Title: Locomotor Function Following Acute Intermittent Hypoxia (AIH) and Transcutaneous Electrical Spinal Cord Stimulation (tSCS) With Gait Therapy Versus Traditional Gait Therapy in Individuals With Spinal Cord Injury

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PROTOCOL TITLE: Locomotor function following acute intermittent hypoxia and transcutaneous electrical spinal cord stimulation with gait therapy versus traditional gait therapy in individuals with spinal cord injury

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9

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	Biostim-5 Spinal Stimulator
IND / IDE / HDE #	NSR
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	36 (up to 75 screened)
Funding Source	Max Nader Center, Craig H. Nielsen Foundation, and the Shirley Ryan AbilityLab Catalyst Grant Program
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☐ Yes ☒ No

OBJECTIVES:

- To determine whether acute intermittent hypoxia therapy (AIH) combined with transcutaneous spinal cord stimulation during ambulation training modulates spinal locomotor networks in individuals with spinal cord injury

- To determine whether acute intermittent hypoxia therapy (AIH) combined with transcutaneous spinal cord stimulation during ambulation training improves locomotor function in individuals with spinal cord injury
- To determine whether ambulation efficiency (improved cardiovascular conditioning) improves with training combination of AIH, transcutaneous spinal cord stimulation and ambulation training in individuals with spinal cord injury

STUDY ENDPOINTS:
Primary endpoints:

- Change in locomotion efficiency as measured by the 6-Minute Walk West (6MWT)

Secondary endpoints

- Change in Ten Meter Walk Test (10MWT) at self-selected velocity and fastest (safe) velocity
- Change in maximum volitional isokinetic and isometric ankle and knee torque as measured by the Biodex dynamometer strength assessment
- Change in transfers
- Change in bilateral lower extremity strength

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):
Transcutaneous Spinal Cord Stimulation: A Transcutaneous Spinal Cord Neurostimulator (BioStim-5 or NeuroEnabling Stimulator System) will deliver transcutaneous electrical spinal cord stimulation. It provides constant current stimulation with a range of 0-250 mA through self-adhesive electrodes (ValuTrode, Axelgaard Ltd., USA) with a diameter of 3.2 cm placed as cathodes on the skin between the spinous processes of the vertebrae. In addition, two 7.5 × 13 cm self-adhesive electrodes serving as anodes (ValuTrode, Axelgaard Ltd., USA) will be placed symmetrically on the skin over the iliac crests. A foam rubber pad will be placed over the cathodes and secured using adhesive tape, and an elastic belt will be wrapped tightly around the trunk above the waist to ensure a constant pressure between the electrodes and the skin. The stimulation waveform will consist of monophasic or biphasic, rectangular 1-ms pulses at a frequency ranged between 0.2 and 40 Hz, with each pulse filled with a carrier frequency of 5 to 10 kHz. The stimulation intensity will vary from 10 to 250 mA and be determined based on participant threshold and maximum motor outputs.

Acute Intermittent Hypoxia (AIH): Intermittent hypoxia will be administered within a clinical research laboratory. Subjects will be fitted with a latex-free full non-rebreather mask with a custom neoprene head strap [Hypoxico Inc., New York, NY, USA]. This mask and oxygen delivery system are commonly used for altitude training. The mask will first provide a normoxic air (room air) mixture (FiO_2 = 0.21) via the mask. The mask is designed to couple with a universal mask circuit connecting to the air mixture system. The purpose of the mask will be to minimize room air entrainment. The non-rebreather mask has an attached reservoir bag where the controlled air mixture (FiO_2 = 0.08 - 0.95) from the generator fills in between breaths, and a valve that largely prevents the inhalation of room or exhaled air. Delivery of air mixtures will be done through adjustment of one-way valves attached to the delivery cylinders. Tubing will extend from the reservoir bag directly to the machine.

Once fitted with the mask, initial recordings of heart rate, blood pressure, and arterial oxygen saturation (SpO_2) will be taken. The sequence of hypoxia will consist of up to 60- 90 seconds of 9-10% O_2 (FiO_2 0.09), alternating with up to 60- 90 seconds of 21% O_2 (normoxic air FiO_2 0.21). The delivery of hypoxia and normoxic air mixtures will be repeated up to 18 times per session

each, for a total of up to 45 minutes, to maintain SpO_2 at 80-90%. Hearth rate and pulse oximetry will be continuously monitored throughout, and recording will be taken at each alteration in sequence. Blood pressure will be taken upon completion of the total sequence.

A pulse oximetry unit will provide continuous monitoring of heart rate and peripheral arterial oxyhemoglobin saturation (SpO2). SpO2 will be maintained at a goal of 80-90% during the hypoxic bouts, however, SpO2 as low as 75% will be accepted. If the SpO2 drops below 75%, we will terminate the hypoxia exposure immediately.

Any subjective symptoms will be recorded and the subject will be monitored throughout the study period for any signs of cardiopulmonary distress.

If there is a dangerous alteration in the cardiopulmonary parameters being assessed, the experiment will be stopped and appropriate care will be provided by the resident on call or nursing staff available at the Shirley Ryan AbilityLab.
All research devices will remain at the Shirley Ryan AbilityLab in a secure research location. Only authorized research personnel will have access to the devices.
All research procedures will be performed at the Shirley Ryan AbilityLab (SRALab) in the Research & Technologies Lab (RT&O).

PROCEDURES INVOLVED:
Study Design: A randomized, controlled crossover trial. We are evaluating the effectiveness of AIH prior to transcutaneous spinal cord stimulation during locomotor training on improving ambulation and standing balance among individuals with paraplegia or tetraplegia due to spinal cord injury. All participants will complete three arms of the study:

1. AIH prior to transcutaneous spinal cord stimulation during locomotor training (AIH + tSCS)
2. Sham AIH prior to sham transcutaneous spinal cord stimulation during locomotor training (SHAM + SHAM)
3. Sham AIH prior to transcutaneous spinal cord stimulation during locomotor training (SHAM AIH + tSCS)

Participants will complete a 4-week washout period between each arm.

Prior to Visit 2, a medical clearance letter describing study procedures and risks will be sent to the subject's physician or clinician to request medical clearance for the subject to participate in the study. Permission to contact the participant's physician or clinician to obtain medical clearance will be obtained during the screening process.

Visit 1: Initial screening session
- Obtain voluntary and informed consent
- Obtain medical clearance from subject's physician
- Inclusion/exclusion criteria checklist reviewed with patient
- Medical history review
    - Patient name
    - Patient date of birth
    - Patient race (voluntary)
    - Patient gender
    - Emergency contact information

- Date of spinal cord injury
- Type and location of spinal cord injury
- AIS level
- Assistive device use
- Orthotic use
- Recent surgery/injuries
- Medications
- Allergies
- Medical History
- Therapy history

- Physical Function Assessment
  - Skin assessment
  - Active and passive range of motion (AROM/PROM) of bilateral lower extremities
  - Assessment of lower extremity spasticity using Modified Ashworth Scale
  - Manual muscle testing of bilateral lower extremities as an assessment of strength
  - Ten Meter Walk Test (10 MWT): Assesses subject walking speed in meters per second for 10 meters. Subjects will repeat each measure 3 times at their normal self-selected walking speed and 3 times at a fast speed while still able to maintain safety. The test may then be repeated without lower extremity orthotics and without assistive devices for a total of up to 18 trials.

Baseline Assessments:

- Standard evaluation of physical function
  - Active and passive range of motion of bilateral lower extremities
  - Assessment of lower extremity spasticity using Modified Ashworth Scale
  - Skin integrity screen
- Assessment of maximum isometric voluntary ankle torque generation: Subjects will be instructed to contract, and for continued voluntary torque production will be encouraged using verbal commands for a period of approximately 5 seconds. The hip will be flexed up to 90-100°, the knee flexed up to 10° and the ankle at 0° plantar flexion, as described in previous studies (Shaffer, Okereke et al. 2000; Pathare, Walter et al. 2005). Axis of ankle rotation will be aligned with the axis of rotation of the dynamometer. The foot will remain secured to a footplate with straps placed at the forefoot and ankle. The knee will be braced to eliminate moments generated by hip adduction/abduction. Subjects will exert constant endpoint forces against the dynamometer with the weight of the limb supported by the device.
- Timed Up and Go Test (TUG): Assesses mobility, balance, walking ability and fall risk. The participant starts seated in a chair with his/her back against the chair back. On command, the participant rises from the chair, walks 3 meters, turns, walks back to the chair and sits down. Timing begins when the command to start is given and stops when the participant returns to a seated position. This test may be repeated up to 3 times during each assessment visit and during each training visit.
- Six Minute Walk Test (6 MWT): The 6MWT is performed as an objective evaluation of functional exercise capacity. The 6MWT is easy to administer, well tolerated, and typically reflective of activities of daily living. The test measures the distance that the patient can walk on a flat, hard surface, indoors, in a period of 6 minutes. The walk test is self-paced and assesses the level of functional capacity. Patients are allowed to stop and rest during the test, however, the timer does not stop. If the patient is unable to

complete the time, the time stopped is noted and reason for stopping prematurely is recorded.
- Ten Meter Walk Test (10 MWT): Assesses subject walking speed in meters per second for 10 meters. Subjects will repeat each measure 3 times at their normal self-selected walking speed and 3 times at a fast speed while still able to maintain safety.
- Spinal Motor Evoked Potentials (MEPs) may be obtained at baseline and during all functional assessment visits while stimulating interspinous spaces with single pulses at each stimulation intensity. MEPs are the electromyographic responses of the peripheral muscles to electrical stimulation of the spinal cord. MEPs will be used to test the integrity of the motor pathways of the spinal cord.

Treatment Sessions
Each participant will complete 5 treatment sessions in each of the 3 arms of the study. Treatment sessions will take place 5 times per week.

Each treatment session may include:
- *Arm 1: AIH + tSCS*
    - May receive up to 45 minutes of AIH and 30 min of locomotion training with transcutaneous spinal cord stimulation.
- *Arm 2: SHAM + SHAM*
    - May receive up to 45 minutes of sham AIH and 30 min of locomotion training with sham transcutaneous spinal cord stimulation.
- *Arm 3: SHAM AIH + tSCS*
    - May receive up to 45 minutes of sham AIH and 30 min of locomotion training with transcutaneous spinal cord stimulation.

Under all of the conditions, the goal during locomotor training is to generate smooth and symmetrical stepping movements. The trained research personnel will provide cues (verbal, visual and tactile) to improve symmetry of gait and avoid compensatory mechanisms. The progression in training refers to gradually increasing gait speed while maintaining improved gait kinematics. Electromyographic (EMG) activity will be collected from the lower extremity muscles bilaterally during maximum voluntary contractions and locomotor training.

Functional Assessment Visits
Occur after completion of each arm
- Refer to Baseline Assessment Visits for repeat of assessments

All visits will be conducted under the supervision of a trained researcher and clinician. Manual assistance or cueing will be provided as necessary for safety and balance. Clinicians will also utilize gait belts and overhead harness systems to ensure patient safety during physical activity. Vital signs will be monitored with use of our wearable sensors before, during and after physical exertion. All subjects will be permitted to stop physical activity or rest at any time during the study. In addition, the following patient reports will be used to assess patient participation and make adjustments as appropriate.
- Rating of Perceived Exertion (RPE): The 15-grade Borg Scale during ambulation training (over ground, treadmill and gravity-eliminated) to monitor RPE. The intensity will be adjusted to ensure patients do not exceed a rating of 17 (very hard).
- Pain scale: Visual Analogue Scale (VAS) for pain will monitor patient discomfort during non-invasive spinal cord stimulation and locomotion training parameters. This is a 10-

point scale. We will stop when the participant states pain that interferes with their safe participation in the research.

Finally, any adverse reactions that result from participation in this study will be documented by the principal investigator on the subject's data file and reported in writing to Northwestern's Office for Protection of Human Subjects.

Video recording and/or pictures of each participant during assessments may be taken during the training and testing sessions. These items may be used to help troubleshoot potential issues. They may also be used for presentations and training of other research personnel. All attempts will be made to ensure the images or videos used are devoid of any identifying information. Each subject may choose to limit if/how these items may be used, as indicated during their consent process.

STUDY TIMELINES

- One (1) screening visit
- One (1) Baseline assessment visit prior to initiating each arm (3 total)
- Fifteen (15) treatment/intervention visits, 5 per each intervention arms
    - The treatment sessions will be up to 5 times per week within each participants' scheduling availability
- One (1) Functional Assessment visit that occurs after all intervention sessions are complete for each arm (POST, 3 total)
- One (1) Functional Assessment visit that occurs 1 week after all intervention sessions are complete for each arm (1 week follow up, 3 total)

We anticipate an ongoing enrollment over 3 years. Investigators will complete this study (primary analyses) 5 years from start date (IRB approval date).

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:

- Participants have been diagnosed with a spinal cord injury below level C2
- ASIA Impairment Scale Grade A-D
- Participants are 18 years of age or older
- Participants are at least 6 months post spinal cord injury
- Participants with paraplegia or tetraplegia secondary to a single spinal cord injury
- Participants are able to provide informed consent
- Participants are not currently receiving regular physical therapy services

Exclusion Criteria

- Individuals less than 18 years of age
- Individuals less than 6 months post spinal cord injury
- Individuals with cerebellar ataxia
- Individuals with multiple spinal cord injury history
- Pregnancy or nursing
- Pacemaker or anti-spasticity implantable pumps
- Active pressure sores
- Unhealed bone fractures
- Peripheral neuropathies
- Painful musculoskeletal dysfunction due to active injuries or infections

- Severe contractures in the lower extremities
- Active urinary tract infection
- Clinically significant depression, psychiatric disorders, or ongoing drug abuse
- Diagnosed with any of the following medical conditions: congestive heart failure, cardiac arrhythmias, uncontrolled hypertension, uncontrolled diabetes mellitus, chronic obstructive pulmonary disease, emphysema, severe asthma, previous myocardial infraction, or known carotid/intracerebral artery stenosis
- Individuals with a tracheostomy or who utilize mechanical ventilation.
- Individuals who are currently enrolled in another interventional research study or in therapy related to lower extremity function and/or walking.
- Participants will be excluded if they have had a botulinum toxin injection to lower extremity musculature within the last 3 months. Participants will need to refrain from lower extremity botulinum toxin injections for the duration of the study. If participants wean off antispasticity medications to successfully complete the responsiveness to AIH screening session, they will need to refrain from the medications for the duration of the study.
- Documented sleep apnea.
- Orthopedic injuries or surgeries that would impact an individual's ability to use the lower extremity.
- Traumatic brain injury or other neurological conditions that would impact the study.

We will not include the following populations:

- Adults unable to consent, unless accompanied by a legally authorized representative.
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

PARTICIPANT POPULATION(S)

Accrual Number:	Category/Group: (Adults/Children Special/Vulnerable Populations)	Consented: Maximum Number to be Consented or Reviewed/Collected/Screened	Enrolled: Number to Complete the Study or Needed to Address the Research Question
Local	Adults	45	36
Study-wide	Single-Center Study	0	0
Total:		45	36

STATISTICAL ANALYSIS PLAN:

All functional gait outcomes will be assessed at three follow-up visits. We will use a linear mixed model with repeated measures to jointly assess changes at INT5, POST and 1WK relative to baseline within each arm as well as assess the changes between arms for each time point. The model will include time points (BL, INT5, POST, and 1WK as a categorical variable) and treatment arm (AIH + tSCS, SHAM AIH + tSCS, and SHAM + SHAM as categorical variable) as fixed effects and subject as a random effect. Linear mixed models provide a better mechanism for handling missing data by using all available data, rather than performing a complete case

analysis, if the data are assumed to be missing at random. The level of significance will be set at alpha = 0.05. Bonferroni corrections will be used to adjust for multiple comparisons.

SAMPLE SIZE AND POWER CONSIDERATIONS:
The sample size calculation will be based on a one-sided paired *t*-test comparing the changes in self-selected speed of the 10 meter walk test from pre- to 1 week post-treatment. Based on the minimum clinically important difference (MCID) for speed previously reported in SCI29, we want to detect a change in speed of 0.06 m/s. The standard deviation of the change from baseline to 1 week post was 0.07 m/s. Therefore, using 0.857 as our effect size, a sample size of n=10 will provide a power of 80% with alpha = 0.05.

References:

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5. Hayes HB, Jayaraman A, Herrmann M, Mitchell GS, Rymer WZ, Trumbower RD. Daily intermittent hypoxia enhances walking after chronic spinal cord injury: a randomized trial. Neurology 2014;82(2):104–13.
6. Labruyère, R. and H. J. A. van Hedel (2014). "Strength training versus robot-assisted gait training after incomplete spinal cord injury: a randomized pilot study in patients depending on walking assistance." Journal of NeuroEngineering and Rehabilitation 11: 4-4.