SPINAL CORD STIMULATION TO INHIBIT AFFERENT FEEDBACK DURING EXERCISE IN HEART FAILURE

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SPINAL CORD STIMULATION TO INHIBIT AFFERENT FEEDBACK DURING EXERCISE IN HEART FAILURE

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Study Product: *Precision Spinal Cord Stimulator System*

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IDE Number:

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IDE	Investigational Device Exemption
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
HF	Heart Failure
MOA	Mechanism of Action

Study Summary

Title	Spinal Cord Stimulation to Inhibit Afferent Feedback during Exercise in Heart Failure
Running Title	SCS during exercise in HF
IRB Protocol Number	14-002521
Phase	Pilot
Methodology	Single blinded, randomized-order study
Overall Study Duration	Two years
Subject Participation Duration	Two visits, at least one week apart, total time = 28-30 hours, includes one overnight stay
Objectives	To determine the influence of lumbar epidural spinal cord stimulation and optimal frequency parameters on blood pressure and its components (cardiac output and systemic vascular resistance) during exercise in HF patients.
Number of Subjects	40
Diagnosis and Main Inclusion Criteria	Heart failure: *Inclusion criteria* for HF patients includes: no history of dangerous arrhythmia's, not pacemaker dependent, body mass index $\leq 35 kg/m^2$, current non-smokers with <15 pack year history, non-pregnant women, and individuals who are able to exercise (i.e. without orthopedic limitations or musculoskeletal disorders).
Study Device	Device: Precision^{TM} stimulation system (or equivalent) , MOA: blocking locomotor afferent feedback to reduce blood pressure and systemic vascular resistance during exercise
Duration of Exposure	Temporary use. Device will be inserted on morning of visit 2, day one and will remain in place until the next morning after exercise: approximate 26-28 hours
Reference therapy	Reference is a placebo
Primary Endpoint	Mean arterial pressure as quantified as the mean computed over the last minute of each frequency challenge on Day 1 and Day 2
Statistical Methodology	The primary outcome measure will be tested using t-tests at the alpha=0.05 level of significance (two-sided). No interim analyses are planned.

1 Introduction

- This document is a clinical research protocol for human research that investigates the use of spinal cord stimulation to reduce systemic vascular resistance and blood pressure in heart failure patients during exercise.
- The described study will be conducted in compliance with the protocol, Good Clinical Practices standards and associated Federal regulations, and all applicable institutional research requirements.

1.1 Background

HF is a complex clinical syndrome involving multiple physiologic systems and is a leading cause of death in North America [1]. It has recently been suggested that the average life-span of a HF patient at the time of hospital discharge is ~5.5 years, with over 17% and 25% of patients having average life-spans of less than six months and one year respectively [2]. The average life-span varies considerably according to age, gender, baseline predicted mortality risk, left ventricular function, and comorbidity burden.

Exercise Intolerance in Heart Failure
Heart failure patients often are burdened with comorbidities involving the pulmonary, metabolic and neuromuscular systems [3, 4]. For example, exercise intolerance, manifested by symptoms of fatigue and dyspnea, is a hallmark feature in HF and is likely influenced by a hyper-active sympathetic nervous system (driven in part by afferent feedback from locomotor muscles). Although mechanisms contributing to exercise intolerance in HF are not completely understood, there is strong evidence to suggest that symptom limited exercise capacity may be an indirect result from alterations in skeletal muscle [5].

Skeletal Muscle Myopathy in Patients with Heart Failure
Skeletal muscle in HF patients demonstrates significant myopathy as the disease progresses, although some of these changes may be inherently due to deconditioning [6]. Alterations in skeletal muscle in HF, including atrophy of muscle fibers, a loss of type I (fatigue-resistant) and gain in type II (fast-fatigable) fiber area and decreased oxidative capacity [7], result in greater glycolytic metabolism during exercise. Enhanced glycolytic metabolic activity in the muscle will consequently increase the firing of mechano- (group III) and metabo- (group IV) receptors which send signals centrally via dorsal column of the spinal cord [8]. A unifying term for the combined influence of mechano- and metabo-reflex mediated responses is the ergoreflex. Globally, this reflex is known to contribute to the cardiovascular and ventilatory responses to exercise in health and disease.

Afferent feedback from Skeletal Muscle Contributes to Increases in Blood pressure
The idea that signals from contracting muscles govern cardiovascular response to exercise dates to seminal studies in the 1930's. Alam and Smirk showed that the increased arterial pressure during exercise was augmented by skeletal muscle ischemia and this response was maintained when exercise stopped but ischemia continued[9]. Since that time, numerous studies in animals[10-12] and humans[13, 14] have established the importance of afferent signaling from skeletal muscle in mediating the increase of sympathetic nerve activity and blood pressure during exercise. Importantly, skeletal muscle afferent activation has been shown to have a

stimulatory effect on sympathetic activity that is greater in HF compared with healthy controls[15]. For example, our laboratory has demonstrated that HF patients on optimal pharmacological treatments demonstrate an increased blood pressure response to metaboreflex stimulation after lower extremity exercise **(Figure 1)**[16]. In fact, it has been suggested that the ergoreflex in HF patients is closely linked to exercise intolerance resulting in increased dyspnea and sensations of fatigue (muscle hypothesis) [17].

Evidence of Blocking Afferent Feedback with Fentanyl on Ventilation in HF

HF patients demonstrate a greater ventilation for a given level of CO_2 production when compared to those without heart failure (high V_E/VCO_2 = low ventilatory efficiency). Reduced ventilatory efficiency in HF patients is known to be related to reduced exercise tolerance, poor prognosis, and increased mortality[18-20]. Recently, we have shown that the increased ventilatory response in HF patients during exercise is driven by augmented afferent feedback from locomotor muscles[21]. When locomotor muscle afferent feedback to the supraspinal centers is inhibited (via intrathecal injection of fentanyl), the ventilatory response to exercise is significantly reduced[22]. These studies demonstrate that locomotor afferent feedback is an important signal in modulating physiological responses during exercise and when blocked can be attenuated and potentially improve exercise capacity.

Impaired Peripheral Vascular Hemodynamics during Exercise in HF

Several studies have indicated that the ability for HF patients to vasodilate peripheral vasculature during exercise is impaired[23-27]. Patients with HF have an increased systemic vascular resistance and reduced limb blood flow during dynamic exercise when compared with healthy controls[23, 25]. Importantly, LeJemtel et al. (1986) demonstrated that maximal limb blood flow did not increase in HF after regional administration of phentolamine, α-adrenergic blockade, during exercise, suggesting the ability of the muscle vasculature to vasodilate is impaired[25]. Overactivation of the sympathetic nerve activity contributes to the reduced ability of the vasculature to vasodilate and thereby limits the reduction in the peripheral vasculature during exercise[28]. Group III/IV muscle afferents are a strong contributor to this excessive sympathoexcitation[29]. Further, spinal cord stimulation of the lumbar spine may inhibit locomotor group III/IV afferent feedback and ultimately improve systemic vascular resistance during exercise in HF.

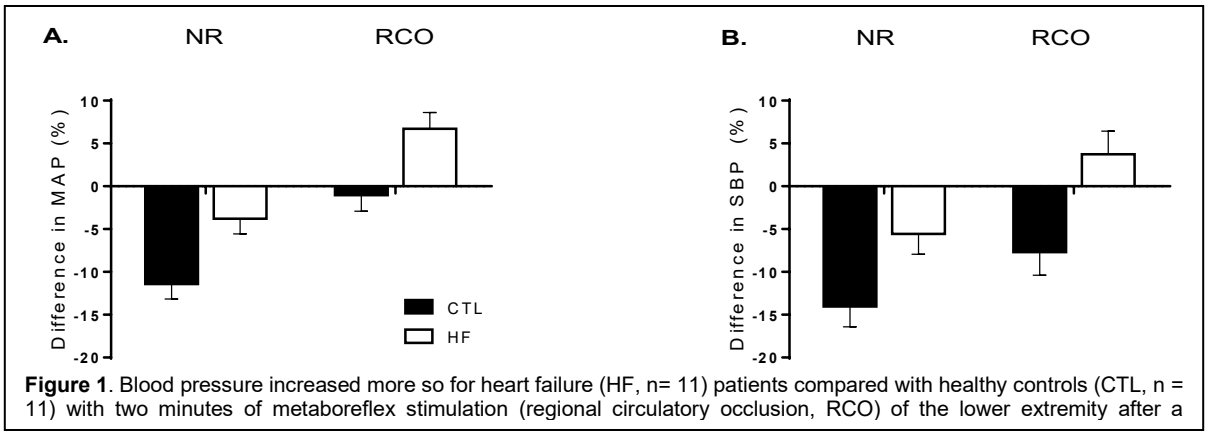


Figure 1. Blood pressure increased more so for heart failure (HF, n= 11) patients compared with healthy controls (CTL, n = 11) with two minutes of metaboreflex stimulation (regional circulatory occlusion, RCO) of the lower extremity after a

Modulating Afferent Feedback via Epidural Spinal Cord Stimulation

Modulation of afferent feedback via spinal cord stimulation has been used successfully for decades as a therapeutic approach for chronic pain; however, this is a novel therapeutic approach for use in patients with HF who demonstrate excessive cardiovascular responses to exercise. Several studies have demonstrated improvements in peripheral blood flow to the lower limbs in patients with peripheral vascular disease. Mechanisms causing the increase in blood flow are currently unclear, but two theories exist. One mechanism is that spinal cord stimulation attenuates sympathetic outflow, reduces vascular resistance and thus increases peripheral blood flow[30, 31]. The second mechanism is that spinal cord stimulation activates the ERK and AKT intracellular signaling pathways and releases GABA in the spinal gray matter that in turn, antidromically activates dorsal root afferent fibers[32]. These fibers increase peripheral vasodilation by releasing calcitonin gene-related peptide (CGRP) onto receptors on the blood vessel walls. In addition, CGRP activates nitric oxide-induced endothelium dependent vasodilation[33-35]. Recent studies also revealed that the capsaicin-sensitive sensory nerves (transient receptor potential vanilloid receptor (TRPV1) containing fibers; including unmyelinated C fibers and thin myelinated Aδ fibers are important in producing the spinal cord stimulation-induced vasodilation[36-38]. This proposal will be the first to investigate the influence of epidural spinal cord stimulation on peripheral locomotor afferent feedback during exercise in HF. Our preliminary results clearly demonstrate that spinal cord stimulation is safe and effective in healthy humans during exercise **(Figure 2).** In addition, we will identify specific stimulation parameters that will optimize inhibition of locomotor afferent feedback and promote optimal cardiovascular responses. In addition, there is also some evidence that somatic afferents from skeletal muscle and the kidney are tonically active and drive a number of cardiovascular and respiratory derangements in resting patients with HF and resistant hypertension, and these afferents are also a target for the proposed therapeutic stimulation.

1.2 Investigational Device

The Precision system will consist of a pulse generator that will not be implanted (external trial stimulator), temporary percutaneous leads, lead extensions, each packaged as a separate kit. The percutaneous 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 heart failure patients.

Class III Device - a device with the following characteristics:

- Risk: high; devices that present serious risk; most typically are implanted and life-supporting or life-sustaining, e.g. replacement heart valves, silicone gel-filled breast implants, cerebral stimulators
- Special FDA controls through Pre-market review: The pre-market review involves a comprehensive evaluation, including data from clinical studies, and is required to ensure safety and effectiveness prior to marketing of the devices. This involves bench and animal tests, clinical trials, the submission of a Premarket Approval Application (PMA).

Category A Device
A Category A device refers to an innovative device believed to be in Class III for which "absolute risk" of the device type has not been established (that is, initial questions of safety and effectiveness have not been resolved, and the FDA is unsure whether the device type can be safe and effective). **Note**: Category A devices ARE NOT eligible for Medicare coverage.

1.3 Clinical Data to Date

Keller-Ross ML, Johnson, BD, Joyner, MJJ, Olson, TP. Influence of the metaboreflex on arterial blood presure in heart failure patients. Am Heart J. In press. Heart failure patients (n=11, 51±15 yrs, mean ± SD) and CTLs (n=11, 43±9 yrs) completed two sessions. For both sessions, participants exercised at 60% of peak work for 4 minutes and then were randomized to either 2 minutes of normal passive recovery (NR) or 2 minutes of RCO. Our results demonstrated that metaboreflex stimulation (via regional circulatory occlusion, RCO) of the lower extremities increased blood pressure for HF patients but not for controls **(Figure 1).**

Furthermore, preliminary data from our laboratory demonstrates that the use of spinal cord stimulation at 100 and 1000 Hz during ischemic exercise and ergoreflex stimulation (RCO) caused a slight decrease in systemic vascular resistance and an increase in cardiac output with no changes in blood pressure. Data is not significant, however due to small sample size. Seven healthy adults (25 ± 2 yrs) participated in 3 sessions of performing ischemic calf-raises for two minutes and then RCO for two minutes (without exercise). Ischemia was produced by use of RCO of the proximal thigh bilaterally **(Figure 2).** The stimulator frequency was randomized to 100 Hz, 1000 Hz and off for the three separate sessions with 15 minutes separating the sessions. Hence, all sessions occurred on the same day. The spinal cord stimulator leads were inserted at L2-L3 interspace and advanced to the inferior aspect of T11. An 8-contact trial spinal cord stimulator was used.

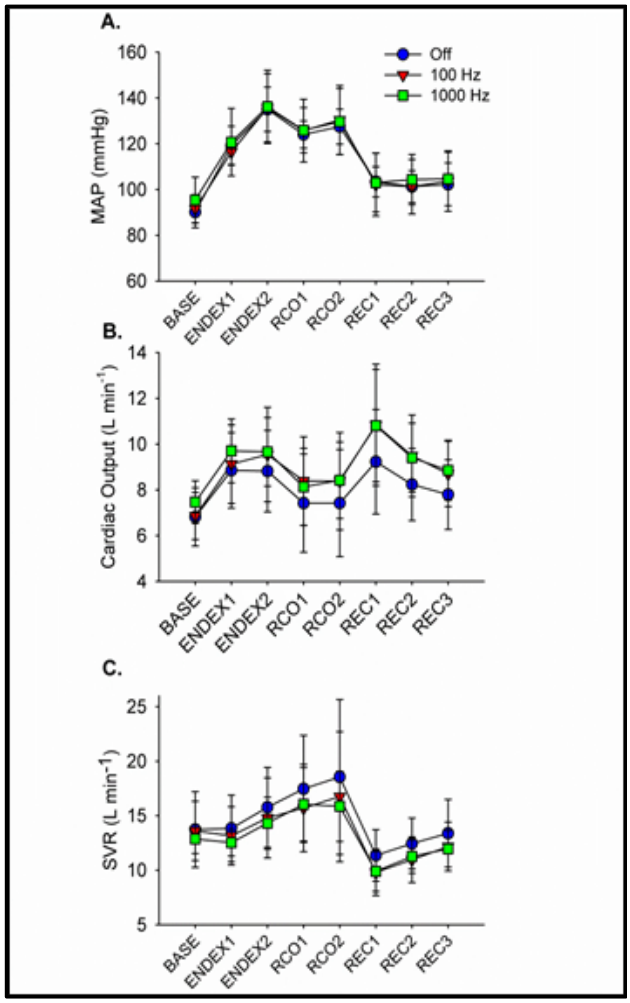


Figure 2. Mean arterial pressure (MAP) *(A)*, cardiac output *(B)* and systemic vascular resistance (SVR) *(C)* during exercise and ergoreflex stimulation in 7 (2 females) healthy adults. Base, resting conditions; ENDEX1, the end of the first minute of ischemic calf-raises; ENDEX2, end of the second minute of ischemic calf-raises; RCO1, end of the first minute of regional circulatory occlusion; RCO2, end of second minute RCO; REC 1, 2 and 3 are recovery time points at one, two and three minutes.

1.4 Study Rationale and Risk/Benefits

1.4.1 Study Rationale

Spinal cord stimulation is used clinically to treat chronic pain disorders [39, 40] and works by modulating afferent input at the dorsal column of the spinal cord [41]. Recently, evidence suggests that lumbar spinal cord stimulation produced a marked improvement in blood flow to lower limbs in patients with peripheral vascular disease [42, 43]. Therefore, the use of spinal cord stimulation may be an innovative technique to reduce the systemic effects of sympathoexcitatory afferent feedback from the active muscle causing a potential reduction in sympathetic activation or an increase in peripheral vasodilation. In this context, the purpose of this proposal is to determine whether epidural spinal cord stimulation can modulate cardiovascular control during exercise in HF. A secondary purpose is to develop optimal stimulation parameters to attenuate sympathoexcitation by attenuating the blood pressure response or reducing systemic vascular resistance during exercise and ultimately improve exercise tolerance in HF. Our rationale is two-fold: **first,** we seek to develop an experimental tool which will permit us to study the contributions of muscle afferents to cardiovascular control during exercise without administering narcotics; and **second**, we seek to explore technologies that may ultimately lead to "device therapy" that will improve exercise tolerance in HF and other patients with excessive sympathoexcitation at rest and during exercise. Currently, there are no minimally invasive devices that provide anti-hypertensive treatment to clinical patients. The risks associated with spinal cord stimulation are very low. Dr. Lamer has implanted over 1000 stimulators in adults at the Mayo Clinic with no adverse events. In addition, we have completed 8 spinal cord stimulation insertions on healthy adults for the intended purposes of this study without adverse effects. The benefits of the outcomes of this study significantly outweigh the risks. This device could prove to be an effective treatment modality for hypertension in clinical patients as well as improve tolerance to exercise (symptoms of dyspnea and fatigue upon exertion) in HF patients.

1.4.2 Anticipated Risks

Exercise: The risks associated with vigorous exercise, usually defined as exercise requiring an oxygen uptake ≥6 METS or 21 ml/kg/min[44] is associated with an increased risk of acute MI[45, 46] and sudden cardiac death[47, 48] compared with less vigorous and sedentary activity. The risk of an acute myocardial infarction (heart attack) during or immediately after an exercise test in patients with suspected cardiac disease is less than or equal to 0.04%.

Arterial Catheters: There is a minor risk of blood vessel spasm, formation of a clot, bruise, infection, or interruption of blood flow to the hand. In the event of a major clot formation in the vessels, surgical treatment may be required. In the event the arterial catheter cannot be successfully placed or needs to be removed, we will be utilizing a finger cuff for non-invasive blood pressure measurements. There are no known risks of this cuff, although, there may be mild discomfort similar to when a blood pressure cuff is inflated around the upper arm.

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

Breathing Gases: There are no known risks associated with breathing the cardiac output gas in the small amounts used in the study.

ECG Electrodes: The adhesives from the electrodes may cause slight irritation to the skin. In rare occasions, the adhesive electrodes may cause an allergic reaction. The subject will be encouraged to let the principal investigator or study personnel know if they are feeling any itching or burning sensations from the electrodes.

Thigh Cuffs: There are no known risks associated with the use of blood pressure cuffs on the thighs as used in this study, although there may be some mild discomfort similar to when you have a blood pressure cuff inflated on your arm.

Spinal Cord Stimulator Placement: Placement of spinal cord stimulator 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. Dr. Lamer has implanted over 1000 stimulators in adults at the Mayo Clinic with no adverse events. 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). In some cases, 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 stimulator. 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.

Spinal Cord Stimulation: Patients may feel mild discomfort from the electrical stimulation.

X-ray and Fluoroscopy: The spinal cord stimulator placement will occur under fluoroscopy. Patients will be exposed to low-levels of radiation. The amount of radiation that will be used has a low risk of harmful effects.

Magnetic Resonance Imaging: There is no radiation associated with MRI, but people who have metal devices like pacemakers cannot have an MRI and will not be able to participate in the study. Some people with claustrophobia may feel too closed in and may not tolerate MRI scanning. If participants feel too confined in the MRI scanner, they can inform the technologist and the MRI scan will be stopped. The MRI machine makes loud knocking sounds when it is scanning. Because of this the subject will be asked to wear earplugs while getting the scan. The earplugs minimize discomfort from noise and keep the noise levels within the safety range.

If a patient is regularly taking blood thinners or anticoagulant medications, to participate they will need to be able to come off them for the study. Their primary care physician will be

contacted to discuss if it is possible for the patient to come off this medications temporarily for the following time periods:

- Coumadin- 6 days prior to the procedure. The INR needs to be normal. Then the patient needs to be off the medication for the trial (2 days), for a total of 8 days off
- Clopidogrel (Plavix)-7 days prior to the procedure. Then the patient needs to be off for the trial (2 days), for a total of 9 days off
- Dabigatran (Pradaxa) -5 days prior to the procedure (total of 7 days off)
- Rivaroxiban (Xarelto) -4 days prior to the procedure (total of 6 days off)
- Apixiban (Eliquis)- 5 days prior to the procedure (total of 7 days off)
- Ticagrelor (Brilinta)- 5 days prior to the procedure (total of 7 days off)
- Aggrenox (Dipyridamole) - 7 days prior to the procedure (total of 9 days)
- Aspirin (ASA) - 6 days prior to procedure. This is a shared decision process. If the patient is taking ASA for secondary prophylaxis, they may remain on ASA

1.4.3 Potential Benefits

We are studying a group of highly symptomatic patients with HF. Spinal cord stimulation may improve exercise capacity, daily activity tolerance, and overall quality of life by reducing fatigue and allowing patients to be more active. Future patients with symptomatic exercise intolerance may also benefit from the results of this study (i.e. other cardiovascular diseases, COPD, etc...) If spinal cord stimulation is found to significantly improve symptoms in HF, without excessive risk, it may become common practice for this population.

2 Study Objectives

2.1 Primary Objective

To determine the influence of lumbar epidural spinal cord stimulation on blood pressure during exercise in HF patients. We will measure the influence of spinal cord stimulation on blood pressure response to lower extremity dynamic exercise with vascular occlusion (to stimulate the mechano- and metabo- reflex, i.e. ergoreflex). ***We hypothesize*** that blood pressure will be lower with spinal cord stimulation during exercise and activation of ergoreflex compared to without stimulation.

2.2 Secondary Objective

To develop optimal frequency parameters for attenuating blood pressure during exercise in HF patients. We will determine the optimal stimulation frequency parameters to attenuate the pressor response in HF. ***We hypothesize*** that blood pressure will be lower during higher frequencies of stimulation (~ 1 KHz) vs lower frequencies (100 Hz).

3 Study Design

3.1 General Design

Forty HF (>18 yrs. of age) will be recruited. The study will include a total of 2 visits. All experiments will take place at the Mayo clinic; at the outpatient radiology for MRI screening,

the Charlton CRU for surgical suite for spinal cord stimulation placement and the Saint Mary's Hospital CRU for clinical exercise laboratory for the exercise protocol and overnight stay.

Study visit 1 will include eligibility screening, consenting process, completion of an activity questionnaire and health questionnaire and performance of a peak VO_2 test. Additionally, subjects will undergo a screening lumbar MRI to ensure that there are no anatomical anomalies in or around the epidural area consistent with standard clinical practice for epidural stimulator lead placement associated with chronic pain syndromes. Study day one will take approximately 3 hours.

Study visit 2 will include an overnight stay in the CRU. Patients will check in to the CRU in the morning of ***day 1, visit 2***. Prior to placement of stimulating electrodes an INR will be checked to ensure safe clotting. An INR of < 1.5 will be required in order to continue with study procedures. An anesthesiologist will place the electrodes in the lumbar/thoracic epidural space in a manner that is standard for the clinical placement of temporary electrodes in humans. This will be done using local anesthesia with (2%) lidocaine and fluoroscopy to guide lead placement. After electrode placement, an arterial catheter will be placed in the radial artery for arterial blood pressure measurements by an anesthesiologist or respiratory therapist from the Anesthesia Clinical Research UnitThe participants will then transfer to the clinical exercise laboratory to start the exercise protocol. Participants will rest 15 minutes prior to starting exercise. Exercise will take place on a vertical bike where they will perform a submaximal cycling exercise at 30% of peak work for 29 minutes. In order to stimulate the mechano- and metabo-reflex (ergoreflex), thigh tourniquets will be placed on the proximal thigh bilaterally and inflated intermittently to pressures of 80 mmHg (See figure 3). In addition, the stimulator frequency will be turned on at two different frequencies ((~100 Hz – ~ 1 KHz, randomized) throughout the exercise. Studies performed in humans with use of spinal cord stimulation have indicated that frequencies up to 10 KHz are safe for humans [49-51]. Measures of arterial blood pressure, heart rate, ventilation (V_E) and gas exchange will be measured continuously throughout the exercise. Cardiac output (via the open-circuit acetylene wash-in technique), arterial blood gases, catecholamines and lactate will be measured intermittently throughout (see experimental paradigm). Systemic vascular resistance will be quantified by calculating MAP/CO.

On day two of visit two, participants will repeat testing from day one with new randomization to determine reliability of testing performed on day one. After the exercise on day two of visit two, the spinal cord stimulator leads will be removed by an anesthesiologist (Dr. Lamer or Dr. Hoelzer). The radial arterial catheter will be removed by an anesthesiologist or a respiratory therapist from the Anesthesia Clinical Research Unit. . Patients are free to leave the hospital once they feel recovered from exercising.

3.2 Primary Study Endpoint

- Mean Arterial Pressure (see operationalized definition in Section 7)

3.3 Secondary Efficacy Endpoint

- Systemic Vascular Resistance

3.4 Primary Safety Endpoints

Data will be collected to determine:

- Incidence of all serious adverse events including unanticipated adverse device effects
- Incidence of device failures and malfunctions

4 Subject Selection, Enrollment and Withdrawal

4.1 Inclusion Criteria

Heart Failure patients with reduced ejection fraction:

- 18-90 yrs.
- Men and women
- History of ischemic or idiopathic dilated cardiomyopathy (duration > 1 yr.), stable for >3 mo and New York Heart Association Class I-III.
- Not pacemaker dependent
- BMI ≤35 kg/m^2
- EF < 40%
- Stable on optimal medications for > 3 mo.
- Current nonsmokers with < 15 pack year history
- Individuals who are able to exercise (i.e. without orthopedic limitations or musculoskeletal disorders)

  Patient Management/Cardiac Medications: Patients will need to be on standardized, state of the art, optimized therapy. This was the approach taken by the large successful NIH supported *HF Action Trial* (Mayo was one of many sites)[52]. Any potential subject that has not been on state of the art therapy will be put on optimized therapy and subsequently maintained on this for a minimum of 3 mo prior to study entry. Changes to the management for whatever reason after "optimization" will require an additional 30 days prior to entry. The standard of care for patients with stable class II - III HF due to systolic dysfunction generally includes the use of ACE inhibitors, diuretics, digoxin and beta-blockers. A-II receptor blockers are frequently used for patients who cannot tolerate ACE inhibitors, usually due to cough. The majority of our preliminary data has been collected on local patients managed at Mayo who are on standard HF medications, although the population and etiology of HF was not as homogenous as proposed in these studies. Although these medications may influence cardiopulmonary interactions in various ways, we feel it is important, practical and safe to study these patients under conditions of optimal care. All standard pharmacotherapeutic agents for HF have effects on the neurohormonal modulation of this disorder. However, concurrent withdrawal of ACE-inhibitor, beta-blocker, digoxin and diuretic would likely be associated with modest decompensation in a high proportion of patients. Accordingly, the impact of our studies will be applicable to a HF population receiving standard optimized therapy. All patients will be managed by their primary care physician or cardiologist with additional review by Dr. Barry Borlaug (Co-Investigator) prior to enrollment to ensure inclusion and exclusion criteria have been satisfied and participation in exercise testing is safe.

4.2 Exclusion Criteria

All participants:

- History dangerous arrhythmias
- Women that are currently pregnant
- Patients taking prescribed opioid medications or have had a fusion or laminectomy at L3 or above.
- Patients with a recent drug-eluding stent
- History of spinal stenosis, lumbar radiculopathy, or peripheral neuropathy will be excluded from this study due to potential complications associated with the spinal cord lead implantation.
- Must not currently be taking blood thinners or anticoagulant medications. If a patient is on such medications, their primary care physician will be contacted to discuss if it is possible for the patient to come off this medications temporarily for the following time periods:
    - Coumadin- 6 days prior to the procedure. The INR needs to be normal. Then the patient needs to be off the medication for the trial (2 days), for a total of 8 days off
    - Clopidogrel (Plavix)-7 days prior to the procedure. Then the patient needs to be off for the trial (2 days), for a total of 9 days off
    - Dabigatran (Pradaxa) -5 days prior to the procedure (total of 7 days off)
    - Rivaroxiban (Xarelto) -4 days prior to the procedure (total of 6 days off)
    - Apixiban (Eliquis)- 5 days prior to the procedure (total of 7 days off)
    - Ticagrelor (Brilinta)- 5 days prior to the procedure (total of 7 days off)
    - Aggrenox (Dipyridamole) - 7 days prior to the procedure (total of 9 days)
    - Aspirin (ASA) - 6 days prior to procedure. This is a shared decision process. If the patient is taking ASA for secondary prophylaxis, they may remain on ASA.

4.3 Subject Recruitment, Enrollment and Screening

Subject Recruitment: The majority of HF patients will be recruited from the Heart Failure (HF) Clinic and the Cardiovascular Health Clinic (CVHC) in the Division of Cardiovascular Diseases of Mayo Clinic, as well as from the surrounding community. Presently, the HF Clinic averages over 150 new patients per month, assesses over 2,000 HF patients per year, and admits over 700 HF patients to the hospital practice per year. The CVHC performs over 40 treadmill exercise tests with gas exchange monthly on patients with reduced LV function. In addition, approximately 30% of our rehabilitation population has reduced LV function.

4.4 Early Withdrawal of Subjects

4.4.1 When to Withdraw Subjects

A patient may be withdrawn from the study at any time, before or after implantation of the spinal cord stimulator, and prior to that subject completing all of the study related procedures. Because of the invasive nature of this study, investigators will do everything

possible to avoid withdrawing patients from this study after implantation. Some reasons to withdraw may include:

- Subject safety issues and adverse device effects or complications
- Failure of the subject to adhere to protocol requirements
- Subject decides to withdraw from the study (withdrawal of consent)

Investigators may choose to replace that subject with a newly enrolled subject in order to maintain sample size.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a patient withdraws from the study for any reason, and cannot or will not complete the investigational aspects of the study, they will be withdrawn from the study with immediate follow-up to be sure of no adverse events related to study procedures.

5 Study Device

The precision system will consist of a pulse generator that will not be implanted, temporary percutaneous leads, surgical paddle 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 heart failure patients.

5.1 Description

Features of the Precision SCS System Include:

- Stimulation electrode field navigation
- Sixteen independent current-controlled electrodes
- High-range parameter capability
- No detectable latex

Implantable Pulse Generator
The precision implantable pulse generator is intended to electrically stimulate the spinal cord. The multi-channel, multi-electrode device capability provides flexibility in conjunction with ease of programming. Because this device is intended for permanent placement in chronic pain patients it is implantable. The device will not be implanted in this study, but will be secured to the patient's skin by adhesive tape until the study procedures are completed.

Percutaneous Leads
The eight-contact percutaneous leads are available in lengths of 30 cm, 50cm, and 70cm. Each lead has eight electrode contacts located near the distal end. Each contact is 3 mm from the adjacent contact. 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 heart failure patients. The physician will be provided with a new Precision Kit for each participant. The physician that will be inserting the leads has been adequately trained to do so and has performed this procedure on over 1000 patients at the Mayo Clinic for chronic pain indications.

Percutaneous Lead Placement in the Epidural Space
1. Position, prep and drape the patient in the usual accepted manner. Inject a local anesthetic at the needle insertion site.

2. Under fluoroscopic guidance, place the insertion needle into the epidural space with the bevel facing up using an angle of 45° or less.
WARNING: The angle of the insertion needle should be 45° or less. Steep angles increase the insertion force of the stylet and also present more of an opportunity for the stylet to pierce the lead and cause tissue damage.

3. Remove the needle stylet from the insertion needle and verify entry into the epidural space using the standard technique.

4. OPTIONAL. Under fluoroscopic guidance, insert the lead blank through the insertion needle and into the epidural space. Advance the lead blank to verify entry into the epidural space, and then withdraw the blank.

5. While holding the lead stylet handle, place the steering cap over the proximal end of the stylet handle with moderate force until it is held in place. Then slowly insert the lead, with stylet, through the insertion needle. The lead stylet should extend to the tip of the lead.

6. OPTIONAL. If exchange of the lead stylet is desired, carefully pull out the existing stylet and insert the preferred stylet. While inserting the stylet into the lead, if resistance is encountered, withdraw the stylet approximately 3 cm, rotate the lead and/or stylet, and gently advance the stylet. If resistance is still encountered, repeat the above procedure.

Connecting the OR cable Assembly
The OR cable assembly is designed for temporary connection of a lead to the Trial Stimulator. A cable extension is provided. When using a Splitter 2x8 prepare two OR Cable Assemblies.

CAUTION: *Do not immerse the OR cable connector or plug in water or other liquids. The OR Cable Assembly is intended for one-time only use; do not resterilize.*

1. If two leads are being implanted, wrap the non-sterile “1-L” and “2-R” labels around the cables at the Trial Stimulator to identify lead connections.

2. Verify that the Trial Stimulator is off.

3. Check that the locking lever on the OR cable connector is in the open position, marked "0".

4. For Percutaneous Leads, remove the steering cap from the stylet and slide the proximal end of the lead with stylet, or splitter, into the open port on the OR cable connector.

5. Push the end of the lead or splitter into the port until it stops. Hold the lead in place while sliding the lever to the locked position, marked "1".

6. Plug the OR Cable Assembly into the corresponding Trial Stimulator port(s) labeled "1-L" (left) and "2-R" (right). Superior (upper or left) leads connect to port "1-L". Inferior (lower or right) leads connect to port "2-R". If only a single lead is being used, connect it to "1-L".

Note: *If using a Splitter 2x8, connect the cable labeled "1-L" to the laser-marked tail, and the cable labeled "2-R" to the unmarked tail.*

7. Proceed to the instructions for "Intraoperative Stimulation Testing" page 23.

Intraoperative Stimulation Testing

Note: *The following steps are for procedural reference only. Please refer to the BionicNavigator Software Guide for detailed stimulation testing procedures and guidelines.*

1. If using a splitter:
• Visually check splitter to leads connection
• Check impedance
Note: *If using the 2x4 Splitter, make note of splitter configuration in the BionicNavigator™ software per Splitter Programming Guide.*

2. After linking the Clinician Programmer to the Trial Stimulator, check impedances to verify that components are properly connected. Lead impedance is measured and displayed for each of the IPG's 16 electrode contacts. Impedances over 4500 Ohms are considered to be resultant from open or unconnected wires, displayed with an X.

3. Using test stimulation, enlist patient feedback to verify lead placement and pain coverage.

Note: *If lead repositioning is necessary, turn stimulation off before proceeding.*

4. Reposition leads as necessary. If using a splitter, gently pull on lead attached to splitter to reposition caudal or disconnect splitter from leads, re-insert stylet, and advance leads to reposition cephalad.

CAUTION: *Do not force stylet into lead.*

5. Steer lead to new position.

6. Remove stylet, wipe proximal ends of leads and reconnect splitter.

7. Check impedances.

8. Repeat steps 1-3 if lead has been repositioned.

9. When the desired paresthesia is achieved:
a) Turn the Trial Stimulator off.
b) Unlock each OR cable connector and disconnect from the lead(s).
c) For percutaneous lead(s) – slowly withdraw the stylet(s).

10. Record the lead position by capturing a fluoroscopic image to be sure the leads have not moved. Retest if necessary.

11. If using a splitter, disconnect splitter from leads. Insert the hex wrench and turn the set screw counter clockwise to loosen.

Note: *• The set screw should only be loosened to an amount sufficient to insert a lead.*

• Do not excessively loosen the set screw. This may cause the set screw to dislodge, rendering the splitter unusable.

5.2 Method for Assigning Subjects to Treatment Groups

- The participants (both HF and Controls) will all undergo the same procedures. The stimulation frequency will be randomized within each trial.

5.3 Preparation and Administration/Implantation of Investigational Device

All participants will receive the same device; there will not be a sham procedure or device. On study visit day one, consent for the study will be obtained as well as other study procedures (Refer to figure 1). On study visit 2, day one, the spinal cord stimulator leads will be implanted in the morning in the CRU at the Mayo Clinic. The device will be on during exercise periods. Participants will exercise on day one and two of study visit two and then the leads will be removed before the patient is released from the study.

5.4 Subject Compliance Monitoring

Subjects will remain in the hospital overnight and will be monitored throughout.

5.5 Prior and Concomitant Therapy

We will collect information on current medications at the baseline visit. There will not be restrictions on medications for heart rate/rhythm and blood pressure that can be used during the study in heart failure patients.

5.6 Packaging and Labeling

All devices and components to be used in this study are market-approved, and will be obtained from the manufacturer Boston Scientific in their original packaging. Labeling includes the device model and serial number.

"CAUTION – Investigational Device. Limited by Federal (or United States) law to investigational use"

The label shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings and precautions and be affixed to the investigational device.

5.7 Masking/Blinding of Study

Participants will be blinded to the frequency of stimulation as well as other stimulation parameters during the study.

5.8 Receiving, Storage, Distribution and Return

5.8.1 Receipt of Investigational Devices

The Precision kit will be obtained from the manufacturer Boston Scientific. Upon receipt of the devices, inventory and logs will be managed by study personnel to maintain device accountability. Any damaged or unusable devices will be exchanged and documented.

5.8.2 Storage

The precision kit will be stored in their original packaging at room temperature in containers by study personnel. They will be marked with the required labels and relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings and precautions.

5.8.3 Distribution of Study Device

The precision kit will be distributed to the implanting physicians and their team before the procedure. The specific serial numbers will be documented. Devices will only be distributed immediately before the procedure.

5.8.4 Return or Destruction of Study Device

At routine intervals and at the completion of the study, there will be a reconciliation of devices shipped, devices utilized, and devices remaining. This reconciliation will be logged

on the Device Accountability form, signed and dated. Any discrepancies noted will be documented, the sponsor-investigator will be notified and an investigation will be conducted to determine the cause of the discrepancy. Devices destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Visit 1

Study visit 1 will include eligibility screening, consenting process, completion of an activity questionnaire and health questionnaire and performance of a peak VO_2 test. Additionally, subjects will undergo a screening lumbar MRI to ensure that there are no anatomical anomalies in or around the epidural area consistent with standard clinical practice for epidural stimulator lead placement associated with chronic pain syndromes. Study day one will take approximately 3 hours.

6.2 Visit 2

Study visit 2 will include an overnight stay in the CRU. Patients will check in to the CRU in the morning of ***day 1, visit 2***. An anesthesiologist will place the electrodes in the lumbar/thoracic epidural space in a manner that is standard for the clinical placement of temporary electrodes in humans. This will be done using local anesthesia with (2%) lidocaine and fluoroscopy to guide lead placement. After electrode placement, an arterial catheter will be placed in the radial artery for arterial blood pressure measurements by an anesthesiologist or a respiratory therapist from the Anesthesia Clinical Research Unit. The participants will then transfer to the clinical exercise laboratory to start the exercise protocol. Participants will rest 15 minutes prior to starting exercise. Exercise will take place on a vertical cycle ergometer where they will perform a submaximal cycling exercise at 30% of peak work for approximately 30 minutes. In order to stimulate the mechano- and metabo-reflex (ergoreflex), thigh tourniquets will be placed on the proximal thigh bilaterally and inflated intermittently to pressures of 80 mmHg at 3 min intervals and deflated for 5 min to allow for wash out (See figure 3). In addition, the stimulator frequency will be turned on at two different frequencies, a high (~1 KHz) and low (~100 Hz) frequency throughout the exercise. Measures of arterial blood pressure, heart rate, ventilation (V_E) and gas exchange will be measured continuously throughout the exercise. Cardiac output (via the open-circuit acetylene wash-in technique), arterial blood gases, catecholamines and lactate will be measured intermittently throughout (see experimental paradigm). Systemic vascular resistance will be quantified by calculating MAP/CO. Barry Borlaug, a HF cardiologist will be available during the experimental sessions.

On day two of visit two, participants will repeat testing from day one with new randomization to determine reliability of testing performed on day one. After the exercise on day two of visit two, the spinal cord stimulator leads will be removed by an anesthesiologist (Dr. Lamer or Dr. Hoelzer).. The radial arterial catheter will be removed by the supervising physician or a respiratory therapist from the Anesthesia Clinical Research Unit. Patients are free to leave the hospital once they feel recovered from exercising.

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.

At least one week will take place between study visit one and two.

Study Procedures

Peak Oxygen Consumption Testing (VO_2 peak) (Visit 1): We will use a modified graded cycle ergometry protocol with increases in intensity of 20 watts / 3 minutes (HF patients) or 40 watts every 3 minutes (CTL) to volitional fatigue. We will use this test to determine specific submaximal workload intensities (30% of peak VO_2) for the subsequent individual study visit. Our laboratory has extensive experience with exercise testing in clinical HF patients.

Measurement of Blood Pressure (Visit 2): We will use an indwelling 20 gauge arterial catheter placed in the radial artery of the non-dominant hand. 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 will be flushed continuously at 3 cc/hr w/sterile saline. This catheter will allow for continuous real-time intra-arterial measurement of beat-to-beat blood pressure. In the event that an arterial line cannot be placed, or it has to be removed during the overnight stay of visit 2, non-invasive continuous blood pressure measurements will be made using the Finapres or Nexfin monitoring systems. Either system utilizes a finger cuff to provide beat by beat blood pressure determination as well as other hemodynamic parameters.

Measurement of Cardiac Output and Systemic Vascular Resistance (All Visits): During the measurement of gas exchange and ventilation as described above, cardiac output will be measured using the open-circuit acetylene (C_2H_2) gas wash-in technique as described by Stout et al. [53] and refined by Gan et al. [54] and Nielson et al. [55] and validated in our laboratory [56]. We have demonstrated that the open-circuit technique for measurement of cardiac output is accurate, reproducible, and sensitive. *Systemic vascular resistance* will be calculated by MAP/CO.

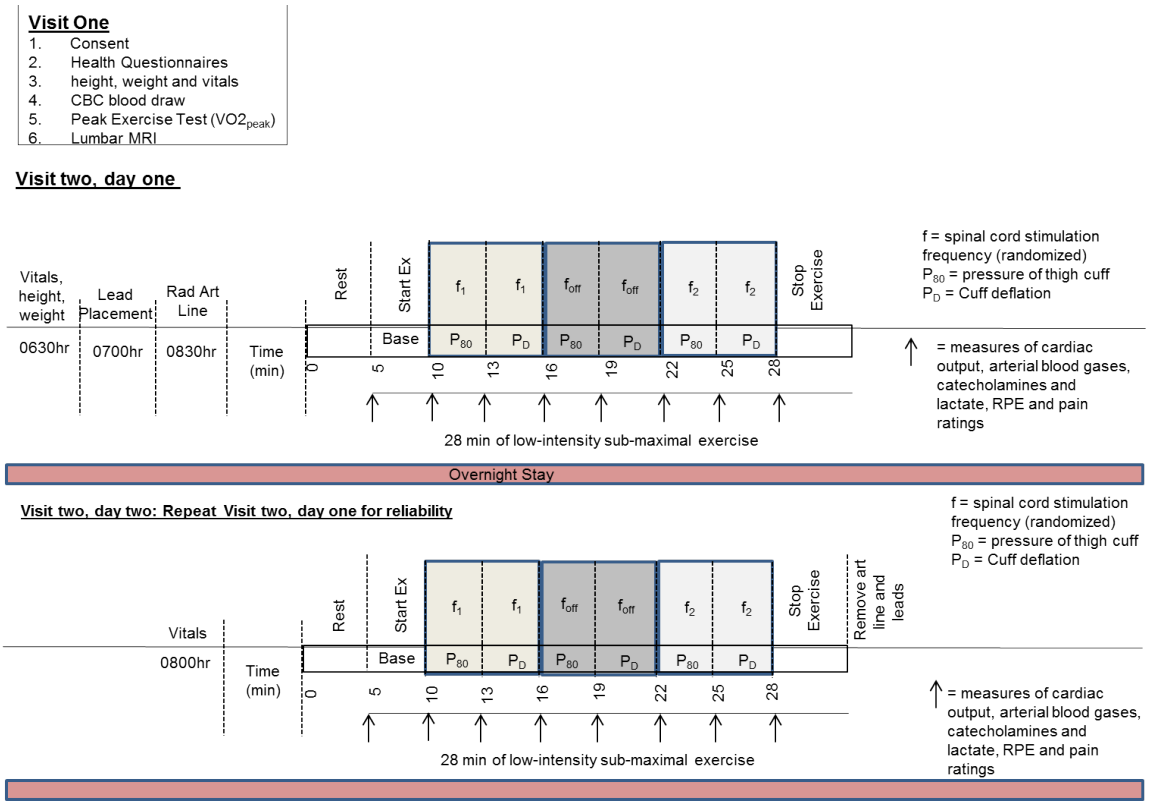
Measurement of Gas Exchange and Ventilation (All Visits): Volume of oxygen consumed (VO_2), volume of carbon dioxide produced (VCO_2), breathing frequency (fb), tidal volume (V_T), minute ventilation (V_E), partial pressure of end-tidal oxygen and carbon dioxide ($P_{ET}O_2$ and $P_{ET}CO_2$, respectively) and derived variables (e.g. V_E/VO_2 and V_E/VCO_2) will be measured using a low resistance open circuit automated metabolic system (Medical Graphics Co., St. Paul, MN) integrated with a mass spectrometer (Perkin Elmer, model 1100). A formal validation of this system has been performed using Douglas bags, Tissot, and calibration gases for measurement of V_E, VO_2 and VCO_2. Volume calibration will be performed with a 3-liter syringe and gas calibration performed with manufacturer recommended gases of known concentration.

Measurement of Arterial Blood Gases, catecholamines, lactate, and heart rate (Visit 2, Day 1 & 2): We will use an indwelling 20 gauge arterial catheter placed in the radial artery of the non-dominant hand. 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 will be flushed continuously at 3 cc/hr w/sterile saline. This catheter will provide access to arterial blood for measurement of blood gases (pH, $PaCO_2$, PaO_2, and oxygen

saturation), catecholamines and lactate. Participants will be instrumented with a 12 lead ECG for the measurement of heart rate and rhythm. Participants will be verbally encouraged to reach maximal effort, determined by the respiratory exchange ratio (RER >1.10) and a rating of perceived exertion ≥ 18 on the Borg 6-20 scale [57].

Measurement of Perceived Exertion and Dyspnea (All Visits): Dyspnea will be measured using the modified Borg analog/visual scale. Because perception of dyspnea consists of sensory (intensity) and affective (unpleasantness) dimensions we will use a scale which provides a number, text description, and picture description of each progressive level of dyspnea during exertion as previous described [58-60]. In addition, we will include measurements of total body fatigue and specific leg fatigue. For this we will use the traditional and well validated Borg scale of perceived exertion. These scales has been used extensively over the last 40 years and are validated for the determination of dyspnea and fatigue during exercise [57]. In addition, we will use the Faces Pain Scale-Revised (FPS-R) during visit 2.

Figure 3. Study Procedures



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Schedule of Events			
Study Activity	**Visit 1**	**Visit 2:day 1**	**Visit 2:day 2**
Consent	X		
History	X		
Physical Exam	X	X	X
Case Report Forms	X	X	X
VO_2 peak exercise test	X		
Exercise	X	X	X
Rating of perceived exertion	X	X	X
Rating of dyspnea (labored breathing)	X	X	X
Rating of pain		X	X
Device Implantation		X	
Device in place		X	X
Stimulation during exercise		X	X
Device removal			X
EKG	X	X	X
Measurements of gas exchange	X	X	X
Measurement of cardiac output with open-circuit acetylene	X	X	X
Arterial line in place / finger cuff		X	X
Concurrent Medications	X	X	X
Adverse Events		X	X
Serious Adverse Events		X	X

7 Statistical Plan

7.1 Sample Size Determination

The sample size is estimated to be 40 participants. The calculation and assumptions made are detailed below.

Statistical Hypotheses
Null hypotheses: The one minute mean MAP measured at times 12, 20 and 28 minutes on day 1 will be equal.

Alternative hypothesis: The contrast testing if the MAP averaged over frequencies 1 and 2 is different than the MAP measured with the device inactive.

Statistical notation: Let mu_f_1, mu_f_2, and mu_f_{0ff} denote the low, high and off frequencies for each patient. The hypotheses of interest, are then as follows:

H0: $(mu\_f_1 + mu\_f_2)/2 = mu\_f_{Off}$
Ha: $(mu\_f_1 + mu\_f_2)/2 < mu\_f_{Off}$

Assumptions:

- Primary endpoint: Mean arterial pressure (MAP) obtained as the one-minute mean pressure measured at the end of each frequency, 80% cuff challenge (12-13 minutes for f_1, 20 – 21 minutes for f_{Off}, and 28-29 minutes for f_2).
- Sample size formula for a one sample t-test
- Two-sided testing at the alpha=0.05 level of significance
- No interim analyses

To estimate the sample size, we assume that the change between the device off setting and the mean MAP for the two active frequencies will be similar to the change observed in a recently completed study examining the effects of Fentanyl. In this study, the mean±SD MAPs at end exercise in the placebo and Fentanyl conditions were 111±13 and with 103±17, respectively. We expect the correlations in the within subject measurements to be high, but we conservatively estimate the correlation to be 0.5 (to allow the SD of the change to be equal to the SD of the pooled estimate) and assume the larger SD will be the pooled estimate (SD = 17) (i.e., estimated difference in HF will be 8±17). This effect size of 0.471 requires 38 participants to achieve 80% power with the assumptions listed above. To account for potential attrition and measurement issues, we will plan to enroll 40 participants.

7.2 Statistical Methods

Descriptive Statistics

Analysis / Interpretation

General Statistical Methods. HF patients will undergo submaximal exercise and ergoreceptor activation with spinal cord stimulation at different frequency parameters to target afferent neural feedback. Continuous variables will be presented as mean±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 as sensitivity analyses to the planned primary analysis. Analyses will be conducted with SPSS (v19 or higher) and The SAS System (v9.4 or higher).

Primary Outcome Analysis. The one minute mean MAP measured at the end of the three frequency challenges on day 1 will be the compared using a blocked (on subject) ANOVA model. The estimated mean MAP for each of the three frequencies will be estimated by the model. The primary hypothesis will test if the pooled effect of the active frequencies (f1, f2) is statistically different from the MAP with the device inactive. This test will be conducted using a type III estimate of the contrast indicated above in the sample size section. This is considered the omnibus test of the device effect. 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 strictly superior in all subjects). Therefore, further analysis will be done to determine the association between the MAP and frequency of spinal cord stimulation to understand the dose-response curve.

Handling of Missing Data

Every effort will be made to ensure missing data is kept at a minimum. When entering data into the database, outliers or invalid data will be investigated to check accuracy. Because of the relatively small size of this study, it should be feasible to keep missing data below 5% and avoid the use of imputation.

Level of Significance and Multiplicity Adjustment

The primary outcome will be tested at the alpha=0.05 (two-sided) level of significance. No correction will be applied to secondary or exploratory analyses conducted (i.e., comparisons of each frequency to the inactive state).

Interim Analysis

There is no plan to conduct an interim analysis or stop early. This is a cross-over design so analysis would be difficult without participants having crossed over to the opposite group.

7.3 Subject Population(s) for Analysis

Subject population for analysis will be any subject (HF patient or control participant) who is randomized, implanted with the device, and completed both halves of the crossover study.

8 Safety and Adverse Events

All adverse events occurring during the study, including those not meeting the criteria of an Unanticipated Adverse Device Effect (UADE) will be recorded on the appropriate case report form. Records of these events will be maintained and reports submitted to the FDA and IRB according to the regulatory requirements. Expected clinical adverse events and nonsignificant (not serious) clinical adverse events will not be reported. Expected clinical adverse events and anticipated adverse device effects are those listed in Section 1.5.2.

8.1 Definitions

Unanticipated Adverse Device Effect (UADE)
A UADE is 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 IDE 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.

Adverse Effect (Event)
Any untoward medical occurrence in a subject involved in clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study related treatment(s).

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as an unanticipated adverse device effect unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the local investigator should instruct each subject to report, to the local investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The local investigator should notify the study regulatory sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the local investigator should become aware of the development of problems, cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets all of the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data.
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or

event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected.

- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event Reporting Period

For this study, the study treatment follow-up period will end on day two of the final visit. No further monitory for adverse events will be performed after the final visit

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Study subjects will be routinely questioned about adverse effects at study visits. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF*)* or in a separate adverse event worksheet. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of the treatment group if applicable or suspected causal relationship to the investigational device or if applicable other study treatment or diagnostic product(s) will be recorded in the subjects' case history. For all adverse effects sufficient information will be pursued and or obtained as to permit; an adequate determination of the outcome, an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable other study treatment or diagnostic product. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Sponsor-Investigator Reporting of Unanticipated Adverse Device Effects and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

The sponsor-investigator will promptly review documented Unanticipated Adverse Device Effects and as necessary shall report the results of such evaluation to FDA within 10 working days and Mayo IRB within 5 working days of initial notice of the effect. Thereafter the sponsor-investigator will submit such additional reports concerning the effect as requested.

8.3.1 Sponsor-Investigator Reporting, Notifying Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

8.3.2 Sponsor-Investigator Reporting: Notifying the FDA

The sponsor-investigator will report to the FDA all unanticipated adverse device effects according to the required reporting timelines, formats and regulations.

The sponsor-investigator will submit a completed FDA Form 3500A to the FDA's Center for Devices and Radiological Health for any observed or reported adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to the DSMB and all participating sub-investigators.

The completed FDA Form 3500A will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the sponsor-investigator first receives notice of the adverse effect.

If the results of the sponsor-investigator's follow-up evaluation shows that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the sponsor-investigator will submit a completed FDA Form 3500A as soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the sponsor-investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of any previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the sponsor-investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

Reporting Process
Unanticipated Adverse Device Effect reports will be submitted on FDA Form 3500A.
The contact information for submitting reports is:

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Deviations from the investigational plan.

The sponsor-investigator shall notify Mayo IRB (see 21 CFR 56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a subject

in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor-investigator is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB notification in accordance with 21 CFR 812.35(a) also is required.

8.4 Unblinding Procedures (Breaking the Blind) (as necessary if the study is blinded)

Every effort will be made to maintain blinding of patient in this study. The study participant will not be able to determine the differences in stimulation frequency parameters of the device.

8.5 Stopping Rules

The study may be stopped if it becomes apparent that patients in the trial (in either group) are developing worsening heart failure symptoms, or needing hospitalization for heart failure which is reasonably felt by the investigators to be related to the spinal cord stimulation.

8.6 Medical Monitoring

It is the responsibility of the sponsor-investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see Section 10 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data comprise all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

9.3 Case Report Forms

A Case Report Form (CRF) will be completed for each subject enrolled into the clinical study. The investigator-sponsor will review, approve and sign/date each completed CRF; the investigator-sponsor's signature serving as attestation of the investigator-sponsor's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not obliterate, erase, or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management

Data will be managed electronically in a secure database to maintain patient data confidentiality and compliance with the Health Insurance Portability and Accountability Act (HIPAA).

Data Processing

Data processing will be performed by study personnel via medgraphics for gas exchange data and lab chart for blood pressure and heart rate analysis.

Data Security and Confidentiality

Data will be encrypted and secured with individual logins and passwords for study personnel, with auditing and logging of changes and modification times.

Data Quality Assurance

Data will be verified at the time of entry into the database using a combination of double-entry, and computerized validation methods to ensure accuracy and reduce outliers or missing data.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for:

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717, whichever is longer.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

As a service to the sponsor-investigator, this study will be monitored during the conduct of the trial by staff from the Mayo Clinic Office of Research Regulatory Support. Clinical trial monitoring may include review of the study documents and data generated throughout the duration of the study to help ensure the validity and integrity of the data along with the protection of human research subjects. This will assist sponsor-investigators in complying with Food and Drug Administration regulations.

10.2 Auditing and Inspecting

The sponsor-investigator will permit study-related monitoring, audits, and inspections by the IRB, the monitor, and government regulatory agencies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The sponsor-investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as a sponsor-investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed and dated by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

This study is being financed primarily by Boston Scientific and Mayo Ventures.

12.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

12.3 Subject Stipends or Payments

Subject remuneration will be $750.

13 Publication Plan

Mayo and Investigators reserve the right to publish the result of work completed under this protocol. Prior review of the proposed publication by Boston Scientific will be provided, but in the interest of free exchange of scientific information, Mayo and Investigators may publish after the expiration of thirty (30) days following mailing of the proposed publication to Boston Scientific. Publication of the results will not include Confidential Information of Boston Scientific without the permission of Boston Scientific. In addition, Boston Scientific shall have the right to publish independently the results of the Study, provided, however, Mayo shall be the first to publish. In addition, any publication of data from the Study by Boston Scientific shall be considered a joint publication with Mayo as the co-author. After the publication of the primary paper, further ancillary studies using data collected in the trial may be analyzed and published by Mayo and Investigators.

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