

ETD Archive

2011

Effect of Lower Body Negative Pressure on Cardiovascular Responses in Males

Michele A. Barton-Verdi
Cleveland State University

Follow this and additional works at: <https://engagedscholarship.csuohio.edu/etdarchive>

 Part of the [Medicine and Health Sciences Commons](#)

[How does access to this work benefit you? Let us know!](#)

Recommended Citation

Barton-Verdi, Michele A., "Effect of Lower Body Negative Pressure on Cardiovascular Responses in Males" (2011). *ETD Archive*. 721.

<https://engagedscholarship.csuohio.edu/etdarchive/721>

This Thesis is brought to you for free and open access by EngagedScholarship@CSU. It has been accepted for inclusion in ETD Archive by an authorized administrator of EngagedScholarship@CSU. For more information, please contact library.es@csuohio.edu.

EFFECT OF LOWER BODY NEGATIVE PRESSURE ON CARDIOVASCULAR
RESPONSES IN MALES

MICHELE A. BARTON-VERDI

Bachelor of Science in Education

The Ohio State University

December, 1990

Master of Education

Grand Canyon University

May, 2009

Submitted in partial fulfillment of requirements for the degree

MASTER OF EDUCATION

at the

CLEVELAND STATE UNIVERSITY

May, 2011

©Copyright by Michele A. Barton-Verdi 2011

This thesis has been approved for the Department of **HEALTH, PHYSICAL EDUCATION, RECREATION, AND DANCE** and the College of Graduate Studies by

Thesis Committee Chairperson, Dr. Kenneth Sparks

Department/Date

Dr. Vida Lock, Ph.D., RN-BC

Department/Date

Dr. Kathleen Little

Department/Date

ACKNOWLEDGEMENTS

This thesis represents the end of a two year journey at Cleveland State University. As I look back over the past two years, I feel very grateful and privileged to have been part of this university, and to have had the opportunity to make wonderful friends. Many people have helped me along with this thesis. Unfortunately, it is not possible to list all of them, but my gratitude extends to all.

To my husband, Dennis, who supports me in everything that I do, I give my deepest thanks. This achievement is as much his as it is mine. To my three children: Ashleigh, Christopher and Joshua, thank you for understanding how important my education is to me. Thank you all for the love and support you have given me throughout this enduring process.

I would also like to thank my committee members Dr. Ken Sparks, Dr. Jill Black (deceased), Dr. Vida Lock and Dr. Kathleen Little for the guidance they have provided throughout my thesis. I would like to thank Dr. Sparks for challenging by example, having high standards, and for having the confidence that I would complete this research. I am grateful for the outstanding guidance and support provided by Dr. Lock who provides an intellectually challenging environment and is committed to the highest quality of learning.

I would like to thank Sue Martensen for always having a smile and for sharing her knowledge and friendship. I would also like to thank Dr. Judith Ausherman for being a mentor, putting things into perspective and for also sharing her expertise in research.

EFFECT OF LOWER BODY NEGATIVE PRESSURE ON CARDIOVASCULAR
RESPONSES IN MALES

MICHELE A. BARTON-VERDI

ABSTRACT

Purpose: The purpose of this study was to assess cardiovascular responses in young males when exposed to three (-10 mmHg, -20 mmHg and -40 mmHg) lower body negative pressures (LBNP).

Methods: The study was limited to 20 healthy, young adult males, ages 18 – 35 years. The protocol involved five, 10 minute phases all at supine rest, 1) LBNP, 0 mmHg; 2) LBNP, -10 mmHg; 3) LBNP, -20 mmHg; 4) LBNP, -40 mmHg; 5) Recovery 0 mmHg. Blood pressure was taken every 3 minutes and EKG was taken every 2 minutes. Cardiac Output, Stroke Volume and heart rate were continuously monitored throughout all stages.

Results: The results indicated a decline in pulse pressure when exposed to LBNP. The more negative pressure applied the more blood pooled in the lower extremities. The baseline mean of pulse pressure for the 20 participants was 60 ± 11.3 , to -40 mmHg 46.5 ± 9.7 . The results of the EKG morphology indicate there was a significant drop in the following: R-R interval; 936.89 ms at 0 mmHg to 800.85 ms at 40 mmHg LBNP, P-R interval; 155 ms at 0 mmHg to 143 at 40 mmHg LBNP, QRS interval 92.58 ms at 0 mmHg to 87.10 ms at 40 mmHg LBNP; Q-T interval 398.58 ms at 0 mmHg to 374.08 ms at -40 mmHg LBNP, Q-Tc interval; 409.03 ms at baseline 0 mmHg to 399.40 ms at -40

mmHg. The Q-T dispersion did not show a significant difference. The P-R axis showed significance from -10 to -40 mmHg and -40 mmHg to recovery. The T axis did not show a significant difference.

Conclusions: The data shows that LBNP induces physiological responses that cause changes in pulse pressure and EKG morphology which replicate the circulatory responses similar to hemorrhage.

TABLE OF CONTENTS

	Page
ABSTRACT.....	v
LIST OF TABLES.....	viii
LIST OF FIGURES.....	ix
CHAPTER	
I. INTRODUCTION.....	1
II. LITERATURE REVIEW.....	8
III. METHODS.....	33
IV. RESULTS & DISCUSSION.....	38
V. SUMMARY & CONCLUSION.....	51
BIBLIOGRAPHY.....	53
APPENDICES	
VI. IRB APPROVAL MEMORANDUM.....	62
VII. AHA/ACSM PREPARTICIPATION SCREENING	
VIII. QUESTIONNAIRE.....	63
IX. INFORMED CONSENT.....	64
X. LOWER BODY NEGATIVE PRESSURE CHAMBER & PRESSURE VALVE W/ RIDGID 6.5 HORSEPOWER SHOP VACUUM CLEANER.....	67

LIST OF TABLES

Table	Page
1. Cardiovascular Measurements	35
2. Classifications of Hemorrhage Severity and Magnitude of LBNP	36
3. EKG Morphology P-R Interval	42
4. EKG Morphology QRS Interval.....	43
5. EKG Morphology Q-T Interval.....	40
6. EKG Morphology Q-Tc Interval.....	45
7. EKG Morphology Q-T dispersion.....	46
8. EKG Morphology P-Axis.....	47
9. EKG Morphology R-Axis	47
10. EKG Morphology T-Axis	48
11. EKG Morphology R-R Interval.....	49

LIST OF FIGURES

Figure	Page
12. Cardiovascular Responses to LBNP.....	39
13. Systolic, Diastolic Blood Pressure & Pulse Pressure Response to LBNP	40

CHAPTER I

INTRODUCTION

The lower body negative pressure (LBNP) model was introduced into the medical community by Stevens and Lamb in 1965 and has been a useful tool to elicit orthostatic stress (Defense Technical Information Center (DTIC), 1979), to study cardiovascular responses to blood loss, blood pressure regulation (Hinghofer-Szalkay et al., 1996; Rhea et al., 1991), and to prevent cardiovascular deconditioning of astronauts (Guell, Braak, & Gharib, 1990). LBNP experiments have been used to evaluate changes in heart rate (HR), SV (SV), CO (CO), blood pressure (BP), pulse pressure (PP), peripheral blood flow, and non-peripheral blood flow during and after the application of LBNP (Hisdal, Toska, & Walloe, 2001). LBNP has also been used to study reflex vasoconstriction responses, and the role baroreceptors play in stabilizing vascular resistance. In surgery, LBNP is used to produce dry operating fields, pulling blood away from the heart (Cooke,

2004). It is also used as an investigative tool during high performance vertical accelerations in aircrafts (Goswami, Loeppky, Szalkay, 2008).

The purpose of LBNP experiments is to force decrease the volume of blood that normally returned back to the heart. The applied negative pressure raises the volume of blood in the lower body, places stress on the cardiovascular system and elicits a number of cardiovascular responses that tend to maintain BP and blood volume in the central area of the body (Russomano et al., 2006). LBNP is a non-invasive procedure which, when conducted in an experimental laboratory environment using a LBNP chamber, can be reversed easily (Goswami et al., 2008).

The LBNP chamber has had many useful applications. Because of the chamber's low fabrication cost and test reproducibility it has been constructed and used for the assessment of the effects of zero G space flight on the tolerance of astronauts (Howden, Tranfield, Lightfoot, Brown, & Swain, 2001). Shifting the volume of blood to the lower half of the body is much more cost effective than a human centrifuge, which can cost up to \$35 million dollars (DTIC, 1979).

The cardiovascular system's response to different levels and durations of LBNP has been widely studied in the last four decades. These experiments have provided physiological data for the United States (U.S.) space flight program. LBNP can be a good indicator of how the cardiovascular system will react to entry and landing of the Shuttle (Charles & Lathers, 1994).

Research has been conducted with LBNP as a mechanism to study physiologic biomarkers for hemorrhagic shock in soldiers (Friedl & Allan, 2004). Acute hemorrhage

and circulatory collapse account for about half of the deaths on the battlefield and on the operating table, a statistic that has not changed much since World War I (Bellamy, 1984). In addition, hemorrhage is the largest cause of death in about 30% of the more than 80% of deaths due to early operations on civilians (Convertino et al., 2004).

Vital signs change relatively late in a human that is suffering from hemorrhage. It is very difficult to determine patients that are compensating from hemorrhage based on blood pressure and temperature alone. Undetected blood loss can increase the death rate in mass-casualty situations, pre-hospital emergency transport, intensive care monitoring of septic patients, and patients undergoing renal dialysis. An undetected decrease in blood volume can lead to life threatening conditions very quickly (Cooke, Rickards, Ryan, & Convertino, 2008). Developing an algorithm to recognize patterns of BP, temperature, other observable and changes prior to cardiovascular deterioration can allow for early detection of blood loss and may prevent death (Cooke et al., 2008).

By investigating the effects of LBNP, identification of signs of hemorrhage such as decreased systolic BP (<100 mmHg), narrow pulse pressure and tachycardia could have tremendous clinical significance in preventing unidentified hemorrhage and its outcomes. Therefore, complete evaluation of cardiovascular responses when exposed to LBNP needs to be thoroughly investigated (Goswami et al., 2008).

Statement of the Problem

This study evaluated cardiovascular responses in young males when exposed to three different lower body negative pressures (-10 mmHg, -20 mmHg, and -40mmHg) as a model to investigate simulated hypovolemia including a reduction in pulse pressure and EKG analysis of variables (ventricular rate, P-R interval, QRS duration, Q-T, Q-Tc, Q-T dispersion, P-R-T axes and R-R variability). Current studies of LBNP did not assess the EKG morphology. The only EKG variable analyzed has been the changes in the R-R interval with simulated hemorrhage using LBNP.

Purpose of the Study

The purpose of this study was to assess cardiovascular responses in young males when exposed to three (-10 mmHg, -20 mmHg and -40 mmHg) lower body negative pressures (LBNP), and to determine if changes occur in EKG morphology.

Hypothesis

1. There will be a decrease in pulse pressure when exposed to lower body negative pressure.
2. EKG Morphology (PR interval, QRS duration, QT/QTc, P-R-T axes and R-R Interval) will change when exposed to lower body negative pressure.

Definition of Terms

CO – the product of heart rate and SV, measured in liters per minute; the amount of blood that is pumped by the heart in 1 minute (Stedman, 2008).

Cardiovascular collapse – can be one or more of the following 1) a quick fall in systolic blood pressure 2) a sudden decrease in heart rate 3) systolic blood pressure below 70 mm Hg and or subject termination due to presyncopal symptoms such as gray out, sweating, nausea or dizziness (Convertino, 2008).

Cardiovascular – related to the heart and blood vessels (CO, SV, blood pressure (Stedman, 2008).

Decompensation - functional deterioration of a previously working structure or system (Stedman, 2008).

Hemorrhage – an escape of blood through ruptured or unruptured vessels walls (Stedman, 2008).

Hemorrhagic shock – Hypovolemic shock resulting from acute hemorrhage, characterized by hypotension, tachycardia; pale, cold, and clammy skin (Stedman, 2008).

Hydrostatic – relating to pressure of fluids or to their properties when in equilibrium (Stedman, 2008).

Hypovolemia – a decreased amount of blood volume in the body (Stedman, 2008).

Lower body negative pressure (LBNP) – external decompression applied to the lower body. It is used to study orthostatic intolerance and the effects of gravitation and acceleration, to produce simulated hemorrhage responses in physiologic research, to assess cardiovascular function, and to reduce abdominal stress during childbirth

(Cooke et al.,2004).

Mean arterial pressure –is a term used to describe the average blood pressure of an individual (Klabunde, 2005).

Non-peripheral – towards the center of the body (Stedman, 2008).

Normotensive – indicating normal arterial blood pressure (Stedman, 2008).

Orthostatic stress – stress relating to an erect posture or position (Stedman, 2008).

Peripheral- relating to or affecting the outer parts, opposite central (Stedman, 2008)

Presyncopal – before the loss of consciousness and postural tone caused by diminished cerebral blood flow (Stedman, 2008).

Pulse pressure – the variation in blood pressure occurring in an artery during the cardiac cycle; the difference between the systolic, or the maximum diastolic, or minimum pressures. A reading of 30-50 is considered the normal range (Stedman, 2008).

Stroke volume – the volume pumped out of one ventricle of the heart in a single beat (Stedman, 2008)

EKG Terms

PR interval – period of time from the onset of the P wave to the beginning of the QRS complex (Klabunde, 2005).

P-R-T axes - direction the cardiac electrical signals that travel toward the EKG leads (Klabunde, 2005).

QRS Duration – length of time for the ventricular myocardium to depolarize (Klabunde, 2005).

QTc Interval – interval between ventricular depolarization (QT interval divided by the square root of the R-R interval) (Klabunde, 2005).

QT Interval – ventricular contraction begins and ends (Klabunde, 2005).

R-R interval – period of time from one R wave to the next (Klabunde, 2005)

Ventricular rate - time interval between QRS complexes (Klabunde, 2005).

CHAPTER II

LITERATURE REVIEW

Lower Body Negative Pressure Used as a Model to Study Hemorrhage

Cooke, Ryan & Convertino, (2004) used LBNP to study progressive hemorrhagic shock in humans because of the high death rate among soldiers due to hemorrhage. If immediate intervention can be determined based on triage algorithms, survival outcome may improve. Physiological compensation to acute hemorrhage with emphasis on cardiovascular responses was evaluated in this study (Cooke et al., 2004). Experimental animal and human studies were used to determine the usefulness of LBNP as a model to study acute hemorrhage. First, the study equated the amount of blood loss to the amount of negative pressure. Second, evaluation of physiological responses to simulated blood loss and LBNP were compared, and lastly mechanisms underlying hemorrhagic shock and cardiovascular collapse were evaluated with emphasis on sympathetic neural activity (Cooke et al., 2004).

The application of LBNP can simulate many of the responses observed in hemorrhage; however, LBNP does not induce tissue trauma or metabolic responses. Classification of hemorrhage severity in humans as: mild, moderate, severe has been equated with the approximate fluid loss by LBNP. From the Convertino et al. study (2004), moderate LBNP of -10 to -20 mmHg is equal to a blood loss of ~400 – 550 ml; LBNP of -20 to -40 mmHg is equal to blood loss of ~500 – 1,000 ml; and LBNP of -40 to -60 mmHg corresponds to more than 1,000 ml of blood loss (Cooke et al., 2004). Thus, physiological responses to hemorrhage and LBNP are similar, suggesting that LBNP can be a useful model to simulate hemorrhage in humans (Cooke, et al. 2004; Convertino, Ludwig, & Cooke, 2004).

In a 2007 study, Convertino et al. found that inspiratory resistance maintains arterial pressure during central hypovolemia which has implications for treatment of patients with severe hemorrhage. Nine healthy male subjects with a mean age of 31 ± 2 yrs, body weight of 69.4 ± 9.1 kg and height of 173.2 cm. were exposed to LBNP to simulate hemorrhage. The protocol consisted of a 5 minute rest period followed by 5 minutes of LBNP at -15, -30, -45, and -60 mmHg and additional increments of -10 mmHg every 5 minutes until the onset of cardiovascular collapse or the completion of -100 mmHg for 5 minutes. Each subject was tested on two separate occasions. The first test was without the use of the Inspiratory Threshold Device (ITD) breathing device and the second test was with the breathing device. Collapse was defined as a decrease in HR, decrease in SBP, gray out, sweating, nausea, dizziness or voluntary termination. The results indicated that at the time of collapse, average BP was 102/77 without the ITD and cardiovascular collapse occurred after 23 minutes and while the ITD breathing device the

average BP was 79/57 and cardiovascular collapse occurred after 31 minutes. In conclusion breathing through the ITD could potentially reduce suffering or death from hemorrhage (Convertino et al., 2007).

In 1998, Halliwill, Lawler, Eickhoff, Joyner and Mulvagh studied the reflex responses to regional venous pooling during LBNP in 16 normotensive subjects (8 males and 8 females) using Medical Anti-Shock Trousers (MAST) medical trousers. During testing procedures HR, BP, breathing, and forearm blood flow were all monitored. Subjects wore segmented MAST medical antishock trousers that were inflated independently in the leg and pelvic regions. The protocol involved a ramped LBNP starting with 10 minutes of rest and LBNP of -10, -20, -30, -40, -50, and 60 mmHg for 5 minutes at each level. The MAST were inflated randomly after the rest period. The test was terminated if any presyncopal signs developed. The results showed that the baseline data did not vary between men and women but that forearm blood flow was higher in men and vascular resistance was higher in women. The MAST did not alter the hemodynamics measured, nor did they produce an increase in central blood volume. This study concluded that blood flow in the legs contribute to the overall responses to LBNP in both males and females (Halliwill et al., 1998).

In 1997, Lightenberg, Blankestijn & Koomans studied the hemodynamic response during LBNP and the role of volume status. Twelve male subjects, aged 19 to 35 years, were selected based on their ability to tolerate 45 mmHg in a pilot experiment. Subjects were placed horizontally in an airtight Plexiglas box up to the level of the iliac crest. Blood samples for hematocrit and plasma rennin activity (PRA) were obtained before and immediately after LBNP. Blood pressure, cardiac index (CI) and SV were continually

monitored. Baseline data was collected for 45 minutes along with the collection of blood samples prior to the application of -45 mmHg LBNP for 60 minutes or until signs of syncope developed. Six of the twelve subjects were able to tolerate 60 minutes of LBNP. The six subjects that showed signs of presyncope were injected with an isotonic saline infusion (25 ml/kg body weight) within 60 minutes of the testing. A second LBNP test was performed on the presyncope subjects using the same protocol. A second trial was performed within a week after the initial experiment on the six subjects that tolerated the 60 minutes of LBNP. They were put on a low sodium diet for 1 week and given 40 mg of furosemide 24 hours before the second experiment.

The comparison of the results of the presyncope group to the LBNP finishers indicated that sodium excretion was in the normal range. Hematocrit, PRA, BP, HR and CI were also normal. The presyncope group that was injected with the saline infusion tolerated LBNP for 60 minutes without presyncope. The saline infusion decreased hematocrit by 2 %. With completion of the LBNP, CI, SBP and PP decreased while HR, PRA and hematocrit increased. The sodium depletion group had significant decreases in CO, SBP, PP while HR increased. PRA increased fourfold, hemotocrit had increased comparable to a fluid loss of 10%. The LBNP proved to have an effect on the reduction in blood volume. The water restricted group had an elevated sensitivity to LBNP whereas the rehydration group had a decreased risk for presyncope (Lightenberg et al., 1997).

Physiologic and Medical Monitoring of Soldiers

Convertino et al. (2004) provided a review of results from the US Army combat casualty care research program where LPNP has been used as an investigational tool to

simulate blood loss (hemorrhage) in humans. With the use of a neoprene kayak skirt a subject was situated into a supine position then the lower body was sealed into the LBNP chamber. The kayak skirt is placed around the waist to provide an airtight seal. The negative pressure was applied to the lower body (below the iliac crest) resulting in forward blood flow away from the upper body (head and heart) to the lower body. This model of LBNP was used to investigate the physiologic signals under controlled conditions inducing hypovolemic hypotension in healthy humans (Convertino et al., 2004). The results from a comparison of data validate that LBNP can be used to simulate hemorrhage in humans and create the physiological responses similar to that of a human in cardiovascular collapse. It was determined that LBNP sequesters blood from the upper body to the pelvis and legs enabling researchers adequate evidence of biomarkers that provide identification of early stages of hemorrhage.

In 2008, Convertino et al. studied medical monitoring of pre-hospitalized civilians during military trauma where treatment is usually based on vital signs (BP, O₂ saturation). Based on the vital signs appropriate interventions are implemented before cardiovascular collapse. For this study, two models of triage decision were tested. Model 1: trauma patient data and analysis of vital signs along with physiologic measurements and Model 2: LBNP used to study central hypovolemia and identification of physiological vital signs with simulated hemorrhage. The results indicated that traditional vital signs such as SBP and O₂ saturation fail to predict immediate triage necessary to prevent cardiovascular collapse. The results of the LBNP study noted that indicators of hemorrhage include reduction in PP, changes in R-R interval, and reduction in tissue oxygenation. For example -20 – 40 mmHg is similar to moderate hemorrhage

of 550 – 1,000 ml of blood or 10 – 20 percent of total blood volume (TBV) (Convertino et al., 2008).

The Cardiovascular System and LBNP

Stevens and Lamb (1965) studied the effects of orthostatic tolerance and varying degrees of LBNP to determine the effects on the cardiovascular system. Thirty eight healthy male subjects (means: age = 23 years, height =175 cm and body weight =71.3 kg). Subjects were placed supine into a LBNP chamber. An intra-arterial needle was inserted into the brachial artery and a polyethylene catheter was advanced into the superior vena cava. Four negative pressures were used: -80, -60, -40 and -25 mmHg over a 20 minute period (5 minutes each). The subjects were then divided into three groups and compared according to the response to the negative pressure. The results showed that the heart rate increased and both CO and SV decreased in all subjects. Both BP and PP had varied responses in subjects especially those that developed presyncopal symptoms. The subjects showing presyncopal symptoms had an abrupt decline in PP and BP. Syncopal symptoms developed at pressures between -60 and -80 mmHg. HR increased from 13 to 67 percent, CO decreased from 20 to 42 percent and SV decreased by 28 to 64 percent (Stevens & Lamb, 1965).

In 1997, Prasad, Hedge and Lazar studied the cardiovascular responses to LBNP of male volunteers in a seated position to study the effects of +Gz stress. Eight healthy male subjects between 25 – 36 years of age participated in the study. The subjects were exposed to -40 mmHg LBNP in steps of -10 mmHg for 5 minutes. The results indicated a significant increase in HR a decrease in SBP, SV, CO; an increase in Diastolic BP with no change in mean arterial pressure. This study elicited the predetermined response

similar to subjects exposed to +Gz. It was concluded that LBNP can be used to study the physiological responses of man when exposed to +Gz (Prasad et al., 1998).

In 1990, Tomaselli, Frey, Kenney & Hoffler studied the effect of a central redistribution of fluid volume in 12 male subjects, ages 30 – 39 years, height 178 ± 5 cm, weight 72 ± 7 kg. Prior to the experiment a 4 ml blood sample was drawn for hematocrit levels. EKG, phonocardiogram (PCG), impedance cardiogram (ZCG), and carotid pulse contour (CPC) were used for instrumentation. Each subject participated in two separate protocols 1 week apart with the order of the protocol reversed for half of the subjects. The control LBNP protocol was 1 minute, -8 mmHg; 1 minute, -16 mmHg; 3 minutes, -30 mmHg; 5 minutes, -40 mmHg; 5 minutes, -50 mmHg. The experimental group started with a 5 minute baseline and 60 minutes of head down tilt followed by return to supine position and the application starting at 5 minutes, -50 mmHg and worked backwards from there. Results indicated that DBP and MAP differed significantly between the control group and the tilt group. The control group increased in DBP, SV, CO, while the tilt group decreased in DBP, HR, SV, CO, peripheral resistance and calf circumference as compared to resting values. Conclusions were that alterations in fluid distributions have different impacts on the cardiovascular system (Tomaselli et al., 1990).

How Does the Heart React to LBNP?

Cardiovascular responses to physical or psychological stressors may not change for all individuals. Marfil, Santaella, Leon, Turpin & Casteller (1999) established that there are individual differences in which the cardiovascular system reacts to stress. Twenty healthy adult male (18 to 25 years) college students were tested according to their cardiovascular reactivity in response to laboratory stressors. Five tasks were given to the

subjects including: mental arithmetic, reaction time measured in response to a loud tone, giving a presentation, a Mirror Trace task and a Cold Pressor task. All tasks lasted 3 minutes with recovery in between tests, SBP, DBP and HR were all measured according to the stressors. The results showed that there was a varied response with BP and HR response. The Reaction Time task produced the largest SBP and HR increases with a minimal DBP response. The Cold Pressor task evoked the largest response DBP, while the HR had minimal change. Stressors can be characterized to elicit a certain hemodynamic response within individuals, however cardiovascular responses to stressors can be quite unpredictable in terms of BP. Specific stressors can be associated with different sympathetic patterns and will elicit diverse responses (Marfil et al., 1999).

Lee, Buchanan, Flatau & Franke (2004) studied the reproducibility of cardiovascular responses to LBNP using two identical trials conducted one week apart. HR variability was measured along with forearm blood flow, HR, SV, and BP. LBNP was graded to -100 mmHg or symptoms of presyncope. The same protocol was used for both tests. Fourteen healthy male subjects (24 ± 1 year, height = 176.8 and height = 83.7 kg.) were placed in the LBNP chamber supine and sealed at the iliac crest with a neoprene skirt. LBNP was increased every 6 minutes by 10 mmHg until presyncope symptoms or -100 mmHg, whichever occurred first. The results indicated that HR responses to LBNP can be reproduced in multiple trials. The cardiovascular responses to LBNP were also consistent with the first trial (Lee et al., 2004).

In 2008, Goswami, Grasser, Roessler, Schneditz and Hinghofer-Szalkay studied the cardiovascular response to LBNP with different seal locations of the chamber. Two different seal locations were tested: iliac crest (IC) and upper abdomen (UA) before and

during LBNP. Fourteen healthy male subjects were used for the testing. LBNP (-40 mmHg) was applied with the seal at either the IC or UA and the negative pressure lasted for 15 minutes. Subjects were tested with both seal locations with 14 days between trials. Twenty minutes prior to testing subjects were injected with Indocyanine green (ICG) to measure blood volume and hepatic blood flow. Plasma volumes were measured from heparinized blood within 1 hr of the test. The results showed that during LBNP HR was higher with the UA seal versus the IC and thoracic impedance increased during the UA seal. There was a reduction in SV with the UA seal. Hemodynamically, the sealing positions influenced the response to LBNP. There was not a significant difference in the effects on CO, peripheral resistance, PP and plasma density. (Goswami et al., 2008).

Cardiac Output During Blood Loss in the Unanesthetized Monkey

Forsyth, Hoffbrand & Melmon (1970) studied regional changes in blood flow during graded hemorrhage in primates. Twelve rhesus monkeys weighing between 3.5 and 6.8 kg, (7 control, 5 restrained in a horizontally tilted primate chair) had flow measurements made using the Rudolph and Heymann microsphere technique before and after 10, 30 and 50% of their measured blood was withdrawn. Throughout the experiment, systemic arterial pressure, central venous pressures, CO, SV and hemocrit were evaluated in both groups of monkeys. The results showed that after a 10% blood loss, arterial pressure was lower in the experimental group than the controls, with minor changes in the kidneys, small and large intestines. The heart received a higher amount of blood and the skin had a lower blood flow. After 30% blood loss, arterial and venous pressures, CO, SV and pH were lower in the experimental group, while HR and respiratory rate were higher. Blood flow fell significantly in the kidneys, skeletal muscle,

small intestine, large intestine, spine and diaphragm. After 50% blood loss, two of the five monkeys were at the point of death; CO, arterial pressure, and total peripheral resistance were all lower than the three living monkeys. Because blood flow to the stomach, large intestine, cecum, lungs, spine and chest wall decreased. Conclusions indicated that the heart and brain are favored in the redistribution of CO during hemorrhage (Forsyth et al., 1970).

LBNP in a Healthy Population

Lower body negative pressure has been used to investigate exercise training in various forms on central hypovolemic tolerance (Convertino, Montgomery, & Greenleaf, 1984; Lightfoot & Tsintgiras, 1995). Because the amount of circulatory stress induced can be finely adjusted, gravitational and hydrostatic concerns are eliminated, and maybe most importantly, it can be instantly reversed, providing a safe recovery. Early use of LBNP was primarily limited to exposing humans to set negative pressures for a specified amount of time and then comparing responses between individuals or groups (Coles, Kidd, & Moffat, 1957; Foux, Siliktar, & Valero, 1976; Frey & Hoffler, 1988; Rhea et al., 1991). With LBNP, exposure is terminated after the attainment of a predetermined negative pressure level or duration of exposure, regardless of the subject's responses. Some researchers have extended LBNP protocols until the subjects exhibited presyncopal signs or symptoms (Murray, Thompson, Bowers, & Albright, 1968).

In an attempt to understand LBNP tolerance, Lightfoot & Tsintgiras (1995) rated three indices used in the literature; duration of exposure (DNP), maximal negative pressure tolerated (MNP), and cumulative stress index (CSI). The primary purpose of their study was to document LBNP tolerance and basic cardiovascular responses in 119

subjects (age = 24 ± 5 yr old; 86 males, 33 females wt= 71.7 ± 12.6 kg; Ht= 173.4 ± 11 cm) and the relationship of various physical characteristics such as age, weight, height, gender and $VO_{2\text{peak}}$ to LBNP tolerance. The second purpose was to examine the validity of three different indices to determine which provided the best indication of LBNP tolerance (Lightfoot & Tsintgiras, 1995).

Subjects were placed individually in an LBNP chamber, sealed at the iliac crest, using a bicycle seat as support. Negative pressure was generated in the LBNP chamber with a vacuum cleaner with the level of negative pressure controlled by a mercury manometer and electrical rheostat. In the majority of exposures (95%), the negative pressure was decreased in -10mm Hg increments every 3 minutes until the onset of presyncopal signs or symptoms. However, in six exposures, a modified 5 minute protocol was used where the negative pressure was decreased from atmospheric to -8 mm Hg for 1 minute, -16 mm Hg for 1 minute, -30 mm Hg for 1 minute, -30 mmHg for 3 minutes, and then decreased in -10 mm Hg increments every 5 minutes thereafter until presyncope. During all LBNP exposures, BP and HR were measured. The test was immediately terminated with the onset of presyncopal signs or symptoms.

Of the 119 subjects used in this study decreases in systolic (SBP) and/or diastolic blood pressure (DBP) were present in 63. A decrease in HR was present in a total of 38 exposures and an increase in forearm blood flow was present during presyncope in four exposures. Additionally, 18 subjects showed severe presyncopal symptoms. Only one of the LBNP exposures in the total of 670 exposures resulted in syncope. Heart rate (HR) was significantly elevated over baseline at -40 mm Hg or at 50% of the MNP. Systolic blood pressure (SBP) was significantly reduced from -50 mm Hg through -90 mm Hg

LBNP. The authors concluded that the average LBNP tolerance for a healthy population is -77 ± 16 mm Hg and that there is no relationship between LBNP and age, weight, height, VO_2 peak, or gender, thus indicating that none of these parameters should be used to predict LBNP tolerance (Lightfoot & Tsintgiras, 1995).

In 2000, Muentner et al. investigated the effect of sleep restriction on orthostatic cardiovascular control in humans. Ten healthy volunteers participated (4 women, 6 men) ages 22-46 years. Subjects reported having 7.7 hr/night sleep on average with occasional naps of .3 to 1.4 hours in duration. Polysomnography was used to assess sleep and monitor brain activity. The protocol consisted of sleep restriction of 4 hours for 4 nights in the sleep laboratory. Data was collected each day and cardiovascular and LBNP testing was performed on the day after the fourth night of sleep restriction. The LBNP protocol consisted of 3 minutes each of -10, -20, -30, -40, -50, and -60 mmHg. The results indicated that sleep restriction did not impair the physiological responses to LBNP, (DBP or mean arterial pressure (MAP)). While HR was lower after sleep restriction, the R-R interval was not affected. It was concluded that lack of sleep does not affect orthostatic tolerance and the ability to maintain physiological responses (Muentner et al., 2000).

In 2002, Schroeder et al. investigated the effect of water ingestion on orthostatic tolerance in healthy subjects. Thirteen healthy subjects (9 men, 4 women) ages 21 to 48 year were included in the study. In a randomized crossover design, each subject underwent the determination of orthostatic intolerance two different times. Subjects were given a tilt table test with the right arm at heart level. After a 15 minute baseline period, subjects were tilted at 30 degrees and drank 50 mL of water at room temperature.

Subjects were then tilted to a 60 degree head up position for 20 minutes. Subjects were then placed in a LBNP chamber for 10 minutes each of pressure at -20, -40, and -60 mmHg while they remained upright in a seated position. The LBNP test was terminated if SBP fell to less than 80 mmHg or if HR was above 150 bpm. The results indicated that drinking 50 ml of water increased orthostatic tolerance within 15 minutes. The average orthostatic tolerance was 31 ± 3 minutes before ingesting water and 36 ± 3 minutes after ingesting 50 ml of water (Schroeder et al., 2002).

Relation of physical characteristics to LBNP tolerance

In 1988, Frey and Hoffler studied the association of age and sex with responses to LBNP. In this study, 21 women and 29 men (ages 29 – 56 years) were exposed to -50 mmHg LBNP. Prior to testing, characteristics of subjects were recorded (age, height, weight and VO_2 peak). Oxygen uptake was collected during a treadmill test using the Bruce protocol. The test procedures were as follows: 5 minutes supine, 0 mmHg LBNP; -8 mmHg, 1 minute; -16 mmHg, 1 minute; -30 mmHg, 3 minutes; -40 mmHg, 5 minutes; -50 mmHg, 5 minutes; and 5 minutes recovery at 0 mmHg.

The results showed that the males had higher SBP and DBP MAP at rest and during LBNP. Calf circumference was measured throughout the test indicating males had a larger increase in blood volume of the legs. The results indicated that the older subjects had smaller HR increases and greater increases in peripheral resistance in comparison to the younger subjects. However, the relationship between physical characteristics and LBNP tolerance was unclear (Frey & Hoffler, 1988).

In a 1977 study Montgomery et al. evaluated the cardiovascular responses of men and women to LBNP. In order to determine reliability of the test results between

genders, six male and four female subjects were measured using impedance plethysmography in the pelvic and leg regions. Both genders were exposed to three, 5 minute exposures of -20, -40, and -60 mmHg LBNP. Females had significantly higher HR and lower leg blood flow than males during the control period. Men had higher mean SBP and DBP and higher pelvic blood flow while women had significantly less blood flow, in the legs and pelvic region during LBNP. Males did not show any signs of syncope at -60 mmHg LBNP, while females showed signs of syncope at -60 mmHg. Thus, females were less tolerant of LBNP (Montgomery et al., 1977).

In a 2000 study, Gotshall evaluated gender differences in tolerance to LBNP. In this study, 18 men and 18 women of similar fitness levels participated. Each woman was to be tested during the second week of her menstrual cycle. During the LBNP testing subjects were sealed at their iliac crest and after 15 minutes of supine control the pressure was reduced to -30 mmHg for 5 minutes, then an -10 mmHg increase in negative pressure was administered every 5 minutes until presyncope was reached. The results showed that women had significantly less tolerance to LBNP than men with 30% less tolerance when expressed using duration and 21% less tolerance to maximal LBNP. Both men and women responded similarly with increases in HR and systemic vascular resistance and decreases in SV and BP. Both men and women had similar responses as presyncope was approached (Gotshall, 2000).

In a 2009 study, Carter, Lawrence, & Klein evaluated whether the menstrual cycle alters sympathetic neural responses to orthostatic stress in young, eumenorrheic women. Thirteen healthy women with regular menstrual cycle of 26 – 30 days participated in the study. Blood was drawn to document levels of estradiol and progesterone on days of

testing. Subjects were tested twice, once during the early follicular (EF) phase and once during the mid luteal (ML) phase of the menstrual cycle. Subjects were supine and sealed in the chamber for five minutes with LBNP was applied at -5, -10, -15, -20, -25, and -40 mmHg. Muscle sympathetic nerve activity (MSNA) was measured in response to orthostatic stress. The findings were that total MSNA was elevated during the ML phase of the menstrual cycle, however, this study was inconclusive on the linkage of the increase of sympathetic baroreflex sensitivity during different phases of the menstrual cycle (Carter et al., 2009).

In a 1987 study, Smith, Hudson & Raven assessed the effect of muscle tension on the cardiovascular responses to LBNP. Eight male subjects were used for the study with a mean age of 28 ± 3 years. Prior to testing a Bruce maximal stress test was used to determine maximal VO_2 . A standard LBNP protocol was used in which the negative pressure was increased: -8 mmHg, 1 minute; -16 mmHg, 5 minutes; -32 mmHg, 3 minutes; -40 mmHg, 5 minutes; and -50 mmHg, 5 minutes. During LBNP, electromyography (EMG) was used to assess the activity of the lower limbs and trunk. Using a strain gauge hand dynamometer to produce tension for 15 seconds to determine maximal voluntary contraction (MVC). The results indicated that the muscle tension affected the tolerance to LBNP. Six out of the eight subjects developed presyncopal symptoms during the relaxed state. When tested a second time there were no presyncopal symptoms during elevated muscle tension levels. The contraction of the forearm muscle when using the hand dynamometer induced a reflex stimulation increasing HR and CO with the application of LBNP (Smith et al., 1987).

In 1998, Lawler, Halliwill, Summer, Joyner, & Mulvach studied leg mass and LBNP tolerance in men and women. Eighteen healthy, non-obese subjects, 8 women and 10 men, ages 18 - 48 yrs, with a wide range of fitness levels ($VO_2 = 29.6 - 59.3$ ml/kg/min) of all subjects were tested. A Dual-emission X-ray absorptiometry (DEXA) scan was used to determine lean muscle mass in the lower extremities. LBNP was used at levels of -10, -20, -30, -40, -50 and -60 for 5 minutes at each level. The results showed that 4 subjects finished the testing with signs of presyncope. Subjects that finished the testing had leg muscle masses averaging 20.3 ± 1.1 kg in men and 13.7 ± 1.6 kg in women. The subjects that did not finish the test had leg muscle masses averaging 22.3 ± 1.2 kg in men and 14.9 ± 1.1 kg in women. Categories were compared according to men with > 21 kg leg mass and women with > 14 kg muscle mass. The author concluded that there was no difference in the responses between the high leg muscle mass and the low leg muscle mass groups. Thus, there was no apparent relationship between leg mass and LBNP tolerance (Lawler et al., 1998).

How Does Age and Fitness Levels Affect LBNP?

Hernandez, Darandilar, & Franke (2005) investigated the effects of age and fitness tolerance to a high level of LBNP. It was predicted that the body's ability to tolerate maximal LBNP would be higher in unfit vs. fit individuals. Tolerance was also determined to be higher in older vs. younger adults (Hernandez et al. 2005). Fitness and age categories were divided into four groups: 20 young adults (< 30 years; 10 males and 10 females; and 60 plus years; 10 males and 10 females). Both age groups were divided into fit and unfit groups based on a Bruce protocol fitness test. Gradual application of LBNP was induced with -10 mmHg increases in LBNP every four minutes. The test was

terminated at a maximum -100 mmHg, symptoms of presyncope, or at the request of the subject. All groups tolerated LBNP similarly. The young fit group responded to LBNP with a higher response in HR. The old unfit group had a higher resting BP and maintained a higher blood pressure throughout the protocol. The older fit group adapted to a reduction in blood volume by decreasing total peripheral conductance. Both groups, young vs. old and fit vs. unfit were comparable in their responses to graded levels of LBNP (Hernandez et al., 2005).

In a 1991 study, Levine et al. investigated physical fitness and cardiovascular regulation with orthostatic intolerance. Twenty four healthy male volunteers, aged 19-32 years, were divided into three groups according to fitness levels based on level of endurance and VO_2 peak. The three levels were high fit: $VO_2 \geq 60$ ml/kg/min and more than 50 miles of running per week or 200 miles of cycling per week; mid fit= VO_2 45-55 ml/kg/min, 30 minutes or more of aerobic exercise per day, 3 times/week; and low fit: $VO_2 \leq 40$ ml/kg/min, with no regular exercise. Subjects were studied on three separate days for determination of VO_2 max, maximal calf vasodilator capacity and carotid baroreflex function and tolerance to LBNP. The LBNP protocol consisted of progressive negative pressure of -8 mmHg for 1 minute, -16 mmHg for 4 minutes, -32 mmHg for 3 minutes, -40 mmHg for 5 minutes, -50 mmHg for 10 minutes and -55 mmHg for a maximum of 30 minutes. LBNP was discontinued with the development of symptoms of presyncope (Levine et al., 1991). The results indicated the high fit subjects had a lower tolerance to LBNP. The subjects with low LBNP tolerance had a higher SV and a decline with SV at LBNP of -40 mmHg. The findings indicated that carotid baroreflex function reflected individual differences in tolerance to LBNP. It was also determined

that orthostatic intolerance was unrelated to fitness level or exercise training (Levine et al., 1991).

How Does Exercise and Training Mode Affect LBNP?

Franke & Taylor (1996) compared different exercise training program (running vs. swimming) in response to LBNP. Seven female runners were compared to 11 female swimmers. Both groups had similar fitness levels as tested by using arm and leg cycle ergometry to determine VO_{2max} . Negative pressures were induced after a four minute control period. Subjects received repeated 2 minute exposures of LBNP at -1.3, 2.7, and 5.7 kPa. This 10 minute cycle was performed 2 different times. The pulse pressure responses to LBNP varied the most indicating different responses in the cardiovascular system to baroreceptor changes, with the runners showing a greater decline in pulse pressure (Franke & Taylor, 1996).

Does Supine Exercise With LBNP Maintain Upright Exercise Capacity?

Watenpaugh et al. (2000) used LBNP during supine exercise to study potential increases in spaceflight fitness. Using LBNP to simulate upright exercise at earth's gravity, treadmill exercises were performed 40 minutes a day in the supine position in a LBNP chamber. Eight relatively fit healthy males, age 30 ± 2 years, were used in this study. The men were randomly assigned to two groups. For 15 days each subject was studied at rest in a 6 degree head down tilt bed (simulates duration of a space shuttle flight). Group 1 was assigned to a LBNP exercise program which incorporated 40 minutes of supine running exercise per day using a bungee cord system on a treadmill exposed to LBNP (average 52 to 67 mmHg). Group 2 did not exercise and remained on bed rest. VO_2 max was recorded pre and post. The results showed that daily supine

exercise during bed rest maintained upright exercise VO₂ max along with running speed and strength of the plantar flexors, while the non-exercise group's exercise capacity diminished by 10% throughout the 15 day study (Watenpaugh et al., 1999).

Comparison of Muscle Sympathetic Nerve Responses and LBNP

Convertino et al. (2004) studied the sympathetic response to LBNP and circulatory shock in 14 males (age = 40 ± 3 ; height = 177 ± 2 cm; and weight = 80.2 ± 2.7 kg.). Each subject underwent 60 minutes of LBNP consisting of a baseline of 12 minutes and exposure to each of the following for 12 minutes each: -15, -30, -45 and -60 mmHg of LBNP. The LBNP was used to simulate hemorrhage and muscle sympathetic nerve activity (MSNA). Measurements included HR, SV, arterial BP and MSNA measured with a nerve traffic analyzer. Each subject breathed 15 breaths/minute paced with a metronome. The results indicated that central hypovolemia was induced and MSNA was directly related to changes in SV. The subjects that experienced symptoms had a significant sympathetic neural response but a low peripheral vasoconstrictive measurement (Convertino et al., 2004).

Rhea et al. (1991) used LBNP to simulate hemorrhage and studied the effects of blood pooling in the legs, abdomen and pelvis to determine sympathetic neural responses to simulated hemorrhage. Thirteen healthy male volunteers between the ages of 20 and 44 years were used in this study. Sympathetic nerve recordings of multiunit postganglionic muscle sympathetic nerve activity (SNA) using the muscle fascicle of the right or left peroneal nerve were taken. LBNP was applied at -5, -10, and -15 mmHg for 3 minutes at each level. The results indicated that sympathetic nerve activity increased as central venous pressure decreased (Rhea et al., 1991).

Analysis of EKG Morphology and Hemorrhage

Van den Bergh, Algra & Rinkel (2004) studied the electrocardiographic (EKG) abnormalities and serum magnesium in patients with subarachnoid hemorrhage (SAH). Sixty two patients were studied that were admitted to the hospital within 72 hours after aneurismal SAH. A standard EKG and serum magnesium measurement were routinely performed at admission. The results indicated that there was hypomagnesemia present in 23 (37%) of the patients that were admitted. Thirty eight patients (61%) had a long QTc duration. Low serum magnesium was related to a long PR interval and a shorter QTc interval. The results were explained by a cellular influx which increased cerebral and cardiac intracellular magnesium, depleting magnesium stores (Van den Bergh et al., 2004).

Sommargren (2002) studied the EKG abnormalities in patients with subarachnoid hemorrhage. The mortality rates for SAH are 30-45% and the median age is 59 years. Classical clinical signs of SAH include onset of severe headache, nausea, vomiting, alterations in consciousness, and EKG abnormalities. Some of the findings in the meta analysis included ST segment elevation, T-wave inversion, prolonged QTc interval, shortened PR interval, decrease in CO, sinus bradycardia, sinus tachycardia and atrial fibrillation.

The research findings of SAH are consistent with the characteristics of an anterior myocardial infarction or ischemia. Timing and data collection influenced the conclusions about the prevalence of abnormalities. The most pronounced changes occurred 72 hours after SAH. It was found that 90% of patients had EKG abnormalities within the first 48 hours. The investigations of hemorrhage and EKG abnormalities is ongoing. Currently,

research has been focused on the release of catecholamines within the myocardium as a cause of the EKG changes. The characteristic findings of autopsies suggest that myocardial damage resembles lesions produced by the infusion of norepinephrine. Additional pathologic changes include elevated levels of cardiac enzymes, such as creatine kinase (Sommargren, 2002).

Ishikawa (1976) studied the influence of alterations in the hematocrit upon the P wave and the QRS complex. This study used 70 patients (33 males & 37 females) with acute anemia whose ages ranged from 9 months to 88 years. The cause of anemia was gastrointestinal bleeding in 68 patients and nasal bleeding in 2. Treatment for anemia consisted of taking iron, vitamin B₁₂, and folic acid or blood transfusions, depending on the severity. Hematocrit was used to represent blood resistivity. Patients were to lay supine in a hospital bed while an EKG was taken.

The results were taken from two EKGs, one at the lowest hematocrit and one at the highest level. The findings were different than predictions indicating QRS and P waves did not always increase due to the varying levels of hematocrit, and there were minimal changes to the P and QRS waves in the anemic patients. Further studies were recommended (Ishikawa, 1976).

Delia, Zaki, Govendir, Church and Malik (1999) studied the effect of acute hemorrhage on QRS amplitude on lead II of the canine EKG. Ten adult racing greyhounds were tranquilized and anesthetized so that six-lead EKG tracings could be recorded after one unit of blood (460 mL) and then a second was taken from the femoral artery of each canine. There was a progressive reduction in the QRS amplitude during the blood loss. The effects of the hemorrhage was reversed promptly by re-infusion and the

QRS amplitude returned to normal. The results indicated that when there was a reduction in blood volume there was a substantial reduction in the QRS voltage because of reduced venous return (Delia et al., 1999).

Stern, Lavy, Carmon and Herishianu (1968), studied the EKG patterns in hemorrhagic stroke. Their investigation included 45 patients in the acute stage of different types of hemorrhagic stroke: subarachnoid, intercerebral and intraventricular. There were 24 males and 21 females, ages 38 to 86 years. A 12 lead EKG was performed during the first 6 hours after admission. Each patient was analyzed for the following: HR, shape of P wave, PR interval, QRS complex, ST segment, T wave and possible U wave, rhythm disturbances, signs of strain, ischemia and infarction with special attention paid to the QT interval. The results indicated EKG abnormalities such as myocardial infarction, ST or T changes, notched P waves, or bundle branch block in 29 of the patients. Eight of the 45 hemorrhagic patients had normal EKGs. The patients with the normal EKGs had a shortened QT interval. Seven of the 45 patients had a long QT interval and this factor was dependent on the specific types of stroke. Changes in the EKG were attributed to vagal stimulation, sympathetic stimulation, adrenaline or myocardial lesions producing catecholamines (Stern et al., 1968).

In a 2010 study, Aygun, Sisman, Nural, Yilmaz and Baydin examined the effect of essential hypertension on the QTc dispersion in patients with intracerebral hemorrhage (ICH). The study group consisted of 47 hypertensive and 30 non-hypertensive patients. The patients were all over 18 years of age presenting with acute ICH and admitted to the emergency department and immediately given a 12 lead EKG. Non-contrast CTs were given to each of the patients to evaluate the size and location of hematomas. The QTc

was calculated using Bazett's formula and prolongation was defined as greater than 440 milliseconds. The results indicated that the QTc in the patients with increased BP had longer QTc and those with normal or low BP had shortened QTc. There was a weak correlation between the size of hematoma and the QTc. It was found that the patients with larger lesions had longer QTc especially when located in the right hemisphere of the brain (Aygün et al., 2010).

Lazar, Manzella, Moonjelly, Wirkowski and Cohen (2008) studied the prognostic value of QT dispersion in patients presenting with acute neurological events. The study involved 140 patients ($72 \pm$ years old, 48% male, 52% female) who were admitted to a hospital with acute neurological events. QTd was calculated from an admission EKG. A complete neurological evaluation was performed on all patients using the National Institute of Health Stroke Scale, the Barthel Index and the Rankin Scale. The degree of neurological impairment as related to the QTd was compared.

The results indicated a change in the QTd in patients with intercerebral hemorrhage, and there was also a trend relating to the age of the subjects. The increase in the QTd was shown to be a predictor in various cardiac arrhythmias, sudden cardiac death, acute cerebrovascular accidents and transient ischemic attacks (Lazar et al., 2008).

Haberthur, Shachinger, Seeberger, and Gysi (2003) studied the effect of non-hypotensive hemorrhage on plasma catecholamine levels and cardiovascular variability in man. This study was comprised of 30 healthy male blood donors aged 19-48 years. Subjects were divided into three age groups: group 1, aged 19-33 years, group 2, aged 34-39 years and group 3, aged 40-48 years. An intravenous access line was kept open in each subject. The first measurement consisted of two, 10 ml blood samples for

determination of epinephrine, and norepinephrine levels. Immediately following 450 ml of blood was donated. Approximately 15 minutes later two 10 ml blood samples were measured for epinephrine and norepinephrine levels. The results indicated there was a rise in plasma norepinephrine which produced a sympathetic response within the cardiovascular system. The blood loss of the subjects represented mild hemorrhage. With the sympathetic activation, changes in BP and HR were detected. Each group of subjects elicited similar responses to the blood donation (Haberthur et al., 2003).

In summary, the literature on LBNP indicateds that the tolerance for a healthy population is -77 ± 16 mm Hg and that there is no relationship between LBNP and age, weight, height, VO_2 peak, gender, or sleep restriction. However, hydration level may increase orthostatic tolerance dependent upon the amount of water consumed prior to test measurements. There were findings that indicate women have less tolerance to LBNP based on the phase of their menstrual cycle. A high fitness level may result in a lower tolerance to LBNP. The type of physical training performed may also cause a greater decline in tolerance to LBNP.

Physiologic responses to LBNP similar to blood loss at levels beyond -20 mmHg and can be used as a model to study hemorrhage. The literature indicates that breathing through an ITD device can reduce suffering or death from hemorrhage. The cardiovascular responses in subjects show that there is an increase in HR and a decrease in CO and SV as negative pressure is applied. The model of LBNP can also be used to investigate physiologic signs of hemorrhage along with biomarkers that can provide identification of early stages of hemorrhage. The blood pools away from the heart to the

legs and pelvic regions causing a decrease in SBP and increase in DBP and a decrease in PP.

CHAPTER III

METHODS

An experimental research study was used to assess the effect of LBNP on cardiovascular responses in young males. The independent variable was LBNP. The dependent variables were cardiovascular responses CO, BP, EKG changes (ventricular rate, PR interval, QRS duration, QT/QTc, P-R-T axes and R-R interval). The study sample was limited to 20 healthy young adult males.

Subjects

Twenty healthy, normotensive, young adult male subjects (18-35 years of age) from Cleveland State University and the Cleveland area volunteered for the study. Each subject was informed of the purpose of the study and any risks associated with participation. All participants were provided written informed consent approved by the Institutional Review Board at Cleveland State University (CSU) (Appendix A). Each subject was administered the AHA/ACSM Pre-participation Screening Questionnaire

(Appendix B) and excluded from the study if there was any history of cardiovascular, metabolic or respiratory disease, or symptoms of any other disease (i.e. diabetes, pulmonary, etc.). The subjects were also eliminated if taking any type of prescription medication that might affect the results of the study. Subjects could not participate if they had any symptoms of chest discomfort, shortness of breath, or had experienced dizziness, fainting or blackouts. Subjects were all to be considered low risk. Informed consent was obtained from each subject prior to participation (Appendix C).

Lower Body Negative Pressure Chamber

The LBNP chamber was a rectangular box made out of plywood. The structure of the chamber was made to endure high levels of LBNP. The dimensions of the chamber was as follows: length 156.5 cm, height 78 cm and width 85 cm. An oval was cut to allow entry of the subject's lower body lying supine. To fully create an airtight seal the subject wore a kayak spray skirt sealed around the rim of the oval. A safety pressure release valve was installed at the side of the chamber. To generate negative pressure, a 6 horsepower vacuum was attached to the chamber at the foot end of the subject (Appendix D) (Esch, Scott, & Warburton, 2007).

The pressure was measured by means of a water manometer connected to the chamber. The subjects sat comfortably on a bike seat inside the box with their legs dangled preventing the subject from sliding down when the suction was applied. The bike seat also allowed the subject to remain at rest rather than exerting force muscularly that might interfere with the pooling of blood to the lower extremities (Loeppky, Venters, Luft, 1978).

Experimental Procedures

Subjects were asked to refrain from any caffeinated beverages for at least three hours prior to testing in the study and were also asked not to engage in physical exercise on the day of the study. Subjects were asked to hydrate the morning of testing not to eat three hours prior to testing. Subjects were asked to wear comfortable, non-restrictive clothing. The protocol involved five, 10 minute collection conditions (Table 1). During each condition the subjects were asked to refrain from talking while data was collected. Data collection was performed according to Table 1.

Table 1. Cardiovascular Measurements.

LBNP	0 LBNP	--10mmHg	-20mmHg	-40mmHg	Recovery 0 LBNP
Blood Pressure	Every 3 rd min.	Every 3 rd min.	Every 3 rd min.	Every 3 rd min.	Every 3 rd min.
Cardiac Output	Continuous	Continuous	Continuous	Continuous	Continuous
EKG	Every 2 nd min.	Every 2 nd min.	Every 2 nd min.	Every 2 nd min.	Every 2 nd min.
Stroke Volume	Continuous	Continuous	Continuous	Continuous	Continuous

Participants were placed supine in the LBNP chamber (Appendix D). 10 minutes baseline data was collected for 10 min. at ambient conditions. After baseline data was collected, subjects were exposed to ten minute intervals of negative pressures at -10, -20, and -40 mmHg for 10 minutes at each pressure followed by recovery at ambient conditions. Throughout all conditions BP, HR, CO, SV and EKG were recorded according to Table 1.

EKG tracings were obtained using a Burdick Atria 3100 12 lead EKG. An Omron digital BP cuff monitor model # HEM-907XL(Omron) was used to monitor BP. Non-

invasive CO and SV was measured using an Impedance Cardiography (ICG) device (Physioflow).

It was predetermined that testing for any subject would be terminated with the onset of presyncopal symptoms such as dizziness, nausea, sweating, sudden fall in SBP pressure, sudden slowing of the HR, progressive elevation of BP, or the subject terminating the experiment due to other discomfort (sweating, nausea or dizziness).

Table 2. Classifications of Hemorrhage Severity and Magnitude of LBNP

Subjects were exposed to LBNP of 20 – 40 mmHg representing moderate hemorrhage, which is an approximate fluid displacement of 500 – 1000 ml according to Table 2.

<u>LBNP</u>	<u>Hemorrhage</u>
10 – 20 mmHg 400 – 550 ml fluid displaced	Mild = 10% of total blood volume
20 – 40 mmHg 500 – 1000 ml fluid displaced	Moderate = 10 – 20% of total blood volume
≥ 40 mmHg ≥ 1000 ml fluid displaced	Severe = 20% of total blood volume

Statistical Analysis

Descriptive statistics were obtained on all measures. Inferential statistics (repeated measures ANOVA) were used to assess treatment differences due to the independent variable (LBNP) on the dependent variables (EKG: ventricular rate, PR interval, QRS duration, QT/QTc, P-R-T axes and R-R variability), BP, PP, HR variability, CO and SV. Since there were more than two levels of an independent

variable, a paired sample *t* test was used to compare all dependent variables at each of the following: supine, P1 (-10 mmHg), P2 (-20 mmHg), P3 (-40 mmHg) and recovery. SPSS (student version 16.0) was used for all analyses with $p < .01$ used as the level of significance

CHAPTER IV

RESULTS & DISCUSSION

Results and Discussion

All twenty subjects completed the experiment uneventfully without presyncopal symptoms. The experimental group of twenty had an average age of 23.4 ± 5.4 yrs., the average height was 175.2 ± 7.8 cm, and average weight was 81.6 ± 26.2 kg.

Cardiovascular responses to decreased LBNP included: HR progressively increasing and SV progressively decreased (figure 1). CO remained relatively unchanged throughout the different pressures. The increase in HR compensated for the decrease in SV to maintain CO.

Cardiovascular Responses

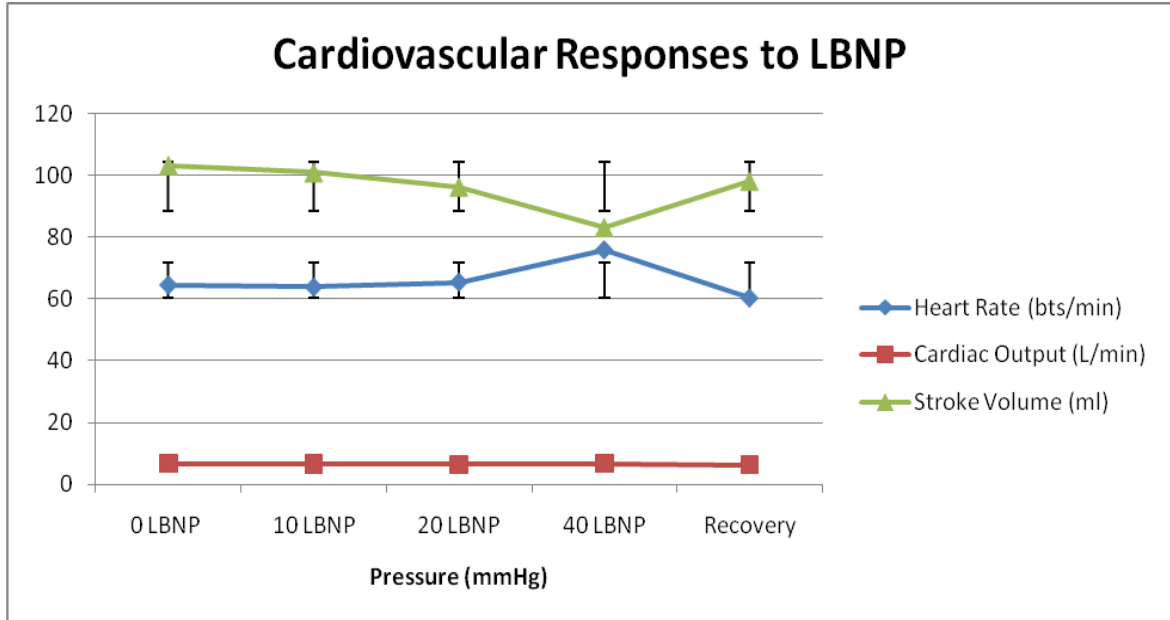


Figure 1. A comparison of HR, and SV and CO at each stage of LBNP

HR changed $64.6 \pm 8.2 \text{ bts} \cdot \text{min}^{-1}$ at 0 mmHg to $75.8 \pm 8.1 \text{ bts} \cdot \text{min}^{-1}$ at -40 mmHg. The increased HR may be partly explained by a decreased central blood volume or the increased tone of the sympathetic nervous system (Cooke et al., 2004).

SV markedly decreased with added LBNP due to the decrease in venous return to the heart. Reduced venous return leads to lower cardiac filling, which is responsible for the increase in the activity of the peripheral sympathetic nervous system. This increases the HR and peripheral vascular resistance through vasoconstriction in proportion to the reduction in SV as supported by the Convertino, Ludwig & Cooke (2004) study. A decrease in ventricular preload can cause a decrease in SV and an increase in HR. (Klabunde, 2005).

With LBNP dropping to -40 mmHg, HR increased to compensate for the reduction in SV so CO could be maintained. Rhea's 1991 findings of simulated

hemorrhage in which there is a decrease in the cardiac preload which decreases CO, causing the sympathetic nervous system to and increase HR to compensate for the reduction.

BP Responses

A comparison of SBP, DBP and PP as related to each stage of progressive LBNP (figure 2). With the application of LBNP, the SBP progressively decreased and the DBP increased. The mean SBP was 126 ± 10.1 at 0 mmHg and decreased to and 114.9 ± 10.1 at -40 mmHg LBNP.

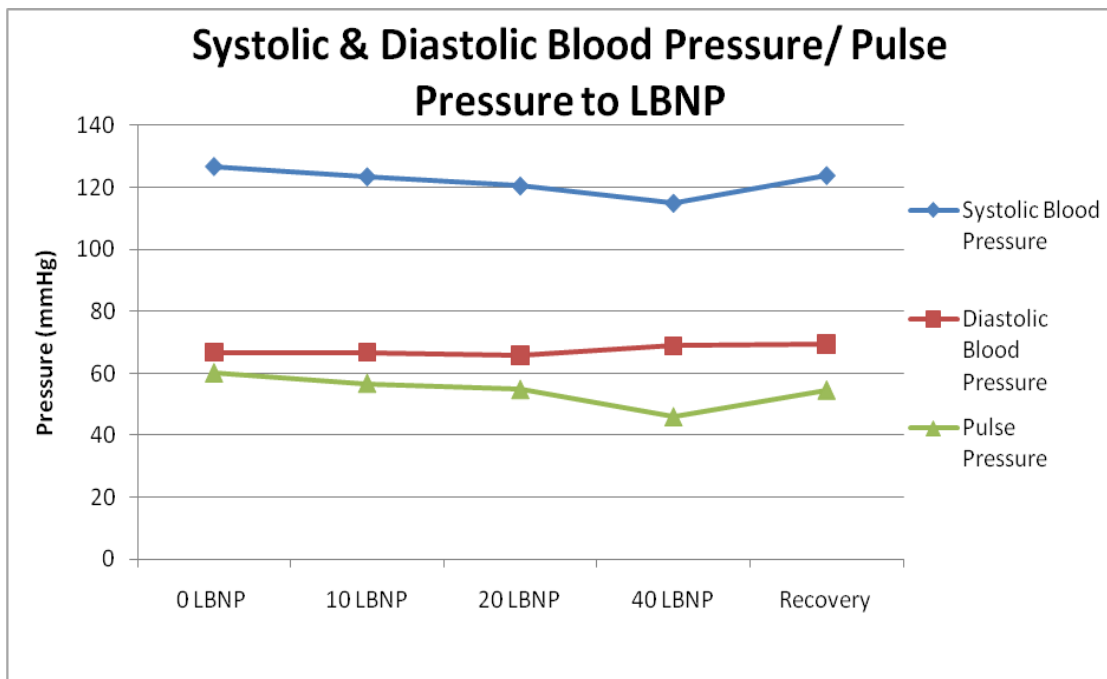


Figure 2. A comparison of SBP, DBP and PP at each stage of LBNP.

The DBP had a varied response; but overall it increased. An increase in either SBP or DBP will increase the MAP. Additionally, under testing conditions, an increase in HR will increase BP. Increased HR leads to increased CO, among other things, which increases BP in support of Marfill et al.,1999.

The varied response in DBP may be due to the autonomic nervous system response and the renin-angiotensin system (Pomeranz et al., 1985). The mean DBP was 66.7 ± 6.3 baseline at 0 mmHg and 68.9 ± 8.9 at -40 mmHg LBNP. The varied response in DBP is supported by the research of Marfil et al. (1999), who noted that there is always a varied cardiovascular response to laboratory stressors within the subject pool.

The PP of all subjects decreased from baseline to -40 mmHg. The mean PP of subjects 0 mmHg was 60 ± 11.3 and at -40 mmHg was 46.5 ± 9.7 . PP declined proportionately to LBNP (Figure 2). The Convertino et al. (2008) study supports the findings that the physiologic response of PP dropping indicates there was simulated blood loss when LBNP of -40 mmHg was applied.

The results support previous studies of Convertino et al. (1984, 2004, 2008) with LBNP up to -40 mmHg indicating that due to the blood volume change and left ventricle end diastolic filling, PP drops. By reducing the end diastolic volume there is a reduction in left ventricle filling (Convertino et al., 2004). Cardiovascular control by baroreflexes lowered the arterial pressure in subjects by increasing HR and increasing vascular resistance. (Convertino et al., 2004).

The greatest responses to LBNP were observed in phase 4 of the testing (-40 mmHg LBNP). Goswami et al. (2008) noted that LBNP up to -40 mmHg (5 minute exposures) could lower PP because of unloading cardiopulmonary baroreceptors, peripheral vasoconstriction in upper limbs, and progressive increases in sympathetic activity. Because of blood pooling in lower body compartments, PP dropped from a mean of 60 bpm down to 46 bpm, which was the most significant change reflected in the data collection in Figure 2.

The subjects elicited the classic cardiovascular responses to moderate hemorrhage (550 – 1000 ml fluid displaced) (Cooke et al., 2004). An increase in the sympathetic activity maintained arterial blood pressure due to the increase in vascular resistance and HR. As HR continued to increase, CO slightly decreased and SV progressively decreased (Figure 1). The hemodynamic responses of the subjects were supported by Goswami et al. 2008.

Electrocardiographic Morphology Changes.

EKG tracings were obtained during each stage and analyzed in respect to changes in PR interval, QRS duration, QT/QTc, QT dispersion, P-R-T axes and R-R interval.

PR Interval

The P-R Interval represents the period of time from the onset of the P wave to the beginning of the QRS complex. The P-R interval normally ranges from 120 to 200 ms (Klabunde, 2005). This represents the time between the onset of atrial depolarization the onset of ventricular depolarization. The mean values of the P-R interval during baseline at 0 mmHg was 151.22 ± 18.53 ms significantly dropping to 143.00 ± 11.29 ms at -40 mmHg and returning back

Table 3. EKG Morphology – P-R Interval

Condition	Mean	STD	Sig. (2-tailed)
0 mmHg LBNP	151.22 ms	± 18.53	.050
-10 mmHg LBNP	152.76 ms	± 19.14	
0 mmHg LBNP	151.22 ms	± 18.53	.086
-20 mmHg LBNP	152.82 ms	± 16.30	
0 mmHg LBNP	151.22 ms	± 18.53	.001*
-40 mmHg LBNP	143.00 ms	± 11.29	
0 mmHg LBNP	151.22 ms	± 18.53	.583
Recovery 0 LBNP	151.70 ms	± 16.75	

*Significant difference ($p < .01$)

to 151.70 ± 16.75 ms at recovery indicating that there were not any conduction defects within the AV node (Table 3). As HR increased, the P-R interval decreased. The results support the previous study of Sommargren (2002) indicating shortened PR intervals due to increased atrial depolarization.

QRS Duration

The QRS duration represents ventricular depolarization. The duration of the QRS normally lasts from 60 ms to 100 ms (Klabunde, 2005). The QRS duration (mean values) continually dropped throughout the experiment from baseline 92.6 ± 6.56 to 87.1 ± 7.46 ms at -40 mmHg (Table 4). This decrease was significant at -20 and -40 mmHg and returned to baseline levels during recovery. The results are supported by Ishikawa (1976) and Delia et al. (1999) indicating a shorter QRS interval with progressive blood loss.

Table 4. EKG Morphology – QRS Interval (ms)

Condition	Mean	STD	Sig. (2-tailed)
0 mmHg LBNP	92.58 ms	± 6.56	.018
-10 mmHg LBNP	91.62 ms	± 6.36	
0 mmHg LBNP	92.58 ms	± 6.56	.000*
-20 mmHg LBNP	89.76 ms	± 6.68	
0 mmHg LBNP	92.58 ms	± 6.56	.000*
-40 mmHg LBNP	87.10 ms	± 7.46	
0 mmHg LBNP	92.58 ms	± 6.56	.391
Recovery 0 LBNP	92.16 ms	± 7.53	

*Significant difference ($p < .01$)

Q-T Interval

The Q-T interval represents both ventricular depolarization and repolarization. This is a rough estimate of the ventricular action potential duration. The Q-T interval is expressed as a corrected Q-T (Q-Tc) interval by taking the Q-T interval and dividing it by the square root of the R-R interval. The Q-T range should be from 200 ms to 400 ms depending on HR (Klabunde, 2005). At a higher HR, the ventricular action potentials are

shorter, decreasing the Q-T interval. The Q-T interval (mean value) during the experiment at baseline (0 mmHg) was 398 ± 31.32 ms baseline dropping to 374 ± 22.01 ms at -40 mmHg which was significant (Table 5). The length of the Q-T interval length varies with HR. An increase in HR would decrease the Q-T interval, the slowing of the HR lengthens the Q-T interval. A shortened Q-T interval can also be related to hypercalcemia as supported by Stern et al.(1968).

Table 5. EKG Morphology – Q-T Interval (ms)

Condition	Mean	STD	Sig. (2-tailed)
0 mmHg LBNP	398.58 ms	± 31.32	.051
-10 mmHg LBNP	396.00 ms	± 32.15	
0 mmHg LBNP	398.58 ms	± 31.32	.147
-20 mmHg LBNP	393.38 ms	± 28.72	
0 mmHg LBNP	398.58 ms	± 31.32	.000*
-40 mmHg LBNP	374.08 ms	± 22.01	
0 mmHg LBNP	398.58 ms	± 31.32	.011
Recovery 0 LBNP	416.36 ms	± 35.24	

**Significant difference ($p < .01$)*

Because the Q-T interval dropped this would indicate an elevated HR compensating for the pooling of blood away from the heart. The Q-T interval from -40 mmHg to recovery increased by 42 ms indicating that there was a slowing of the HR as the subject recovered. The Q-T interval increased to 416.36 ± 35.24 ms during recovery. The findings are supported by the research of Stern et al. (1968), noting that EKG changes may be indicative of vagal stimulation, sympathetic stimulation, adrenaline or myocardial lesions producing catecholamines.

Q-Tc Interval

The Q-Tc represents the interval between ventricular depolarizations. Normal Q-Tc intervals are less than 440 ms (Klabunde, 2005). The Q-Tc duration (mean values)

during the experiment was 409 ± 19.01 ms at baseline dropping significantly to 399 ± 14.47 ms at -40 mmHg (Table 6).

Table 6. EKG Morphology – Q-Tc Interval (ms)

Condition	Mean	STD	Sig. (2-tailed)
0 mmHg LBNP	409.03 ms	± 19.01	.051
-10 mmHg LBNP	405.79 ms	± 19.38	
0 mmHg LBNP	409.03 ms	± 19.01	.147
-20 mmHg LBNP	403.02 ms	± 16.87	
0 mmHg LBNP	409.03 ms	± 19.01	.000*
-40 mmHg LBNP	399.40 ms	± 14.47	
0 mmHg LBNP	409.03 ms	± 19.01	.076
Recovery 0 LBNP	411.07 ms	± 20.19	

*Significant difference ($p < .01$)

The decrease in the Q-Tc represents a lengthened ventricular depolarization. . If the Q-Tc interval would have increased beyond 440 ms this would have indicated a severe medical condition. However, all mean values were within the normal conduction range. The results support the study of Aygun et al. (2010) indicating QTc under 440 ms represent a Class I hemorrhage (0 – 15% total blood volume) using the ATLS classification in which the body can compensate for this type of blood loss. According to Cooke et al. (2004), a negative pressure of -40 mmHg represents moderate hemorrhage or 550 – 1000 ml of blood loss which would account for changes at -40 mmHg (Table 2).

QT Dispersion

QT dispersion or QTd most likely represents a measure of myocardial repolarization. QTd is defined generally as the difference between the longest and the shortest QT interval in a set of ECG leads. QTd in normal subjects is usually between 27 and 65 ms (Klabunde, 2005). The Q-Td started at 37.34 ± 27.20 ms baseline and decreased to 30.54 ± 19.39 ms at -40 mmHg LBNP (Table 7).

Table 7. EKG Morphology – QTd Interval (ms)

Condition	Mean	STD	Sig. (2-tailed)
0 mmHg LBNP -10 mmHg LBNP	37.34 ms 35.36 ms	± 27.20 ± 23.94	.022
0 mmHg LBNP -20 mmHg LBNP	37.34 ms 31.88 ms	± 27.20 ± 19.49	.016
0 mmHg LBNP -40 mmHg LBNP	37.34 ms 30.54 ms	± 27.20 ± 19.39	.019
0 mmHg LBNP Recovery 0 LBNP	37.34 ms 33.36 ms	± 27.20 ± 20.73	.014

All subjects stayed in the normal range throughout the protocol and no significant changes were noted. The non significant change in QTd supports the research of Lazar et al., 2008 indicating that increases in the QTd would indicate sudden cardiac death, congestive heart failure or end stage renal disease.

P-R-T Axes

The P-R-T axes were all within the proper range which is -30 to +90 degrees. The three axis measurements are determined by the direction in which the electrical signals generated by the heart traveled toward the leads of the EKG.

P Axis

(Table 8) shows the effect of LBNP on the P axis. The P axis at baseline was 49.97 ± 24.94 and increased to 64.62 ± 14.66 at -40 mmHg LBNP which was a significant change.

Table 8. EKG Morphology – P Axis (degrees)

Condition	Mean	STD	Sig. (2-tailed)
0 mmHg LBNP	49.97 degrees	± 24.94	.532
-10 mmHg LBNP	51.46 degrees	± 27.28	
0 mmHg LBNP	49.97 degrees	± 24.94	.201
-20 mmHg LBNP	54.29 degrees	± 23.24	
0 mmHg LBNP	49.97 degrees	± 24.94	.001*
-40 mmHg LBNP	64.62 degrees	±14.66	
0 mmHg LBNP	49.97 degrees	± 24.94	.620
Recovery 0 LBNP	48.94 degrees	± 27.09	

*Significant difference ($p < .01$)

R Axis

Table 9 shows the effect of LBNP on the R axis. There was a significant change from baseline to -40 mmHg.

Table 9. EKG Morphology – R Axis (degrees)

Condition	Mean	STD	Sig. (2-tailed)
0 mmHg LBNP	73.08 degrees	± 15.68	.892
-10 mmHg LBNP	73.14 degrees	± 15.61	
0 mmHg LBNP	73.08 degrees	± 15.68	.381
-20 mmHg LBNP	73.70 degrees	± 16.11	
0 mmHg LBNP	73.08 degrees	± 15.68	.001*
-40 mmHg LBNP	77.06 degrees	± 14.25	
0 mmHg LBNP	73.08 degrees	± 15.68	.860
Recovery 0 LBNP	72.99 degrees	± 15.74	

*Significant difference ($p < .01$)

T Axis

The T axis did not change with increased LBNP (Table 10).

Table 10. EKG Morphology – T Axis (degrees)

Condition	Mean	STD	Sig. (2-tailed)
0 mmHg LBNP	55.02 degrees	± 16.08	.666
-10 mmHg LBNP	55.34 degrees	± 16.40	
0 mmHg LBNP	55.02 degrees	± 16.08	.538
-20 mmHg LBNP	55.60 degrees	± 16.53	
0 mmHg LBNP	55.02 degrees	± 16.08	.559
-40 mmHg LBNP	55.84 degrees	± 17.24	
0 mmHg LBNP	55.02 degrees	± 16.08	.107
Recovery 0 LBNP	56.43 degrees	± 16.20	

Because of the mid level, incremental, short duration phases this caused leg interstitial fluid pressure changes, plasma volume and whole body capillary fluid transport to be affected. The sympathetic reflex is initiated by increased venous return and increased arterial filling. Because the arterial walls are stretched this increases HR by stimulating both the SA node and the atrial stretch receptors. With the stimulation of the SA node, depolarization waves emerge and travel through the atria. The P-R-T axes all traveled through a wave of depolarization producing positive voltage in the EKG. Because the left or right ventricle did not increase in activity the axis changes were normal.

R-R Interval

Table 11 shows a change in the R-R interval as LBNP increased. When LBNP went from 0 to -20 mmHg there was minimal change in the R-R interval. However, from

Table 11. EKG Morphology – R-R Interval (ms)

Condition	Mean	STD	Sig. (2-tailed)
0 mmHg LBNP	936.89 ms	± 117.51	.474
-10 mmHg LBNP	944.72 ms	± 122.97	
0 mmHg LBNP	936.89 ms	± 117.51	.789
-20 mmHg LBNP	932.04 ms	± 137.33	
0 mmHg LBNP	936.89 ms	± 117.51	.000*
-40 mmHg LBNP	800.85 ms	± 100.10	
0 mmHg LBNP Recovery 0 LBNP	936.89 ms 1003.81 ms	± 117.51 ± 129.25	.000*

*Significant difference ($p < .01$)

baseline (936.89 ± 117.51 ms) to -40 mmHg (800.85 ± 100.10 ms) there was a significant drop in the R-R interval. Table 11 also shows that from baseline (936.89 ± 117.51 ms) to recovery (1003.81 ± 129.25 ms) there was a significant change in the R-R interval.

The R-R interval supported the Convertino et al. (2008) study suggesting the potential use of HR variability as an assessment tool for fluid loss. The R wave amplitude dropped with progressive LBNP indicating that there were changes in central blood volume and the response of the sympathetic nervous system.

In summary, the EKG findings showed that the PR interval decreased as HR increased. The QRS duration decreased due to the fluid shift in the body. The Q-T interval the (ventricular action potentials) are shorter due to the increase in HR. The Q-Tc interval decreased due to the lengthened ventricular depolarization. The QT dispersion did not change. Significance in the QTd would have indicated a severe medical condition. There was only an approximate fluid displacement of 500 – 1000 ml of fluid being representative of a moderate blood loss. The P-R-T axes were all within proper range of -30 to +90 degrees. There was a significant change in the P and R axis,

which could have been due to activity of the ventricles. The R-R interval decreased as LBNP increased because of central blood volume changes.

CHAPTER V

SUMMARY & CONCLUSION

Summary/Conclusions

Lower body negative pressure induces blood pooling in the lower body. The blood volume shift causes a reduction in venous return to the heart. Cardiovascular adjustments must be made to compensate for the decreases in venous return in order to maintain CO and adequate BP. The overall short term response to LBNP depends on a combination of the above listed factors and any combination of physiological factors that vary from individual to individual.

There was a significant decline in PP when exposed to LBNP (-10, -20, -40 mmHg). EKG morphology (PR interval, QRS duration, QT/QTc, P-R- axis and R-R interval) changed with the application of LBNP: PR interval decreased, QRS duration decreased, Q-T decreased, Q-Tc decreased, Q-Td no change, P axis increased, R axis increased, and R-R interval decreased. There was support for both hypotheses in this experiment showing a decrease in PP when exposed to LBNP and the EKG morphology changed when subjects were exposed to LBNP.

Limitations

The limitations of this study include a narrow range of LBNP. Using LBNP beyond -40 mmHg would elicit even greater cardiovascular responses, reflex changes and enhance higher activity levels of baroreceptors. The study was limited to young adult males. Females were eliminated from this study due to the possibility of pregnancy and fluctuations in results due to changes in hormonal levels throughout the menstrual cycle. The opening of the chamber (34 inches in diameter) limited this study to non-obese subjects.

Future Research Recommendations

Studies need to be conducted to assess the effects of catecholamines of graded LBNP and EKG morphology. The frequency and duration of EKG abnormalities along with graded negative pressure above -40 mmHg LBNP needs to be evaluated. Also, serum levels of various electrolytes need to be investigated related to simulated hemorrhage and EKG changes.

Since acute hemorrhage accounts for about 50% of the deaths of soldiers in combat (Convertino et al., 2004), additional research needs to be done evaluating combinations of vital signs and EKG morphology during LBNP up to -70 mmHg, to develop early detectable warning signs of hemorrhage triage purposes.

In conclusion, the results from this study indicate that HR, CO, SV, SBP, DBP and PP can be used as biomarkers for blood loss. Testing conditions influenced hemodynamic responses related to EKG. These observations underscore the need to understand the factors that affect change in EKG morphology and LBNP exposure.

BIBLIOGRAPHY

- Aygun, D. Sisman, B., Nural, M., Yilmaz, O., & Baydin, A. (2010). Effect of essential hypertension on QTc dispersion in patients with intracerebral hemorrhage. *Turkish Journal of Medical Science*, 40, 541-547.
- Bellamy, R. F. (1984). The causes of death in conventional land warfare: Implications for combat causality care research. *Military Medicine*, 149, 55-62.
- Carter, J., Lawrence, J., Klein, J. (2009). Menstrual cycle alters sympathetic neural responses to orthostatic stress in young, eumenorrheic women. *American Journal of Endocrinology and Metabolism*, 297, E 85 – E 91.
- Charles, J. B., & Lathers, C. M. (1994). Summary of lower body negative pressure experiments during space flight. *Journal of Clinical Pharmacology*, 34, 571-583.
- Coles, D., Kidd, B., & Moffat, W. (1957). Distensibility of blood vessels of the human calf determined by local application of subatmospheric pressures. *Journal of Applied Physiology*, 10, 461-468.
- Convertino, V.A., Ludwig, D. A., Cooke, W.H. (2004) SV and sympathetic responses to lower-body negative pressure reveal new insight into circulatory shock in humans. *Autonomic Neuroscience: Basic and Clinical* 111, 127-134.
- Convertino, V. A., Cooke, H. W., Salinas, J., & Holcomb, J. B., (2004). *Advanced Capabilities for Combat Medics*, 16, 1-10.
- Convertino, V. A., Montgomery, L. D., & Greenleaf, J. E. (1984). Cardiovascular responses during orthostatic: effect of an increase in VO₂ max. *Aviation, Space and Environmental Medicine*, 55, 702-708.

Convertino, V. A., Ryan, K.L., Rickards,. C. A. Cooke, W. H., Idris, A. H., et al (2007).

Inspiratory resistance maintains arterial pressure during central hypovolemia: implications for treatment of patients with severe hemorrhage. *Critical Care Medicine*, 55, 305-311

Convertino, V. A., Ryan, K. L., Rickards, C. A., Salinas, J., McManus, J. G., & Cooke,

W. H. et al. (2008). Physiological and medical monitoring for en route care of combat casualties. *Journal of Trauma, Injury, infection, and Critical Care*,(April Supplement), S342-S353.

Cooke, W. H., Rickards, C. A., Ryan, K. L., & Convertino, V. A (2008). Autonomic

compensation to simulated hemorrhage monitored with heart period variability. *Critical Care Medicine*, 36, 1892-1899.

Cooke, W. H., Ryan, K. L., & Convertino, V. A. (2004). Lower body negative pressure

as a model to study progression to acute hemorrhagic shock in humans. *Journal of Applied Physiology*, 96, 1249-1261.

Defense Technical Information Center (DTIC). (1979). *A Lower Body Negative Pressure*

Box for +Gx Simulation in the Upright Seated Position (Defense Logistics Agency). Alexandria, VA: Department of Defense.

Delia,P. Zaki, S., Govendir,M., Church, D. & Malik, R. (1999). Effect of acute

hemorrhage on QRS amplitude of the lead II canine electrocardiogram. *Australian Veterinary Journal*, 77, 298-300.

Esch, B.,Scott, J. & Warburton, D.,(2007). Construction of a lower body negative

chamber. *Advances in Physiology Education*, 37, 76-81.

- Forsyth, R. P., Hoffbrand, B. I., & Melmon, K. L. (1970). Redistribution of CO during hemorrhage in the unanaesthetized monkey. *Circulation Research*, XXVII, 311-320.
- Foux, A., Seliktar, R., & Valero, A. (1976). Effects of lower body negative pressure (LBNP) on the distribution of body fluids. *Journal of Applied Physiology*, 41, 719-726.
- Franke, W. D., & Taylor, K. A. (1996). Exercise training mode affects the hemodynamic responses to lower body negative pressure in women. *European Journal of Applied Physiology*, 73, 169-174.
- Frey, M. A., & Hoffler, G. W. (1988). Association of sex and age with responses to lower body negative pressure. *Journal of Applied Physiology*, 65, 1752-1756.
- Friedl, COL. E., USA, & Allan, J. H. (2004). Physiological research for the warfighter. *USARIEM*, Oct/Nov/Dec, 33-43.
- Goldsmith, R. S., Francis, G. S., Crowley, A. W., & Cohn, J. N. (1982). Response of vasopressin and norepinephrine to lower negative body pressure in humans. *American Journal of Physiology - Heart Circulation Physiology*, 243, 970-973.
- Goswami, N., Grasser, E., Roessler, A., Schneditz, D., & Hinghofer-Szalkay, H. (2008). The cardiovascular response to lower body negative pressure in humans depends on seal location. *Physiological Research*, 58, 311-318.
- Goswami, N., Loeppky, J. A., & Szalkay, H. H. (May 2008). LBNP: Past protocols and technical considerations for experimental design. *Aviation, Space, and Environmental Medicine*, 79, 459-471.

- Gotshall, R. W. (2000). Gender differences in tolerance to lower body negative pressure. *Aviation, Space, and Environmental Medicine*, 71, 1104-1110.
- Guell, A. Braak L., & Gharib, C. (1990). Cardiovascular deconditioning during weightlessness simulation and the use of lower body negative pressure as a countermeasure to orthostatic intolerance. *The Physiologist*, 3 (1), S-31 – S-33.
- Haberthur, C., Shachinger, H., Seeberger, M., & Gysi, C., (2003). Effect of non-hypotensive hemorrhage on plasma catecholamine levels and cardiovascular variability in man. *Clinical Physiology and Functional Imaging*, 23, 159-165.
- Halliwill, J., Lawler, L., Eickhoff, T., Joyner, M. and Mulvagh, S. (1998). Reflex responses to regional venous pooling during lower body negative pressure in humans. *Journal of Applied Physiology*, 84 (2) 454-458
- Hernandez, J. P., Darandikar, A., & Franke, W. D. (2005). Effects of age and fitness on tolerance to lower body negative pressure. *Journal of Gerontology*, 60A, 782-786.
- Hinghofer-Szalkay, H. G., Vidas, M., Sauseng-Felleger, G., Konig, E. M., Lichardus, B., & Jezova, D. (1996). Head-up tilt and lower body suction: Comparison of hormone responses in healthy men. *Physiology Research*, 45, 369-378.
- Hisdal, J., Toska, D., & Walloe, L. (2001). Beat-to-beat cardiovascular responses to rapid, low level LBNP in humans. *American Journal of Physiological Regulation Integrative Comprehensive Physiology*, 281, R213-R221.
- Howden, R., Tranfield, P.A., Lightfoot, J.T., Brown, S.J., Swaine, I.L. (2001). The reproducibility of tolerance to lower-body negative pressure and its quantification. *European Journal of Applied Physiology*; 84: 462-8.

- Ishikawa, K. (1976). Influence of alterations in the hematocrit upon the P wave and the QRS complex. *Chest*; 69: 762-768.
- Klabunde, R. E. (2005). *Cardiovascular Physiology Concepts*. Philadelphia: Lippincott Williams & Wilkins.
- Lawler, L., Halliwill, J., Summer, J., Joyner, M., & Mulvagh, S., (1998). Leg mass and lower body negative pressure tolerance in men and women. *Journal of Applied Physiology*, 85 (4), 1471-1475.
- Lazar, J., Manzella, S., Moonjelly, J., Wirkowski, E., & Cohen, T., (2003). The prognostic value of QT dispersion in patients presenting with acute neurological events. *Journal of Invasive Cardiology*, 15, 31-5.
- Lee, K., Buchanan, D., Flatau, A., & Franke, W. D. (2004). Reproducibility of the HR variability responses to graded lower body negative pressure. *European Journal of Applied Physiology*, 92, 106-113.
- Ligtenberg, G., Blankestijn, P., & Koomans, A. (1997). Hemodynamic response during lower body negative pressure: The role of volume status. *Journal of the American Society of Nephrology*, 9; 105-113.
- Lightfoot, J. T., & Tsintgiras, K. M. (1995). Quantification of tolerance to lower body negative pressure in a healthy population. *Medicine and Science in Sports and Exercise*, 27, 697-706.
- Levine, B.D, Buckey, J.C., Fritsch, J.M., Yancy, C.W., Watenpugh, D.E., Snell, P.G., et al. (1991). Physical fitness and cardiovascular regulation: mechanisms of orthostatic intolerance. *Journal of Applied Physiology*, vol. 70, (1), pp. 112-122.

- Loeppky, J.A., Venters, M.D, Luft, U.C.,(1978). Blood volume and cardiorespiratory responses to lower body negative pressure (LBNP). *Aviation, Space, Environmental Medicine*, 39, 1297-1307.
- Marfil, M., Santaella, M., l Carment F., Leon, A., Turpin, G., Castellar, J. (1999). Individual differences associated with cardiac difference response: psychophysiological and personality variables. *Psychology in Spain*, 3 (1), 54-62.
- Montgomery, L.D.,Kirk, P.A., Payne, R.L.,Gerber, S.D.,Newton, P.J. & Williams, B.A. (1977). Cardiovascular responses of men and women to lower body negative pressure. *Aviation, Space and Environmental Medicine*, 48, 138-145.
- Muenter, N., Watenpaugh, W., Wasmund, S., Wasmund, S., Maxwell, S., & Smith, M. (2000). Effect of sleep restriction o orthostatic cardiovascular control in humans. *Journal of Applied Physiology*, 88: 966-972.
- Murray, R. H., Thompson, L. F., Bowers, J. A., & Albright, C. D. (1968). Hemodynamic effects of graded hypovolemia and vasodepressor syncope induced by lower body negative pressure. *American Heart Journal*, 76, 799-811.
- Omron (n.d.). *Omron Company*. Retrieved December 2, 2009, from www.omronwebstore.com
- Pomeranz, B., Macaulay, R.J.B., Caudill, M.A., Kutz, I, Adam, D, Gorpdon, D. et al. (1985). Assessment of autonomic function in humans by HR spectral analysis. *American Journal of Physiology* 248, H151-H153.
- Prasad, A. K., Hedge, K.S., & Lazar, M., (1997). Cardiovascular responses to application of lower body negative pressure of male volunteers in seated position. *Indian Journal of Physiological Pharmacology*, 42 (2), 239-244.

- Rhea, R., Hamdan, M., Clary, M., Randels, M., Dayton, P., Srauss, R., et al. (1991). Comparison of muscle sympathetic responses to hemorrhage and lower body negative pressure. *Journal of Applied Physiology*, 70, 1401-1405.
- Russomano, T., Beck, L., Petrat, G., May, F., Thompson, S., & Allan, J. et al. (2006). Development of a lower body negative pressure box with an environmental control system for physiological studies. *Advances in Space Research*, 38, 1233-1239.
- Schroeder, C. Bush, E., Norcliffe, L., Luft, F., Tank, J. et al. 2002. Water drinking acutely improves orthostatic tolerance in healthy subject. *Circulation*, 106: 2806-2811.
- Smith, M. L., Hudson, D. L., & Raven, P. B. (1987). Effect of muscle tension on the cardiovascular responses to lower body negative pressure in man. *Medicine and Science in Sport and Exercise*, 19, 436-442.
- Sommargren, C. (2002). EKG abnormalities in patients with subarachnoid hemorrhage. *American Journal of Critical Care*, 11, 48-56.
- Stedman, (2008). *Stedman's Medical Dictionary for the Health Professions and Nursing* (6th ed.). Philadelphia, PA: Lippincott Williams & Wilkins.
- Stern, S., Lavy, S., Carmon, A., and Herishianu, Y., (1968). EKG Patterns in Hemorrhagic Stroke. *Journal of Neurological Science*, 8: 61-67.
- Stevens, P., & Lamb, L. (1965). Effects of lower body negative pressure on the cardiovascular system. *American Journal of Cardiology*, 4, 506-515.

- Tomaselli, C., Frey, M., Kenney, R., & Hoffler, G. (1990). Effect of a central redistribution of fluid volume on response to lower body negative pressure. *Aviation, Space & Environmental Medicine*, 61: 38-42.
- Van den Bergh, W, Algra, A.,& Rinkel, G.(2004). EKG abnormalities and serum magnesium in patients with subarachnoid hemorrhage. *Stroke*, 35 (3), 644-8.
- Watenpaugh, D., Ballard, R., Schneider, S., Lee, S., Ertl, A., William, J., et al. (1999). Supine lower body negative pressure exercise during bed rest maintains upright exercise capacity. *Journal of Applied Physiology*, 89, 218-227.

APPENDICES



Cleveland State University

Office of Sponsored Programs and Research
Institutional Review Board (IRB)

Memorandum

To: Kenneth Sparks Principal Investigator or Advisor
C&F

From: Rich Piiparinen, GA
Office of Sponsored Programs & Research

Date: March 11, 2010

Re: Results of IRB Review of your project number: 29075-SPA-HS
Co-Principal Investigator or Student: Michele Barton
Entitled: The Effect of Lower Body Negative Pressure on Cardiovascular Responses in Young Males

The IRB has reviewed and approved your application for the above named project, under the category noted below. Approval for use of human subjects in this research is for one year from today. If your study extends beyond this approval period, you must again contact this office to initiate an annual review of this research. ***This approval expires at 11:59 pm on 3/5/2011.***

By accepting this decision, you agree to notify the IRB of: (1) any additions to or changes in procedures for your study that modify the subjects' risk in any way; and (2) any events that affect that safety or well-being of subjects.

Thank you for your efforts to maintain compliance with the federal regulations for the protection of human subjects.

Approval Category:

Date: 3/6/2010

- Exempt Status. Project is exempt from further review under CFR 46.101:
- Expedited Review: 4

cc: Project file

Mailing Address: 2121 Euclid Avenue, PH-3rd Floor • Cleveland, Ohio 44115-2214
Campus Location: Parker Hannifin Hall • 2258 Euclid Avenue • Cleveland, Ohio
(216) 687-3630 • Fax (216) 687-9382

APPENDIX B

Name _____

Date _____

AHA/ACSM Pre-participation Screening Questionnaire

Assess Your Health Needs by Marking all *true* statements

History

You have had:

- A heart attack
- Heart Surgery
- Cardiac Catheterization
- Coronary angioplasty (PTCA)
- Pacemaker/implantable cardiac
- Defibrillator/rhythm disturbance
- Heart valve disease
- Heart failure
- Heart transplantation
- Congenital heart disease

Recommendations:

If you marked any of the statements in this section, consult your healthcare provider before engaging in exercise. You may need to use a facility with a medically qualified staff.

Other health issues:

- You have musculoskeletal problems. (*Specify on back*)*
- You have concerns about the safety of exercise. (*Specify on back*)*
- You take prescription medication (s). (*specify on back*)*
- You are pregnant

Symptoms

- You experience chest discomfort with exertion.
- You experience unreasonable breathlessness.
- You experience dizziness, fainting, blackouts
- You take heart medications.

Cardiovascular risk factors

- You are a man older than 45 years.
- You are a woman older than 55 years or you have had a hysterectomy or you are postmenopausal.
- You smoke.
- Your BP is greater than 140/90 mm Hg.
- You don't know your BP.
- You take BP medication.
- You don't know your cholesterol level.
- You have a blood cholesterol >240 mg/dl.
- You have a blood relative who had a heart attack before age 55 (*father/brother*) or 65 (*mother/sister*).
- You are diabetic or take medicine to control your blood sugar.
- You are physically inactive (*i.e., you get less than 30 minutes of physical activity on at least 3 days/week*).
- You are more than 20 pounds overweight.
- None of the above is true.

If you marked two or more of the statements in this section, you should consult your healthcare provider before engaging in exercise. You might benefit by using a facility with a professionally qualified staff to guide your exercise program.

You should be able to exercise safely without consultation of your healthcare provider in almost any facility that meets you needs.

- Proceed with test if musculoskeletal problems are minor, concerns about safety of exercise are normal, and prescription medications are not for cardiac, pulmonary, or metabolic disease.

Risk Status (Low, Moderate, High): _____

Appendix C

The effect of lower body negative pressure (LBNP) on cardiovascular responses in young males

Informed Consent

Purpose and Explanation of Testing Procedures

This study is being implemented by Dr. Kenneth Sparks, Director of the Human Performance Laboratory, Michele Barton, graduate student, and Dr. Milind Mehta from Cleveland State University, Department of Health, Physical Education, Recreation and Dance.

The purpose of this study is to measure your cardiovascular responses of blood flow, BP and electrocardiography (ECG) when you are exposed to lower body negative pressure. This means that you will lie down with your lower body (up to your lower rib area) placed in a sealed box. The box is attached to a vacuum cleaner. When the vacuum cleaner is turned on it produces a suction or negative pressure on your lower body area that is in the box. Lower body negative pressure (LBNP) has been studied since 1965 to reproduce orthostatic stress (changes in BP with different body positions). It has been used to study cardiovascular responses to changes in blood pressure and to prevent loss of physical conditioning of astronauts while in space. The LBNP device applies negative pressure to the lower limbs, this forces fluid from the upper body to shift to the lower body, this helps to prevent loss of physical conditioning during flight in space. LBNP is a non-invasive procedure that increases the blood volume in the lower body and reduces central blood volume and central venous pressure. The negative pressure is generated by attaching a vacuum cleaner attached to the chamber or sealed box (previously described) and controlled by a manual rheostat valve and monitored with a mercury manometer. The pressure can be quickly eliminated to restore normal pressure by simply turning off the vacuum cleaner. The body quickly recovers from LBNP effects within 30 seconds.

On the day of testing subjects you will be asked to refrain from any caffeinated beverages at least three hours prior to the study and will also be asked not to engage in physical exercise on the day of the study. The protocol involves seven, five minute conditions: (sitting, standing, supine (lying down) at 0 mmHg in LBNP, supine LBNP 10 mmHg, supine LBNP 20 mmHg, supine LBNP 40 mmHg, and supine recovery 0 mmHg. BP and ECG will be taken during the fifth minute of each stage. CO (the amount of blood pumped by the heart per minute) and HR will be continually monitored throughout all stages. You will be placed in the LBNP chamber after collection of data during sitting and standing. You will then be exposed to 0, 10, 20, and 40 mmHg LBNP for 5 minutes while in the supine position, and 0 mmHg LBNP during recovery. Throughout all conditions your BP, HR, ECG and CO will be measured and recorded. BP will be taken

using a BP cuff attached to your upper arm, The ECG (12 leads) will be taken using an electrocardiogram with chest and limb electrodes attached. Your CO will be measured using a device that uses electrodes placed on your skin at various locations for calculating your CO.

Potential Risks and Discomfort

Potential risks associated with exposure to LBNP include low BP, swelling of the legs, nausea, dizziness, and fainting.

In order to minimize the potential risks, you will be monitored for BP, ECG, and HR changes. Trained personnel will be present during testing if emergency care is needed. Furthermore, during the experimental trials, if your SBP falls below 90 mmHg and/or your HR falls 5 – 10 beats below baseline values you will be immediately removed from exposure. Following removal from exposure, you will be placed in a supine position with your legs elevated while sipping water at liberty and vitals will be monitored until BP and/or HR values return to normal.

Responsibilities of the Participant

You will need to complete a medical history. The information you submit and contained therein will be used in the determination of your eligibility for participation in the study.

Potential Benefits:

There are minimal benefits to be obtained by you other than participating in research to increase scientific knowledge. Risk-benefits status: Based on the precautions to minimize risk previously noted, the investigators view this as a low risk protocol that may provide important data for determining changes in cardiovascular responses with pooling of blood in lower body.

Confidentiality:

Any information obtained during your test will be treated as confidential and will not be revealed to any individual without your consent. However, information obtained during your test may be used for research purposes with your right to privacy retained.

The medical and research information recorded about you will be used within Cleveland State University as part of this research. Tests and procedures done solely for this research study may be placed in your file to indicate your participation in this study.

Upon completion of the study, you may have access to the research information recorded about you. Any publication of data will only use group data and not identify individuals who participated in the study.

Freedom of Consent:

Your participation in this study is voluntary. You are free to stop at any time, if you so desire.

Inquiries:

Any questions about the procedures used in this project are welcomed. If you have any doubts or questions please ask for further explanation or call Dr. Kenneth Sparks at 216-687-4831.

Patient Acknowledgement:

The procedures, purposes, known discomforts and risks and possible benefits to me and to others have been explained to me. I have read the consent form or it has been read to me and I understand it. I have had an opportunity to ask questions that have been answered to my satisfaction. I voluntarily consent to participate in this study and I have been given a copy of this consent form.

I understand that if I have any questions about my rights as a research subject I can contact the Cleveland State University, Institutional Review Board at 216-687-3630.

Signature of Participant

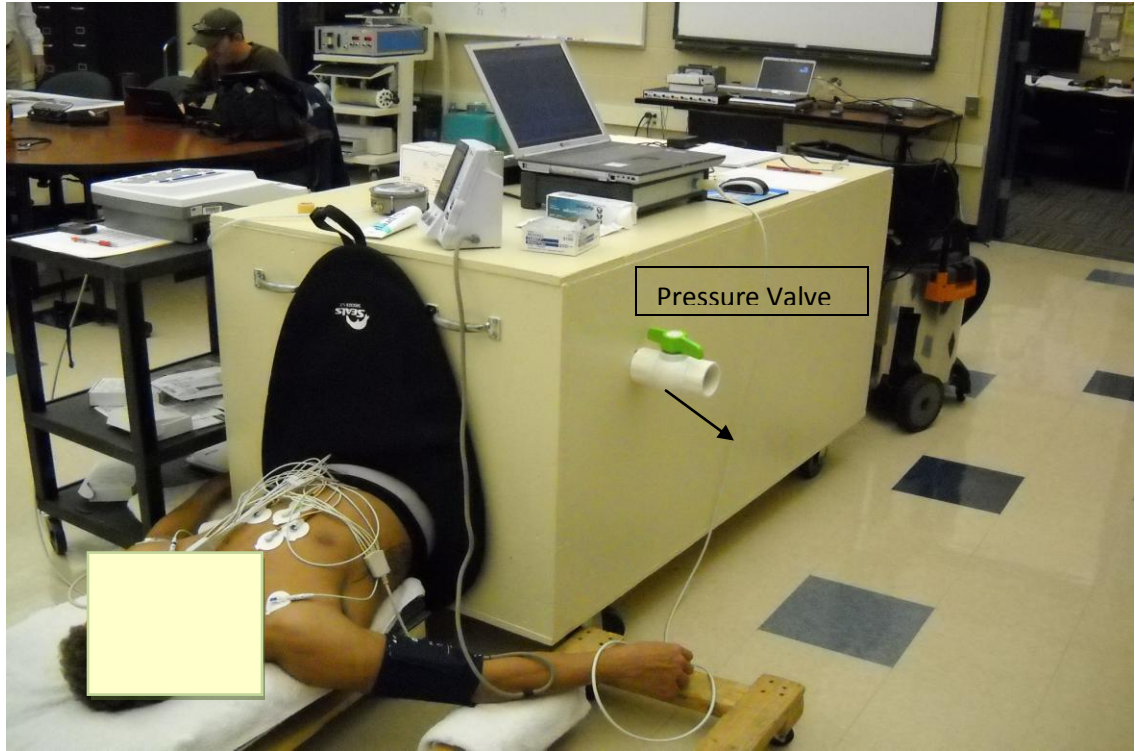
Date

Signature of Witness

Date

Appendix D

Subject Supine in Lower Body Negative Pressure Chamber (LBNP Pressure Valve) ↘



Ridgid 6.5 Horsepower Shop Vacuum Cleaner attached to LBNP Chamber

