Official Title: Repetitive Acute Intermittent Hypoxia for Spinal Cord Repair

NCT ID Number: NCT03780829

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KEY SUMMARY INFORMATION ABOUT THIS STUDY

You are being invited to take part in a research study that is being funded by the Department of Veterans Affairs. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive. Taking part in this study is completely voluntary.

This research study is investigating the effects of breathing low oxygen (hypoxia) and upper limb training on arm and hand function. In this study, you will be breathing low levels of oxygen for repeated short intermittent periods of time (also known as repeated acute intermittent hypoxia, rAIH) followed by training to improve upper-extremity function in individuals with chronic incomplete cervical spinal cord injuries. This study also involves the use of TMS (transcranial magnetic stimulation) and is not FDA approved for how it is being used in this study.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

By doing this study, we hope to learn how to facilitate recovery of arm and hand movements by using repetitive intermittent hypoxia and exercise training. Your participation in this research could vary. If you choose to participate in experiment one, you will be asked to participate in 2 sessions lasting approximately 2 hours. If you choose to participate in experiment two, you will be asked to participate in approximately 7 sessions lasting 2 hours. For our first aim, you may be asked to participate in 2 sessions that last 2 hours/day. For this aim, your total research time is 4 hours. For the second aim, we may ask you to participate in 7 sessions for 2 hours a day that can be spread out across 3 months.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

This study is being conducted to determine if repetitive intermittent hypoxia (r-AIH) and exercise training can enhance the beneficial effects of arm and hand training on improving limb function in persons with spinal injury. Your participation may help medical research determine methods for improving hand movement and function. The information obtained from your participation may help others in the future. For a complete description of benefits, refer to the Detailed Information section of this form.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

As with any experimental procedure, there may be adverse events that are currently unknown and some of these unknown risks could be permanent, severe, or life threatening. Procedures in this study may cause all, some or none of the risks or adverse events listed. Rare, unknown, or unforeseeable (unanticipated) risks also may occur. There are no direct benefits to you from your taking part in this research study. However, the information we get from this study might help us treat future patients. The most common risks of participation are:

- Mild discomfort at the stimulation site and associated muscles
- Hypoxia may result in feeling light-headed, dizzy, changes in vision, changes in spasticity, or euphoria (a feeling or state of intense excitement and happiness).

- Upper limb exercise training may experience changes in spasms or spasticity, soreness, and fatigue that may last up to three days.

Please see "POSSIBLE RISKS OR DISCOMFORTS" below for all risks and discomforts.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits, or rights you would normally have if you chose not to volunteer.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of the study is (Principal Investigator) [redacted] the principal investigator. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his/her contact information is: [redacted]

DETAILED INFORMATION ABOUT THE STUDY

WHAT IS THE PURPOSE OF THIS STUDY?

The study is being conducted to look at recovery of arm and hand movements by using rAIH and exercise training. You are being asked to participate in a research study investigating the effects of intermittent hypoxia and upper limb training on arm strength and function. Other studies suggest that rAIH and exercise training may improve arm and hand motor function in persons with spinal cord injury.

HOW LONG WILL I BE IN THE STUDY?

This research study is expected to take approximately 2 years. Your individual participation in the project will take anywhere from 2 days 2 hours each day to 7 days (2 hours each day) depending on which experiment you are in. These days can span out across weeks and months if needed.

WHAT WILL HAPPEN IF I TAKE PART IN THE STUDY?

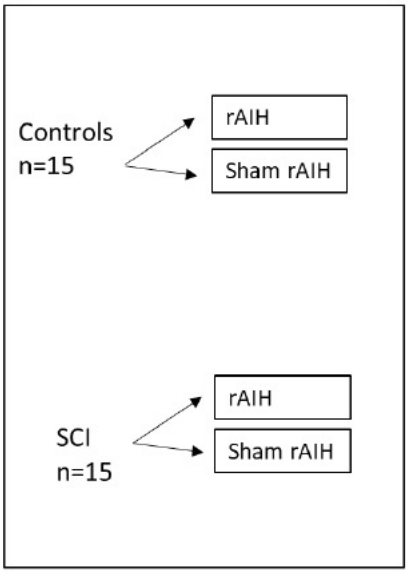
We anticipate screening at the Hines VA and at the VA-leased space on the 20th floor of Shirley Ryan Ability Lab in [redacted] Lab. We project screening 90 participants (45 controls and 45 SCI). We plan to enroll 15 controls and 15 subjects with spinal cord injury (SCI) in experiment 1 and 30 controls and 30 SCI in experiment 2.

There are 2 experiments in this study:

Experiment 1. Experiment 1 is a crossover study. A crossover design is a type of randomized trial where each subject will have one of the study treatments, and then will later cross over to the other treatment condition. The order in which they undergo each of the treatments during the trial will differ subject-by-subject. After screening eligibility, you will be asked to complete 2 testing sessions lasting approximately

2 hours each separated by a few days. One session will include rAIH and the other will use sham rAIH. The order in which you have the rAIH visit and the sham rAIH visit will vary. This means that you will be assigned to one of those conditions without knowing which order you will have rAIH or sham rAIH. We will use rAIH or Sham rAIH for about half an hour and then measure your hand function.

Experiment 1 (Crossover design)

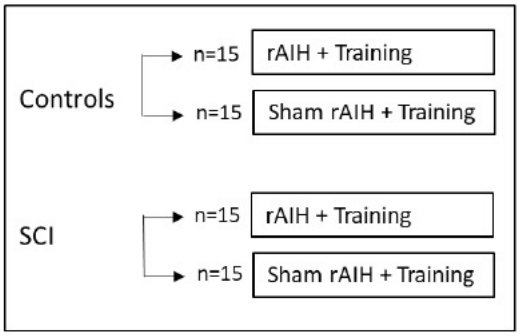


In Experiment 1 the following procedures will be conducted:

- rAIH
- Sham rAIH (Placebo treatment not hypoxia)
- Transcranial Magnetic Stimulation (TMS) stimulation on your scalp
- Recording of your muscle activity
- An assessment of your hand function

Experiment 2. Experiment 2 is a controlled study. You will be asked to complete 7 sessions, and for all 7 of those sessions you will be randomly assigned to a group that will receive either rAIH with training or sham rAIH with training. You will participate in 1 session of baseline measurements, 5 training sessions, and 1 session of post- intervention measurements. Each intervention and training session will last approximately 2 hours. You will be asked to complete a minimum of 3 training sessions per week.

Experiment 2 (Controlled design)



In Experiment 2 the following procedures will be conducted:

- rAIH + training or sham rAIH + training
- TMS stimulation on your scalp
- Recording of your muscle activity
- An assessment of your hand function
- Arm and hand exercise training

For SCI participants only:

- You will also be asked to complete 2 surveys: (1) self-care subscale of the Spinal Cord Independence Measure Version III (SCIM) and (2) The Capabilities of Upper Extremity (CUE)

You can participate in Experiment 1, Experiment 2, or both.

The measurements are described in detail below in **"Study Procedures"**.

STUDY PROCEDURES

If you are interested in participating, we will first review our eligibility criteria with you, the informed consent, complete an intake questionnaire including past medical and surgical history.

Screening Procedures for all participants: During the in-person screening session, which may last up to 1 hour, you may be asked to complete:

- The Informed Consent
- A general screening and medical intake questionnaire
- A strength assessment of your arms and hands
- A variety of hand positions (making a cylinder, lateral key pinch or tip to tip pinch)
- A questionnaire to evaluate if your injury is complete or incomplete (SCI only)
- Testing to determine your response to TMS

To evaluate your responsiveness to TMS, we will deliver a few stimulations to your brain and record the response from the muscle being tested. This is done to see if we can get specific recordings from different muscles. During this testing you might feel movement or a twitch in your muscles.

We will encourage you to ask any questions you may have during this time.

Experimental Procedures for all participants:
If you complete the screening procedures and qualify for the study, you will be asked to participate in Experiment 1, Experiment 2, or both. These experiments will take place at the Hines VA building 128 room A150 or in the VA-leased lab space at Shirley Ryan AbilityLab located at 355 E Erie St Chicago, IL 60611. The research staff will work with you to schedule times when you are available.

Depending on the experiment and group combination that you are allocated to, you may be asked to complete any of the below tasks:

Acute Intermittent Hypoxia (AIH): During these sessions, we will take measurements of your heart rate, oxygen levels, and blood pressure. We will then fit you with a mask that will be placed over your mouth and nose. Tubing will be attached to the front of the mask. The session will last approximately 30-45 minutes with 60-90 seconds of lower oxygen (tubing attached, 9-10% oxygen level), alternating with 60-90 sec of normal room air (no tubing attached). We will monitor for any signs or symptoms of lightheadedness, dizziness, spasms, or unexpected changes in heart rate, oxygen levels, or blood pressure. You will not be told whether you are receiving low oxygen or normal oxygen during the session.

Normal Room Air (Sham AIH): During these sessions, we will take measurements of your heart rate, oxygen levels, and blood pressure. We will then fit you with a mask that will be placed over your mouth and nose. Tubing will be attached to the front of the mask. The session will last approximately 30-45 minutes with 60-90 seconds of normal room air (with tubing attached to the mask) and 60-90 sec of normal room air (without the tubing attached to the mask). We will monitor for any signs or symptoms of lightheadedness, dizziness, spasms, or unexpected changes in heart rate, oxygen levels, or blood pressure. You will not be told whether you are receiving low oxygen or normal oxygen during the session.

Electromyography (EMG): Recording electrodes will be attached to either the surface of your skin over selected muscles or to the muscle directly using sterile needles to record the activity within these muscles. Customized equipment will be attached to your arms and fingers to measure your strength and ability to move.

Transcranial Magnetic Stimulation (TMS): A wire coil will be placed over your head. When activated, this coil will generate a magnetic pulse over a specified area of your head. You may also feel a small twitch of the muscles in your arm, face or your hand. Several series of pulses will occur over the course of the session.

Cervicomedullary Motor Evoked Potentials (CMEPs): We will deliver pulses of electrical stimulation near the mastoid process, which is the bone behind the ear. These pulses may feel strange but should not feel uncomfortable.

Chedoke Arm and Hand Activity Inventory (CAHAI): We will examine the ability of your hand and harm to perform certain tasks.

Jebsen Taylor Hand Function Test (JTT): We will examine your hand function by using simulated activities of daily living.

9 Hole Peg test (9HPT): We will examine your hand function by asking you to move small pegs from one side of a board to the other side.

Strength (Force): We will assess the strength you can produce with your arm and hand

For SCI participants:
Surveys: The following two questionnaires will be given to you before the first training session and after the last training session. You do not have to answer any questions you do not want to. They will each take approximately 5 minutes to complete:

(a) Self-care subscale of the Spinal Cord Independence Measure- Version III (SCIM).
In this questionnaire we will ask you about your ability to complete basic daily functions using your upper such as feed, bathe upper body, dress upper body, and groom.

(b) The Capabilities of Upper Extremity Questionnaire (CUE).
In this questionnaire, we will ask you about your ability to perceive how much function you have with your hands and arms by your ability to reach or lift, pull and push with arms, moving and positioning arm and wrist, and the ability to use hands and fingers.

WHAT IS EXPECTED OF ME IF I TAKE PART IN THIS STUDY?

- Keep your study appointments.
- If you miss an appointment, please contact the investigator or research staff to reschedule as soon as you know you will miss the appointment.
- Tell the investigator or research staff if you believe you might be pregnant or might have gotten your partner pregnant.
- Complete your diaries as instructed.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- While participating in this research study, do not take part in any other research project without approval from the investigators. This is to protect you from possible injury from things such as extra blood drawing, extra X-rays, or potential drug interactions. Taking part in other research studies without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other studies.

We may request copies of medical records from outside non-VA facilities. A VA Form Letter 10-212 will need to be signed for each different non-VA entity from which records will be requested.

WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE IF I TAKE PART IN THIS STUDY?

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur.

There is always a chance that any procedure can harm you. Risks of the usual care you receive are not risks of this study. Those risks are not included in the consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

Risks of AIH:
Hypoxia-associated reduction in inspired oxygen can result in lightheaded sensation, dizziness, reduced vision, increased spasticity, or euphoria. The experiment will be stopped immediately if participants experience any of these symptoms.

Risks of Muscle Activity Recording (EMG):
Mild discomfort, such as an itching sensation may be felt under the electrodes that register the response in your muscles. The possibility of this is infrequent (occurring in 1-10%, or 1-10 out of 100 people). We will clean the area with alcohol and use standard, hospital grade electrodes.

Risks of Transcranial Magnetic Stimulation (TMS):

There is the rare possibility (occurs in less than 1%, or less than 1 out of 100 people) that TMS could cause a seizure. When assessing your eligibility to participate in this research, we ask specific questions that help us to determine whether or not you would be more likely to experience this particular risk. We will exclude from the study those individuals who are at increased risk for this complication.

Additional, infrequent risks (< 2%) associated with TMS include mild headache, mild discomfort at the stimulation site and associated muscles, weakness, tingling, and a feeling of tiredness.

During TMS testing the coil may get warm. It may feel about the same as a heating pad on low or medium setting. This may be uncomfortable but should not be painful. The frequency of this event depends of the stimulation intensity and number of pulses tested.

In the unlikely event of a seizure the rapid response team will be called or 911 will be called.

For Women of Child-bearing Potential

Magnetic fields attenuate (weaken) rapidly with distance, and it is unlikely that a fetus might be affected by the use of TMS. However, the effects of TMS during pregnancy are unknown. For this reason, we have decided to exclude women who are currently pregnant. This is because the effects of TMS on an unborn child are not known. There may be unforeseeable (unanticipated) risks to the participant (or to the unborn child) if the participant is pregnant or becomes pregnant during the study.

Before performing TMS procedures in each session, female participants will be asked about their pregnancy status, and they will be informed that the effects of TMS during pregnancy are unknown. Participants who are uncertain about their pregnancy status and want to participate in the study will be offered a urine pregnancy test prior to undergoing any TMS procedures. For these individuals, at each research visit, we will document pregnancy status and offer a urine pregnancy test if warranted.

Medically acceptable form of birth control while participating in the study are any of the following:

- Complete abstinence (not having sexual intercourse with anyone)
- An oral contraceptive (birth control pills)
- Norplant
- Depo-Provera
- A condom with spermicide
- A cervical cap with spermicide

Risks of CMEPs:

Mild discomfort, such as an itching sensation may be felt under the electrode that stimulates your wrist or under the electrodes that register the response in your muscles. The possibility of this is infrequent (occurring in 1-10%, or 1-10 out of 100 people). A higher stimulus intensity will be used near the bone behind the ear (mastoid process) to create a motor response in the muscles of the upper and lower limbs. This might result in some discomfort for some participants. In order to keep the discomfort at a minimum, stimulation will start at a very low intensity and increase slowly to each person's tolerance.

Risk of Breach of Confidentiality:

As with any research, there is always a minor risk of a breach of confidentiality. That is, in very rare cases, people not associated with this research study may, inadvertently, see your identifiable research results. We will do everything in our power to prevent this from happening by keeping all research records in locked files. Identifiable electronic information related to your participation will be stored on restricted access password protected servers.

Participation in research may involve a loss of privacy. Your research records will be kept as confidential as possible.

POTENTIAL BENEFITS

There are no direct/personal benefits to you from your taking part in this research study. However, the information we get from this study might help others with your condition(s).

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO JOIN THIS STUDY?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. This is not a treatment study. Your alternative is not to participate in this study. This will not affect your care or benefits at Hines VA. Your decision will not have any impact on your participation in other studies and will not result in any penalty or loss of benefits to which you are otherwise entitled.

You can leave the research study at any time, and it will not be held against you. You may withdraw, at any time, your consent for participation in this research study. Identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

We may include information about your study participation in your medical record.

HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

This research study involves the recording of current identifiable medical information. The information that will be recorded will be limited to information concerning the purpose of this research and your safety. All records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a case number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records.

As with any research, there is always a minor risk of a breach of confidentiality. That is, in very rare cases, people not associated with this research study may, inadvertently, see your identifiable research

results. We will do everything in our power to prevent this from happening by keeping all research records in locked files. Identifiable electronic information related to your participation will be stored on restricted access password protected servers.
In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law.

You will not be identified by name in any publication of the research results unless you, a POA, or an LAR sign a separate consent form giving your permission (release).

There are times when we might have to show your records to other people. For example, someone from the Office of Human Research Protections (OHRP), the Government Accountability Office, the Office of the Inspector General, the US Food & Drug Administration (FDA), the VA Office of Research Oversight, VA Office of Research and Development, the VA Institutional Review Board (IRB), our local Research and Development Committee, authorized members of the Human Research Protection Program, and study monitors may look at or copy portions of records that identify you.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time. The study is listed as Repetitive Acute Intermittent Hypoxia for Spinal Cord Repair with ClinicalTrials.gov Identifier: NCT03433599

Health Information Portability and Accountability Act (HIPAA)

There are rules to protect your private information. Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form, you provide your permission called your 'authorization,' for the use and disclosure of information protected by the Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. The study team may also collect other information including your name, address, date of birth, and information from your medical records.

The research team may also need to disclose the information to others as part of the study progress. Others may include the following: the Office of Human Research Protections, the Government Accountability Office, the Office of the Inspector General, the VA Office of Research Oversight, VA Office of Research and Development (sponsor), the VA Institutional Review Board (IRB), the US Food & Drug Administration (FDA), study monitors, authorized representatives of the Hines VA Research Administration and Hines Human Research Protections Program.

Your health information disclosed pursuant to this authorization may no longer be protected by Federal laws or regulations and may be subject to re-disclosure by the recipient.

While this study is being conducted you will not have access to your research related health records.

This will not affect your VA healthcare, including your doctor's ability to see your records as part of your normal care and will not affect your right to have access to the research records after the study is completed.

You can revoke this authorization, in writing, at any time. To revoke your authorization, you must write to the Release of Information Office at Hines VA, or you can ask a member of the research team to give you a form to revoke the authorization. Your request will be valid when the Release of Information Office receives it. If you revoke this authorization, you will not be able to continue to participate in the study. This will not affect your rights as a VHA patient to treatment or benefit outside of the study.

If you revoke this authorization, the investigator ([redacted]) and his research team can continue to use information about you that was collected before receipt of the revocation. The research team will not collect information about you after you revoke the authorization.

Treatment, payment or enrollment/eligibility for benefits cannot be conditioned on you signing this authorization. This authorization will expire at the end of the research study unless revoked prior to that time.

WHAT ARE THE COSTS TO ME IF I TAKE PART IN THIS STUDY?

You will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

Payment Offered for Participation: If you agree to take part in this research study, we will pay you the following for your time and effort: $10 per hour. If the session lasts 0-1 hour you will be paid for the full one hour ($10). If the session lasts longer than an hour the payment will be prorated based on the time. All payments will be made by direct deposit via Electronic Funds Transfer (EFT). The EFT process will use your social security number. Veterans who are unable to utilize this option (i.e., do not have a bank account or the ability to get a Direct Express Debit card) may not be able to receive compensation. You will have an opportunity to discuss these options before you consent to participate in the study.

WHAT WILL HAPPEN IF I AM INJURED BECAUSE OF MY BEING IN THE STUDY?

If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you or your insurance unless the injury is due to non-compliance by a study participant with study procedures or if the research is conducted for VA under contract with an individual or non-VA institution.

If you have additional questions, please contact the Study Investigator, or contact Hines VA and ask for the ACOS/Research.

You do not give up any of your legal rights and you do not release the VA from any liability by signing this form.

If you should have a medical concern or get hurt or sick as a result of taking part in this study, call:

DURING THE DAY:

[redacted] _____ at _[redacted]__and

AFTER HOURS:

[redacted] _____ at _[redacted]_.

You do not give up any of your legal rights and you do not release the VA from any liability by signing this form.

DO I HAVE TO TAKE PART IN THE STUDY?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. This is not a treatment study. Your alternative is not to participate in this study. This will not affect your care or benefits at The Hines VA. Your decision will not have any impact on your participation in other studies and will not result in any penalty or loss of benefits to which you are otherwise entitled.

RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION

The researcher may remove you from the study if he/she believes that staying in the study is no longer in your best interest. If you stop being in the study, the study staff and the study doctor will stop collecting your health information. Although they will stop collecting new information about you, they may need to use the information they have already collected to evaluate the study results. If you start the study and then you cancel your permission, you will not be able to continue to participate in the study. We will tell you about any new information or changes in the study that might change your decision to stay in the study. You may be asked to sign a new consent form if this occurs.

WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS?

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the Edward Hines, Jr. VA Hospital IRB office at [redacted]. This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the Edward Hines, Jr. VA Hospital IRB Office if you have questions, complaints, or concerns about the study or if you would like to obtain information or offer input.

FUTURE USE OF DATA AND RE-CONTACT

The data collected as part of this research study, even if identifiers are removed, will not be used or distributed for future research studies.

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

Dr./Mr./Ms_____ _____has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

By signing this document below, you voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it. A copy of this signed consent will also be put in your record.

I agree to participate in this research study as has been explained in this form.		
_____ Participant's Name	_____ Participant's Signature	_____ Date

I agree to participate in this research study as has been explained in this form.		
_____ Participant's Name	_____ Participant's Signature	_____ Date (coordinator initial ____)
_____ Witness #1 Name	_____ Witness #1 Signature	_____ Date
_____ Witness #2 Name	_____ Witness #2 Signature	_____ Date
_____ Name of Person Obtaining consent	_____ Signature of Person Obtaining Consent	_____ Date