Consent to Participate in a Research Study

TITLE: Spinal Cord Stimulation to Inhibit Afferent Feedback during Exercise in Hypertension

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You are invited to participate in a research study looking at whether stimulating the spinal cord through electrical signals can benefit people with high blood pressure while they exercise. You were selected as a possible participant because you have high blood pressure and are currently not taking medications for blood pressure or are taking a blood pressure medication that is on the inclusion list for this study. Your participation is completely voluntary.

To allow you to make an informed decision as to whether or not you want to take part in this research study, this document describes the purpose of the study, your rights and obligations, and the possible benefits and risks of participating in the study. Please take time to read the following information carefully. Feel free to talk with your doctor, family, or friends before deciding if you would like to take part. Please ask your study doctor if there is anything that is not clear or if you would like more information. Once you have decided that you want to take part, you will be asked to sign this consent form. You will be given a copy of this form to keep, and the original will stay at the study site.

This study is being conducted by Dr. Manda Keller-Ross and the Department of Physical Medicine and Rehabilitation. Boston Scientific is providing the stimulation devices used in the protocol and is providing partial funding for the study. A representative from Boston Scientific, the company who is supplying the stimulator leads and device, may be present during spinal cord stimulation part of the study.

Study Purpose

Spinal cord stimulation is a technique used to reduce pain for individuals with conditions that cause chronic pain. This is a very common and safe technique performed in pain clinics. Because of how spinal cord stimulation works to decrease pain, we believe that it may also work to reduce blood pressure during exercise.

The purpose of this study is two-fold. The first purpose is to determine if the change in blood pressure during exercise is different between older men and women. To determine this difference, blood pressure cuffs will be placed on both thighs during an exercise routine and inflated periodically. This provides information from the nerves of your muscles and how they affect the body's response to exercise. A blood pressure cuff will be placed on one of the fingers of your hand to measure blood pressure. We may also take manual blood pressures throughout the study.

The second purpose is to explore how well spinal cord stimulation lowers the increased blood pressure, changes in heart function, and changes in blood circulation that occur during exercise in individuals with high blood pressure. This study is looking at whether stimulating the spinal cord affects how blood pressure changes during exercise in individuals with high blood pressure.

If any new information arises that may change your mind about participating in or continuing with the study, we will tell you about it.

Study Length
If you choose to take part in the study, your participation will last up to 6 weeks.

Study Procedures
There will be a total of 3 visits. It is required to complete the Study Day 1 before participating in Study Days 2 and 3. At least one week will separate each study visit.

Study Day 1 –Consenting process, VO_2 test and lumbar MRI or Computed Tomography (CT) Scan (~2.5 hrs.)
You will be asked to report to the clinical research unit on the 1st floor in the Phillips-Wangensteen Building. The study procedures will be explained to you and all of your questions about the study will be answered. If you are still interested in participating in the study, you will sign the consent form and you will participate in the following tests and procedures:

- Your medical records will be screened and your medical history will be taken in order to confirm that you are eligible for the study.
- You will have your height and weight obtained by a study team member, and they will also check your blood pressure, heart rate, and breathing rate.
- You will have a blood draw for a complete blood count and to determine how well your blood is clotting. A total of two teaspoons of blood will be drawn from your arm during this study visit.
- You will complete a questionnaire about how active you are.
- You will breathe into a mouthpiece that will be similar to breathing into a scuba mask for the entire time that you are doing the exercise test.
- You will then perform an exercise test on a bike while breathing into a mouthpiece. Typically, the exercise test takes between 8 and 12 minutes. The following things may happen during your exercise test:
    - The amount of oxygen in your blood will be monitored using a small sensor that sits on your finger.
    - Your blood pressure will be monitored with a device that measures moment to moment changes in pressure. This will be measured by a sensor placed on one of your fingers.
    - Your heart rate will be measured through an electrocardiogram (ECG), which measures your heart rate using small, adhesive metal tabs that will be stuck to your skin, called electrodes.
    - You may also have electrodes stuck to the skin on both legs to measure your muscles' response to exercise.

- If you agree to participate in the spinal cord stimulation session, you will finish the visit by having an MRI or CT scan of your lower back at Fairview. This is done to confirm that there are no reasons why you would not be able to have the spinal cord stimulator leads inserted into the spine.
    - If you have a contraindication to MRI, you will have the option to undergo one CT scan procedure of your lower back to assess eligibility.
- If you feel you may need medication to help you undergo a MRI or CT scan, we will contact a study team physician to get medication prescribed for you. The physician will likely prescribe either Ativan or Valium. You will be asked to avoid solid foods for 6 hours and liquid up to 2 hours prior to taking the medication.
- If you are a minor or a pregnant woman you are not able to participate in the study.
- If you are female you may have to take a urine pregnancy test to confirm you are not pregnant prior to the MRI or CT scan. You may not be eligible for this study if you have participated in any other study that also included radiation exposure within the past 12 months, and you are responsible for informing the investigator of such involvement prior to beginning the proposed study.
- If you are taking prescribed medications you may be asked to take home a pill count sheet to document your medications during the duration of the study.

<u>Dynamic Exercise Only Session –Exercise with Intermittent Thigh Blood Pressure Measurements (~ 2 hrs)</u>

You will be asked to check in on the 1st floor of the Clinical Research Unit in the Phillips-Wangensteen Building. You will not need to fast prior to this exercise session.

- Electrodes will be placed on your skin to measure your heart rate and your muscles' response to exercise.
- You will be seated on a stationary bike and we will begin set-up of study procedures, including recordings of the amount of oxygen in your blood using finger sensor, blood pressure using finger sensor, heart rate and muscle activity using the electrodes.
- We will wrap blood pressure cuffs, which look like sleeves, around each of your upper thighs.
- You will breathe into a mouthpiece that will be similar to breathing into a scuba mask for the entire time that you are doing the exercise test.
- After a short period of rest, you will begin to exercise intermittently at a low intensity, this means that during exercise, you will still be able to talk. Occasionally, the cuffs on your thighs will be inflated. You will feel more pressure on your thighs as these cuffs are inflated. When you exercise, your muscles will release energy. This energy will be trapped in the muscle when the cuffs are inflated. You will also be asked to breathe the same non-toxic gas mixture (acetylene and helium) at various time points over the course of the study for 8 to 10 breaths to measure the amount of blood flowing through your heart and lungs.

<u>Dynamic Exercise and Stimulation Visit – Spinal Cord Stimulation during Exercise with Intermittent Thigh Blood Pressure Measurement (4-6 hrs.)</u>

You will be asked to check in at the University of Minnesota Medical Center, Fairview.

- A nurse will check your vitals.
- The anesthesiologist/neurosurgeon will speak with you and review the spinal cord stimulator procedure and the risks associated with the procedure. He will also review your MRI or CT scan results with you.
- The spinal stimulator leads (the part of the stimulator that is implanted during the procedure) will then be placed in the Operating Room.
    - You will be asked to lie on your abdomen (prone position).
    - Your back will be washed with a sterilizing solution (Chloraprep) and then draped with a sterile cloth to keep the area clean and prevent infection.
    - An x-ray machine called a fluoroscope will be used to take an x-ray of your spine to guide the placement of the leads.
    - Your lower back will be injected with a drug called lidocaine or a similar drug that is indicated by the physician will be injected into the skin of your lower back for the purposes of reducing the amount of pain associated with the procedure. Then another needle will be placed into the area around your spine.
    - Once the needle is properly positioned, the spinal stimulator will be passed through the needle and placed in the correct position. A second wire may be placed in the same manner.
    - Once these wires are placed, they will be connected to a power source and an electric current will be applied. This is a light, often pleasant tingling sensation felt in the legs and back.
    - Once the placement is completed, the needles will be removed from your back and the stimulator leads will be left in place and secured with tape.
    - When the experiment is complete, the leads will be easily removed by gently pulling them out. There is little to no pain involved with the removal, and it takes approximately 30 seconds.
- A thin tube called an arterial catheter will be inserted into a blood vessel in your wrist to constantly measure blood pressure. Blood samples will also be drawn through this tube intermittently. Eight tablespoons of blood will be drawn from your arm throughout the duration of this study visit. Prior to the placement of the tube, a drug called lidocaine or a similar drug that is indicated by the physician will be injected into the skin in that area to reduce the amount of pain associated with the procedure. An ultrasound machine might be used to put in the tube. The tube will be secured to your arm with an adhesive or nonadhesive bandage. You will be able to walk after the insertion of spinal cord leads and the tube in your blood vessel. The study team will walk with you to the exercise laboratory after these procedures. If you would prefer to go by wheelchair we will have one available.
- The exercise portion of the study will then begin. You will be breathing into a mouthpiece for the duration of the test. After a period of rest, you will begin exercising. Exercise will consist of sitting on a stationary bike, and exercising at a low-intensity for approximately 15-20 minutes. The blood pressure sleeves will be placed on your upper thigh and inflated intermittently. You will perform this exercise 3 times with 15-20 minutes of rest in between. The stimulator will be turned on to two different levels (high and low) during two exercise bouts and during one bout of exercise it will be turned off.

You might be able to tell that the stimulation feels different, but you will not be told which one is high frequency and which one is low frequency. You will feel a light, tingling feeling in your lower legs.

- Heart rate and oxygen content in your blood will be monitored using electrodes and a finger sensor.
- After the exercise is completed, the spinal cord stimulator wires and blood vessel tube will be removed.
- You will have the option of eating lunch prior to leaving for the day.

<u>The dynamic exercise and dynamic exercise and stimulation visits will be randomized between study day 2 and study day 3.</u>

Risks of Study Participation

This study has the following risks:

Exercise: The risks associated with vigorous exercise include abnormal heartbeats, shortness of breath and in very rare circumstances, worsening of high blood pressure symptoms, heart attack, stroke, or death.

Arterial Catheters: There is a minor risk of sudden blood vessel contraction, formation of a clump of blood in your blood vessel, bruises where the tube is inserted, infection at the site of the tube insertion, or interruption of blood flow to the hand. In the event of the formation of a major clump of blood in the blood vessels, surgical treatment may be required.

Blood draw: The risks of drawing blood include pain, bruising at the site of the blood draw, or in rare cases, infection at the site of the needle stick.

Breathing Gases: There are no known risks associated with breathing the non-toxic acetylene and helium gases for the measurement of blood flowing through the heart and lungs) in the small amounts used in the study.

ECG Electrodes: The adhesives from the electrodes may cause slight irritation to the skin. On rare occasions, the adhesive electrodes may cause an allergic reaction.

Thigh Cuffs: There are no known risks associated with the use of blood pressure cuffs on the thighs as used in this study.

Spinal Cord Stimulator Placement: Placement of the spinal cord stimulator will occur under medication that blocks sensation at the site of the needle insertion. 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. Soreness at the needle site may occur once the anesthesia wears off. On extremely rare occasions, nerve root/spinal cord trauma with the placement may occur that may lead to paralysis. There is also a risk that the needle may puncture the tough membrane surrounding the spinal cord, which can cause a headache called a "spinal headache." Spinal headaches can occur a day or two after the procedure. If you get a headache, contact the investigators regarding treatment.

The spinal cord stimulator devices have been cleared as safe and effective in the United States by the U.S. Food and Drug Administration (FDA). However, this is a new use of spinal cord stimulation, and the use of spinal cord stimulation to lower blood pressure has not been cleared by the FDA because of the experimental nature of this study. The devices we will be using for this study are provided by Boston Scientific.

Lidocaine, or A Similar Drug Indicated by The Physician, Administration for Anesthesia: A 2% solution of lidocaine will be used to block pain in the area of the insertion of the stimulator wires. The risks of injecting the lidocaine include pain, bruising at the site of the injection, or in rare cases, infection at the site of the needle stick.

Spinal Cord Stimulation: There may be mild discomfort from the electrical stimulation.

X-ray, Fluoroscopy and CT: As part of this study you will undergo one fluoroscopy procedure and *one CT scan if you are unable to have a MRI.* These procedures involve exposure to ionizing radiation. This radiation exposure is not necessary for your medical care and is for research purposes only. The average amount of radiation that the average person would receive from these procedures is 3 times that received from natural sources of radiation by a Minnesota resident in one year (3 mSv). **Risks of MRI**

MRI machines use a strong magnet and radiofrequency magnetic fields to take images of your body. The scanning process is similar to an x-ray or CT scan, but MRI does not use ionizing radiation (high-energy radiation that can potentially cause damage to DNA) like x-rays or CT scans. The risks associated with MRI scans are:

Projectiles: Objects with magnetic properties can be pulled into the magnet and turn into projectiles. To minimize this risk we ask that subjects remove all metallic items (watches, cell phones, hair pins, etc.) prior to entering the scanner and by controlling access to the scanner.

Claustrophobia: The scanner is a long narrow tube that may cause some people to feel claustrophobic. Either sedative or muscle relaxant will be administered to some participants with the indication of claustrophobia.

Hearing Damage: The noise generated by the operation of the scanner during a study is loud enough to cause hearing damage if you do not wear hearing protection. Hearing protection is required and is provided by the investigator.

Nerve Stimulation: Some people experience localized tingling, twitching, or muscle contractions during MRI scans. This is expected, but if it is uncomfortable please notify the investigator.

Disruption of Devices: Some devices can be damaged by magnetic fields and should not be brought into the scanner room. This includes some implanted devices such as pacemakers, cochlear implants, insulin pumps, nerve stimulators, etc. If you have any implanted device notify the investigator.

Heating of Devices: The radiofrequency waves used in MRI can heat conductive materials such as metal implants (screws, plates, rods, wires, artificial joints, etc.), certain tattoo inks, certain clothing fabrics, jewelry, medication patches, wigs, etc. You will be asked to remove

these items if possible. If they cannot be removed you will be asked to provide more information to allow MRI staff to be able to make determination on the safety of proceeding with the scan.

A thorough pre-scan questionnaire will allow us to minimize the risk of device disruption and heating. You will be in constant contact with the investigator and should notify the investigator immediately, via the squeeze ball, if you notice anything unusual, become claustrophobic, think that your hearing protection is not adequate, or if you experience nerve stimulation that is uncomfortable.

In addition, there is a risk of unknown effects related to participation in MRI research. Long-term effects of exposure to high magnetic fields are unknown. Most people experience no short-term ill effects from the strong magnetic field, but some people report dizziness, mild nausea, headache, a metallic taste in their mouth, or sensations of flashing lights. These symptoms, if present, subside shortly after leaving the magnet. If any sensations experienced during participation cause discomfort or pain, notify the researcher right away and your participation will stop and you will be taken out of the magnetic field. The risks of exposure to high magnetic fields are unknown for fetuses. Therefore, if you are a female who is capable of becoming pregnant, and you have any reason to believe that you might be pregnant, you should not participate in this study. With the use of sedatives you 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.

Discontinuation without Subject Consent
Under certain conditions, the study may be discontinued without your consent. If a condition arises that puts you at risk, we will stop the study immediately. This is for your safety.

Benefits of Study Participation
There are no direct benefits for participating in this study.

Notification of Significant New Findings

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

Alternatives to Study Participation
The alternative to participating in this study is to not participate or to withdraw from the study at any time after you have consented to participate.

Study Costs/Compensation
You will not be billed for any of the procedure that will be completed as part of the study.

You will be compensated for participating in this study. If all three study visits are completed, you will receive up to $325. You will not be compensated for visits that you do not complete.

Compensation will be released to you in the form of a gift card at the end of the visits. Study visit compensation breakdown: Initial session: $75.00, Dynamic Exercise session: $50.00 and Dynamic Exercise and Spinal Cord Stimulation: $200.00. The compensation is for the time you spend in the study.

If you start the study but stop prior to study completion, you will be compensated for the time that you did spend participating in the study.

Research-Related Injury
In the event that this research activity results in an injury or if you feel that you have suffered a research-related injury, notify a member of the study staff immediately. Treatment will be available including first aid, emergency treatment, and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury and that you may be eligible for reimbursement of some medical care costs, let the study physicians know right away.

Incidental Findings

The pictures created during this study are for research purposes. However, a Radiologist trained in reading the pictures will review all pictures collected during this study and the investigator in charge of this study will share your results with you and your physician. The pictures may also be placed in your medical record.

Confidentiality
The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. Your record for the study may, however, may be reviewed by Boston Scientific, who manufactures the spinal cord stimulation device, the Food and Drug Administration (FDA), and by departments at the University with appropriate regulatory oversight. In any publications or presentations, data will be de-identified and not include any information that would make it possible to identify you as a subject. The MRI may be included in your medical record, but any other information will not. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide us with that permission.

A description of this clinical trial is available on http://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that could identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Protected Health Information (PHI)
Your PHI created or received for the purposes of this study is protected under the federal regulation, known as HIPAA. Please refer to the attached HIPAA authorization for detail concerning the use of this information.

Voluntary Nature of the Study
Participation in this study is voluntary. Your decision whether or not to participate in this study will not affect your current or future relations with the University, Fairview or Boston Scientific. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

Who do I contact if I have question, concerns or feedback about my experience?
This research has been reviewed and approved by an Institutional Review Board (IRB) within the Human Research Protections Program (HRPP). To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625-1650 or go to www.irb.umn.edu/report.html. You are encouraged to contact the HRPP if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

☐ If you check this box then you are indicating to the study staff that you would like to participate in visit one (excluding the MRI and blood draws for CBC and INR) and the Dynamic exercise arm of this study *only*. This means that you will not participate in the Spinal Cord Stimulation and Exercise arm of the study. The amount that you will be paid for participating in the study will be reduced because the time that you are involved in the study will be less. You will be paid up to $100 for the study completion, $50 for visit one and $50 for the Dynamic exercise.

Statement of Consent

I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Name of Subject _____

Signature of Subject _____

Date _____

Signature of Person Obtaining Consent_____

Date _____