ACUTE HEMODYNAMIC RESPONSES TO ELECTRICAL MUSCULAR STIMULATION WITH BLOOD FLOW RESTRICTION IN DAILY WHEELCHAIR USERS

by

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ABSTRACT

INTRODUCTION: Individuals with disabilities that use wheelchairs as their primary mode to carry out activities of daily living (ADL), and those affected by spinal cord injury (SCI), have been found to live less-active lives than their able-bodied counterparts, often experiencing physiological changes in the body that can contribute to the development of chronic diseases. Autonomic dysreflexia (AD), marked by a sudden increase in blood pressure (BP) from an unfavorable external stimulus on the lower extremities, is a possible condition that can experienced within this population. Electrical muscular stimulation (EMS) combined with blood flow restriction (BFR) on the lower extremities may lead to hemodynamic adaptations and increases in muscle fiber hypertrophy, improving overall function and quality of life. **PURPOSE:** The purpose of the study is to compare acute hemodynamic and skeletal muscle responses to EMS with and without the addition of BFR among individuals that primarily use wheelchairs for ADL. **METHODS:** 10 everyday wheelchair users were recruited from University of Alabama Adapted Athletics program to participate in three conditions. Conditions included sessions of EMS only, BFR only, and combined EMS and BFR on the lower extremities for varying lengths of time. EMS stimulated the quadriceps muscles into extension for 30 seconds at a time with 5 seconds of rest in-between, for a duration of 20 minutes. BFR was inflated at 40% of limb occlusion pressure (LOP) for 8 minutes on and off with 4 minutes of deflation between inflation times. Measurements taken pre- and post-trial included blood lactate (mmol) as well as blood flow measures of the posterior tibial artery and vastus medialis (VM) muscle cross-sectional area (VM CSA) using ultrasonography. BP and heart rate (HR) were

measured noninvasively and continuously during each condition as well as analyzed in 5-minute increments. BP was closely monitored for the purpose of safety in observing any possible incidences of AD among participants. Blood lactate, posterior tibial artery blood flow parameters, and VM CSA from pre- to post-trial were statistically analyzed by the use of one- and two-way analysis of variance (ANOVA). HR, systolic BP (SBP), diastolic BP (DBP) and mean arterial pressure (MAP) were analyzed by the use of a two-way ANOVA. Percent change was used to analyze HR, SBP, DBP, and MAP with timepoints from pre- to during the trial (10-15 minutes from start) and pre- to recovery time post-trial (5 minutes following the end) for each condition. **RESULTS:** Blood lactate increased over time within both the EMS+BFR (1.0 ± 0.1 vs. 1.4 ± 0.1; t= -2.73, p= 0.023) as well as BFR only (0.9 ± 0.2 vs 1.5 ± 0.4; t= -2.94, p= 0.017) conditions. There was a significant decrease in posterior tibial artery distance (0.215 ± 0.00 vs. 0.207 ± 0.00; t=2.47, p= 0.036) and area (0.037 ± 0.000 vs. 0.034 ± 0.000; t=2.67, p= 0.026) over time within the BFR only condition. Across all conditions, changes in HR (expressed as a percentage change from baseline) were lower post- compared to during the trial (mean difference [MD], 95% confidence interval [CI]): -5.3% (-10.4, -0.1), with the greatest differences observed within the EMS+BFR condition: -11.3% (-21.1, -1.5). Similar responses were observed for SBP (-18.4% [-27.1, -9.7]) and DBP (-22.9% [-37.7, -8.0]) in the EMS+BFR condition. There were no significant changes in MAP over time or by condition. **CONCLUSIONS:** EMS+BFR acutely increased blood lactate over time. The BFR only condition also acutely increased blood lactate as well as decreased posterior tibial artery distance and area over time. Compared to baseline, HR increased during the trial across all conditions, but was significantly lower 5 minutes following the trial in the EMS+BFR condition only. Similar responses were observed for SBP and DBP for the EMS+BFR condition only. There were no observed incidences of AD in any of the

conditions, with more favorable cardiovascular responses during and following the EMS+BFR trial. Collectively, our findings support the efficacy and safety of using BFR in combination with EMS with the goal of improving vascular health and function among everyday wheelchair users.

DEDICATION

This thesis is dedicated to all those that guided, supported, and encouraged me through my efforts in completing this project. In particular, my professors and advisors in both the undergraduate and graduate exercise science programs here at University of Alabama. This project is also dedicated to my teammates, amazing coaches, family, and friends who motivated and encouraged me on a daily basis, and through all the trials and tribulations that have been a part of this journey.

LIST OF ABBREVIATIONS

AD	Autonomic dysreflexia
ADL	Activities of daily living
ANOVA	Analysis of variance
BFR	Blood flow restriction
BMI	Body mass index (kg/m^2)
BP	Blood pressure
CI	Confidence interval
cm	Centimeters
CSA	Cross-sectional area
DBP	Diastolic blood pressure
DVT	Deep vein thrombosis
ECRL	Extensor carpi radialis longus
EDC	Extensor digitorium communis
EMS	Electrical muscular stimulation
EMS+BFR	Electrical muscular stimulation and blood flow restriction
FDA	Food and Drug Administration
FMD	Flow mediated dilation

GH	Growth hormone
HR	Heart rate
Hz	Hertz
kg	Kilograms
LOP	Limb occlusion pressure
M	Mean
MAP	Mean arterial pressure
mA	Milliamperes
MD	Mean difference
mmHg	Millimeter of mercury
mmol	Millimole
η^2 partial	Partial eta squared
PA	Physical activity
SBP	Systolic blood pressure
SCI	Spinal cord injury
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
TAMV	Time averaged mean velocity
VM	Vastus medialis
VM CSA	Vastus medialis cross-sectional area

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

A REVIEW OF THE LITERATURE ON SPINAL CORD INJURY ELECTRICAL MUSCULAR STIMULATION AND BLOOD FLOW RESTRICTION

Introduction

Individuals with disabilities that use wheelchairs as their primary mode to carry out activities of daily living (ADL), as well as those that have been affected by a spinal cord injury (SCI), have been found to be less active than able-bodied individuals. This population is often faced with increased risk of cardiovascular disease, such as lower limb thromboses, and other chronic diseases (1). Those that rely on wheelchairs for activities of daily life experience changes in the body such as decreases in muscle mass, increases in adiposity, and loss of neural innervation (1). This decrease in neural function and lack of physical activity leads to muscle atrophy in the lower body, significantly affecting everyday activities, overall health, and quality of life. External stimulation of the lower extremities through electrical muscular stimulation (EMS) may improve overall function and could contribute to improved quality of life through the maintenance of muscle mass (2). Stoner et al. state, “many forms of electrically stimulated exercise therapy have been used to train the legs in persons with SCI and have been shown to evoke improvements in exercise capacity, blood composition and metabolic profiles, blood flow parameters, total peripheral conductance, and femoral artery diameter”. This suggests that incorporation of EMS into a regular fitness routine for daily wheelchair users may significantly reduce the likelihood of lower extremity vascular complications.

The use of blood flow restriction (BFR) exercise as a form of treatment in clinical practices has become well-known and may lead to improvements in overall health and function. Blood flow restricted resistance training has created hypertrophic responses in the body, most significantly, due to metabolic by-product accumulation. Whole blood lactate and muscle cell lactate accumulation due to BFR results in increased growth hormone (GH) and enhanced cellular protein synthesis (4). Additionally, BFR has been shown to be a beneficial training option to promote muscle hypertrophy, as well as increased vascular compliance (5). Therefore, pairing EMS with BFR may lead to synergistic hemodynamic adaptations and increases in muscle fiber hypertrophy in individuals that use wheelchairs for activities of daily living, providing a means of improving health and quality of life.

Daily Wheelchair Users, Spinal Cord Injury, and Physical Activity

It is very well known that regular physical activity (PA) contributes greatly to improving health and reducing overall mortality. Individuals that utilize wheelchairs to carry out ADL, and those that have been faced with SCI, are often less-active than able-bodied individuals; resulting in physiological changes that can contribute to cardiovascular disease, lower-limb thrombosis, and other chronic diseases (1). Those with reduced ambulatory function often go through changes in body composition and metabolism; including decreases in muscle mass, increases in adiposity, and loss of autonomic control of cardiovascular functions (6-8). In addition, those that have a SCI and are sedentary have been found to have less compliant arteries than age-matched able-bodied individuals (9). This can lead to development of hypertension, atherosclerosis, stroke, heart failure, and overall poor cardiovascular health. Changes in neural innervation can lead to muscular

atrophy, ultimately contributing to negative changes within the body. Some of these adverse changes can include reduced blood flow as well as alterations to metabolism, muscle mass and cholesterol (6-8). The sedentary lifestyle that is adopted by many daily wheelchair users and those with SCI often result in poor cardiovascular and functional fitness, increasing cardiovascular mortality risk (10). Overall, this can impair activities of daily living and decrease quality of life.

Physical activity has been found to be a great predictor of maximal work capacity in daily wheelchair users. Increases in PA levels in this population has the potential to greatly improve total work capacity. Those with SCI have been found to experience many benefits from exercise training. A report by Hopman in 1986 found a mean value of 20% improvement in maximal oxygen uptake and 40% physical work capacity from 4-20 weeks of regular cardiovascular training. Current evidence suggests that improvements in cardiovascular pathologies in those with SCI were the result of increased PA and organized exercise programs (1). Daily wheelchair users and those with SCI that engage in greater amounts of PA and exercise may experience improvements in health overall, contributing to enhanced quality of life.

Electrical Muscular Stimulation

Electrical muscular stimulation (EMS) is a non-invasive therapeutic practice that involves the simulation of the musculature through sticky electrodes that are placed on the surface of the skin. EMS has been used in many clinical and therapeutic settings as a form of treatment to reverse vascular changes from SCI (19), improve muscular strength (20), and provide improvements in exercise capacity (21, 22). In addition, EMS is known to improve body composition and metabolic profiles (23, 24), blood flow parameters (25-27),

total peripheral conductance (28), and femoral artery diameter (27). These physiological adaptations improve overall physical function and increased quality of life. A study by Stoner et al. found that home-based EMS-induced resistance exercise therapy has the potential to improve flow mediated dilation (FMD) and arterial range in those with complete SCI, suggesting an enhancement of endothelial function (3). In addition, a study by Sabatier et al. discovered that electrically stimulated resistance training, specifically in spinal cord injured individuals, increases muscular endurance and muscle cross-sectional area (CSA) (19). Bochkezanian et al. discovered that a program of 12 weeks of high-intensity EMS of the knee extensor muscles significantly enhanced knee extensor torque, quadricep CSA, and reduced symptoms of spasticity (29). This research demonstrates just a few examples of the benefits that are elicited by the use of EMS training. In this thesis study, EMS will provide muscular contraction that will mimic the muscular activity that able-bodied individuals experience while exercising. The use of EMS training could drastically improve overall work capacity and cardiovascular health in individuals that use wheelchairs to carry out activities of daily living, contributing to greater quality of life.

Blood Flow Restriction

BFR involves the application of occlusion over the proximal portion of a limb, applying pressure that may or may not reduce arterial inflow while restricting venous return of blood distal to the application site of the occlusion (12). Resistance exercise training at low intensity with BFR has been found to increase muscle strength to a similar extent as high-intensity resistance training (13). Muscle hypertrophy has been found to occur at as low as 20% of 1RM with moderate vascular occlusion (14). This low-intensity occlusion training can benefit those that may not be able to engage in high-intensity

resistance training by allowing positive training adaptations with very little muscle damage (15). Taking part in resistance training at lower intensities with BFR may reduce the strain that is placed on the joints of the limb while still benefitting from physiological training adaptations (30). Mechanisms of BFR adaptations include hypoxia induced recruitment of fast-twitch fibers, greater duration of metabolic acidosis eliciting a greater hormonal response, enhanced growth factor expression and intracellular signaling, metabolic adaptation to the fast glycolytic system, the production of reactive oxygen species ultimately leading to tissue growth, intracellular swelling leading to tissue growth, and activation of myogenic stem cells (16). A study conducted by Shimizu et al. analyzed the effects of BFR on vascular endothelial function, peripheral blood circulation, and muscular strength in the elderly population. Their results displayed increases in plasma concentration of vascular endothelial growth factor, said to improve endothelial function; as well as increases in GH, peripheral blood circulation, norepinephrine, and lactate following one bout of low-intensity resistance training with BFR (31). To date, the literature on the feasibility of BFR specifically in individuals with lower extremity impairments is very limited. Benefits of BFR training among daily wheelchair users may be substantial, including the improvement of muscular strength and endurance, motor function and independence, and cardiovascular health through aerobic exercise (17). Potential safety issues with the use of BFR in this population include the development of deep vein thrombosis (DVT) or autonomic dysreflexia (AD). A study by Stavres et al. looking at the feasibility and safety of BFR in those with SCI, suggests that all subjects were able to safely perform exercise conditions with BFR without any signs or symptoms of acute AD or DVT (17). The study found that specifically those with SCI can handle a

single bout of BFR at 125% venous occlusion pressure, exhibiting similar physiological responses to able-bodied individuals (17). In addition, Stavres et al. found that with BFR exercise in those with SCI, lower limb blood volume was increased, and perfusion was maintained, while also experiencing increases in osmotic pressure gradient that resulted in cell swelling. Further research should explore the effect of varying exercise intensity, as well as the safety, feasibility, and physiological responses to BFR among different levels of SCI (17). It appears that when safety precautions are taken, BFR exercise training could have the potential to greatly improve muscular strength, endurance, and cardiovascular health in individuals with lower-level physical impairments. This could drastically improve overall health and lead to increased function and quality of life in those that primarily use wheelchairs to carry out tasks of daily living.

Electrical Muscular Stimulation and Blood Flow Restriction

Although literature and research on the use of EMS paired with BFR is limited, one study that utilized this technique found promising results. Gorgey et al. (32) analyzed the effects of pairing EMS and BFR on muscle CSA, torque, and hand function on the forearm muscles of tetraplegic individuals; as well as on FMD and blood flow velocity on the brachial artery of both paraplegics and tetraplegics. The study was broken down into two small studies, study A and study B. Study A examined only the CSA, torque, and function changes with EMS and BFR compared to just EMS in the extensor carpi radialis longus (ECRL) and extensor digitorium communis (EDC) forearm muscles. The participants of this sub-study were 9 men with incomplete tetraplegia, above the injury level of C8, with greater than 2 months in time injured. The participants went through 6 weeks of training twice weekly for 30 minutes consisting of electrical stimulation of both

the forearm extensor muscles. The right forearm received EMS paired with BFR, while the left forearm received only EMS. Each forearm was electrically simulated for a total of 40 repetitions of extension, with a contraction relaxation of 5 seconds work to 5 seconds of rest. The amplitude of the current, ranging from 0 to 200 milliamperes (mA), was increased until the wrist was stimulated into extension without finger extension. The BFR cuff on the right arm, paired with EMS, was inflated at 30% greater than resting systolic blood pressure (SBP) for almost 8 minutes while contractions were taking place. The participants took part in pre- and post- assessment visits to gather measurements. Measurements included ECRL and EDC muscle CSA by ultrasound and tape measure, torque by the Biodex isokinetic dynamometer, and hand functional tests. Heart rate (HR) measurements were taken every minute by the Polar HR monitor, and blood pressure (BP) was taken at the beginning and end of every exercise session.

Study A results showed that following 6 weeks of training, ECRL CSA increased in the EMS and BFR forearm by 17% from pre- to post-intervention. No change was found in CSA of the EMS only forearm. Additionally, specific tension increased when frequency changed from 20 to 80 hertz (Hz) in the EMS and BFR forearm when an amplitude current of 150 mA was used. When looking at functional grasp and release, there were no statistical differences following training between EMS and BFR compared to EMS only in the tasks assigned.

Study B focused on the effects of EMS and BFR on FMD and blood flow velocity of the brachial artery in comparison to just BFR. This sub-study included participants that were both tetraplegic and paraplegic, with injury levels ranging from C3 to L2. The right forearm of the participant received EMS and BFR, and the left forearm received BFR

only. The parameters of EMS on the right forearm were the same as study A, increasing amplitude to elicit wrist extension without finger extension. 30 contractions were then carried out, with 5 seconds of contraction to 5 seconds of rest. Measurements of resting brachial artery diameter and blood flow velocity of the right and left arms were taken prior to the start. Blood flow parameter measurements including brachial artery diameter and blood flow velocity were then taken with ultrasound prior, during, and immediately following BFR occlusion. The BFR protocol consisted of 3 minutes of rest with no occlusion, 3 minutes of cuff occlusion, and another 3 minutes measuring reactive hyperemia. Blood flow parameters were taken every 30 seconds during time with no cuff occlusion, and every minute during cuff occlusion.

The results of study B found that there were no differences in the baseline diameters or the resting blood flow velocity of the brachial artery between the EMS and BFR and the BFR arms. Following cuff occlusion however, compared to baseline, the brachial artery diameter and blood flow velocity increased in both forearms. FMD was found to have increased in the EMS and BFR arm compared to the BFR only arm.

Overall, the results of the study found that EMS and BFR led to noticeable improvements in muscular hypertrophy and electrically evoked strength. Hand function was also observed with the use of this technique, decreasing the time, and increasing speed of tasks. Additionally, improvement in FMD during EMS and BFR may lead to improvements in muscle size. EMS with BFR was concluded to be safe and feasible when used in rehabilitation for those with SCI.

The use of EMS and BFR on the upper extremities, as done in the study by Gorgey et al. (32) may provide results that are different than our current study, utilizing EMS and

BFR on the lower extremities. These differences could be due to the fact that the lower extremities in individuals with disabilities often experience muscular atrophy from disuse. As mentioned previously, individuals that experience limitations in ambulatory function go through alterations in the body from disuse and loss of function such as decreases in muscle mass, alterations in metabolism, and vasculature changes such as stiffening of the arteries (1). Gorgey et al. (32) mentioned an additional study, conducted by Stoner et al. (33) that analyzed upper vs lower extremity arterial function following SCI. Stoner et al. found that individuals that experience SCI often have greater decreases in FMD and arterial range below the lesion level compared to above (33). The article states, "Patients with paraplegia mostly rely on upper body function for performing daily activities. Because individuals with SCI actively use their upper extremities, blood flow patterns may be such that the blood vessels retain their functional function status because of normal shear stressor activity" (34, 35). The results of the Gorgey et al. study additionally found that there was a greater lactate accumulation in paralyzed muscle from the EMS condition (32). Therefore, utilizing EMS in combination with BFR in the lower extremities may also lead to great lactate accumulation.

Overall, the lower limbs of those that use wheelchairs for ADL often experience disuse atrophy and loss of function, leading to decreased muscle mass and metabolic activity, as well as altered properties of the muscles and vasculature. Therefore, unlike the upper extremities, the lower extremities may experience different levels of fatigue as well as neuromotor and metabolic activity. The results of the current study may vary drastically, due to the use of the untrained limbs of those that use wheelchairs for ADL. On the other hand, the use of EMS and BFR in combination has the potential to increase

muscle hypertrophy and strength as well as improve vasculature, contributing to improved function, especially among individuals that use wheelchairs for ADL. Such improvements may also contribute to improving one's overall quality of life.

Last, Gorgey et al. study (32) also reported that despite including participants with high lesion levels (above C8 and C3-L2), there were no experienced incidences of AD. This finding is noteworthy to mention as it provides support for the safety of our current study and the feasibility of the use of EMS+BFR in this population.

CHAPTER 2

PURPOSE

BFR has been shown to create hypoxic environments in occluded limbs that leads to a buildup of metabolites. This accumulation of metabolites elicits increases in GH, which contributes to increases in muscle CSA, i.e., *hypertrophy,* observed with long-term (training) adaptations to resistance exercise. Pairing EMS with BFR may lead to synergistic hemodynamic and skeletal muscle adaptations, producing even greater increases in muscle fiber hypertrophy than either modality alone. It is critical to understand whether combined EMS and BFR elicits greater hemodynamic and skeletal muscle responses acutely when compared to either modality alone, for understanding potential synergistic effects that may be observed with longer-term training adaptations. Therefore, the purpose of this study was to compare acute hemodynamic and skeletal muscle responses to EMS with and without the addition of BFR among individuals that primarily use wheelchairs for ADL. Acute hemodynamic responses were analyzed by determining alterations in blood flow and lumen diameter, as well as changes in HR, BP, muscle CSA and metabolic stress after EMS with or without BFR. Over time, this method of training may have the potential to lead to increased blood vessel function and muscle hypertrophy. Therefore, the specific aims and corresponding hypotheses are as follows:

Specific Aims and Hypotheses

Aim 1: Determine whether the addition of BFR treatment during EMS on daily wheelchair users significantly enhances hemodynamic responses—increased arterial blood flow post-occlusion (i.e., reactive hyperemia), lumen diameter—in the lower limbs of wheelchair users, as well as increases in HR and BP compared to either of the conditions (EMS or BFR) alone.

We *hypothesized* that the combination of EMS+BFR will elicit greater hemodynamic responses, i.e., reactive hyperemia and lumen diameter, as well as increases in HR and BP among wheelchair users when compared to EMS or BFR alone.

Aim 2: Determine whether the addition of BFR with EMS induces greater skeletal muscle responses—muscle cell swelling (increases in muscle CSA) as seen through ultrasound circumference measurements —in the occluded limbs of wheelchair users compared to either of the conditions (EMS and BFR) alone.

We *hypothesized* that the combination of EMS+BFR will induce greater skeletal muscle responses, i.e., muscle cell swelling measured by changes in muscle CSA, in the occluded limbs of wheelchair users when compared to either of the conditions (EMS and BFR) alone.

Aim 3: Determine whether the addition of BFR with EMS elicits greater skeletal muscle metabolic stress—increases in blood lactate levels—among wheelchair users compared to either of the conditions (EMS and BFR) alone.

We *hypothesized* that the combination of EMS+BFR will elicit greater skeletal muscle metabolic stress, i.e., increases in blood lactate levels, among wheelchair users compared to either of the conditions (EMS and BFR) alone.

Aim 4: Determine whether the addition of BFR at 40% occlusion with EMS can safely be utilized among wheelchair users below the level of T6—without eliciting any incidences of AD.

We *hypothesized* that the combination of EMS+BFR may be used safely among wheelchair users below the level of T6—without eliciting any incidences of AD.

Significance of the Thesis

The use of EMS and BFR methods respectively have been proven to improve the musculature, vasculature, and overall health of those that use wheelchairs on a daily basis. The use of EMS+BFR in conjunction over time may lead to increased blood vessel function and muscle hypertrophy that will contribute to improved health and quality of life.

The use of EMS+BFR specifically in the lower extremities of those that use wheelchairs for ADL is a method that has not been greatly examined. Although this has been explored in the upper extremities of those with para- and tetraplegia, the use of EMS and BFR in the lower extremities may provide different results due to disuse atrophy and loss of function. The current study utilized participants with a wide range of disabilities, duration of injury, and included the participation of both genders. The use of the Finapres NOVA (Finapres Medical Systems B.V., Netherlands) in our study provided non-invasive, continuous, real-time measurements of arterial hemodynamic parameters that are both detailed and accurate.

Longitudinal studies further pursuing the use of this method should focus on the long-term adaptations that occur with continued use of EMS+BFR training in this population. Utilizing the findings of our study in carrying out a long-duration training

program may provide great physiological benefits and may lead to improvements in function in this population. This may help attenuate the progression of muscular atrophy and many other physiological adaptations that occur from disuse of the lower extremities. If future longitudinal studies demonstrate that EMS+BFR leads to improvements of the vasculature and muscles in this population, standardized, long-term training programs should be developed. This should be a program that is easily obtainable, accessible, and affordable for the personal in-home use of individuals that use wheelchairs daily. This may include using devices and equipment such as low-cost personal EMS units or BFR bands. The safety and validity of the use of that equipment should be verified before carrying out the training in unsupervised settings. The development of such a training program may have the potential to greatly improve the function and quality of life of many individuals throughout this population.

CHAPTER 3

METHODS

Participants

Participants in the study included adults that use a wheelchair as their main mode of completing activities of daily living. Participants were required to have a lower extremity physical impairment, specifically below the level of T6 for the purpose of reducing the risk of AD, and as mentioned previously must also use a wheelchair primarily on a daily basis. An *a priori* power analysis was conducted using G*Power (version 3.1.9.7) with an effect size of 0.71 based off current BFR research and past literature of studies done within this population (3). To achieve this effect size at an alpha level of 0.05 and power (1-β) of 0.80, a sample of 9 participants was required. Thus, a sample of 10 participants recruited from the University of Alabama Adapted Athletics program were utilized for this study (Table 1). All participants considered for inclusion were required to be between the years of 18 and 45, and have no signs, symptoms, or diagnoses of cardiovascular, metabolic, or renal disease. Participants must have had no reports of health complications for at least 6 months prior to the start of the study. Health complications for this study were defined as cardiovascular health issues that may put the participant at risk for the study, which included but were not limited to DVT, cardiovascular disease, uncontrolled hypertension (SBP ≥130 mmHg or DBP ≥80 mmHg) (36), blood-clotting disorders, or any episode of AD. In addition, individuals with a SBP of greater than 150 mmHg prior to the start of each study visit were excluded. In all of the screened

participants, one individual did not meet the above study eligibility criteria, was excluded, and did not participate in any part of the study. Although there were no instances, if at any time during the visit the participant experienced SBP greater than 160 mmHg, the experimental visit was to be immediately discontinued. Finally, individuals that were taking antihypertensive medications (or medications used to treat hypertension) were also excluded.

Table 1 Participant characteristics (N=10)

Participant ID	Age	Height (cm)	Weight (kg)	Body Fat (%)	BMI	BP (mmHg)	Level	Milliamperage (mA)
1	23	160.02	58.6	11.9	22.9	105/70	T11-T12 ◊	45
2	23	160.02	61.7	5.4	24.1	127/72	L4*	20
3	27	191.77	106.1	21.3	29.1	132/74	L3†	46
4	20	182.88	93.6	17.6	27.9	119/67	L5*	27
5	22	175.26	85	12.2	27.6	114/67	T12 ◊	65
6	23	132.08	41	11.9	23.6	106/68	L4*	10
7	23	161.29	55.5	9.8	21.3	106/64	L2-L3†	58
8	18	144.78	54.8	25.4	26.2	113/66	L4-L5*	20
9	19	165.1	82.8	21.0	30.3	111/70	L3-L4*	23
10	27	154.94	49.7	13.5	20.6	108/71	L4-L5*	15
Minimum	18	132.1	41.0	5.4	20.6	105/64	-	10
Maximum	27	191.8	106.1	25.4	30.3	132/74	-	65
Mean	22.5	162.8	68.9	15.0	25.4	114/69	-	32.9
Std. Deviation	2.99	17.48	21.42	6.14	3.34		-	19.12

*Congenital disability, ◊ complete level injury, † incomplete level injury

Experimental Design

The proposed study was conducted using a randomized, crossover, repeated measures experimental design. Participants that were screened for inclusion completed 3 study visits consisting of different data experimental conditions over a 1–3-week time frame. Participants were asked to come in for their visit around the same time of day (within a 1- or 2-hour window) for each visit, to reduce variability in BP and hemodynamic responses. Visits were separated by at least 72 hours to ensure adequate recovery time from the physiological effects of BFR.

Study Measurements

Prior to participation in the study, all participants went through an examination by Dr. Brett Bentley for medical clearance to ensure safety. All measurements and data collection were gathered in the University of Alabama Exercise Physiology Laboratory in Wade Hall. During the first visit, participants gave their informed consent and were asked to fill out a 24-hour fluid and physical activity recall form. Participant anthropometric measurements were taken at the start of visit one. Weight (kg) and height (cm) measurements were be performed using methodology and equipment specifically for individuals with SCI and/or wheelchair users. Participants mounted a wheelchair scale (Adam Equipment, Oxford, CT) while seated in their wheelchairs, the weight (of participant and wheelchair) was recorded, and the participants were then asked to safely transfer to an examination table. The weight of the wheelchair alone was then measured and recorded. The participant's body weight was calculated as the difference between the weight obtained for the participant in their wheelchair and the wheelchair alone. Participants were then asked to transfer to the medical procedure chair. Since included participants were required to be daily wheelchair users, the following procedures occurred to ensure safe transfer of the participant to the medical procedure chair: 1) The wheelchair was aligned parallel to the medical chair and the wheels were locked to stabilize the wheelchair. 2) The medical examination table had the ability to raise up and down. It was lowered all the way down to facilitate ease of participant transfer. 3) At least 1 member of the research team, who was present at the time of this procedure, was available to assist with transfer to the medical procedure chair if needed. The height of the participant was then measured using a tape measure while they were in the supine position on the

examination table. Participants did not exercise during any visit but sat upright in the medical procedure chair throughout the duration of the visit to maintain consistency of anatomical positioning and to decrease the risk of AD. Body composition measurements, such as body fat percentage (%) and body mass index (BMI), were taken by conducting a bioimpedance analysis with a handheld OMRON analyzer (Omron Electronics, Kyoto, Japan) while participants were in the upright seated position on the medical procedure chair. Baseline resting BP and HR were taken at visit 1. Resting BP was then taken at the start of each subsequent visit. BP was measured 3 times in the left arm at the brachial artery, 1-minute apart, with an automated BP monitor (Welch Allyn Spot Vital Signs, Hill-Rom, Chicago, IL). The BP readings were collected, and if within 5 mmHg for both SBP and DBP, the average of 3 BP readings were used (36). Participants were outfitted with HR monitors during each visit, as well as the Finapres NOVA device during each visit for noninvasive, continuous hemodynamic monitoring of HR and BP taken at the finger. Different timepoints were used for the statistical analyses of HR, SBP, DBP, and MAP. Timepoints from pre- to 10-15 minutes from start were used to reflect responses from within the trial, and from pre- to 5 minutes following the end of the trial to reflect recovery responses. Baseline blood lactate levels were evaluated immediately following baseline BP measurement. Baseline blood flow and muscle CSA measurements of the right leg were then taken using ultrasonography (Philips IU22, Stockton, CA). Blood flow measurements were taken at the posterior tibial artery. Muscle analysis provided the VM CSA. B-mode ultrasonography was used to gather images of the VM which were then traced on the computer by the imaging program Image-J (version 1.53) to gather CSA values. The measurement site was measured on each participant halfway from the patella

to the bottom of the BFR cuff and was marked with a skin marker by a dashed line horizontally across the participant's thigh. To ensure consistency in data collection, all measurement site locations were gathered, and were taken in the same location across all visits. Measurements that were taken during each visit included pre- and post-trial blood flow analysis and muscle CSA; lactate (mmol) levels pre- and post-trial; HR pre-, post- and 5 minutes following with the HR monitor; and BP prior to, immediately following, every 5 minutes throughout, and 5 minutes following completion of the trial for each condition. As mentioned previously, HR and BP were measured continuously as well with the Finapres NOVA (Figure 1).

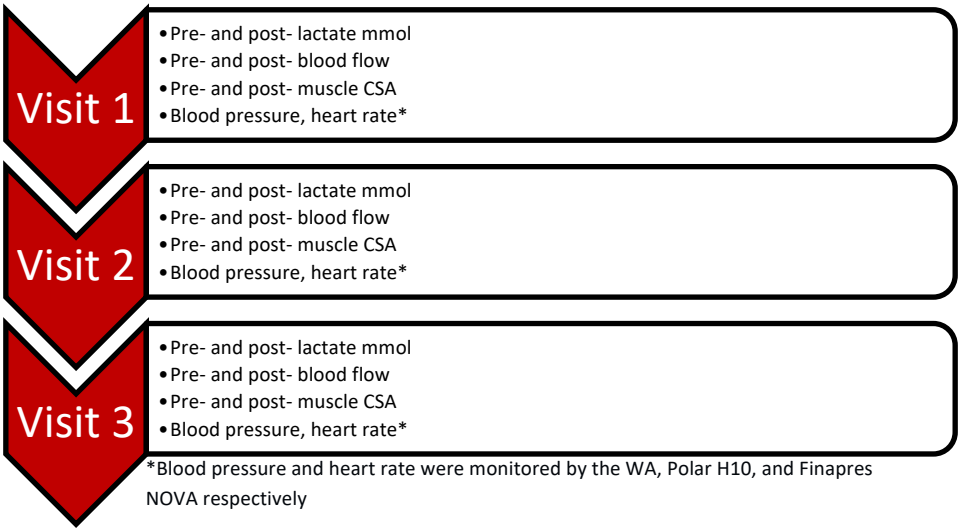

Figure 1 Measurements taken during each visit

Study Visits

Participants engaged in three separate experimental visits: EMS (EMS only), BFR (BFR only), and EMS+BFR (Figure 2). For all participants, the order for the EMS, BFR, or EMS+BFR applications was randomized on Microsoft Excel prior to participation in the

study to eliminate training/learning bias. Therefore, participants were randomized into one of the three conditions (Figure 2) for visit 1 and had baseline measurements gathered prior to the application of either the BFR, EMS, or EMS+BFR condition. This was followed by application of the corresponding condition, which lasted a duration of 20 minutes. Re-evaluation of the aforementioned variables took place immediately following completion of the trial protocol. During the second and third visits, participants were asked to re-initial their original consent document if they wished to continue participation and filled out another 24-hour recall form at each visit. They then followed the same procedures as visit 1, but took part in one of the other two remaining conditions not already participated in. The third visit evaluated the final remaining application.

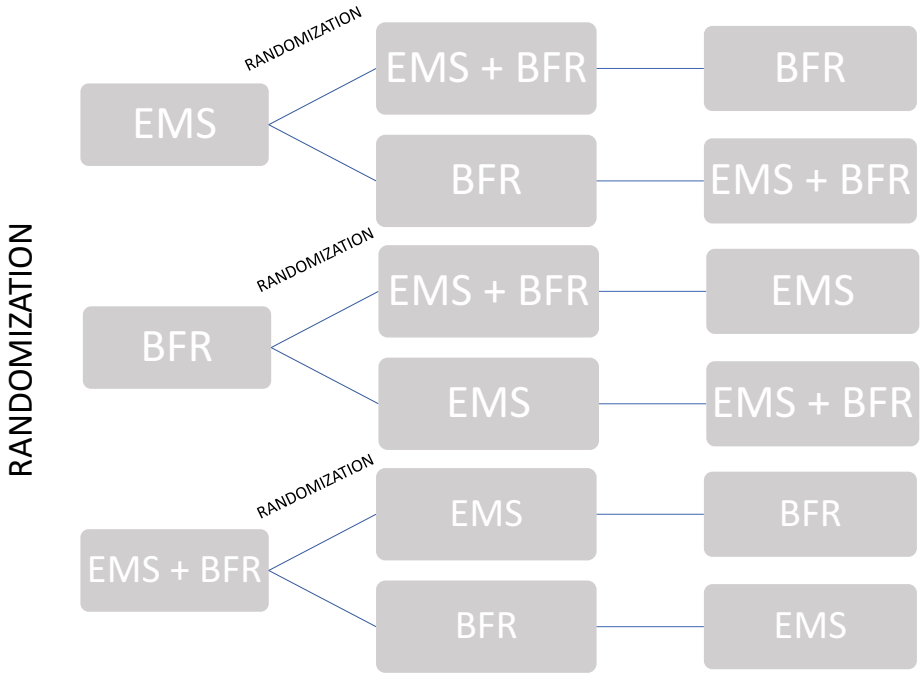

Figure 2 Randomization of participant conditions

Blood Flow Restriction Application

The Delfi PTS II (Delfi Medical, Vancouver, B.C., Canada) is the BFR device that was used for this study. The device is a Food and Drug Administration (FDA) approved blood flow restriction/tourniquet system that is commonly used in physical therapy, athletic training, and in research. This BFR device uses an inflatable tourniquet, much like a BP cuff, to induce vascular occlusion in a limb. The system first determined pressure needed for 100% arterial occlusion and used this information to calculate user-specific occlusion percentage. This specific system has a sensor that regulates pressure during muscular movement to maintain a constant pressure, rather than allow a spike in pressure during exercise. The BFR application was applied to both the combined EMS+BFR group as well as the group with only BFR. For the BFR application, the BFR cuff was applied to the participant's right thigh, approximately 1/3 of the way down the participant's thigh. The thigh was measured from the superior border of the patella to the inguinal crease to determine BFR cuff placement ⅓ of the way down the thigh. BFR cuffs were administered to participants according to size per the manufacturer's recommendation. The cuff was then inflated to 40% of pre-determined limb occlusion pressure (LOP) for 8 minutes. The cuff remained inflated for the full 8 minutes, was followed by 4 minutes of deflation, and then another 8 minutes of inflation following the deflation period. Although longer occlusion times have been determined to be safe, standard clinical protocol for BFR use suggests a standard occlusion time of 8 minutes.

Electrical Muscular Stimulation Application

EMS was performed during combined EMS+BFR visits, as well as EMS only visits. The EMS device that was used in this study was the "InTENSity Select Combo II"

model DI2195 (Richmar Medical Company, Clayton, MO). The device utilized an internal rechargeable battery that was charged on a daily basis. The condition utilized 4 total (2-inch x 2-inch) EMS electrodes, placed proximally on the vastus lateralis and rectus femoris and distally on the vastus lateralis and vastus medialis of the dominant leg, per standard EMS protocol for training the quadriceps. Proximally, the electrodes were placed within an inch above the BFR cuff, and distally within an inch above the patella. The stimulation was performed using a frequency 30Hz and 400 microsecond biphasic pulses with a ramp up time of 3 seconds, contraction time of 30 seconds, and a relaxation time of 5 seconds. The stimulation pattern was continuous for the duration of each treatment, which was 20 minutes. The mA range for the device was from 0-100, but for each participant was slowly increased from 0 one point at a time until extension of the leg or an increase of mA did not elicit further seen muscular contraction. The mA was recorded for each participant and was kept consistent in both sessions of EMS use.

Minimizing risk of Autonomic Dysreflexia

Possible symptoms of AD include headache, piloerection (goosebumps), profuse sweating above level of SCI with lack of sweating below that level, hypertension, and bradycardia (18). Steps that were taken to reduce the risk of AD incidence consisted of the exclusion of individuals with injury level at or above T6, those with SBP greater than 150mmHg prior to the start of the study, and those that experienced SBP greater than 160mmHg at any point during the study. Although there were no incidences of SBP at or greater than 160mmHg, if the participant did experience a BP at that level during the trial, it was to immediately be stopped (18). Prior to the start of each data collection visit, participants were asked to completely void the bladder as an additional safety precaution.

Participants were seated in an upright position on the medical examination table throughout the trial, BP was continuously monitored with the Finapres NOVA, and participants were monitored for the development of any symptoms of AD (18).

Statistical Analyses

Blood lactate, blood flow parameters, muscle CSA

To evaluate if there are significant differences between pre- and post-trial among variables of blood lactate, blood flow parameters, and muscle CSA for each condition, and between conditions, a two-way repeated measures analysis of variance (ANOVA) was used. For significant effects, pairwise comparisons with Bonferroni multiple comparison adjustments were explored. To evaluate the post- to pre- change among variables of blood lactate, blood flow parameters, and muscle CSA for each condition, a one-way repeated measures ANOVA was used. Due to the multiple number of groups and timepoints, a paired samples t-test was used to individually determine if there were differences in timepoints pre- to post-trial within each individual condition for variables of blood lactate, blood flow parameters, and muscle CSA.

HR, SBP, DBP, MAP

A one-way ANOVA with a Bonferroni post-hoc analysis was performed to evaluate pre-trial HR, SBP, DBP, and MAP values measured at the start of each condition. Results revealed significant differences in pre-trial values between the 3 conditions. To account for these differences, change scores, expressed as the percentage change from pre-trial ([(post-pre)/pre] × 100), were calculated and used to analyze HR, SBP, DBP and MAP data. The timepoints of interest were: pre- to during the trial (10-15 minutes from

start) and pre- to recovery time post-trial (5 minutes following the end) for each condition. Two-way-ANOVAs were used to evaluate changes in these variables by condition, time, or condition by time interactions. For significant main and interaction effects, pairwise comparisons with Bonferroni multiple comparison adjustments, were further explored.

For statistical analyses of all study variables, an alpha level of 0.05 was used to determine statistical significance. The data results are being reported as mean (M) ± standard deviation (SD) for blood lactate, blood flow parameters, and VM CSA. HR, SBP, DBP and MAP data results are being reported as mean difference (MD) and confidence interval (CI). Partial eta squared values (η^2 partial) were considered in addition to alpha level, as many large values of η^2 partial ($\eta^2 > 0.14$) were found throughout our data. This suggests that even though our data was underpowered due to sample size, there was a large effect of time or condition on the variables. Statistical Processes for the Social Sciences (SPSS) software (version 28) and Microsoft Excel (version 16.58) were used to complete the analysis of the data gathered from the study.

CHAPTER 4

RESULTS

Blood lactate, posterior tibial artery distance and area, volume flow, time averaged mean velocity (TAMV), or VM CSA: Main Effects

When conducting a two-way ANOVA, there was no significant difference observed when analyzing the average response of blood lactate, posterior tibial artery distance and area, volume flow, time averaged mean velocity (TAMV), or VM CSA pre- vs. post- by each condition or by time (Table 4).

Interactions: When conducting a two-way ANOVA, there was no time × condition interaction throughout any of the groups for blood lactate, posterior tibial artery distance and area, volume flow, TAMV, or VM CSA (Table 4).

The one-way ANOVA and paired samples t-tests results for each outcome will be discussed in greater detail below.

Paired Samples T-Test:

When analyzing mean change within each individual condition through a paired samples t-test, within the BFR only condition, there was a significant increase found in blood lactate (Figure 3), a significant decrease in posterior tibial artery distance and area, and a trending significant decrease in volume flow pre- to post- within the BFR only condition (Table 2). Within the combined EMS+BFR condition there was a significant increase found in blood lactate (Figure 3). There was no significant change in blood lactate over time within the EMS condition (Table 2). There was no significant change in posterior tibial artery distance and area or volume

flow pre- to post- within the EMS only and EMS+BFR conditions (Table 2). For TAMV and VM CSA, when analyzing within each individual condition for mean change, there was no difference seen over time within any of the conditions (Table 2).

Table 2 Paired samples t-test: lactate, blood flow parameters and muscle cross-sectional area (N=10):

Variable	Condition	Pre-Condition	Post-Condition	*t Stat*	*P*
Lactate (mmol)	EMS	1.3 ± 0.7	2.3 ± 6.6	-1.01	0.331
	BFR	0.9 ± 0.2	1.5 ± 0.4	-2.94	**0.017**
	EMS + BFR	1.0 ±0.05	1.4 ± 0.1	-2.73	**0.023**
Post. Tib. A. Dist. (cm)	EMS	0.222 ± 0.002	0.226 ± 0.004	-0.77	0.460
	BFR	0.215 ± 0.0003	0.207 ± 0.0002	2.47	**0.036**
	EMS + BFR	0.207 ± 0.00003	0.216 ± 0.0007	-1.26	0.241
Post. Tib. A. Area (cm^2)	EMS	0.040 ± 0.0005	0.043 ± 0.0008	-0.89	0.396
	BFR	0.037 ± 0.00003	0.034 ± 0.00002	2.67	**0.026**
	EMS + BFR	0.034 ± 0.000004	0.037 ± 0.00008	-1.28	0.234
TAMV (cm/s)	EMS	7.7 ± 73.6	4.3 ± 9.0	1.61	0.142
	BFR	6.1 ± 20.8	5.1 ± 12.9	1.49	0.169
	EMS + BFR	7.1 ± 75.2	5.4 ± 24.4	0.88	0.403
Vol Flow (cc/min)	EMS	17.0 ± 290.4	13.0 ± 286.9	0.65	0.530
	BFR	13.7 ± 109.5	10.5 ± 63.0	1.99	0.078
	EMS + BFR	14.7 ± 347.2	12.7 ± 178.7	0.41	0.694
VM CSA (cm^2)	EMS	8.6 ± 15.9	8.2 ± 16.9	0.62	0.552
	BFR	8.1 ± 17.1	8.5 ± 20.0	-0.54	0.599
	EMS + BFR	9.4 ± 21.8	9.0 ± 12.0	0.49	0.637

BFR, Blood flow restriction. EMS, Electrical muscular stimulation.
EMS + BFR, Blood flow restriction and electrical muscular stimulation combined.
TAMV, Time-averaged mean velocity. VM CSA, Vastus medialis cross-sectional area.
* Greenhouse-Geisser correction applied.

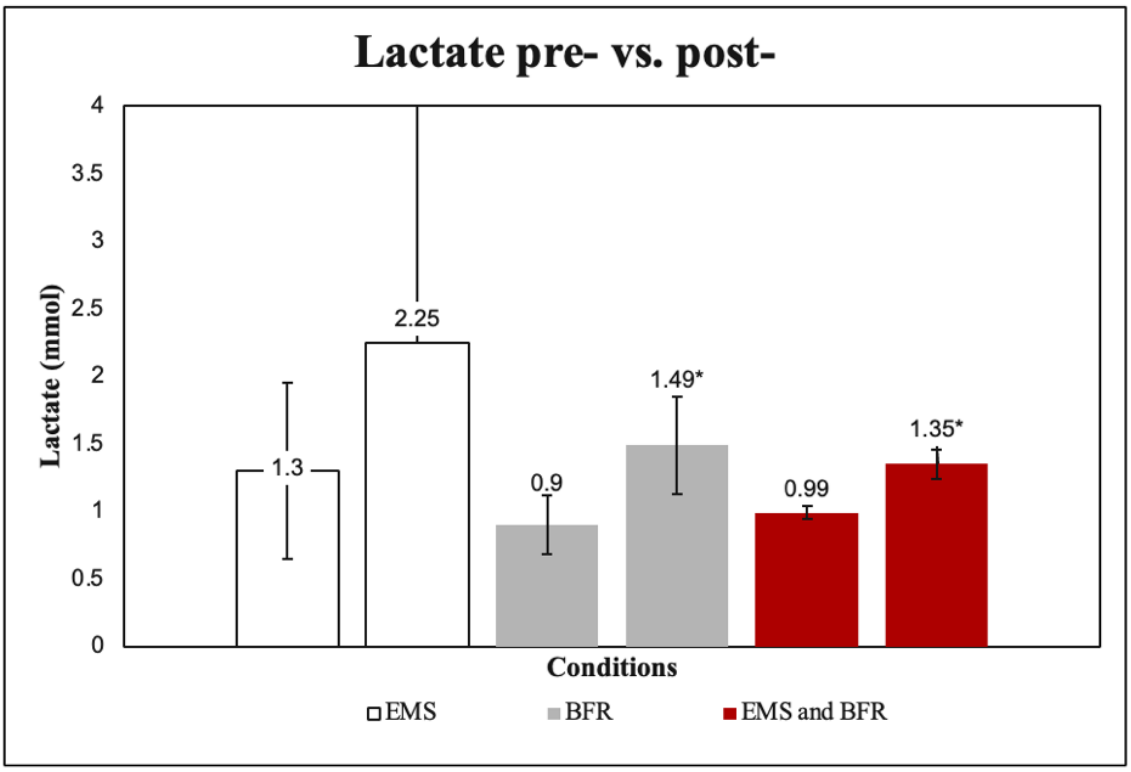

Figure 3 Changes in blood lactate (mmol) over time, broken down by condition
*Significantly different than pre- condition ($p<0.05$)

One-Way ANOVA

There was no significant difference in the mean value of pre- vs. post- change in blood lactate, posterior tibial artery distance and area, volume flow, TAMV, or VM CSA between conditions when utilizing a one-way ANOVA (Table 3).

Table 3 One-way repeated measures ANOVA: lactate, blood flow parameters and muscle cross-sectional area (N=10):

			Condition Effect		
Variable	**Condition**	**Descriptive Statistics**	***F***	**η^2 partial**	***P***
Lactate (mmol)	EMS	0.95 ± 2.9	0.30	0.32	0.600*
	BFR	0.59 ± 0.6			
	EMS + BFR	0.36. ± 0.4			
Post. Tib. A. Dist.	EMS	0.004 ± 0.015	3.07	0.25	0.071
(cm)	BFR	-0.009 ± 0.011			
	EMS + BFR	0.009 ± 0.023			
Post. Tib. A. Area	EMS	0.002 ± 0.008	2.88	0.24	0.082
(cm^2)	BFR	-0.003 ± 0.004			
	EMS + BFR	0.003 ± 0.008			
TAMV	EMS	-3.4 ± 6.7	0.72	0.07	0.502
(cm/s)	BFR	-1.0 ± 2.2			
	EMS + BFR	-1.7 ± 6.2			
Vol Flow	EMS	-4.0 ± 19.5	0.06	0.01	0.946
(cc/min)	BFR	-3.2 ± 5.0			
	EMS + BFR	-2.0 ± 15.7			
VM CSA	EMS	-0.39 ± 2.01	0.44	0.05	0.653
(cm^2)	BFR	0.35 ± 2.04			
	EMS + BFR	-0.35 ± 2.25			

BFR, Blood flow restriction. EMS, Electrical muscular stimulation. EMS + BFR, Blood flow restriction and electrical muscular stimulation combined. TAMV, time-averaged mean velocity. CSA, cross-sectional area. η2 partial, Partial eta effect size.

*Greenhouse-Geisser correction applied.

Table 4 Two-way repeated measures ANOVA: lactate, blood flow parameters and muscle cross-sectional area (N=10):

				Treatment Effect			Time Effect			Interaction		
Variable	**Condition**	**Pre-treatment**	**Post-treatment**	**F**	**$\eta^2_{partial}$**	***P***	***F***	**$\eta^2_{partial}$**	***P***	***F***	**$\eta^2_{partial}$**	***P***
Lactate (mmol)	EMS	1.3 ± 0.8	2.3 ± 2.6	2.09	0.19	0.179*	3.70	0.29	0.291	0.30	0.03	0.600*
	BFR	0.9 ± 0.5	1.5 ± 0.6									
	BFR and EMS	0.9. ± 0.2	1.4 ± 0.3									
Post. Tib. A. Dist (cm)	EMS	0.222 ± 0.05	0.226 ± 0.06	0.75	0.08	0.415*	0.16	0.02	0.697	3.07	0.25	0.071
	BFR	0.215 ± 0.02	0.207 ± 0.01									
	BFR and EMS	0.207 ± 0.01	0.216 ± 0.03									
Post. Tib. A. Area (cm^2)	EMS	0.040 ± 0.02	0.043 ± 0.03	0.81	0.08	0.395*	0.29	0.03	0.603	2.88	0.24	0.082
	BFR	0.037 ± 0.01	0.034 ± 0.004									
	BFR and EMS	0.034 ± 0.002	0.037 ± 0.01									
TAMV (cm/s)	EMS	7.7 ± 8.6	4.3 ± 3.0	0.17	0.02	0.845	2.71	0.23	0.134	0.72	0.07	0.502
	BFR	6.1 ± 4.6	5.1 ± 3.6									
	BFR and EMS	7.1 ± 8.7	5.4 ± 4.9									
Vol Flow (cc/min)	EMS	17.02 ± 17.0	13.00 ± 16.9	0.44	0.05	0.652	0.99	0.10	0.347	0.06	0.01	0.946
	BFR	13.66 ± 10.5	10.49 ± 7.9									
	BFR and EMS	14.71 ± 18.6	12.69 ± 13.4									
VM CSA (cm^2)	EMS	8.6 ± 4.0	8.2 ± 4.1	1.24	0.12	0.312	0.10	0.01	0.765	0.44	0.05	0.653
	BFR	8.1 ± 4.1	8.5 ± 4.5									
	BFR and EMS	9.4 ± 4.7	9.0 ± 3.5									

BFR, Blood flow restriction. EMS, Electrical muscular stimulation. BFR+EMS, Blood flow restriction and electrical muscular stimulation combined. TAMV, Time-averaged mean velocity. CSA, cross-sectional area. η2 partial, Partial eta effect size.

* Greenhouse-Geisser correction applied.

HR, SBP, DBP, and MAP: Main Effects

When analyzing percent change in HR, SBP, and DBP with a two-way ANOVA, there was a main effect of time (Table 5). Across all conditions, the average percent change in HR in the 5 minutes following the trial was lower than percent change 10-15 minutes within the trial (Table 5). Across all conditions, there was a statistically significant difference between average percent change in SBP as well as DBP in the 5 minutes following the trial and 10-15 minutes within the trial (Table 5). There was no main effect of condition observed for HR, SBP, or DBP. There was no main effect of time observed for MAP over time or between conditions (Table 5).

Interactions: When analyzing percent change in HR, SBP, and DBP with a two-wav ANOVA, there was a significant interaction of time × condition (Table 5). There was no interaction of time × condition observed for MAP (Table 5).

The two-way ANOVA results for each outcome will be discussed in greater detail below. Of note, several variables that were trending towards significance had large η^2 partial values, suggesting a large effect of condition, time, or condition × time interaction (Table 5). It is also noteworthy to mention that safety precautions to prevent incidences of AD were successful, as no episodes of AD were observed pre, during, or post-trial for any condition, including BFR at 40% of LOP.

Heart Rate

Percent changes in HR from pre-trial were not different 10-15 minutes within the trial or in the 5 minutes following the trial in the BFR only and EMS only conditions (Table 5). During the combined EMS+BFR condition, percent changes in HR were significantly higher 10-15 minutes within the trial compared to the 5 minutes following the trial (-11.3% [-21.1, -1.5])

(Figure 4). Although not significant, in the 5 minutes following the trial, percent change in HR during the BFR condition was higher than during the EMS+BFR condition (10.4% [-0.3, 21.1]) (Figure 4).

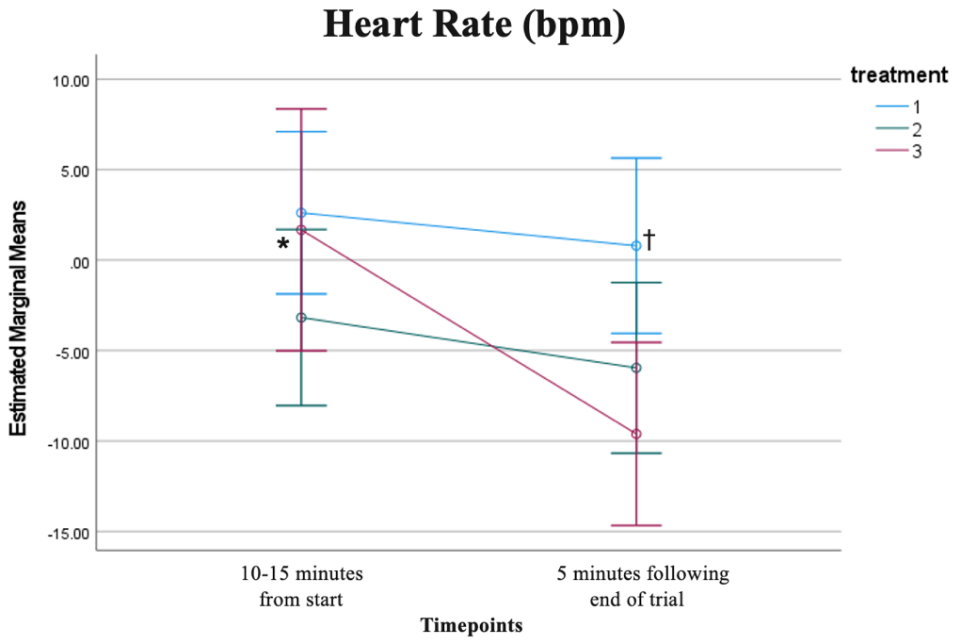

Figure 4 Heart rate response (% change) from pre- to within trial and following the trial

Treatment 1=BFR, 2=EMS, 3=EMS+BFR (combined). Time 1: Timepoint pre- to 10-15 minutes from start (% change). Time 2: pre- to 5 minutes following the end of the trial (% change).

* % change from baseline different within the trial compared to post-trial for EMS+BFR, p=0.030.

† BFR tended to be different than EMS+BFR, p=0.057

Systolic Blood Pressure

Percent changes in SBP from pre-trial were not different 10-15 minutes within the trial or in the 5 minutes following the trial in the BFR only and EMS only conditions (Table 5). Within the combined EMS+BFR condition, percent changes in SBP were significantly higher 10-15 minutes within the trial compared to the 5 minutes following the trial (-18.4% [-27.1, -9.7]) (Figure 5). Percent change in SBP in the 5 minutes following the trial during the BFR condition was higher than during the EMS+BFR condition (15.9% [0.002, 31.7]) (Figure 5).

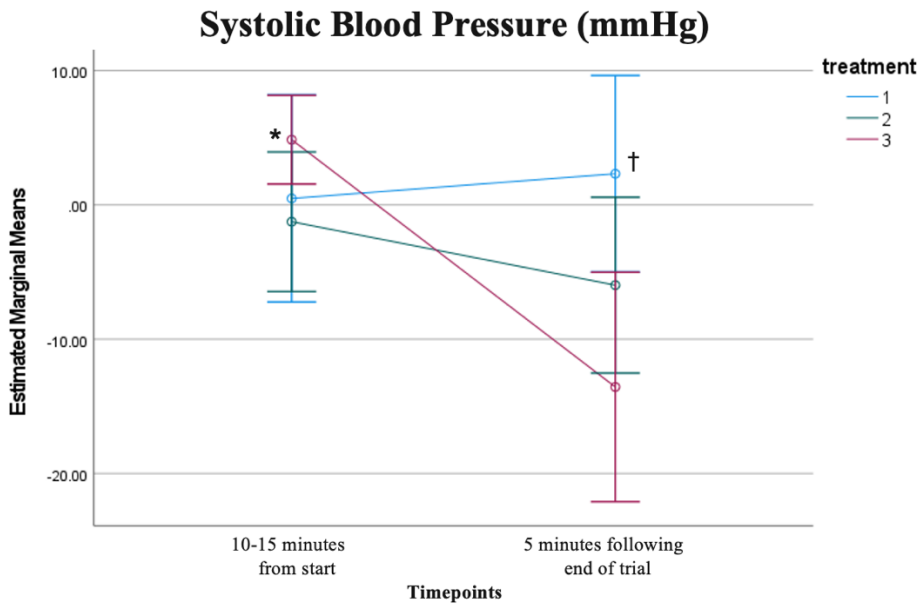

Figure 5 Systolic blood pressure response (% change) from pre- to within trial and following the trial

Treatment 1=BFR, 2=EMS, 3=EMS+BFR (combined). Time 1: Timepoint pre- to 10-15 minutes from start (% change). Time 2: pre- to 5 minutes following the end of the trial (% change).

* % changes were significantly higher within the trial compared to post-trial, p=0.002.

† marginally significantly higher than EMS+BFR, p=0.05.

Diastolic Blood Pressure

Percent changes in DBP from pre-trial were not different 10-15 minutes within the trial or in the 5 minutes following the trial in the BFR only or EMS only conditions (Table 5). Within the EMS+BFR condition, percent changes in DBP were significantly higher 10-15 minutes within the trial compared to the 5 minutes following the trial (-22.9% [-37.7, -8.0]). Percent change in DBP in the 5 minutes following the trial during the BFR condition was higher than during the EMS+BFR condition (22.0% [-1.4, 45.4]), but did not reach statistical significance (Table 5).

Mean Arterial Pressure

Percent changes in MAP from pre-trial were not different 10-15 minutes within the trial or in the 5 minutes following the trial in the BFR only and EMS only conditions (Table 5).

Although the time × condition interaction was not significant, within the EMS+BFR condition, changes in MAP were significantly higher 10-15 minutes within the trial compared to 5 minutes following the trial (-3.9% [-6.9, -0.9]). No other differences were observed.

Table 5 Two-way repeated measures ANOVA: Heart rate, systolic and diastolic blood pressure, mean arterial pressure % change from pre- to timepoints of 10-15 minutes from start and 5 minutes following completion of trial (N=9).

		10-15 min	20-15 min	Condition Effect			Time Effect			Condition*Time		
Variable	**Condition**	**from start**	**from start**	**F**	**η^2 partial**	***P***	***F***	**η^2 partial**	***P***	***F***	**η^2 partial**	***P***
Heart Rate	BFR	71.4 ± 6.9	70.2 ± 7.9	2.056	0.227	0.165	5.912	0.458	**0.045**	5.15	0.424	**0.021**
(bpm)	EMS	74.9 ± 10.1	72.6 ± 8.1									
	BFR and EMS	71.9 ±8.2	70.7 ± 9.0									
Systolic BP	BFR	130.8 ± 15.2	133.0 ± 13.1	1.584	0.185	0.240	13.901	0.665	**0.007**	10.668	0.604	**0.002**
(mmHg)	EMS	138.9 ± 10.4	132.6 ± 15.4									
	BFR and EMS	129.2 ± 13.9	125.2 ± 12.8									
Diastolic BP	BFR	79.1 ± 9.4	80.6 ± 8.4	2.154	0.235	0.153	26.767	0.793	**0.001**	6.866	0.495	**0.008**
(mmHg)	EMS	82.2 ± 13.4	75.7 ± 18.1									
	BFR and EMS	76.6 ± 8.5	72.9 ± 7.1									
Mean Arterial	BFR	98.8 ± 12.6	100.8 ± 11.0	1.924	0.216	0.183	3.463	0.331	0.105	4.726	0.403	0.063*
Pressure	EMS	104.7 ± 11.5	97.7 ± 14.8									
(mmHg)	BFR and EMS	95.9 ± 9.5	92.3 ± 8.2									

BFR, Blood flow restriction. EMS, Electrical muscular stimulation. BFR+EMS, Blood flow restriction and electrical muscular stimulation combined.
BP, blood pressure. bpm, beats per minute. mmHg, millimeters mercury. η2 partial, Partial eta effect size.
* Greenhouse-Geisser correction applied.

CHAPTER 5

DISCUSSION, LIMITATIONS, & CONCLUSION

Discussion

The primary objectives of the study were to determine whether the addition of BFR treatment during EMS on daily wheelchair users has an increased effect on hemodynamics, skeletal muscle swelling, and skeletal muscle metabolic stress responses in the lower limbs of wheelchair users compared to either of the treatments (EMS or BFR) alone.

When analyzed within each individual condition for mean change with a paired samples t-test, there was a statistically significant increase in blood lactate (mmol) over time within the EMS+BFR as well as BFR only conditions (Figure 3). HR (Figure 4), SBP (Figure 5), and DBP percent changes within the EMS+BFR condition from pre-trial were significantly higher within the trial compared to following the trial. There were no other statistical differences observed by the EMS+BFR condition over time, between conditions, by mean change, or by interaction in any of the variables previously discussed. The results indicate that an acute bout of BFR combined with EMS as opposed to other trials creates an increased metabolic stress response, while somewhat affecting HR, SBP, and DBP, and without affecting the vasculature and skeletal muscle swelling responses.

When analyzed individually for mean change through a paired samples t-test, the BFR only condition resulted in an acute increase in blood lactate (mmol) (Figure 3) as well as a decrease in posterior tibial artery distance and area over time. Although not significant, in the 5 minutes following the trial, percent changes in HR (Figure 4), SBP and DBP during BFR were higher than those observed during EMS and BFR. Thus, the use of BFR on its own was shown to have an acute effect on metabolic stress response while affecting artery distance, area, and marginally changing blood volume flow over time. There were no other statistically significant results to report on the EMS only condition. Across all conditions, the average change in HR was lower following the trial than within the trial.

Similarly, although observed in a study with able-bodied participants as opposed to daily wheelchair users, a bout of low-intensity resistance exercise with blood flow occlusion resulted in elevated blood lactate mmol levels in comparison to exercise with no occlusion (15, 31). Although there have been differences observed in the physiology of individuals with lower-limb impairments such as decreased muscle metabolism, loss of neural function leading to reductions in muscle mass and density, and increased arterial stiffness (6-9), our results reflect a very similar response to the response of BFR utilized in able-bodied populations. Similar to our results, in the study by Stavres et al., when BFR was used in lower extremity exercise in those with incomplete SCI, there was no observed difference in lactate between conditions of exercise with and without BFR (17). One limitation is that that the measure of blood lactate collected in the current study was taken within a minute of completion of the trial and reflected whole-body lactate versus measuring the accumulation seen exclusively at the muscle. Blood lactate mmol levels may have been significantly higher within the muscle in comparison to whole body lactate (15). As seen throughout the

literature, whole body blood lactate as well as muscle cell lactate accumulation from the use of BFR has been found to result in increased GH and enhanced cellular protein synthesis (4). While our results reflected acute increases in lactate, research on long-term training effects of EMS+BFR in this population may show that the combination may contribute to an enhanced effect of muscle hypertrophy.

There was a statistically significant decrease in both posterior tibial artery distance and area over time, within the BFR only condition. There were no other significant changes in distance or area by condition or time × condition, and no significant changes in TAMV or volume flow over time, by condition, or time × condition. Somewhat similarly to results of the current study, Renzi et. al. observed a decrease in FMD, which was expressed as percent change in popliteal artery diameters from baseline to maximum, from acute bouts of low intensity walking exercise with the use of BFR in able-bodied individuals (37). However, this was found to be significant after multiple weeks of training and not measured from an acute bout as seen within our current study. When utilizing EMS+BFR in para- and tetraplegics, Gorgey et. al. (32) observed that brachial artery diameter and blood flow velocity increased following cuff occlusion in forearms with combined EMS+BFR and in forearms with BFR only. FMD was also found to have increased in the EMS+BFR forearm compared to the BFR only condition (32). While there have been observed increases in vessel diameter or area in response to BFR in other literature, as mentioned previously, our findings report significant decreases. Furthermore, in contrast to our results, one study by Stoner et al., found increases in FMD and arterial range during the use of only EMS on the lower extremities of those with SCI (33). So, while our results did not reflect increases in artery distance and area, Stoner et al. provide evidence that EMS on its own may lead to

improvements in arterial health in this population. The study also observed that those that have experienced SCI often have greater decreases in FMD and arterial range below the lesion level compared to the upper extremities (33). Upper extremities may experience normal shear stress activity on a daily basis in comparison to lower extremities, contributing to the retention of function that leads to typical blood flow patterns (34, 35). It has been found that individuals with SCI have abnormal vascular control such as prolonged recovery of blood flow following ischemia, as well as reduced sensitivity (38). This could be due to reduced vasodilation from increases in muscle sympathetic nervous activity, impairment of β-adrenergic vasodilation, or impairment of nitric oxide release (38, 39). Additionally, the impairment of nitric oxide induced vasodilation, metabolic changes in blood vessels from inactivity, or neurological impulse interruption, could be a possible explanation for the lack of sensitivity to the BFR trial (39, 40, 41).

There was no significant difference in VM CSA over time within each condition, between conditions, or by interaction throughout the groups. In contrast to our findings, one study observed that VM CSA increased acutely after the use of EMS+BFR when utilizing BFR at different pressures in able-bodied adults (42). Additionally, in the study mentioned previously by Gorgey et al. on the use of EMS+BFR on para- and tetraplegics, increases in muscle CSA in the ECRL and EDC wrist extensor muscles with the combination of EMS+BFR compared to EMS alone was observed following multiple weeks of this exercise treatment (32). This supports the idea that with continued use, the combination of EMS and BFR has the potential to greatly enhance adaptations of muscle hypertrophy. It is possible that an increase in BFR occlusion pressure may acutely increase muscle CSA, especially in everyday wheelchair users. However, it has been suggested that additional pressure has led

to no greater increase in muscle swelling (42), or intramuscular metabolites (43). Due to these findings, it is still not clear whether progressive increases in occlusion pressure will drive changes in development of muscle CSA and hypertrophy. Multiple studies have demonstrated that long term training with the use of EMS has resulted in increases in muscle CSA (19, 29). The lack of observed increase in muscle CSA within our study could be due to possible decreased metabolic activity from disuse and atrophy of the affected muscles in the legs of our participants as opposed to the muscles of able-bodied individuals (6-8). Additionally, our study only analyzed the acute effects of treatment, and may not have been of sufficient stimulus intensity to elicit this type of response. When considering the training stimulus, which in our study was EMS, exercise intensity may have needed to be increased. Loenneke et al. state that those that take part in low-intensity resistance training with BFR see greater increases in cellular swelling, strength, and hypertrophy than those engaging in light exercise such as walking with BFR (44). Because our study mimicked an acute bout of low-intensity exercise, an increase in intensity of training and long-term continued use of BFR may elicit a greater response of increased metabolite accumulation, cellular swelling, or muscle CSA.

Across all conditions, the average percent change in HR, was lower following the trial than within. During the combined EMS+BFR condition, percent changes in HR, SBP, and DBP from pre-trial were significantly higher within the trial compared to following, suggesting that the use of EMS and BFR in combination increases HR, SBP, and DBP. Although there may have been changes in HR and BP over time within trials, there were no observed adverse effects on the cardiovascular system with EMS+BFR, and no instances of AD.

A study by Head et al., utilizing the combination of EMS+BFR at 40% and higher occlusion pressures on able-bodied individuals, although not statistically meaningful, produced increases in HR when using EMS+BFR as opposed to EMS on its own. The conditions of the study did not produce any unexpected effects on the cardiovascular system during any of the treatments (42). Our study produced similar results in that the percent changes in HR from pre- to within trial and following the trial were not different within the conditions of EMS and BFR on their own, but EMS+BFR led to greater percent changes in HR 10-15 minutes within the trial versus in the 5 minutes following the trial. As seen in the study by Renzi et al, the use of BFR on able-bodied individuals while walking has been shown to increase HR in order to maintain cardiac output (37). Other research has also shown patterns of increased HR with the application of BFR (45, 46). These results suggest the possibility that EMS+BFR has a synergistic effect on elevating cardiac output.

The study by Stavres et al. investigating the feasibility and safety of BFR on individuals with incomplete SCI found increases in MAP, and SBP over exercise bouts with and without BFR, but showed no exercise pressor response, cardiovascular strain, or difference between conditions (17). A similar response was also observed in a sample of able-bodied individuals where BFR was utilized while walking, also resulting in a significant increase in SBP, DBP, and MAP (37). These observed responses are similar to the results found in our study. There was a significant percent change over time for HR, SBP, and DBP, however no significant differences were seen between treatments. Specifically, within the EMS+BFR condition, there was a higher percent change in SBP and DBP at during the trial versus following. Overall, this demonstrates that EMS+BFR with 40% occlusion elicits a mild pressor response, causing increases in HR, SBP, and DBP.

In contrast to other findings, our study produced no change in MAP over time, by condition or between conditions. One study that included a sample of para- and quadriplegics utilized functional neuromuscular stimulation to carry out graded knee extensions and found that both groups observed increases in MAP. However quadriplegic subjects experienced much lower MAP values than paraplegics (47). Although our sample included individuals with many varying levels of disability, low MAP could suggest peripheral vasculature or vasomotor dysfunction. Although not all participants in our study have experienced an SCI, everyday wheelchair users face the potential for arterial remodeling. Blood vessels can become hypersensitive to α-adrenergic receptor stimulants (48) and norepinephrine, leading to a higher increase in BP (49). Stiffening of the arteries may also occur, affecting arterial pressure. This remodeling occurs as a result of decreased arterial diameter and increased thickness of artery walls (50). Overall, while our subjects experienced increased in BP, there was no significant change in MAP.

The conditions of our study produced increases in HR, SBP and DBP. Constant BP measurement was utilized for the monitoring of possible instances of AD, in which there were no events or adverse effects. Gorgey et. al. also constantly monitored BP for safety purposes and did not observe any instances of AD in any of their participants within any of their conditions, particularly with the combination of EMS and BFR (32). Considering there were no incidences within our study of AD with BFR at 40% LOP, these results promote the feasibility and safety of the use of EMS+BFR within this population. Future uses of EMS in conjunction with BFR above the level of 40% may be a safe practice.

Limitations

The purpose of the study was to determine if EMS in conjunction with BFR has an increased effect on hemodynamics, muscle swelling and blood lactate, however, the study was faced with multiple limitations. The recruited sample size of the study was quite small, due to limited access to individuals in the unique population of everyday wheelchair users. Additionally, in some participants, the stimulation of EMS on the quadriceps muscles had little to no effect, and after multiple minutes of stimulation would not elicit a response in muscular contraction. Perhaps an unknown mechanism regarding altered muscle metabolism and contractile properties in participants with SCI may be at play. While our study analyzed the acute response due to the various treatments, this may not have created a great enough response to show potential changes when EMS and BFR are utilized longitudinally.

It is important to discuss the fact that the sample of individuals used for the study were elite athletes from the University of Alabama Adapted Athletics program. Because this group of individuals is very well-trained, the participants may have had a different response to the conditions of the study than everyday wheelchair users that are untrained and sedentary. As mentioned previously, those that are sedentary may have less compliant arteries and reduced metabolic response of the musculature. Future studies should utilize EMS+BFR on individuals from a wide range of physical activity engagement and trained status to see the comparison of responses.

The use of EMS+BFR, demonstrated to be utilized safely without any additional cardiovascular strain or incidences of AD, may be able to be used at greater BFR pressures and EMS intensities to improve lower extremity musculature and blood vasculature. It is

important to further investigate EMS+BFR responses in this population longitudinally to truly know the potential applications of this form of therapy in practice. Further research in this area has the potential to greatly improve overall quality of life.

Conclusions

The findings of our study have supported the safety of the use of BFR in combination with EMS in everyday wheelchair users. The use of EMS+BFR was found to acutely increase blood lactate over the time of the trial, where the BFR only condition increased blood lactate and decreased posterior tibial artery distance and area. Our results demonstrate that EMS+BFR with 40% occlusion elicits a mild pressor response, causing increases in HR, SBP, and DBP. The study was found to be a good support for the safety and use of BFR in combination with EMS in the population of everyday wheelchair users.

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APPENDIX

THE UNIVERSITY OF ALABAMA® | Office of the Vice President for Research & Economic Development
Office for Research Compliance

July 1, 2021

Lauren Hopps
Department of Kinesiology
College of Education
The University of Alabama
Box 870312

Re: IRB Protocol # 21-02-4239-A "Acute Hemodynamic Responses to EMS with BFR in Paraplegic Individuals"

Ms. Hopps:

The University of Alabama Medical Institutional Review Board has reviewed the revision to your previously approved full board protocol. The board has approved the minor change in your protocol.

Please remember that your approval will expire on May 5, 2022.

Should you need to submit any further correspondence regarding this proposal, please include the assigned IRB application number. Changes in this study cannot be initiated without IRB approval, except when necessary to eliminate apparent immediate hazards to participants.

Good luck with your research.

Sincerely,

[redacted]

Carpantato T. Myles, MSM, CIM, CIP
Director & Research Compliance Officer

Jessup Building | Box 870127 | Tuscaloosa, AL 35487-0127
205-348-8461 | Fax 205-348-7189 | Toll Free 1-877-820-3066

Project Title: Acute hemodynamic responses to EMS with BFR in paraplegic individuals.

Consent to Participate in a Research Study

Please read this informed consent carefully before you decide to participate in the study.

Consent Form Key Information: This study aims to:

- To determine changes in blood flow at two different areas using electrical muscle stimulation with and without blood flow restriction on both legs
- To compare muscle size change using electrical muscle stimulation with and without blood flow restriction

Purpose of the research study: The primary purpose of this study is to compare blood flow, blood vessel size and muscle size in the legs while using Electrical Muscle Stimulation (EMS) with and without Blood Flow Restriction (BFR) in paraplegics or those that use wheelchairs on a daily basis. Information obtained from this study can be used to help physical therapists, athletic trainers, and strength coaches to help determine who they should or should not use BFR for.

What you will do in the study: You will do things in the following order:

Session 1

On the first visit, you will fill out the answers to questions that ask you about your age, your overall health, any medicines you take, and any sickness you may have. Depending on your answers to the questions, you may not be able to take part in the study. If this happens, this will be explained to you and any questions you have will be answered, and the investigator will remove you from the study. You will not be punished in any way.

If you meet the criteria and you agree to take part in this study,
you will be asked to do these things:

You will fill out a form that tells us what exercise you did and how much sleep you got during the previous day.

You will be asked to use the restroom and empty the bladder before starting the study session.

We will measure your height and weight.

You will have your body fat estimated by a handheld BIA machine. You will hold the handheld device with both hands. This will estimate your body fat.

Your blood lactate levels will be taken before and after treatment by gathering a drop of blood through a simple finger stick method.

You will be equipped with a heart rate monitor throughout the duration of treatment. The monitor is an elastic band that will wrap around the chest with the actual device positioned on the chest plate. Resting blood pressure will be measured using a finger cuff recording device. Blood pressure will be recorded pre, during, and post treatment. This will provide a continuous measure of blood pressure and heart rate. This will be repeated at each session.

For the first session, upon arrival, you will be asked to fill out a 24-hour history form about your diet and water intake. You will then lie in a chair while we use an ultrasound machine to look at your blood flow and muscle thickness. We will take three measurements with the ultrasound machine: two on your dominant thigh and one at your dominant ankle. These measurements will be taken after 5 minutes of time spent laying down and immediately following treatment.

During this session you will either have EMS treatment with or without the BFR cuff on both of your thighs, or just a treatment of BFR without EMS. EMS treatments will last 20 minutes. If you have the BFR it will be inflated to 40% of your total blood flow occlusion for your thighs. Blood flow restriction is done with a cuff similar to a blood pressure cuff, it is used to limit the blood flow to the area below the cuff. BFR treatment will include inflation of the cuff for 8 minutes, will then be deflated for 4 minutes, and then inflated again for 8 minutes.

During session 2, upon arrival, you will be asked to use the restroom and fill out a 24-hour history form about your diet and water intake. Your blood lactate levels will be taken by gathering a drop of blood through a finger stick method before and after the treatment.

For the second session, you will lie in a chair while we use an ultrasound machine to look at your blood flow. We will take the same three measurements: two on your dominant thigh and one at your dominant ankle. These measurements will be taken before and immediately following the treatment. This session will include application of one of the other two remaining treatments. Meaning, if your first session included EMS and BFR, this session will include either just EMS or just BFR.

During session 3, upon arrival, you will be asked to again to use the restroom and fill out a 24-hour history form about your diet and water intake. Your blood lactate levels will again be taken by gathering a drop of blood through a finger stick method before and after the treatment.

For the third session, again, you will lie in a chair while we use an ultrasound machine to look at your blood flow. We will take the same three measurements: two on your dominant thigh and one at your dominant ankle. These measurements will be taken before and immediately following the treatment. This session will include application of the final remaining treatment. For example, if your first session included EMS and BFR, and second session included just EMS, this session will include just BFR.

Time required: The study will require 4-5 hours of your time, in total. The first session will take around 2-3 hours, while the other sessions will take around 1-2 hours.

Risks: There are no known risks associated with the use of an EMS unit.

Potential BFR risks associated with this study are very low. Based on previous BFR studies there been very few notes of health issues related to its use, which is not different from the chance of

experiencing these issues without the use of BFR, showing that BFR is not likely to be the cause of these problems. Although very unlikely, Autonomic Dysreflexia (AD), a sudden onset of high blood pressure, is a possible risk. A previous BFR study has shown that out of nine participants, none experienced any signs of AD. Other research done has shown a very low risk of blood clotting within the blood vessels, or clots within the vessels of the lungs. Excessive muscle damage has also been found to have a very low incidence in BFR treatments as well. There is a lot of research available showing that BFR use actually improves blood vessel health and blood flow, which are very good effects. Previous studies, as well as surgeons, have completely stopped blood flow for up to 2 hours without problems. For this study, we will only be partly limiting blood flow for 8 minutes at a time; so the risks for any problems is small. You may also experience slight numbness or "pins and needles", which will be gone when the cuff is removed. Also, you may find the blood flow restriction device to be uncomfortable and you may experience some pain. There is also a small risk of muscular injury. Please note that this study uses an investigational device, meaning the BFR system used in this study is being used in an experimental manner and is not FDA approved for the activity we are looking at in this study.

Electrical muscle stimulation also has very low risk. EMS is only used to flex the muscle that the electrode stickers are attached to. You may experience slight discomfort from irritation from the stickers on the skin, or low level electricity from the EMS. Many studies have look at EMS with no problems.

You will be observed during and after testing, and testing will be stopped if you show any signs/symptoms such as chest pains, lightheadedness, confusion, nausea, or cold, clammy skin, or if you feel for any other reason you need/want to stop. Following each treatment, you will need to use the Deep Vein Thrombosis fact sheet provided to check your legs for any changes. A research member will be reaching out to you 24-48 hours to ensure that no new symptoms have come up. In case of accident or illness, a CPR certified individual will provide proper care, until emergency medical services arrive.

How will risks be minimized? Risks will be minimized by:

- Only allowing you to participate in the study if you are healthy and without disease.
- Following the BFR protocol.
- Stopping a test if you show any signs or symptoms of possible illness.
- Asking you how you are feeling during the test.

Someone trained in CPR will be present for all sessions, and we are only 5 minutes from a hospital if an emergency occurs. In the event that this research activity results in an injury, treatment will be available, including first aid and emergency treatment as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. We will not confirm whether you have health insurance coverage. Therefore, if you are not covered and you become injured as described above, you will be responsible for any costs you incur for treatment. Neither the Principal Investigator nor the University of Alabama will provide payment of costs associated with any injury due to your participation in this study.

You will be informed if significant new findings arise that might affect your desire to continue in the study.

Benefits: Though the participants of this study will not be compensated, the information gathered from their participation will be beneficial to society in several ways. Because the blood flow responses of BFR and EMS on paraplegic athletes are not well known yet, this information can help us understand what is happening during BFR and EMS application.

Confidentiality: Your privacy will be protected by asking you medical related questions in a private room or a site of your choosing.

During testing, your privacy will be protected by reducing the entrance of individuals into the laboratory to only those people who are working on the study and/or those people who normally work in the laboratory and have a desk there.

Medically-related information collected about you while you are exercising will not have your name on it.

Voluntary participation: Your participation in the study is completely voluntary. You can choose not to be in the study. If you start the study, you can stop at any time. There will be no effects on your care or your relations with the University of Alabama.

Right to withdraw from the study: You have the right to withdraw from the study at any time without penalty.

How to withdraw from the study: If you want to withdraw from the study, you may tell the researcher and leave the room as you deem fit. There is no penalty for withdrawing.

Compensation/Reimbursement: You will receive no payment for participating in the study.

Using data beyond this study:

The information collected from you for this study could be helpful to future researches when this study is done. Our research team would like to make your information available for future use in studies that are looking at:

- Blood flow restriction
- Electrical muscular stimulation
- Spinal cord injury

You will not be asked for permission for the use of your information in future studies, however your information will not be connected to your name or any other piece of identifying data.

Additionally, future researchers will not attempt to identify you. The de-identified data from this study will ultimately be provided along with others in the creation of a large data set.

If you have questions about the study or need to report a study related issue please contact, contact:

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If you have questions about your rights as a participant in a research study, would like to make suggestions or file complaints and concerns about the research study, please contact: Ms. Tanta Myles, the University of Alabama Research Compliance Officer at (205)-348-8461 or toll-free at 1-877-820-3066. You may also ask questions, make suggestions, or file complaints and concerns through the IRB Outreach Website at http://ovpred.ua.edu/research-compliance/prco/. You may email the Office for Research Compliance at rscompliance@research.ua.edu.

Project Title: Acute hemodynamic responses to EMS with BFR in paraplegic individuals.

Agreement:

€ I agree to participate in the research study described above.

€ I do not agree to participate in the research study described above.

Signature of Research Participant Date

Print Name of Research Participant

Signature of Investigator or other Person Obtaining Consent Date

Print Name of Investigator or other Person Obtaining Consent

Re-affirmation of consent:

Visit #2 Participant's Initials:_____

Re-affirmation of consent:

Visit #3 Participant's Initials:_____