A Pilot Study to assess
Spinal Cord Stimulation to Inhibit Afferent Feedback during Exercise in Hypertension

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Study Summary

Title	*A Pilot Study to Assess Spinal Cord Stimulation to Inhibit Afferent Feedback during Exercise in Adults with HTN*
Short Title	*SCS to Inhibit Afferent Feedback during Exercise*
Protocol Number	*1604M86961*
Phase	*Pilot Data*
Methodology	*Single blinded, randomized – order study*
Study Duration	*Two years*
Study Center(s)	*Single-center*
Objectives	*To investigate the exercise blood pressure response during a lower-extremity dynamic exercise in postmenopausal women with hypertension and to determine if lumbar epidural spinal cord stimulation reduces blood pressure during exercise in postmenopausal women and men with hypertension.*
Number of Subjects	*40*
Diagnosis and Main Inclusion Criteria	*Hypertension: Men and postmenopausal women between the ages of 40-90 years old. Hypertension as defined by BP ≥130/80 and diagnosed by a physician*
Statistical Methodology	*A two factor (condition x time) repeated measures ANOVA with sex as a between subjects factor.*

List of Abbreviations

AE	adverse event
BP	blood pressure
CITI	Collaborative Institutional Training Initiative
CO	cardiac output
CT	computed tomography
CVD	cardiovascular disease
DSMB	data safety monitoring board
ECG	electrocardiogram
EPR	exercise pressor response
EXER	exercise
FSH	follicle-stimulating hormone
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
HTN	hypertension
IRB	institutional review board
MAP	mean arterial pressure
MRI	magnetic resonance imaging
PI	principal investigator
RCO	regional circulatory occlusion
REC	recovery
RER	Respiratory Exchange Ratio
RPE	rating of perceived exertion
SAE	serious adverse event
SCS	spinal cord stimulation
SVR	Systemic Vascular Resistance
VE	ventilation
VO2	volume of oxygen uptake
VCO2	volume of carbon dioxide produced

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Introduction

1.1. Background and Significance

Health Issue Addressed

Hypertension (HTN) is a silent, invisible killer that rarely causes symptoms and is one of the key causes for cardiovascular disease (CVD). Sympathetically mediated cardiovascular responses to exercise (over activation of group III/IV skeletal muscle afferents, sympathoexcitation) are exaggerated in adults with HTN (10). These abnormally large changes in hemodynamics during exercise (exercise-induced HTN) increase the risk for adverse cardiovascular or cerebrovascular events during or immediately following a bout of exercise (6, 18, 23). Importantly, HTN used to be considered a man's disease, however, women following menopause, are now at a greater risk for CVD compared with men (23). Despite the greater increase of HTN in postmenopausal women, the sex difference in the exercise pressor response (EPR) in adults with HTN is unclear. Further, treatment guidelines for HTN management remain inconsistent, particularly for young and aged women (23). Therefore, there is a *critical need* to understand if the EPR is differentially regulated in postmenopausal women with HTN and to determine an effective early intervention that can target exercise-induced hypertension in these women.

Gap in Knowledge Addressed

Generally, suggested non-pharmacological methods utilized to treat HTN usually include change in diet and exercise, but unfortunately, exercise is risky for HTN patients that experience exaggerated sympathoexcitation in response to exercise (6, 10, 18). So, there is a large gap in knowledge in regards to the best non-pharmacological method for reducing BP in HTN patients. As such, we propose a novel treatment that is in current use for pain disorders(12), but may serve as a promising treatment for HTN. Spinal cord stimulation (SCS) works by modulating afferent input at the dorsal column of the spinal cord and causes vasodilation in the peripheral blood vessels (5). Therefore, the use of SCS can be an innovative technique to reduce systemic effects of sympathoexcitatory afferent feedback from the active skeletal muscle, and thereby increase peripheral vasodilation and reduce blood pressure (BP) in adults with HTN. This will be a pilot study and the generated data will justify conducting larger clinical trials.

Sex Differences in HTN

The prevalence of HTN is higher in men until after menopause in women when the prevalence of HTN surpasses that of age-matched men(23). In the world, 25% of adult women are hypertensive, and in the United States, >75% of women over 60 years of age are hypertensive (4, 21). Aging is associated with elevated sympathetic activity. As such, sympathetic activity was found to be lower in women than in men among subjects <49 yrs., but the same in men and women among those that were ≥50 yrs(14). Importantly, sympathetic activity is greater in postmenopausal compared with age-matched premenopausal women(14). *In summary, the prevalence of HTN is higher in older women and sympathetically mediated increases in BP may be of more importance, demonstrating the need for investigating sex differences in the exercise blood pressure response in adults with HTN.*

Exercise Pressor Reflex in HTN

HTN can be characterized by chronic elevations in sympathetic nerve activity(13) which contributes to the abnormal augmented exercise pressor reflex(19). The afferent arm of this reflex is composed of mechanically (group III) and metabolically (group IV) sensitive skeletal muscle afferents which are known to become overactive or more sensitive in HTN (7, 15). As such, the autonomic response to exercise is altered, generating exaggerated increases in BP, heart rate, and SVR. Therefore, the risk for experiencing a cardiovascular or cerebrovascular event during or immediately after exercise is greatly elevated (6, 10, 18). This circumstance is regrettable as it limits the safety of exercise as a

treatment for HTN; a treatment with demonstrated potential for lowering BP and improving cardiovascular health (3).

Current Treatments in HTN

Despite the extensive list of major morbidity and mortality trials of antihypertensive agents (20), guidelines remain inconsistent for HTN management. Although a large variety of pharmacologic agents that, alone and in combination, are highly effective in lowering BP, ~50% of adults with HTN cannot be controlled with the drug treatment and lifestyle modification alone (1). Importantly, exercise is a treatment to lower BP and improve cardiovascular health, however with the increased risk of adverse cardiovascular or cerebrovascular events during or immediately following a bout of exercise, it limits the safety of exercise as a prescription. Further, while antihypertensive methods are similar between men and women, HTN may be less well controlled in older women (23). *There is, therefore, a critical need to determine a non-pharmacological treatment that can be used as an adjunct to exercise and lifestyle modifications for adults with HTN.*

Spinal Cord Stimulation

Modulation of afferent feedback via SCS has been used successfully for decades as a treatment for chronic pain. Each year, more than 14,000 SCS implantations are performed worldwide(22). This proposal however, seeks to test SCS as a novel non-pharmacological therapy for adults with HTN. The putative mechanism is that lumbar SCS produces vasodilation in the vasculature of the lower limbs and feet, mediated by antidromic activation of sensory fibers and decreased sympathetic outflow(22). Initial experiments to investigate the influence of SCS on BP in young healthy, demonstrated that SCS is safe and effective in young healthy adults during exercise (Figure 2). *This protocol will be the first to investigate the influence of epidural SCS on peripheral locomotor afferent feedback (group III/IV) during exercise in HTN and if there is a sex difference in the response to SCS.*

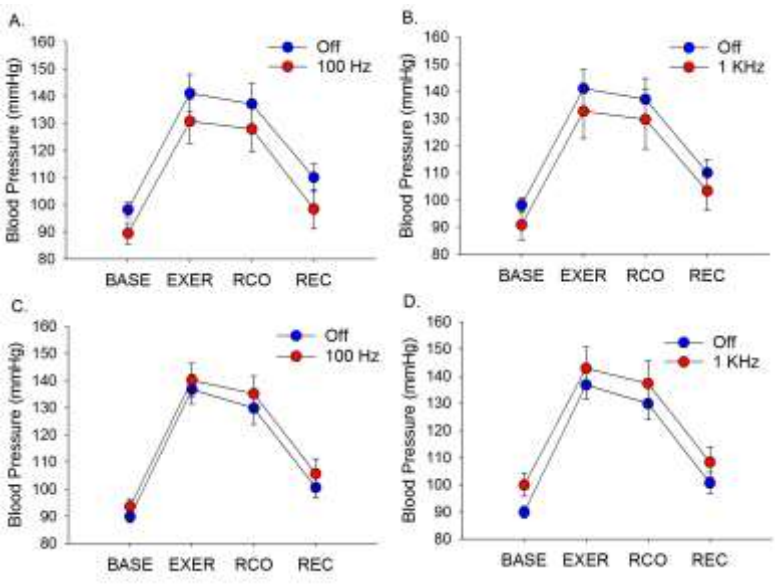


Figure 2. Spinal cord stimulation reduced mean arterial pressure (MAP) in healthy young women ***(A & B)*** (n=3), but not men ***(C & D)*** (n=5) throughout exercise and recovery ($p<0.05$). There was no difference between 100 Hz and 1 KHz frequencies ($p>0.05$). Base: resting, EXER: at the end of 2 minutes of ischemic calf-raises, RCO: regional circulatory occlusion (post-exercise), REC: 3 min of recovery

1. Specific Aims/Study Objectives

Specific Aim 1

To investigate the EPR during a lower-extremity dynamic exercise in postmenopausal women with HTN. There is evidence to suggest that 1) premenopausal women have a blunted EPR compared with young men and postmenopausal women and 2) hormone therapy reduces the EPR in postmenopausal women. *Hypothesis:* postmenopausal women with HTN, not receiving hormone therapy, will have a greater EPR compared with men with HTN during a lower-extremity exercise.

Specific Aim 2

To determine if lumbar epidural SCS reduces BP during the EPR in postmenopausal women with HTN. Considerable evidence has accumulated over the last decade demonstrating that the EPR contributes appreciably to the abnormally augmented cardiovascular response to exercise in HTN. *Hypothesis:* SCS will cause a greater reduction in the EPR in hypertensive postmenopausal women compared with hypertensive men and this attenuation will be greater with high frequency stimulation.

2. Investigational Device

The Precision Spectra system will consist of a an external trial (ETS) spinal cord stimulation system , temporary percutaneous leads and lead extensions, each packaged as a separate kit. The percutaneous and surgical paddle leads function as a component of the Precision SCS system by delivering electrical stimulation to the nerve structures in the dorsal aspect of the spinal cord. Although this has typically been indicated for reductions in pain in chronic lumbar and lower leg pain patients, we will implant the leads in the same region of the lumbar spine, but will assess how spinal cord stimulation modulates blood pressure and systemic vascular resistance in adults with HTN.

Features of the Precision spectra SCS System Include:

- Stimulation electrode field navigation
- 32 independent current-controlled channels of stimulation (32 contacts + the implantable pulse generator)
- Two 16 contact Infinion leads
- High-range parameter capability
- No detectable latex

Leads

The percutaneous leads function as a component of the Precision SCS system by delivery electrical stimulation to the nerve structures in the dorsal aspect of the spinal cord, resulting in an inhibition of pain sensation.

Percutaneous Leads

The Infinion™ 16 percutaneous lead is available in lengths of 50 cm and 70 cm. Each lead has 16 contacts located near the distal end. Each contact is 3 mm in length and is spaced 1 mm from the adjacent contact.

The intended purpose of this device is to investigate if spinal cord stimulation of the lumbar spine can modulate blood pressure and systemic vascular resistance in hypertension patients. The physician will be provided with a new Precision Kit for each participant. The physicians that will be inserting the leads have been adequately trained to do so and are already performing this procedure at the University of Minnesota for chronic pain indications.

3. Study Design

1.2. Study Design

This is a single center study conducted at the University of Minnesota, enrolling up to sixty subjects (30 men and 30 post-menopausal women). Subjects will be a assigned to one of the two study arms, (Dynamic Exercise or Spinal Cord Stimulation) and then crossover to the other arm after the initial assignment is complete. However, if the screening MRI/CT or blood work determines the subject is not a candidate for spinal cord stimulation or if the participant decides they would like to participate in the

exercise arm of the study but not the spinal cord stimulation arm, then they will be assigned to the Dynamic Exercise arm only.

1.3. Study Duration

The subjects will participate in two study visits that will be approximately one week apart. Subject participation in the study is up to 4 weeks. Study enrollment is anticipated to take approximately 2.5 years.

2. Study Population

2.1. Inclusion Criteria

Subjects will be eligible to participate in the study if all of the following conditions exist:

1. Men and post-menopausal women between the ages of 40-90 years old
2. Hypertension defined as BP ≥ 130/80, diagnosed by a physician
3. Ability of the patient to provide consent

2.2. Exclusion Criteria

Subjects will be excluded from participation in the study if any of the following conditions exist:

1. Unstable or uncontrolled cardiopulmonary disorders other than hypertension, as determined on the medical evaluation questionnaire.
2. History of dangerous arrhythmias (arrhythmias requiring treatment or requiring physician supervision)
3. Currently taking specific anti-hypertensive medications that may affect the exercise pressor response or influence the effect of spinal cord stimulation. We have attached a list of medications that will allow participants to be eligible for the study and medications that will exclude individuals from the study. The inclusive/exclusive exhaustive list our study team collated was done so with guidance from Dr. Paul Drawz, Nephrologist.
4. History of spinal fusion or laminectomy at L3 or above
5. Current prescription opioid usage
6. At physician discretion which will be documented on the case report form.

2.3. Recruitment

All materials used in study recruitment will be approved by the Institutional Review Board (IRB) prior to implementation. Study recruitment will utilize various methods in order to maximize the opportunity to recruit potential subjects for the study.

1. Fliers will be posted at the University of Minnesota Hospital/Clinic waiting rooms and at the VA Medical Center (once approved through the VA) and may be advertised using various media outlets including newsletters, campus email and announcements in the Twin Cities. Information from the recruitment fliers will be posted on the monitors and the Clinic and Surgery Center (CSC) at the University of Minnesota. In addition, fliers will be posted in community centers and libraries in the metro area upon approval from center sites.

2. We would like to use general recruitment mailings through the Fairview Research Administration, using data supplied by CTSI informatics, as well as through the University of Minnesota Physicians to

recruit adults with hypertension in the age range of 40-79 in the metro area. We propose to mail 210 people a month for each month of the study duration. A recruitment letter (attached) and the recruitment flier will be sent out to identified individuals.

3. ResearchMatch will be used to identify and email individuals who are interested in participating in our study.

4. We will post recruitment through our lab research website (Cardiovascular Research & Rehabilitation Lab on the Department of Rehab Med website) and social media. It will systematically be updated to reflect the latest IRB approved protocol. The link on the Cardiovascular Research & Rehabilitation Lab will be sent to professional websites and posted on social media. Patients will self-identify by e-mailing or contacting the researchers.

3. Study Visits

3.1. Pre-Screening

Interested adults will be pre-screened by a study team member over the phone. Adults that are interested in the study will be invited to schedule a screening visit.

A schedule of Assessments for the study visits is provided in **Figure 1**.

Figure 1: Schedule of Assessments

Procedure	Telephone pre-screening	Screening Session	Dynamic Exercise Session	Dynamic Exercise and SCS Session
Eligibility Screening	X			
Consenting Process		X		
Activity and Health Questionnaire		X		
VO_2 Max		X		
Women: Confirmation of Menopause[1]		X		
CBC and INR		X		
Lumbar Screening MRI or CT[2]		X		
Pill count sheet to track medication		X		
Vitals (HR and BP), Height, Weight		X	X	X
ECG		X	X	X
SCS Leads Implantation				X
Radial Arterial Line Insertion				X
Exercise 30% VO_2 Peak			X	X
Blood draws				X
Follow-up phone call to assess for adverse events (3 – 6 days post visit)				X

[1] FSH lab test required if no history of oophorectomy

[2] For women if no history of oophorectomy and FSH testing results are not available at the time of MRI

3.1.1. *Screening and Baseline*

After consenting to the study, subject demographics and eligibility will be confirmed by the principal investigator (PI). Subject Eligibility assessments include:

- Vitals (blood pressure and heart rate), height and weight
- Participants can be taking up to 2 medications on the Inclusion list in Medication table
- Medical history
- For Women: confirmation of menopause by FSH, or history of oophorectomy
- Complete blood count (CBC) and INR (determine any anticoagulation concerns)
- Completion of Activity and Health questionnaire
- VO_2 peak testing
- Screening Lumbar MRI or CT
- Patients will be asked to track their medication using the pill count sheet
  For women for whom menopause has not been confirmed: A urine pregnancy test

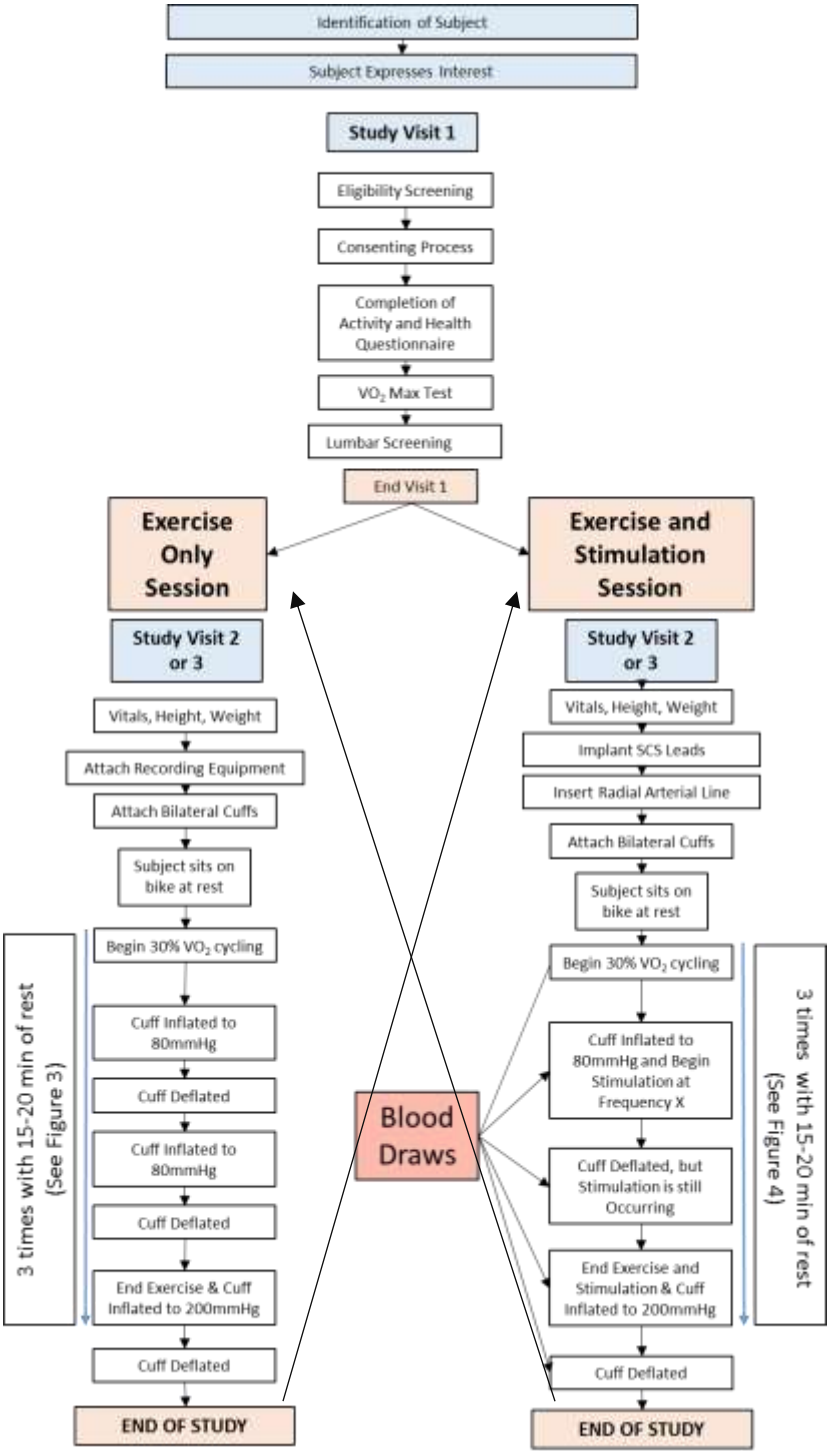
A screening lumbar MRI or CT is done to ensure that there are no anatomical anomalies in or around the epidural area consistent with standard clinical practice that would prevent epidural stimulator lead placement. If the participant is contraindicated for MRI, they will have the option to undergo a CT scan to assess eligibility. If the participant requests a medication before the MRI or CT, a study team physician will be contacted and the medication will be prescribed and administered. Medication such as, Ativan or Valium (0.5 mg to 20 mg) will be prescribed to the participant. The participant will be asked to not consume solid foods for 6 hours prior to taking medication and liquids for 2 hours up to taking medication.

Subjects will be assigned to one of the study arms once screening is complete. However, if the MRI or CT determines they are not able to undergo spinal cord stimulation, they may only participate in the Dynamic Exercise session.

Screening for the study will continue until each study arm has 20 post-menopausal women and 20 age-matched men, and to allow or subject attrition for a total of 60 enrolled subjects.

Figure 2 indicates the flow of events for the Dynamic Exercise Study and Spinal Cord Stimulation Study. Specific timelines for both study arms are provided in Figures 3 and 4.

Figure 2: Flow of Events



Dynamic Exercise Session

1. Vitals, height and weight
2. Submaximal exercise on a cycle ergometer with bilateral lower extremity pressure cuffs intermittently increased at pressures of 80 mmHg for 3 min during exercise and 200 mmHg for 2 min post exercise, 3xs with 15 minutes of rest in between (see figure 3).
3. Blood pressure will be measured continuously via noninvasive finger plethysmography.
4. Gas exchange and ventilation will be measured via automated metabolic system (Medical Graphics Co., St. Paul, MN).

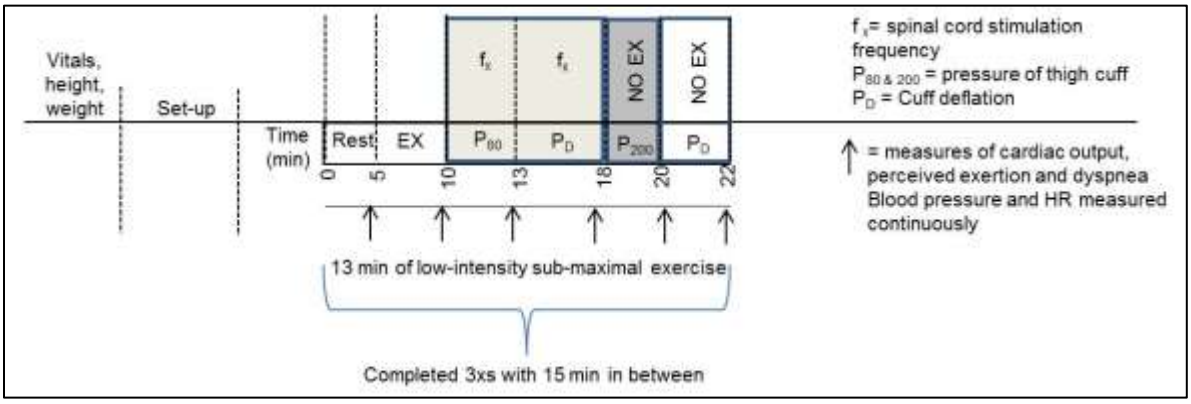


Figure 3. Protocol for Dynamic Exercise Arm

3.1.1. *Dynamic Exercise and Spinal Cord Stimulation Session*

Exercise and Stimulation Session

1. Vitals, height and weight
2. SCS lead placement
3. Radial arterial line insertion
4. Exercise 30% VO_2 Peak with Stimulation
5. Blood draws
6. Lead removal
7. Adverse Event assessment

Follow-up: A phone call to the participant will be placed 2-3 days after the study to confirm that no adverse events have taken place as a result of the study.

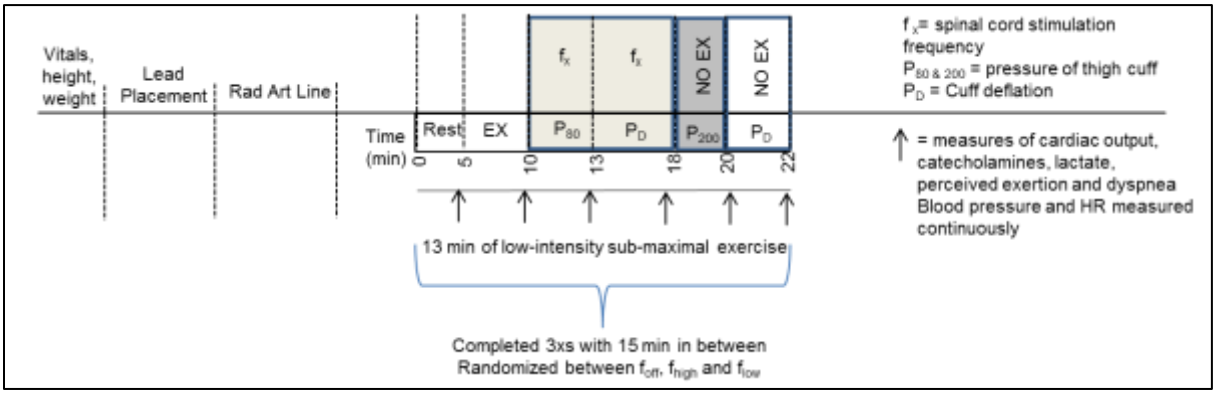


Figure 4. Protocol for Exercise and Spinal Cord Stimulation Session

Spinal Cord Stimulation (SCS) Trial Lead Placement

SCS leads will be temporarily placed in the lumbar/thoracic epidural space in a manner that is standard for the clinical placement of trial leads in humans. Insertion of the lumbar SCS leads and arterial catheter will be conducted by qualified anesthesiologist or neurosurgeon.

SCS lead placement will occur in a sterile environment. This is done using local anesthesia with (2%) lidocaine or a similar drug and fluoroscopy to guide lead placement. Subjects lay prone and their low back is injected with lidocaine to numb the area. Another needle is placed into the epidural space within the spinal canal. Once the needle is properly in position, the SCS leads are passed through the needle and placed in the correct position via fluoroscopy (Figure 5A). A second lead may be placed in the same manner. Once the leads are placed, they will be connected to an external trial stimulator that provides stimulation current to the implanted lead. Stimulation produces a light, often pleasant tingling sensation in the legs and back, also known as paresthesia. Once the placement is complete, the needles are removed from the back and the stimulator leads left in place and secured with transparent tape (Figure 5B). Once the experiment is complete, the leads are removed by gently pulling them out by the physician with a bandage applied to the wound site.

Figure 5A. Fluoroscopy image of lumbar SCS leads in the epidural space of the spine

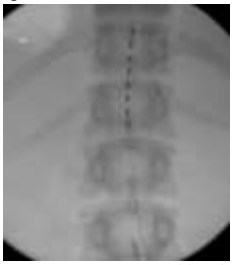


Figure 5B. Image of lumbar spine, post SCS procedure

Arterial catheter placement

An indwelling 20 gauge arterial catheter will be placed in the radial artery of the participant's nondominant hand by an anesthesiologist or an anesthesiology resident. The catheter will be placed (after an Allen's test demonstrates adequate ulnar blood flow) using aseptic technique via ultrasound guidance after local anesthesia with lidocaine. It is flushed continuously at 3 cc/hr w/sterile saline.

After electrode placement, an arterial catheter is placed in the radial artery for intra-arterial BP recording. The subjects are then escorted to the exercise laboratory to start the exercise protocol (described below).

Upon completion of the study, the arterial line will be removed by a physician or a UMP nurse who is trained to in managing and removing arterial lines. Pressure will be held on the arterial site for 10 min. These procedures will take place in the Phillips Wangensteen Building (PWB) M Health Clinical Research Unit (CRU).

Anesthesiologists have extensive experience with arterial line and lead placement and removal as well as blood draws. Anesthesiology residents are well trained to place arterial lines and have experience with this procedure.

Transport of participants from surgical suite to exercise suite. The leads will be secured to the participant's skin via transparent adhesive (tegaderm) (Figure 5B), to have a visual of the implant site at all times. The arterial line will be secured to the arm via tegaderm, a gauze roll or coban upon physician discretion. The arterial line will be connected to one of the transducers of a portable flowtrac device

(Edwards Life Sciences, Irving CA) for continuous blood pressure monitoring during transport. The second transducer of the flowtrac device will be connected to an AD equipment (ADInstruments Inc.,Colorado Springs, CO) to measure the pressure waveform online and later help with the BP data analysis offline. The participant will be transported via wheelchair to the PWB M Health CRU via a service corridor which allows for aboth a direct rouite and one that is out of the general public walkway. The PWB M Health CRU iswhere the exercise lab is located. The participant will be escorted by the PI of the study and an anesthesiologist, anesthesiology resident or Dr. Park. Continuous blood pressure and heart rate will be monitored throughout the exercise portion of the study. The PI has extensive experience with exercise studies in clinical populations, in particular, those with heart conditions.

Exercise 30% VO2 Peak with Stimulation

Exercise takes place on a cycle ergometer where the subject will cycle at 30% of peak work. In order to further stimulate group III/IV afferents, thigh tourniquets are placed on the proximal thigh bilaterally and inflated intermittently to pressures of 80 mmHg. The stimulator frequency is turned off, and on at two different frequencies (100 Hz and 1 KHz) (randomized) throughout the exercise. Blood pressure, heart rate, ventilation (VE) and gas exchange are measured throughout the exercise. Cardiac output, catecholamines and lactate are measured intermittently throughout. The rationale for these measures is described below.

After the exercise, the SCS leads and radial arterial catheter are removed.

4. Measures

Peak Oxygen Consumption Testing (VO2 peak) and submaximal exercise (Both studies) A modified graded cycle ergometry protocol will be used to determine workload during the visit. Intensity will increase by 40 watts/3 minutes until volitional fatigue (9).

After SCS lead insertion on a subsequent visit, subjects will be escorted to the exercise laboratory where they will exercise on a cycle ergometer at a low intensity (30% VO2peak) (8)..

Cardiac Output and SVR (Both Studies): Cardiac output (CO) will be measured using noninvasively with device Nexfin (Edwards Life Sciences, Irving CA) during the dynamic exercise session and invasively with the flowtrac device during the dynamic exercise and stimulation session (Edwards Life Sciences, Irving CA). Cardiac output will be measured to provide a complete picture of vascular resistance, SVR=BP/CO.

Gas Exchange and Ventilation (VE) (Both Studies): VO2, volume of carbon dioxide produced (VCO2), and VE will be measured using a low resistance open circuit automated metabolic system (Medical Graphics Co., St. Paul, MN).Gas exchange and VE parameters will provide information regarding exercise performance and metabolic workload during exercise testing. These measures are indicative of health status in patients (16).

Perceived Exertion and Dyspnea (Both Studies): Measurements to determine if perceived exertion and dyspnea are reduced with SCS. Dyspnea will be measured using the modified Borg analog/visual (0-10) scale (2). Perceived exertion will be measured by rating of perceived exertion (RPE) scale on the Borg (6-20) scale (2). Labored breathing (dyspnea) and sensations of fatigue (perceived exertion) are two common complaints in patients with CVD.

Intra-arterial BP (Spinal Cord Stimulation Study): This catheter allows for continuous real-time intra-arterial measurement of beat-to-beat BP. Blood pressure is the primary outcome measure. As such, intra-arterial BP recording is considered the most accurate(17).

Catecholamines, lactate and blood gases (Spinal Cord Stimulation Study): The arterial catheter provides access to arterial blood for these measurements. Catecholamines (epinephrine, norepinephrine and dopamine) are a measurement of sympathetic activity, lactate is a metabolic by-product from muscle contraction and blood gases will provide information on arterial O_2 and CO_2 during exercise.

ECG (Both Studies): Subjects are instrumented with a 12 lead ECG for the measurement of heart rate and rhythm. These measurements are crucial for understanding if SCS reduces sympathetic activity and metabolite production during exercise.

5. Analysis Plan

General Statistical Methods. Subjects will undergo submaximal exercise and ergoreceptor activation with SCS at different frequency parameters to target afferent neural feedback. Continuous variables will be presented as means ±SD. Categorical variables will be presented as number (% population). Distribution normality will be assessed and transformations or non-parametric methods will be used as appropriate. Analyses will be conducted with SPSS (v19 or higher).

Primary Outcome Analysis. The one-minute mean BP measured at the end of the three frequency challenges will be compared using a repeated measures (on subject) ANCOVA model. The primary hypothesis will test if the pooled effect of the active frequencies (f1, f2) is significantly different from the BP with the device inactive. Post hoc comparisons of the individual frequencies will also be conducted as a part of the optimization approach. It is not known if the dose-response relationship is monotonic (i.e., higher frequency is superior in all subjects). Therefore, further analysis will be done to determine the association between the BP and frequency of SCS to reveal the dose-response curve.

Additional analysis will be conducted on an age-matched subgroup consisting of 10 postmenopausal women and 10 age-matched men.

6. Data and Safety Monitoring Plan

6.1. Data

Authorized study staff and investigators who have gone through HIPAA, CITI, and other data security training through the University of Minnesota will be collecting, managing, and analyzing data. Cardiovascular variables will be monitored through by use of an electrocardiogram, an intra-arterial catheter using flowtrac (Edward Life Sciences) and data from these instruments will be outputted to PowerLab (AD instruments) for offline analysis. Cardiac output and systemic vascular resistance will be measured and recorded by using the flowtrac device (Edwards Life Sciences, Irving CA). Gas exchange and ventilation variables by use of a low resistance open circuit automated metabolic system. After each study visit, subject data will be labeled by way of a random numbering system in order to anonymize the data. The data will be stored and locked in a filing cabinet. There will be a list that will link random numbering with the subject names in a computer file on a University of Minnesota computer that is secured with needing a password to access. Only study team members will be able to access this data.

In accordance with governmental regulations, study records will be kept for a minimum of three years following the completion of the study. After that time and if there is no longer a need for the records, the records will be destroyed.

6.1.1. *Confidentiality*

Each subject's data will be coded so that it is not identifiable to the person. The code will be secured in a locked file and on computer which will have a secure password. Blood samples will be stored in the Genomics Center in coded format.

6.2. Potential Risks

- Maximal Exercise Testing Protocol: A graded exercise protocol will be used on an upright cycle ergometer to volitional fatigue. The protocol will be discontinued immediately if any one of the following occur:

  1) subject desire to stop,
  2) drop in systolic blood pressure > 10 mmHg with increasing workload when accompanied with evidence of ischemia,
  3) severe angina,
  4) sustained ventricular tachycardia,
  5) ST segment elevation > 1.0 mm in leads without diagnostic Q waves,
  6) technical difficulties in monitoring ECG or systolic blood pressure or
  7) completion of data collection.

  The protocol will also be discontinued if any two of the following occur:
  1) failure of heart rate to increase with increasing workload,
  2) plateau in VO_2,
  3) RER > 1.10,
  4) perceived exertion > 18 (Borg 6-20 point scale),
  5) systolic blood pressure > 250 mmHg, and 6) increased nervous system symptoms (e.g. ataxia, dizziness or syncope).

  Risks of maximal exercise include: leg pain and fatigue, shortness of breath and general exhaustion.

- Spinal Cord Stimulator Placement: Placement of spinal leads will occur under local anesthesia (2% lidocaine). Therefore, minimal pain will be felt with electrode placement. There may be bruising or bleeding at the needle puncture site. There is a risk for infection at the insertion site which is extremely rare in healthy patients. Soreness at the needle site may occur once the local wears off. This is typically very minor and either requires no treatment or simple over-the-counter treatments. On an extremely rare occasion, nerve root/spinal cord trauma with the placement may occur that may lead to paralysis.
  - There is also a less than 1% risk of dural puncture and a "spinal headache." Spinal headaches may be present for 1-5 days and usually resolve with conservative therapy (rest, fluids, and analgesics such as ibuprofen or acetaminophen). A procedure known as a "blood patch" may be needed where the subject's own blood will be injected using similar techniques as the placement of the leads. This procedure is safe and very effective in treating spinal headaches. This risk is lower when the procedure is performed by a highly experienced individual.
  - There is no increased risk of walking with a spinal cord stimulator. Indeed, walking distance is used as a measure for patient outcomes with spinal cord stimulation(11). Less is known about exercise and SCS. In our previous study at the Mayo Clinic, however, patients were able to endure an intense ischemic exercise with SCS without adverse events (unpublished).
- Placement of arterial catheters: Risks of placing a catheter include infection or clot. These complications are extremely rare and unlikely to occur in ambulatory subjects undergoing catheterization for a few hours. A more common complication is a hematoma at the site of the

catheter placement. The physician may use ultrasound to guide the placement of the catheter, which significantly reduces this risk.

- Surface Electrodes (electrocardiography, ECG): The adhesive from the electrodes may cause slight irritation to the skin. In rare occasions, the adhesive electrodes may cause an allergic reaction.
- Magnetic Resonance Imaging: Subjects will undergo an MRI safety screening questionnaire to ensure they have no contraindications to the MRI environment. This proposal includes post-menopausal women only, however pregnancy screening will be done prior to the lumbar MRI only if menopausal status hasn't been confirmed at the time of screening.
- X-ray, CT, and Fluoroscopy: The placement of spinal leads will occur under fluoroscopy. Subjects will be exposed to low-levels of radiation. The amount of radiation that will be used has a low risk of harmful effects. The average amount of radiation that the average person would receive from fluoroscopy is approximately 1/3 (1mSv) and CT is 2 and 2/3 times (8mSv) of that received from natural sources of radiation by a Minnesota resident in one year (3 mSv).
- Sedative Use: With the use of sedatives a participant may experience dizziness, daytime drowsiness, dry mouth, change in appetite, blurred vision, diarrhea, or constipation, burning or tingling in the hands, arms or legs and unsteadiness. In rare cases of over-sedation, cardiovascular or respiratory depression may occur.
- Risks of transport from hospital to PWB CRU are minimized by: the study team, including the PI and physician transporting the participant safely between the two buildings using the service corridor which allows for both a direct route and one that is out of the general public walkway. Details of the transport of participant are located in section 3 of protocol.

6.3. Adverse Event Reporting

The investigators will observe for adverse events at each session and conduct an interview at of each session to determine whether an adverse event has occurred since the previous session. In addition, a follow-up phone call will be placed to each subject 2-3 days after the completion of the exercise and stimulation session to determine if any adverse events had occurred after the participant left the study.

6.3.1. *Serious Adverse Events (SAE) –*

A SAE is defined as any untoward medical occurrence, whether related to the study device or procedure or not, that meets one or more of the following criteria:

- Results in death
- Is life-threatening
    - Refers to an event in which the subject was at risk of death at the time of the event: it does not refer to and event that hypothetically might have caused death if it were more severe.
- Requires hospitalization > 24 hours
- Requires prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in fetal distress, fetal death, or congenital anomaly or birth defect

The relationship of the SAE to the study device and/or procedure will be evaluated by then investigator according to the following definitions:

- Unrelated: AE is not related to the study-specific devices or procedures
- Probably Related: AE has a strong temperal relationship to the study –specific devices or procedures, or another etiology is unlikely
- Unknown: Relationship of the study-specific devices or procedure and alternative etiology is unknown

Data for those SAEs determined to be “probably related” to the study devices or procedures, whether “expected” or “unexpected” will be collected and an emergent DSMB meeting will be held to determine if the study stopping rule criteria has been met. (section 7.4 and 7.5)

Otherwise all SAEs will be reported in summary form at the time of IRB continuing review.

6.3.2. *Unexpected Adverse Device Events (UADE)*

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Problems/events that are unanticipated and involve new or increased risk to subjects should be reported to the IRB within 5 working days if, in the opinion of the PI, they are possibly, probably or definitely related to the research procedures.

Those serious, unanticipated problems/events that the PI deems unlikely or not related and do NOT meet the IRB’s definition of UPIRTSO and should be reported in summary form at the time of IRB continuing review.

6.3.3. *Expected Adverse Events (AE)*

Those adverse events identified as Potential Risks (section 9.2) will be collected and reported in summary form at the time of IRB continuing review Data and Safety Monitoring Board (DSMB)

The DSMB will consist of one physician, one faculty member familiar with spinal stimulation and one biostatistician. None of the Board members will be directly involved with the study. The DSMB will meet semiannually to review all reportable events. If a SAE related to the study devices or procedures occur, an emergent DSMB meeting will held to assess whether the event meets the stopping rule criteria.

6.3.4. *Stopping Rules*

If a SAE occurs, that is deemed by the PI as being **related to the study devices or study procedure**; the study will be put on hold and reviewed by the DSMB to determine whether the study can continue.

6.4. Protocol Deviations/Violations

Any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency shall be reported to the IRB within 5 working days after the emergency occurred. Otherwise, deviations not meeting UPIRTSO criteria should be reported in summary form at the time of IRB continuing review.

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