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Co-Investigators:	Timothy Brennan, MD Mark Dyken, MD Seth Holwerda, PhD Gary Pierce, PhD Rahul Rastogi, MD Saul Wilson, MD
Title of Study:	Investigating Mechanisms of Human Spinal Cord Stimulation for the Purpose of Treating Restless Leg syndrome
Study Center:	University of Iowa
Estimated number of subjects:	50 adults between the ages of 18-80

I. Introduction

The overall goal of this proposed study is to evaluate the underlying mechanisms of neural control of blood flow in the lower extremities in humans with restless leg syndrome (RLS). At least 15% of the general public suffers from RLS and many more may go undiagnosed. This unfortunate disorder leads primarily to a disturbing sensation within the patient's lower extremities that requires movement for relief (1, 2). The central hypothesis of our study is that physiological changes in lower limb blood flow as a result of thoracolumbar epidural Spinal Cord Stimulation (SCS) lead to the relief of RLS.

Patients aged 18-85 years with (n=25) and without RLS (n=25) that have recently having undergone Spinal Cord Stimulation (SCS)implantation (thoracolumbar) for chronic pain will be recruited from the Departments of Anesthesia and Neurosurgery, University of Iowa Hospitals and Clinics. The rationale for studying both RLS patients and non-RLS patients with chronic back pain is to initially test the effectiveness of Spinal Cord Stimulation (SCS) on lower limb blood flow in the absence of symptoms of RLS. In the non-RLS patients, we could determine if SCS does in fact alter limb blood flow. We hypothesize that RLS patients have altered muscle sympathetic nerve activity (MSNA) and blood flow correlating to severity of RLS symptoms, which will then be modulated by Spinal Cord Stimulation (SCS), allowing for resolution of symptoms in RLS with MSNA-mediated improvements in leg blood flow. We also hypothesize that SCS in RLS patients will reduce 24-hour ambulatory blood pressure in parallel with reductions in MSNA.

II. Background

Epidural spinal cord stimulation (SCS) is an exciting clinical therapy employed by a wide range of physicians. In the United States, the primary indication for implantation is chronic pain. In Europe, the primary indication is angina. Clinical observations have provided inferences about the underlying mechanisms evoked by (SCS) that explain its effectiveness; however, a gap in the literature remains in regards to the physiological mechanisms of how SCS works for relieving pain due to the limited number of basic science research groups involved in studies related to SCS. Nonetheless, the high efficacy of SCS for the treatment of chronic pain of the trunk and limbs continues to be highlighted in meta-analyses and published reviews (4, 5).

As pain is the most common reason for implantation in the United States, there is significant expertise and interest in the mechanisms of SCS for relieving pain by Dr. Tim Brennan and Dr. Rahul Rastogi in the Department of Anesthesia. There is also great interest in further understanding mechanisms of spinal cord stimulation with regard to pain and motor behaviors within the Department of Neurosurgery, by Dr. Chandan Reddy and Dr. Marshall Holland. As a result of these synergistic interests, there has been a great partnership between the Departments of Anesthesia and Neurosurgery leading this charge, which led to recent and ongoing publication regarding the role of high frequency SCS performed in human patients here at the University of Iowa (3).

Restless leg syndrome (RLS), also known as Willis-Ekbom disease, is a common disorder of periodic limb movement that affects up to 15% of the population and is characterized by a distressing urge to move the lower extremities during sleep or rest (4, 5). While many cases are able to be treated effectively by community family physicians, the more severe cases require expertise provided by specialized neurologists. This unfortunate disorder leads primarily to a disturbing sensation within the patient's lower extremities that requires movement for relief (6, 7). RLS is often categorized as primary or secondary. Primary RLS is more likely to occur in younger people (peak age of onset approximately 20 years of age) and often has a strong family history with up to 60% of patients having a family member with the disease. The more prevalent secondary RLS develops in adulthood (peak onset of 40 years of age) and is typically associated with chronic disease such as iron deficiency, chronic renal failure, diabetes mellitus, liver disease, rheumatologic conditions, peripheral neuropathy, and even pregnancy. As the growth of the proportion of elderly increases, so to shall the prevalence of the chronic diseases that predispose the development of RLS (2).

Treatment of this disease has proven to be highly difficult. As the understanding of its pathophysiology continues to be delineated there is hope that further pharmacotherapy can be developed (8-10). Dopamine agonists remain the mainstay of pharmacotherapy (11)and is well established as a peripheral vasodilator (12). Previous studies have demonstrated peripheral vasodilation effects of spinal cord stimulation (13, 14). We believe that there is an underlying common mechanism between vasodilation and symptomatic relief of RLS. This study provides us with a unique opportunity to not only explore a potential novel therapy, but also delineate the underlying neural mechanism of blood flow control that could be exploited

for other physiological and pathophysiological investigation. To our knowledge, this will be the first study to test the novel idea of using epidural SCS to treat symptoms of RLS.

III. Statement of Compliance

This study will be conducted in compliance with the protocol, Good Clinical Practice and the applicable Food and Drug Administration and other Department of Health and Human Services regulatory requirements.

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection and Good Clinical Practice training.

IV. IRB Oversight

Human Subjects Office / IRB
J. Andrew Bertolatus, MD
Hardin Library, Office 105
600 Newton Rd
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V. Location of Study Procedures

University of Iowa
200 Hawkins Drive
Iowa City, Iowa 52242

VI. Main Hypothesis

We hypothesize that epidural SCS will reduce symptoms in patients with RLS, and that this reduction is due to decreases in MSNA and improvement in leg blood flow.

Aim 1: To determine the extent to which epidural SCS decreases MSNA and improves lower limb blood flow and arterial stiffness inpatients treated with thoracolumbar epidural SCS for chronic back pain.
Hypothesis 1a: Thoracolumbar epidural SCS will abolish MSNA as measured by peroneal nerve microneurography to the lower limbs in patients with chronic back pain.
Hypothesis 1b: Thoracolumbar epidural SCS will increase femoral artery blood flow as measured by Doppler ultrasound and calf blood flow as measured by venous occlusion plethysmography after SCS in patients with chronic back pain.
Hypothesis 1c: Thoracolumbar epidural SCS will decrease leg arterial stiffness as measured by femoral-dorsalis pedis pulse wave velocity after SCS in patients with chronic back pain.

Aim 2: To determine the extent to which epidural SCS decreases MSNA and improves leg blood flow and arterial stiffness and reduces symptoms in patients with RLS.
Hypothesis 2a: Thoracolumbar epidural SCS will increase femoral artery and calf blood flow and reduce leg arterial stiffness inpatients with RLS.
Hypothesis 2b: Thoracolumbar epidural SCS will improve severity of clinical symptoms in patients with RLS.

Aim 3: To determine the extent to which SCS decreases 24-hour ambulatory blood pressure.
Hypothesis 3: Thoracolumbar epidural SCS will decrease 24-hour ambulatory blood pressure to a greater extent in patients with RLS compared with patients without RLS.

VII. Main Screening Criteria

Patients aged 18-85 years with and without RLS that have recently having undergone Spinal Cord Stimulation (SCS)implantation (thoracolumbar) for chronic pain will be recruited from the Departments of Anesthesia and Neurosurgery, University of Iowa Hospitals and Clinics.

VIII. Recruitment procedures

Patients will be identified as potential subjects in Neurosurgery or Pain clinic. The potential subject will then be approached by a member of the research team to discuss the study. After the study is thoroughly explained and all questions are answered, the subject will be asked to sign a formal written consent.

Patients will be drawn from the general pool of patients undergoing spinal cord stimulation for chronic pain. Of this pool for already implanted patients, those patients who additionally have restless leg syndrome (RLS) will serve as the experimental population, while those patients who do not meet criteria for RLS will serve as the control population.

IX. Inclusion Criteria

- All subjects will be between the ages of 18-85.
- All subjects will have the mental capacity to understand and decide to participate in the research.
- All subjects will recently have undergone or are planning to undergo SCS implantation (thoracolumbar region) for chronic pain, as defined by standard clinical criteria used by the UIHC Pain Clinic for neuromodulation therapy (having failed conservative measures, surgery, and other interventional pain procedures).

Group 1 and 2 will be divided based on if they have Restless Leg Syndrome (n=25) or do not have Restless Leg Syndrome (n=25, control group).

X. Exclusion Criteria

- <18 or >85 years of age
- Non-English speakers

XI. Study Procedures

For RLS subjects will be instructed to discontinue their RLS medications 48 hours prior to visits #1 & #2.

For Visit 1: The subject will arrive to the CRU for their appointment which will take 4 hours. The subject will have been fasting for 8 hours, refrain from moderate or vigorous exercise for at least 24 hours, refrain from drinking alcohol for at least 24 hours prior to the visit. Any female subjects will undergo a urine pregnancy test prior to the study beginning. If the pregnancy test is positive, the subject will no longer be eligible to continue with the study. DEXA scan will be done. Subject will be asked to wear comfortable clothes that doesn't contain any metal or reflective surfaces as this may skew the results. Subjects will lay on the table. The procedure will take 10-15 minutes. An IV catheter will be placed in the subject's arm by a RN, after 20 minutes the nurse will draw blood from the IV catheter to measure sugar, insulin, cholesterol, and catecholamine. A blood pressure cuff will be placed around the subject's upper arm and blood pressure will be recorded 2-3 times. 3 EKG stickers will be placed on the subject's chest so that heart rate and rhythm can be monitored. A non-invasive tonometer probe will be placed on the subject's wrist, arm, neck, upper/inner thigh, and ankle to record the pulse at these sites. The blood flow to the subject's arm or leg may also be measured by placing a probe on the skin over the femoral artery of the leg or the brachial artery of the arm. Transcutaneous recordings will be captured to measure oxygen and carbon dioxide by placing monitors on the subject's chest and foot. Calf blood flow using venous occlusion plethysmography (VOP): VOP will be used to measure calf blood flow (CBF) responses to local ischemia to test endothelium-dependent dilation of calf resistance arteries. Briefly, subjects lie supine and have blood pressure cuffs (venous occlusion) placed around upper thigh and pediatric blood pressure cuffs around ankle. CBF will be measured by placing a gallium-in-silastic strain gauge around the widest part of the calf which measures small changes in calf volume during periodic inflation (8 secinflated:4 sec deflated) of upper thigh cuffs to 40 mmHg (which temporarily prevents venous outflow and measures arterial inflow into calf) and continuous ankle inflation of a blood pressure cuff to 250 mmHg. VOP is a well-established and validated technique for measuring limb response to ischemia in human subjects and is expressed in ml/100 ml tissue/min. Calf vascular conductance, to determine blood flow adjusted for mean arterial pressure, will be calculated as blood flow/mean arterial pressure, expressed as ml/min/100mmHg. If the subject is taking any morning medications, the research team may ask the subject to not take them in the morning but bring them with to the study and take at the end of the visit. At the end of visit 1, the participant will be sent home with a 24-hour ambulatory blood pressure monitor (AMBP) that will be worn for 2 days; one with the stimulator on and one with the stimulator off.

For visit 2: The subject will arrive to the CRU for their appointment which will take 4 hours. The subject will have been fasting for 8 hours, refrain from moderate or vigorous exercise for at least 24 hours, refrain from drinking alcohol for at least 24 hours prior to the visit. Any female subjects will undergo a urine pregnancy test prior to the study beginning. If the pregnancy test is positive, the subject will no longer be eligible to continue with the study. An IV catheter will be placed in the subject's arm by a RN, after 20 minutes the nurse will draw blood from the IV catheter to measure sugar, insulin, cholesterol, and catecholamine. A non-invasive tonometer probe on will be placed on the subject's wrist, arm, neck, upper/inner thigh, and ankle to record the pulse at these sites. The blood flow to the arm or leg may also be measured by placing a probe on the skin over the femoral artery of the leg or the brachial artery of the arm. Transcutaneous recordings will be captured to measure oxygen and carbon dioxide by placing monitors on the subject's chest and foot. The subject's heart rate will be measured by using an ECG and the subject's blood pressure will be monitored indirectly with an automatic cuff device on one of the subject's fingers. The sympathetic nervous system activity to the subject's leg muscles will be measured by a tiny microelectrode placed in a nerve in the right leg located just below the knee on the outer part of the leg. When the nerve is stimulated, an involuntary twitching or tingling sensation of the lower leg or foot will occur. The sensation will disappear when the stimulation is stopped. When the nerve is located 2 tiny sterile microelectrodes will be inserted through the skin. VOP (venous occlusion plethysmography) testing to measure calf blood flow. If the subject is taking any morning medications, the research team may ask the subject to not take them in the morning but bring them with to the study and take at the end of the visit. If DEXA scan hasn't been completed during visit 1, it will be completed during visit 2. Subject will be asked to wear comfortable clothes that doesn't contain any metal or reflective surfaces as this may skew the results. Subjects will lay on the table. The procedure will take 10-15 minutes.

Ambulatory blood pressure cuff visit: A visit for the placement of a Continuous ambulatory blood pressure cuff may be added for any willing participants. A subset of participants will only be completing the Continuous ambulatory blood pressure cuff study and will sign a separate consent form. Participants will complete a diary (data collection sheet) while wearing the blood pressure cuff that will include time of activities, sleep, and time of SCS activation and deactivation. Participants will be given a shipping box with postage to return the blood pressure cuff and diary if unable to physically return to the Clinical Research Unit. The time of this visit will take place at the convenience of the participant. While wearing the Continuous ambulatory blood pressure cuff, participants will refrain from any RLS medications (48hours).

Enrolled subjects are eligible to come back for a third unscheduled visit to complete study related interventions that were not completed during the scheduled two visits if they wish.

XII. Possible Risks of the Study

Emotional or psychological: There are no foreseeable emotional or psychological risks with this study. But there is risk of inadvertent disclosure of PHI which could cause emotional or psychological risk.

Physical: The nerve recording procedure (microneurography) occasionally may result in the leg muscles feeling tired. Also, the patient may have a pins-and-needles feeling or a greater sensitivity to touch in the leg. However, these side effects rarely occur and do not usually last more than a couple of minutes. The ambulatory blood pressure monitor may cause some discomfort and could potentially bruise or scratch the participant's arm, though this is not very common.

The potential risk and discomfort from the blood draw may result in any of the following to occur slight bruising, pain, a temporary feeling of faintness, and rarely an infection at the site of the blood draw.

The pulse wave velocity has no known risks associated with the use of the non-invasive pulse transducer, but the ECG electrodes that are used may cause minor irritation to the skin

Fasting for 8 hours prior to participating in the study may cause dehydration. You will be encouraged to drink plenty of water, subjects may experience hunger and irritability. if the subject would experience nausea, vomiting, or fainting the subject will be instructed to stop fasting.

Legal or social: There are no foreseeable legal or social risks with this study.

XIII. Adverse Event Reporting:

The University of Iowa requires Investigators to collect and report to the University of Iowa IRB if any of the following occur:

- An unanticipated problem involving risks to subjects or others is any event or problem that:
  1) was unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB- approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied AND
  2) suggests that the research places subjects or others (those not directly involved in the research such as research staff or family members) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized AND
  3) is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research).
  4) Serious adverse drug event (either expected or unexpected) occurring in a UI subject
  5) If a subject is enrolled by U/VAHCS investigators, the investigator must report to the UI IRB either serious adverse drug events or unexpected adverse drug events. By definition, these events must be associated with the use of the drug.
  6) An unexpected adverse drug event is any adverse drug experience (associated with the use of the drug), the frequency, specificity, or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information provided to the subjects and the IRB

- A serious adverse drug event is any adverse drug experience (associated with the use of the drug) occurring at any dose that results in any of the following outcomes:

  1) Death
  2) Life-threatening adverse drug experience
  3) Inpatient hospitalization or prolongation of existing hospitalization
  4) A persistent or significant disability/incapacity
  5) A congenital anomaly/birth defect
  6) Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

- Receipt of new information
  During the course of a study, researchers may become aware of new information that would impact a subject's decision to participate or continue participating in the research study. For example, interim analyses of data may identify a trend which impacts the safety of subjects or may identify early efficacy (benefit) of one of the interventions under study. In addition, results from other research studies or changes in standards of practice or care may affect conduct of a study and would need to be communicated to research subjects.

- Noncompliance
  Noncompliance is a failure to follow the federal regulations with respect to protection of human subjects in research or failure to follow the determinations of the IRB with respect to conduct of the research as approved by the IRB.

Once per year, the IRB is required to review and approve all non-exempt research projects at intervals appropriate to the degree of risk, but not less than once a year. This is called "continuing review." Continuing review for non-exempt research is required to occur as long as the research remains active for long-term follow-up of the research subject, even when the research is permanently closed to the enrollment of new subjects and all subjects have completed all research-related interventions and to occur when the remaining research activities are limited to collection of private identifiable information.

Adverse Event Collection:

The clinical research team is responsible for collecting and recording the research data. As the results are collected, all adverse events will be identified after an informed consent is signed by the subject or their legally authorized representative (LAR) and the medication is initiated.

Throughout the study, during all follow-up visits, in addition to the medical chart review, adverse events are to be elicited by the investigator (or designate) by asking the subject non-leading questions. All AEs and SAEs will be reported to the principal investigator (PI) and the PI will determine the final relationship of the event to the investigational product.

XIV. Data Management

The following people/agencies may have access to subject data/records:

- Study team
- Federal government regulatory agencies
- Auditing departments of the University of Iowa
- The National Institute of Health

To protect confidentiality, we will assign each subject a study ID. All records will be in a locked cabinet in a locked office or password protected computer system. Data and records will be managed as follows:

- Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.) - Whenever possible, subject identifying information will be blacked out on all paper or hard copy records and replaced with the subject's unique study identifier. Paper records will be stored in a locked file cabinet in the study team's locked office.
- Electronic records (computer files, electronic databases, etc.) – All electronic data bases will only be accessed by the study team and available only with a username and password assigned to study team by the PI.

XV. Subject Safety

- To minimize risks all subjects are carefully pre-screened and screened trying to identify any factors that could contribute to increased risk.
- All testing is completed at University of Iowa Hospitals and Clinics by a very experienced and well-trained staff and monitored by the Principal Investigator.
- All confidential information is kept in locked offices and password protected computers only available to study team members.
- The participant has contact information and study team members available 24/7.

XVI. References

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14. Wu M, Linderoth B, Foreman RD. Putative mechanisms behind effects of spinal cord stimulation on vascular diseases: a reviewof experimental studies. Auton Neurosci. Feb 29 2008;138(1-2):9-23.