uptake was significantly steeper in the supine and -6° head-down tilt positions compared to upright. Others have similarly shown that cardiac output is increased during supine exercise up to 160W compared to upright exercise (Leyk, Essfeld et al. 1994). However, these data are in disagreement with several other studies that have shown no difference between the cardiac output and oxygen uptake relationship during upright and supine exercise (Blomqvist and Stone 1977; Poliner, Dehmer et al. 1980). Therefore, further investigation is required to determine the extent to which posture influences cardiac output.

Peripheral Blood Flow

Since lower limb arterial pressure is influenced by the height of the arterial column, which increases in proportion to subject height, one would expect a correlation to exist between subject height and the decrement in peak oxygen uptake. Figure 5-1 shows that as subject's height increases so does the percent difference between peak oxygen uptake in the -6° head-down tilt positions. Others have seen similar correlations between the height of the hydrostatic column and cycle time in men and women (Egana, Green et al. 2006). In taller subjects the hydrostatic pressure gradient is larger (Watenpaugh and Hargens 1977), which when tilted may cause a greater decrease in hydrostatic pressure and perfusion pressure compared to the shorter subjects. This could explain the correlation between subject height and reductions in peak oxygen uptake seen in this study.

As previously mentioned muscle blood flow is not only determined by perfusion pressure but also vascular conductance. During conditions of low perfusion pressure an increase in vascular conductance can maintain adequate blood flow (Rowell 1993). Tschakovsky and Hughson (Tschakovsky and Hughson 2000) observed that passive arm elevation above the heart caused transient vasodilation at rest. However results from the current study suggest that during strenuous exercise when the muscle vasculature is already maximally dilated the decrease in perfusion pressure from supine or -6° head-down tilt positions cannot be fully compensated for by further dilation of the local vasculature. In 2007 Walker et al. (Walker, Saunders et al. 2007) demonstrated that the vasodilatation, which occurred during exercise above heart level did not fully compensate for the reduction in arterial perfusion pressure, leading to a reduction in exercising muscle blood flow.

The differences in lower limb arterial pressure during the supine and -6° head-down tilt position can only influence blood flow if their change is greater than the change in venous pressure. Strenuous exercise like that during a graded exercise test allows for venous pressure to remain very low, despite an upright posture, due to the decreased transmural pressure caused by the muscle pump and the presence of venous valves (Rowell 1974). It is important to mention that while venous pressure during upright exercise may be very low there is a potentially lower venous pressure during supine and -6° head-down tilt exercise. Laughlin and Joyner (Laughlin

and Joyner 2003) have proposed that the absence of a venous hydrostatic column may render the muscle pump ineffective. Potentially this change in venous hydrostatic pressure combined with the drop in pressure during muscle relaxation decreases intramuscular venous pressure below the critical opening pressure of the vessel. If venous pressure does decrease below this point the venous vessel will collapse and flow will be impeded until pressure rises above the critical opening pressure. This concept is supported when comparing research examine the influence of the muscle pump on limb blood flow. Several studies using dogs, which have a very small hydrostatic column, have found no muscle pump effect(Dobson and Gladden 2003; Hamann, Valic et al. 2003; Valic, Buckwalter et al. 2005), while others using upright humans have examined the presence of a contributing muscle pump (Shiotani, Sato et al. 2002; Lutjemeier, Miura et al. 2005). Therefore, it may be the combined decrease in arterial perfusion pressure and the lack of an effective muscle pump, may be contributing to the decreased exercise tolerance measured in the current study.

Lactate Threshold

The observed decrease in estimated lactate threshold in during supine exercise compared to upright is likely the result of an earlier recruitment of more motor units. Researchers have shown that when a muscle is exercised above the heart there is an increased integrated surface electromyogram response compared to exercise performed below heart level, suggesting an increase in motor unit recruitment (Tachi, Kouzaki et al. 2004). Hobbs and McCloskey (1987) have previously demonstrated an inverse relationship between muscle perfusion pressure and integrated surface electromyogram response to exercise (Hobbs and McCloskey 1987). The increased motor unit recruitment may involve increased contribution of type II fibers, which have been shown to contain more LDH_5 (M-LDH) isoforms of lactate dehydrogenase (Brooks 2000), and therefore contribute to the earlier lactate accumulation observed in the current study.

Limitations

Several limitations exist that may have influenced the results of the current study. First, is the reproducibility and validity of the protocol used during each peak exercise test. Potentially, subjects were not reaching a true maximal oxygen uptake value and were terminating the test prematurely. Early pilot data examining the reproducibility of the current protocol, in both upright and -6° head-down tilt positions, demonstrates no significant change between peak exercise tests over the course of 3 different testing sessions. However, at this time it is uncertain that subjects reached a true maximal oxygen uptake, using only volitional fatigue and RER values as termination criteria. Poole et. al (Poole, Wilkerson et al. 2008) have previously shown that maximal oxygen uptake can be drastically underestimated when using a RER criteria of 1.10 or 1.15 like that used in the current study.

A second limitation to the current study is the measurement of cardiac output via the single-breath exhalation technique during exercise. Several researchers have found that at rest and during exercise pulmonary capillary blood flow measured via the single-breath exhalaton technique underestimates cardiac output by approximately 1 L/min (Ramage, Coleman et al. 1967; Sadeh, Miller et al. 1997). Therefore, the results of the curent study allow only for the comparison of cardiac output between the three peak exercise tests, not the direct comparison with cardiac output measured in other studies. Also little is known on how a negative hydrostatic column like that created via -6° head-down tilt posture would change the relationship between pulmonary capillary blood flow and left ventriclar cardiac output. While these are limitations of the current study, it does not minimize the observed relationship between -6° head-down tilt exercise and central cardiovascular performance.

A third potential limitation is the lack of stroke volume data measured at higher intensities of exercise, particulary during peak exercise. While stroke volume at 100-watts is an important comparision, data pertaining to maximal exercise will allow for a better understanding of central cardiovascular performance in microgravity under conditions of high intensity work. The high breathing frequency that occurs at maximal work rates makes the protocol for the single-breath exhalation technique difficult and often impossible for most subjects. Therefore only a 100-watt comparison was made in the current study. In addition to the limited stroke

volume data is the lack of limb blood flow measurements that will further explain the mechanism behind the decreased exercise tolerance observed with supine and -6° head-down tilt exercise.

Future Directions

This study has demonstrated a decrease in peak oxygen uptake in the supine and -6° head-down tilt positions, despite a maintained and/or significantly increased central cardiovascular performance. Future work will need to address these findings from both peripheral and central cardiovascular directions.

First, continued research should examine the influence of the negative hydrostatic pressure gradient created by -6° head-down tilt exercise on limb blood flow, particularly femoral artery blood flow, and the changes within the microcirculation. The use of Doppler ultrasound to measure femoral artery blood flow (Hoelting, Scheuermann et al. 2001) and near-infrared spectroscopy to measure muscle capillary O_2 extraction (Ferreira, Lutjemeier et al. 2006; Harper, Ferreira et al. 2006) during head-down tilt exercise conditions will provide useful information pertaining to the limitations to exercise in acute microgravity.

Second, based on the findings of the current study, future research should examine if the acute increase in stroke volume with -6° head-down tilt exercise influences the cardiovascular adaptations that occur with chronic exercise training.
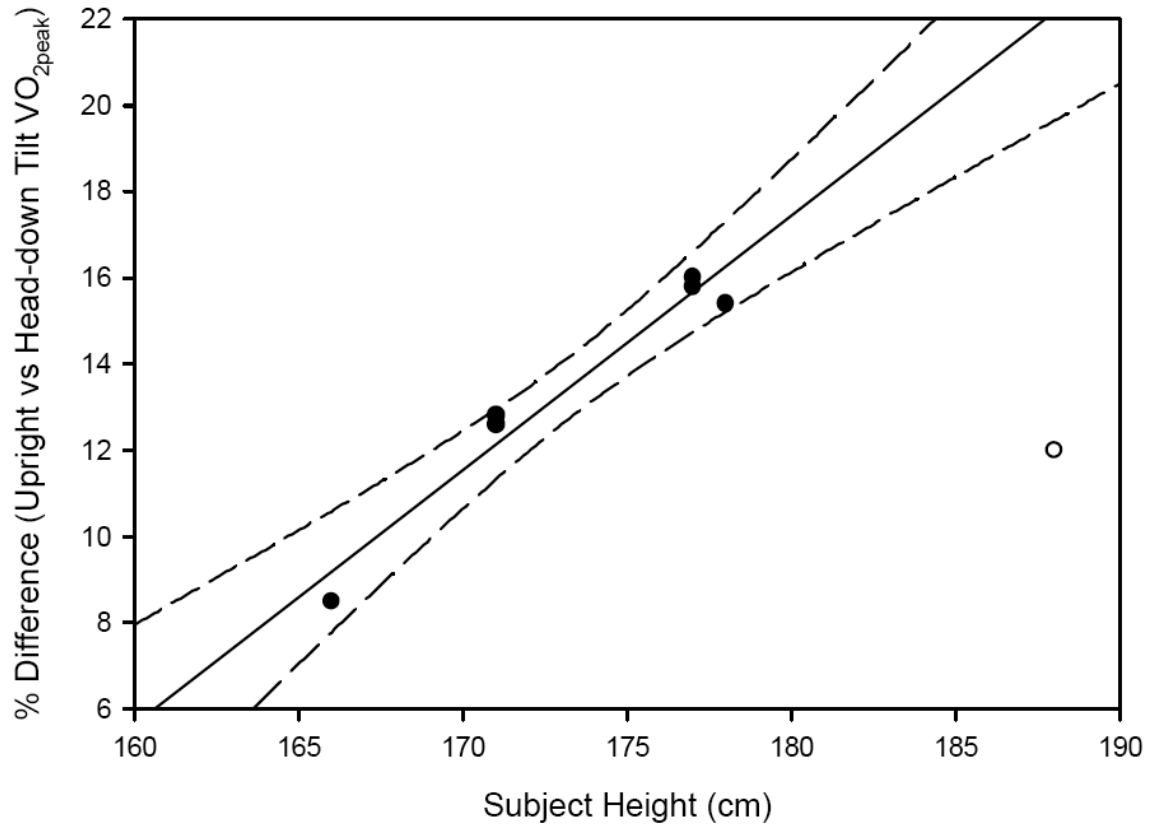
Conclusion

The measurement of peak oxygen uptake and exercising stroke volume in the -6° head-down tilt position prior to microgravity deconditioning may prove useful for future space research and missions. Acute microgravity exposure at rest has been shown to increase several central cardiovascular variables (Fortney, Schneider et al. 1977; Nixon, Murray et al. 1979; Blomqvist, Nixon et al. 1980; Poliner, Dehmer et al. 1980; Gaffney, Nixon et al. 1985). The data from this study suggests that despite the maintained or improved central cardiovascular performance the work capacity of an astronaut would be decreased immediately at onset of exposure to a microgravity environment. As the time of exposure to a microgravity environment

increases the deconditioning of the cardiovascular system (Fortney, Schneider et al. 1977; Levine, Zuckerman et al. 1997) will further decrease the already compromised astronaut's work capacity caused by the initial change in gravitational stress. Improved assessment of an astronaut's ability to perform strenuous work in a microgravity setting before a mission may allow for more effective pre-flight and in-flight training programs to be designed.

In summary, the key finding of this study is that peak oxygen uptake is acutely reduced in the supine and -6° head-down tilt exercise positions when compared to upright, despite an increase in sub-max stroke volume in the latter position. This reduction in exercise performance is likely the result of decreased muscle blood flow via reductions in muscle perfusion pressure and an ineffective muscle pump. With measurement of exercise performance during -6° head-down tilt an assessment of acute microgravity work capacity and cardiovascular performance can be made.

Figure 5-1 VO$_2$ – Height Correlation

**Correlation between subject height and the percent difference between upright and -6°
head-down tilt peak oxygen uptakes. One subject (open circle) was excluded from the
correlation on the criteria that his data fell outside of the 95% confidence interval of
the other subjects (closed circles). r = 0.973, P<0.05.**

References

Astrand, P. O., T. E. Cuddy, et al. (1964). "Cardiac Output during Submaximal and Maximal Work." <u>J Appl Physiol</u> **19**: 268-74.

Bar-Shlomo, B. Z., M. N. Druck, et al. (1982). "Left ventricular function in trained and untrained healthy subjects." <u>Circulation</u> **65**(3): 484-8.

Blomqvist, C. G., J. V. Nixon, et al. (1980). "Early cardiovascular adaptation to zero gravity simulated by head-down tilt." <u>Acta Astronaut</u> **7**(4-5): 543-53.

Blomqvist, C. G. and B. Saltin (1983). "Cardiovascular adaptations to physical training." <u>Annu Rev Physiol</u> **45**: 169-89.

Blomqvist, G. C. and L. H. Stone (1977). Cardiovascular Adjustments to Gravitational Stress. <u>Handbook of Physiology. The Cardiovascular System</u> Bethesda, Md. : Baltimore, Md., American Physiological Society. **sect. 3 vol. III:** 1025-1063.

Brooks, G. A. (2000). <u>Exercise physiology : human bioenergetics and its applications</u>. Mountain View, Calif., Mayfield Pub.

Chapman, C. B., J. N. Fisher, et al. (1960). "Behavior of stroke volume at rest and during exercise in human beings." <u>The Journal of Clinical Investigation</u> **39**: 1208-13.

Cheng, C. P., Y. Igarashi, et al. (1992). "Mechanism of augmented rate of left ventricular filling during exercise." <u>Circ Res</u> **70**(1): 9-19.

Dobson, J. L. and L. B. Gladden (2003). "Effect of rhythmic tetanic skeletal muscle contractions on peak muscle perfusion." <u>J Appl Physiol</u> **94**(1): 11-9.

Downey, A. E., L. M. Chenoweth, et al. (2007). "Effects of inspiratory muscle training on exercise responses in normoxia and hypoxia." <u>Respir Physiol Neurobiol</u> **156**(2): 137-46.

Egana, M., S. Green, et al. (2006). "Effect of posture on high-intensity constant-load cycling performance in men and women." <u>Eur J Appl Physiol</u> **96**(1): 1-9.

Egana, M., S. Smith, et al. (2007). "Revisiting the effect of posture on high-intensity constant-load cycling performance in men and women." <u>Eur J Appl Physiol</u> **99**(5): 495-501.

Ehsani, A. A., J. M. Hagberg, et al. (1978). "Rapid changes in left ventricular dimensions and mass in response to physical conditioning and deconditioning." <u>Am J Cardiol</u> **42**(1): 52-6.

Feigl, E. O. (1974). Cardiac Muscle Mechanics. <u>Physiology and Biophysics; Circulation, Respiration, and Fluid Balance</u>. T. C. Ruch and H. D. Patton. Philadelphia, W.B. Saunders Company. **2:** 33-48.

Ferreira, L. F., B. J. Lutjemeier, et al. (2006). "Effects of pedal frequency on estimated muscle microvascular O2 extraction." <u>Eur J Appl Physiol</u> **96**(5): 558-63.

Fitzpatrick, R., J. L. Taylor, et al. (1996). "Effects of arterial perfusion pressure on force production in working human hand muscles." <u>J Physiol</u> **495 (Pt 3)**: 885-91.

Folkow, B., P. Gaskell, et al. (1970). "Blood flow through limb muscles during heavy rhythmic exercise." <u>Acta Physiol Scand</u> **80**(1): 61-72.

Folkow, B., U. Haglund, et al. (1971). "Blood flow in the calf muscle of man during heavy rhythmic exercise." <u>Acta Physiol Scand</u> **81**(2): 157-63.

Fortney, S. M., V. S. Schneider, et al. (1977). The Physiology of Bedrest. Handbook of Physiology. Environmental Physiology. New York, American Physiological Society. **sect 4:** 889-939.

Gaffney, F. A., J. V. Nixon, et al. (1985). "Cardiovascular deconditioning produced by 20 hours of bedrest with head-down tilt (-5 degrees) in middle-aged healthy men." Am J Cardiol **56**(10): 634-8.

Gauer, O. H. and H. L. Thron (1965). Postural Changes in Circulation. Handbook of Physiology. Circulation. W. F. Hamilton and P. Dow. Bethesda, American Physiological Society. **3 Sect. 2:** 2409-2439.

Gledhill, N., D. Cox, et al. (1994). "Endurance athletes' stroke volume does not plateau: major advantage is diastolic function." Med Sci Sports Exerc **26**(9): 1116-21.

Goodman, J. M., P. P. Liu, et al. (2005). "Left ventricular adaptations following short-term endurance training." J Appl Physiol **98**(2): 454-60.

Hamann, J. J., Z. Valic, et al. (2003). "Muscle pump does not enhance blood flow in exercising skeletal muscle." J Appl Physiol **94**(1): 6-10.

Hargens, A. R., C. M. Tipton, et al. (1983). "Fluid shifts and muscle function in humans during acute simulated weightlessness." J Appl Physiol **54**(4): 1003-9.

Harper, A. J., L. F. Ferreira, et al. (2006). "Human femoral artery and estimated muscle capillary blood flow kinetics following the onset of exercise." Exp Physiol **91**(4): 661-71.

Hobbs, S. F. and D. I. McCloskey (1987). "Effects of blood pressure on force production in cat and human muscle." J Appl Physiol **63**(2): 834-9.

Hoelting, B. D., B. W. Scheuermann, et al. (2001). "Effect of contraction frequency on leg blood flow during knee extension exercise in humans." J Appl Physiol **91**(2): 671-9.

Hoffler, W. G., S. A. J. Bergman, et al. (1977). The Apollo-Soyuz Test Project Medical Report. In-Flight Lower Limb Volume Measurements. Washington, DC, United States. National Aeronautics and Space Administration. Johnson Space Center.,.

Hopper, M. K., A. R. Coggan, et al. (1988). "Exercise stroke volume relative to plasma-volume expansion." J Appl Physiol **64**(1): 404-8.

Kakurin, L. I., V. I. Lobachik, et al. (1976). "Antiorthostatic hypokinesia as a method of weightlessness simulation." Aviat Space Environ Med **47**(10): 1083-6.

Katz, A. M. (1977). Physiology of the Heart. New York, Raven Press.

Koga, S., T. Shiojiri, et al. (1999). "Kinetics of oxygen uptake during supine and upright heavy exercise." J Appl Physiol **87**(1): 253-60.

Laughlin, M. H. (1987). "Skeletal muscle blood flow capacity: role of muscle pump in exercise hyperemia." Am J Physiol **253**(5 Pt 2): H993-1004.

Laughlin, M. H. and M. Joyner (2003). "Closer to the edge? Contractions, pressures, waterfalls and blood flow to contracting skeletal muscle." J Appl Physiol **94**(1): 3-5.

Levine, B. D., L. D. Lane, et al. (1991). "Left ventricular pressure-volume and Frank-Starling relations in endurance athletes. Implications for orthostatic tolerance and exercise performance." Circulation **84**(3): 1016-23.

Levine, B. D., J. H. Zuckerman, et al. (1997). "Cardiac atrophy after bed-rest deconditioning: a nonneural mechanism for orthostatic intolerance." Circulation **96**(2): 517-25.

Leyk, D., D. Essfeld, et al. (1994). "Postural effect on cardiac output, oxygen uptake and lactate during cycle exercise of varying intensity." Eur J Appl Physiol Occup Physiol **68**(1): 30-5.

Liu, Y., E. Menold, et al. (1997). "Validation of the acetylene rebreathing method for measurement of cardiac output at rest and during high-intensity exercise." Clin Physiol **17**(2): 171-82.

Lutjemeier, B. J., A. Miura, et al. (2005). "Muscle contraction-blood flow interactions during upright knee extension exercise in humans." J Appl Physiol **98**(4): 1575-83.

Martin, W. H., 3rd, J. Montgomery, et al. (1987). "Cardiovascular adaptations to intense swim training in sedentary middle-aged men and women." Circulation **75**(2): 323-30.

Nielsen, H. V. (1983). "Arterial pressure-blood flow relations during limb elevation in man." Acta Physiol Scand **118**(4): 405-13.

Nixon, J. V., R. G. Murray, et al. (1979). "Early cardiovascular adaptation to simulated zero gravity." J Appl Physiol **46**(3): 541-8.

Poliner, L. R., G. J. Dehmer, et al. (1980). "Left ventricular performance in normal subjects: a comparison of the responses to exercise in the upright and supine positions." Circulation **62**(3): 528-34.

Poole, D. C., D. P. Wilkerson, et al. (2008). "Validity of criteria for establishing maximal O2 uptake during ramp exercise tests." Eur J Appl Physiol **102**(4): 403-10.

Ramage, J., E. Coleman, et al. (1967). "Rest and Exercise Cardiac Output and Diffusing Capacity Assesed By a Single Slow Exhalation of Methane, Acetylene, and Carbon Monixide." Chest **92**(1): 44-50.

Ray, C. A. and K. J. Cureton (1991). "Interactive effects of body posture and exercise training on maximal oxygen uptake." J Appl Physiol **71**(2): 596-600.

Ray, C. A., K. J. Cureton, et al. (1990). "Postural specificity of cardiovascular adaptations to exercise training." J Appl Physiol **69**(6): 2202-8.

Rerych, S. K., P. M. Scholz, et al. (1980). "Effects of exercise training on left ventricular function in normal subjects: a longitudinal study by radionuclide angiography." Am J Cardiol **45**(2): 244-52.

Robinson, B. F., S. E. Epstein, et al. (1966). "Control of heart rate by the autonomic nervous system. Studies in man on the interrelation between baroreceptor mechanisms and exercise." Circ Res **19**(2): 400-11.

Rowell, L. B. (1974). "Human cardiovascular adjustments to exercise and thermal stress." Physiol Rev **54**(1): 75-159.

Rowell, L. B. (1984). "Reflex control of regional circulations in humans." J Auton Nerv Syst **11**(2): 101-14.

Rowell, L. B. (1986). Human circulation : regulation during physical stress. New York, Oxford University Press.

Rowell, L. B. (1993). Human cardiovascular control. New York, Oxford University Press.

Rowell, L. B. (1997). "Neural control of muscle blood flow: importance during dynamic exercise." Clin Exp Pharmacol Physiol **24**(2): 117-25.

Sadeh, J., A. Miller, et al. (1997). "Noninvascie Measurement of Cardiac Output by an Acetylene Uptake Technique and Simultaneous Comparison with Thermodilution in ICU Patients." Chest **111**(5): 1295-1300.

Scher, A. M. (1974). Control of Cardiac Output. Physiology and Biophysics; Circulation, Respiration, and Fluid Balance. T. C. Ruch and H. D. Patton. Philadelphia, W.B. Saunders Company. **2:** 170-184.

Shapiro, L. M. and R. G. Smith (1983). "Effect of training on left ventricular structure and function. An echocardiographic study." Br Heart J **50**(6): 534-9.

Shiotani, I., H. Sato, et al. (2002). "Muscle pump-dependent self-perfusion mechanism in legs in normal subjects and patients with heart failure." J Appl Physiol **92**(4): 1647-54.

Stegall, F. H. (1966). "Muscle Pumping in the Dependent Leg." Circulation Research **19**.

Stegall, F. H. (1966). "Muscle Pumping in the Dependent Leg." Circulation Research **19**: 180.

Stray-Gundersen, J., T. I. Musch, et al. (1986). "The effect of pericardiectomy on maximal oxygen consumption and maximal cardiac output in untrained dogs." Circ Res **58**(4): 523-30.

Tachi, M., M. Kouzaki, et al. (2004). "The influence of circulatory difference on muscle oxygenation and fatigue during intermittent static dorsiflexion." Eur J Appl Physiol **91**(5-6): 682-8.

Thadani, U. and J. O. Parker (1978). "Hemodynamics at rest and during supine and sitting bicycle exercise in normal subjects." Am J Cardiol **41**(1): 52-9.

Thornton, W. E., V. Hedge, et al. (1992). "Changes in leg volume during microgravity simulation." Aviat Space Environ Med **63**(9): 789-94.

Thornton, W. E., W. G. Hoffler, et al. (1977). Biomedical results from Skylab. Anthropometric Changes and Fluid Shifts. Washington, DC, United States. National Aeronautics and Space Administration. Johnson Space Center.,.

Tipton, C. M. and American College of Sports Medicine. (2006). ACSM's advanced exercise physiology. Philadelphia, Lippincott Williams & Wilkins.

Trappe, T., S. Trappe, et al. (2006). "Cardiorespiratory responses to physical work during and following 17 days of bed rest and spaceflight." J Appl Physiol **100**(3): 951-7.

Tschakovsky, M. E. and R. L. Hughson (2000). "Venous emptying mediates a transient vasodilation in the human forearm." Am J Physiol Heart Circ Physiol **279**(3): H1007-14.

Valic, Z., J. B. Buckwalter, et al. (2005). "Muscle blood flow response to contraction: influence of venous pressure." J Appl Physiol **98**(1): 72-6.

Walker, K. L., N. R. Saunders, et al. (2007). "Do vasoregulatory mechanisms in exercising human muscle compensate for changes in arterial perfusion pressure?" Am J Physiol Heart Circ Physiol **293**(5): H2928-36.

Watenpaugh, D. E. and A. R. Hargens (1977). The Cardiovascular System in Microgravity. Handbook of Physiology. Environmental Physiology. New York, American Physiological Society. **sect 4:** 631-674.

Wilson, A. F., S. Savariryan, et al. (1996). "Almost simultaneous measurement of cardiovascular and gas exchange variables during maximal exercise." Med Sci Sports Exerc **28**(4): 436-43.

Wright, J. R., D. I. McCloskey, et al. (1999). "Effects of muscle perfusion pressure on fatigue and systemic arterial pressure in human subjects." J Appl Physiol **86**(3): 845-51.