Study name: **Effects of RLIC on Motor Learning in Middle-Aged and Older Adults**

Name of legacy study protocol in Washington University HRPO system: **Remote Limb Ischemic Conditioning to Enhance Learning**

ClinicalTrials.gov ID: **NIHR01HD086930-Aim3**

NCT03582943

PI: Catherine Lang
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314-286-1945

Study Protocol

Latest revision of document: 6/20/16

Remote Limb Ischemic Conditionin

PI: Catherine Lang
IRB ID #: 201403019

Project Details

1. Demographics

1.1 Project Title:
Remote Limb Ischemic Conditioning to Enhance Learning

1.2 Short Title (required):
Remote Limb Ischemic Conditionin

1.3 Project is primarily:
Biomedical

1.3.a Does this study require review under ICH-GCP?
No

1.4 Type of Study:
Phase 1(I)

1.5 Select how you plan to obtain consent:
- Sign a consent document or a consent letter

2. Source(s) of Support

2.1 Source(s) of Support

Type/Source	Grant Title	Name of PI on Grant	Status
Federal Agency NIH, National Institutes of Health	Ischemic conditioning as a neurorecovery agent post stroke	Catherine Lang	AWARDED

Attachment Name	Category	Version	Date Attached
SubmittedApp_20150122.pdf	Grant from funding source or private foundation/association	1	06/20/16

3. Research Team

3.1 Principal Investigator

Name	E-mail	Title
Catherine Lang	langc@wusm.wustl.edu	Prof of Physical Therapy

3.2 Team Members

Research Team Members

Role	Name	Role Desc	Student	Email	Title	School	Department
PI	Catherine Lang, PHD, PT		No	langc@wusm.wustl.edu	Prof of Physical Therapy	School Of Medicine	Program In Physical Therapy
	Marghuretta Bland, CI, DPT, MS-			blandm@wusm.wustl.edu	Assoc Prof of Physical Therapy	School Of Medicine	Program In Physical Therapy
	Jeffrey Gidday, PHD			gidday@wudosis.wustl.edu	Sr Scientist	School Of Medicine	Neurosurgery
	Jin-Moo Lee, MD, PHD			leejm@neuro.wustl.edu	Norman J Stupp Prof of Neurology	School Of Medicine	Neurology
	Gina Malito, BS			gmalito@email.wustl.edu	Physical Therapist/Clinic Associate	School Of Medicine	Program In Physical Therapy

	Anna Mattlage, PHD			mattlagea@wusm.wustl.edu	Staff Scientist	School Of Medicine	Program In Physical Therapy
	Swati Surkar, PHD			ssurkar@email.wustl.edu	Postdoc Research Associate	School Of Medicine	Program In Physical Therapy
	Allison Tsui, BS			allisontsui@email.wustl.edu	PT Aide, Grad Student		Program In Physical Therapy
	Kimberly Waddell, BS, MS			waddellk@wusm.wustl.edu	Predoctoral Trainee	Arts & Sciences	Program In Physical Therapy
	Shelby Wilson, BS			shelby.wilson@wustl.edu		School Of Medicine	Physical Therapy Program-pp-dpt

Team Member Financial Interest

Name	Financial Interests
Catherine Lang, PHD, PT	none
Marghuretta Bland, CI, DPT, MS-	none
Jeffrey Gidday, PHD	none
Jin-Moo Lee, MD, PHD	none
Gina Malito, BS	none
Anna Mattlage, PHD	none
Swati Surkar, PHD	none
Allison Tsui, BS	none
Kimberly Waddell, BS, MS	none
Shelby Wilson, BS	none

4. Other Institutional Reviews/Requirements

4.1 Do any of the objectives of this study involve the diagnosis, prevention, screening, evaluation, treatment or support of cancer patients?
No

4.2 Are more than 30% of the patients involved in this study likely to have an active cancer diagnosis?
No

4.3 Will any subject be asked to undergo a radiation therapy procedure (including external beam therapy, brachytherapy, or radiopharmaceutical therapy)?
No

4.4 Does your study involve the administration of radiopharmaceuticals (radioactive drugs) for research purposes?
No

4.5 Will any participant be asked to undergo any of the following:

- a standard radiology procedure involving ionizing radiation (includes X-rays, fluoroscopy, DEXA, CT)
  OR
- a standard nuclear medicine examination with FDA-approved radioactive drugs (including bone scans, radionuclide ventriculogram (RVG or MUGA), myocardial perfusion imaging, FDG-PET)
- DO NOT include MRI or ultrasound

No

4.6 Will the study involve any of the following activity at WUSM or any BJC hospitals, even if subjects or their insurance will not be billed for the item or service, and regardless of the study funding source (including studies with departmental or no funding)?

- Procedures, tests, examinations, hospitalizations, use of Pathology services, use of clinic facilities or clinical equipment, or any patient care services, including services conducted in the Clinical Research Unit; or
- Physician services or services provided by non-physicians who are credentialed to bill (ARNPs, Physician Assistants, etc.)

Yes

4.7 Does this project involve administration of recombinant DNA (gene therapy) or microorganisms?
No

4.8 Does this study involve the use of human embryonic stem cells or human induced pluripotent stem cells?
No

4.9 Does this study involve research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero?

No

4.10 Will a Certificate of confidentiality be used for this research?
No

4.11 Does this project need to be registered on ClinicalTrials.gov?
No

4.12 Title that should appear in Epic (and will be visible in the patient medical record):
N/A-study does not need to go into Epic

4.13 Select one person from the study team that should appear in Epic as the contact person for this study:
Marghuretta Bland

4.14 Do you want to request that an ordering tool be built for your study in Epic?
No

4.15 Would you like to submit a request for the Epic team to consider your study for the use of BPA (Best Practice Advisory) in Epic?
No

4.16 Would you like to submit a request for the Epic team to build your questionnaires in Epic for the purposes of recruitment?
No

4.17 Will any external monitors require access to this study in Epic?
No

4.19 Mark all that apply to your study:

1. Protocol

1.1 Is there a separate, written protocol that will be submitted in addition to this form? (Note: a grant application is not considered to be a protocol)
Yes

Attachment Name	Category	Version	Date Attached
RLIC_protocol.docx	Intervention: Separate Written Protocol	9	10/15/15

1.1.a Who initiated/provided the protocol?
WUSTL Investigator

1.1.b Protocol#:

1.1.c Protocol Version#:
8

1.1.d Protocol Date
09/28/2015

1.1.e Provide a list of the amendments for this study (this may be left blank if none). Any amendments previously listed should not be removed.

1.2 Select up to three key words below that best describe this research study:
- Neurology
- Physical Therapy

1.3 Provide a short summary/abstract of the purpose and procedures of the study proposed in this IRB application.

- DO NOT include information on studies not proposed in this application.
- Use LAY terminology only. This must be easily understandable by IRB community members and nonscientists.
- DO NOT cut and paste technical abstracts from source of support applications that may not be understood by a general audience.

The purpose of this study is to determine if remote limb ischemic conditioning (RLIC) can serve as an agent to enhance motor performance and learning in humans. Our immediate goal is to test if remote limb ischemic conditioning paired with training results in greater improvements in performance and learning compared to sham conditioning paired with training in neurologically-intact adults. Our long-term goal is to determine if remote limb ischemic conditioning can improve rehabilitation outcomes for people with stroke.

RLIC will be achieved by wearing blood pressure cuff which is alternately inflated and deflated. This study will have two randomly assigned groups and will use a repeated measures design. Group one will consist of neurologically intact subjects who receive RLIC treatment to 20mmHg above their systolic BP and group two will consist of neurologically intact subjects who receive a sham treatment. Study procedures include: RLIC treatment, questionnaires, balance training, and arm motor training. The study consists of 7 visits plus two follow up appointments and will last up to 6 weeks. Visits will last from 0.5-2.5 hours, depending on the visit.

1.8 Check all materials/methods that will be used in recruiting participants:

- Telephone script
- Ads/Brochures/Posters/News Release/Fliers
- Email or letters
- Website or Social Media (printed pages)
- Existing Registry/database
  - Other Existing Registry/database - Volunteer For Health

Attachment Name	Category	Version	Date Attached
RLIC_Phone_Correspondence-1.rtf	Recruitment Script: Phone	4	07/05/16
Lang 201403019 - Centerwatch - Ellen Sutter.rtf	Recruitment: Website	1	09/29/16
201403019 website.rtf	Recruitment: Other	1	10/29/15
RLIC_poster_elderly (3)_updated20170620.rtf	Recruitment Materials: Ads/Brochures/Posters/News Release/Fliers	11	06/21/17
Sutter_Facebook_Post.rtf	Recruitment: Website	6	09/29/16
Sutter_Age_Poster_updated20170620.rtf	Recruitment Materials: Ads/Brochures/Posters/News Release/Fliers	4	06/21/17

1.9 Will you use a screening log or other record that would include information on people who do not consent to participate in the study?

Yes

Attachment Name	Category	Version	Date Attached
Blank_ScreeningForm.xlsx	Screening: Screening Log	3	10/30/17

1.9.a Will the screening log be shared with individuals outside of the research team?

No

1.10 Describe where the consent discussion will occur (check all that apply):

- Private room or area

1.11 Participants and/or their legally authorized representative will have (check all that apply to the consent process and explain process in Question 1.12 below):

- As much time as they desire to consider enrolling in the study, including:
  - An opportunity to thoroughly review the consent materials with knowledgeable members of the research team, and with family and/or friends as appropriate
  - Sufficient time to have all of their questions answered

1.12 Provide a description of the enrollment and consent process in sequential order and address EACH of the bulleted points below:

- Describe each study population separately including control population
- Describe when recruitment and consent materials are used
- Indicate how much time individuals will have to consider participation
- Use THIRD person active voice. For example, "the principal investigator will identify potential participants, the study coordinator will discuss the study with participants over the telephone and schedule the first study visit, etc..."
- Describe the steps that will be taken by the research team to minimize the possibility of coercion or undue influence during the consent process

Enrollment process:
Study staff will distribute approved flyers to various locations in the St. Louis area (e.g., Barnes Jewish Hospital, Washington University, local cafes etc.); these materials will include information about study procedures, time commitment, compensation, and how to contact Dr. Lang's research laboratory. Study team members will get permission at each site before leaving flyers. If a participant calls in response to an advertisement, a research team member will answer any questions related to the study, will ask 8 screening questions (no PHI), offer to send potential participants a copy of the consent form, and will encourage them to call if they have questions.

Consent Process:
A member of the research team will meet with the potential participant individually at the beginning of the first visit to go over the consent document. The research team member will place a copy of the consent in front of the potential participant and will review each section of the document. The research team member will then give the potential participant time to read the document and encourage the individual to ask questions. If the individual does not wish to sign the consent, the research team member will thank the individual for his or her time and the meeting will conclude. If the individual needs more time to think about participating, he or she may take the consent form home and schedule a second visit if he or she decides to participate. If the individual signs the informed consent, the research team member will make a copy of the consent and give it to the individual before the conclusion of the first visit. If the potential participant displays any signs of impairment, suggesting that he or she is not capable of providing consent, the research team member will stop the consent process, as this person would not be eligible for this study. Individuals who express that they are not interested in participating will not be contacted further.

1.14 Will participants be randomized?

Yes

1.15 Will any of the following be used to collect information from the participant or others?

- Screening questions or screening/eligibility questionnaires
- Surveys
- Questionnaires
- Stimuli
- Any other written assessments

Yes

Attachment Name	Category	Version	Date Attached
RLIC_Demographic_Data_Collection_Form.docx	Subject Data Collection Instruments	2	01/09/15
PIC_Side_Effects_Questionnaire.docx	Subject Data Collection Instruments	1	03/04/14
Borg_Exertion_Scale.pdf	Subject Data Collection Instruments	2	03/11/14
RLIC_Treatment_Guess_Form.docx	Subject Data Collection Instruments	6	10/15/15

1.16 Does this project involve creating any audio, video, or photographs?
No

1.17 Does the study include any form of deception (e.g., providing participants with false information, misleading information, or withholding information about certain study procedures)?
Examples:

- Procedure includes a cover story that provides a plausible but inaccurate account of the purposes of the research.
- Participants will be provided with false information regarding the particular behaviors of interest in the research.
- Procedures include a confederate pretending to be another participant in the study.
- Participants will be told that the research includes completion of a particular task, when in fact, that task will not be administered.
- Study is designed to introduce a new procedure (or task) that participants are not initially told about.

No

1.18 Indicate any payments or reimbursements to participants (check all that apply)

- Cash
- Check

1.19 Does this study have a plan to have an individual or committee review combined data from all participants on a periodic basis (such as summary or aggregate safety and/or efficacy data)?
Yes, but it's not described in an attached protocol

The study investigators and study staff will meet weekly to review accrued data, data confidentiality, adherence to protocol design, recruitment, and subject complaints. In addition, this study is one aim of an entire grant, and the grant has a Data Safety Monitoring Committee to meet the NIH requirments. The Data Safety Monitoring Committee does review this study as well as the other studies (seperate IRB Protocols)

1.20 What have you done to minimize any risks?

- Adverse event monitoring

1.25 Will any data from this project be stored for use in future research studies?
No

1.26 Does this project involve the collection or use of biological samples?
No

1.27 Are you requesting institutional certification to contribute human data or samples to a repository or database for broad sharing (public or restricted access)?
No

2. Participants

2.1 Will there be any adult participants?
Yes

2.1.a How many adult participants do you expect to consent or enroll under a waiver for this project?
143

2.1.b What is the age of the youngest adult participant?
18.0

2.1.c What is the age of the oldest adult participant?
No age limit

2.2 Will there be any minor participants?
No

2.3 Will there be any emancipated minor participants?
No

2.7 Do you plan to recruit/enroll non-English speaking people?
No

2.8 Do you propose to enroll any of the following in this study as participants?

- Employee of the PI or employee of a research team member
- Individual supervised by PI or supervised by member of research team
- Individual subordinate to the PI or subordinate to any member of the research team
- Student or trainee under the direction of the PI or under the direction of a member of the research team

No

2.9 Is this project about pregnant women?
No

2.10 Will this project involve fetuses?
No

2.11 Does this project involve the use of fetal tissue from any source?
No

2.12 Does this project recruit adult participants who may be incompetent or have limited decision-making capacity on initial enrollment into the study?
No

2.13 Does this project involve prisoners as participants?
No

3. Performance Sites

3.1 Indicate type of site(s) where research will occur (check all that apply):

- Academic Institution

3.2 Where will project procedures take place (check all that apply)?

- School of Medicine

3.3 Is this project also being conducted by other researchers at their own sites (e.g. a multi-site collaborative project)?
No

4. Drugs/Devices

4.1 Does this project involve:

	Yes	No
Drug(s) (including radioisotopes)	○	◉
Use of contrast agent(s)	○	◉
Other substance injected, ingested, or applied to the body	○	◉
Testing a Device (Including companion devices, software, mobile health devices, assays, not FDA approved or outside approved indications, etc.)	○	◉
Combination product (as determined by the FDA - must have FDA documentation identifying this as a combination product)	○	◉

4.2 Does this project involve a drug washout (asking participant to stop taking any drugs the participant is currently taking)?
No

4.3 Will any participants receive a placebo in place of standard therapy?
No

5. Privacy & Confidentiality

5.1 Indicate your plans to protect the privacy interests of the participants during the conduct of the study (check all that apply):

- Only the minimum necessary private information is collected for the purposes of the study
- Any procedures or interventions conducted as part of the study will be conducted in private setting to the extent possible
- Recruitment/consent will occur in a private setting
- Participants will be able to ask questions in a private setting

5.2 Are you collecting or using the Social Security Number of any participants for any purpose?
Yes

5.2.a Provide the intended usage of SSN:
- To provide compensation to participants

5.3 Project uses paper or hard copy consents, surveys, data collection forms, research subject binders, or other hard copy materials (check all that apply):
Yes
- All materials are stored in secured environment
- Access is limited to research team members only

5.4 Project collects, stores and/or transmits electronic data on mobile devices, desktop computers, servers including cloud servers, email, or any other information in electronic form (check all that apply):
Yes
- Data in Redcap
- Password protected
- Access is limited to research team only

5.5 Project collects or uses biologic specimens (check all that apply):
No

5.6 Identify any additional protections in place for data and or samples (check all that apply):
- No additional protections

Remote Limb Ischemic Conditioning to Enhance Performance and Learning

Study Objectives	The objective of this research study is to determine if remote limb ischemic conditioning (RLIC) can serve as an agent to enhance motor learning. The immediate goal is to test the combination of RLIC with motor training in neurologically intact, middle-aged and older adults. The long term goal is to determine if RLIC, when compared to sham treatment, augments the learning that occurs during a rehabilitation training exercise in people who have motor deficits following stroke.
Background Rationale	It is now understood that the nervous system has remarkable adaptive capacity. Specifically, the central nervous system retains its ability to reorganize in structure and function in response to behavioral experience in neurologically intact people and in individuals with neurological injury. Motor learning guides the adaptation of the central nervous system and is an essential component of effective training paradigms. There is a growing body of literature which suggests that inducing a transient state of systemic ischemia has the potential to induce spinal plasticity, strengthen spared pathways to motoneurons, and lead to improved motor recovery following neurological injury.[1,2] Specifically, daily systemic ischemic conditioning has been shown to improve both forelimb and respiratory motor function in rodent models of chronic cervical spinal injury.[1,3] Moreover, systemic ischemic conditioning resulted in increased ankle strength (single session)[2] and augmented walking speed and endurance (5 sessions)[4] in humans with motor incomplete spinal cord injuries. In a related area of research, it has been shown that ischemic conditioning administered *peripherally* represents a strategy for harnessing the body's endogenous protective capabilities against lethal levels of ischemia. With this technique, applying brief ischemia and reperfusion to a remote organ or tissue results in significantly reduced damage from subsequent exposures to ischemia. For example, applying a tourniquet and creating ischemia in a rat's hindlimb for 10 minutes reduced the extent of cardiac abnormalities following a sustained ischemic insult.[5] This same phenomenon has been shown in humans. Applying an inflated blood pressure cuff to the upper or lower limb has shown efficacy for protection in people undergoing cardiac surgeries,[6,7] undergoing elective surgery to repair abdominal aortic aneurysm,[8] experiencing MI,[9] and with symptomatic intracranial arterial stenosis.[7] The mechanisms underlying the neuroplastic and neuroprotective effects of ischemic conditioning are not fully understood. At this time, the literature indicates that there are both humoral and neural mechanisms responsible for the protection and the plasticity. It is clear that ischemic conditioning results in widespread physiological effects and that the observed effects work through multiple mechanistic pathways. The next translational step is to investigate whether combining ischemic conditioning with behavioral training has the ability to augment motor learning. Specifically, we will employ remote limb ischemic conditioning (via inflation/deflation of a blood pressure cuff) with the objective of activating the endogenous pathways shown to elicit neuroplasticity. If eventually effective, RLIC could have profound effect on the rehabilitation and recovery of motor function in people with stroke. It is important to first start this translational investigation in neurologically intact people in order to determine optimal protocols for people with stroke.

	The purpose of this study is to test if remote limb ischemic conditioning will enhance motor learning in neurologically intact middle-aged and older adults who are of a similar age and present with similar comorbidities as persons with stroke. . We previously found that combining behavioral training and RLIC facilitated motor learning in healthy young adults under 40.[10]The primary aim of this study is to determine if training + RLIC facilitates the learning of motor tasks in an older population beyond the healthy young population that we have previously tested.
Study Design	Between subjects repeated measures design. Please refer to Figure 1.
Groups	Group 1: Neurologically Intact Subjects + RLIC conditioning Group 2: Neurologically Intact Subjects + sham conditioning Subjects who qualify and consent will be randomly assigned to either group 1 or 2.. Allocation will be concealed from those responsible for assessing subjects for eligibility and entry into the study (e.g. sequentially numbered, opaque, sealed envelopes).
Number of Subjects & Power Analysis	Based off of our pilot data on the balance training task we need the following total sample sizes moving forward (see Table 1 below) to achieve at least 80% power to detect the mean differences of change scores (posttest – pretest) between the two treatment groups (RLIC vs. sham) based on a two-sample t-test at a significance level of 0.05. The standard deviations for change scores are assumed to be 2.5 seconds and 1.9 seconds for the RLIC and sham groups, respectively. Moving forward, we will recruit 10 subjects per group (n=40). This will give us the ability to detect differences on the balance task of at least 3 seconds or more. Differences less than 3 seconds (and smaller effect sizes) are unlikely to be clinically-relevant in future target populations. We continue to request permission to enroll 130 subjects total 51 of whom have already been enrolled) to allow for screen failures and participants who do not complete all study visits. Table 1. Power analysis Mean difference of change score — Total sample size (assume equal sample size in each group) 7 seconds — 12 (with actual power 93%) 6 — 12 (with actual power 85%) 5 — 15 4 — 21 3 — 30 2 — 63 1 — 237
Inclusion & Exclusion Criteria	**Inclusion Criteria** 1) At least 18 years old. 2) Cognitive skills sufficient to actively participate. **Exclusion Criteria** 1) History of neurological condition, ADD, ADHD, balance impairment, or vestibular disorder. 2) History of sleep apnea. 3) History of lower extremity condition, injury, or surgery which could compromise performance on motor training task. 4) Any extremity soft tissue, orthopedic, or vascular injury which may contraindicate RLIC. 5) Any cognitive, sensory, or communication problem that would prevent completion of the study.

	6) Current use of medication for, or treatment with: systemic inflammation, spasticity, selective serotonin reuptake inhibitors. 7) Current intensive weight lifting or interval training exercise. 8) Current substance abuse or dependence. 9) If participant lives further than one hour away and is unwilling to travel for assessment and treatment sessions.
Concomitant Medications/Training	Medications for the management for other co-morbid conditions not listed in the exclusion criteria are permitted. Regular, light exercise is permitted. See exclusion criteria for exercise that is not permitted.
Order of Experiment/ Study Visits	This study involves 9 total visits. Participants will be in the study for up to 6 weeks. The first 2 visits (D1 and D2) will take approximately 1.5 hours and 1 hour, respectively, and consist of RLIC/sham conditioning alone. The following 5 visits (D3-D7) will take approximately 2.0-2.5 hours and consist of RLIC/sham conditioning followed by motor training. The final two visits (F/U1 and F/U2) take place two and four weeks after D7 and will last approximately 30 minutes each. Please refer to Figure 1 for details about study visits. **D1**: A trained clinical interviewer will provide informed consent and conduct a structured clinical interview. Eligible participants will be asked to complete descriptive measures. Next, researchers will assess pretest performance on the two outcome measures. After the pretest, subjects will undergo one set of RLIC or sham conditioning. **D2**: Subjects will undergo one set of RLIC/sham conditioning. **D3-7:** One set of RLIC or sham conditioning will be performed and then behavioral training will commence. **F/U1-2**: Posttest performance will be assessed on the two outcome measures. Participants will <u>not</u> receive RLIC or sham conditioning during the follow-up visits. During the second follow-up session, participants will fill out a survey indicating whether they think that they received RLIC or sham treatment.
Conditioning Parameters	Remote limb ischemic conditioning will be achieved via blood pressure cuff inflation to 20 mmHg above the subject's resting systolic blood pressure on the dominant upper extremity. Sham conditioning will be achieved via blood pressure cuff inflation to 10 mmHg under the subject's resting diastolic blood pressure, on the dominant upper extremity. One set of RLIC or sham conditioning consists of 5 cycles of alternating 5 minutes of inflation, 5 minutes of deflation. One set of RLIC/sham conditioning will be performed per day onD1 and D2 and onD3-7. RLIC will always be performed before beginning behavioral training on D3-D7. Subjects will be blinded to their group assignment (RLICvs. sham).
Behavioral Training Parameters	Participants will received behavioral training on D3-D7 on a balance training task (15 minutes; rest breaks as needed) The balance training task is a lower extremity standing balance task.[11] The balance task requires subjects to stand on a movable platform (stability platform, model 16030L, Lafayette Instrument) and to keep the platform in a balanced, horizontal position.[11] This is a lab-based test. This motor task was selected because it simulates the balance required for

	daily function, and can be easily modified to the appropriate level of difficulty in accordance with each subject's motor abilities.
Descriptive measures	Demographic information, including age, dominant side, gender, ethnicity, race, level of physical activity, first day of last menstrual cycle, height, body weight, employment status, education level, living status, co-morbidities, and current medications will be collected on all subjects during D1.
Primary Outcome Measures	The outcome measure is change in balance score on the balance task. Performance on the balance task will be quantified by the identifying the number of seconds in a 30-second trial that an individual is able to maintain the platform within ±3° of horizontal. 5 trials are averaged for the baseline, after the intervention, and at follow-ups. Balance change scores will be computed as the difference from the end of intervention minus the baseline (in seconds).
Data Analysis	Data will be analyzed using a mixed model analyses examining group differences and interactions between group and various subject characterisitcs. Our first hypothesis is that both the RLIC and sham groups will demonstrate improved performance on the balance task and arm task, with practice (main effect of time). Secondly, we hypothesize that RLIC will facilitate motor learning to a greater extent than the sham group, so that subjects given RLIC will demonstrate greater improvements in performance on the balance task and arm task than individuals given sham treatment (group x time interaction). Additional analyses are planned per the funded project and include explorations into how various subject characteristics influence/interact with the RLIC vs. sham conditioning. These factors include age, sex, BMI, and the presence/absence of cardiovascular comorbidities and medications.
Safety Considerations & Monitoring	The risks of participating in the rehabilitation intervention are minimal and are similar to the risks encountered during routine physical and occupational therapy services. The most likely risk during motor training tasks is fatigue. Fatigue will be monitored with the RPE scale during each session and rest breaks will be given as needed. There is also a small risk of falling during participation in the balance task portion of this study. Subjects will be permitted to use a handrail as needed for safety during the balance task and a trained research assistant will be immediately adjacent to the subject at all times. In order to monitor for safety, we will continuously monitor for headaches, pain, lightheadedness, dizziness, altered vision, respiratory distress, cyanosis, and spasms. We will record and monitor heart rate, blood pressure, and oxygen saturation before, during, and after each set of RLIC. Sessions will be terminated if heart rate <40 bpm or >160bpm, systolic BP <85mm Hg or >160mmHg, or if O_2 saturation <75%. Moreover, during the second follow up session, all subjects will be asked to fill out a questionnaire related to the presence of adverse effects that resulted from participation in this study.
Investigators	PI: Catherine Lang PT, PhD
Number of Centers	1 center: Washington University School of Medicine
Key References	Please see the reference list.

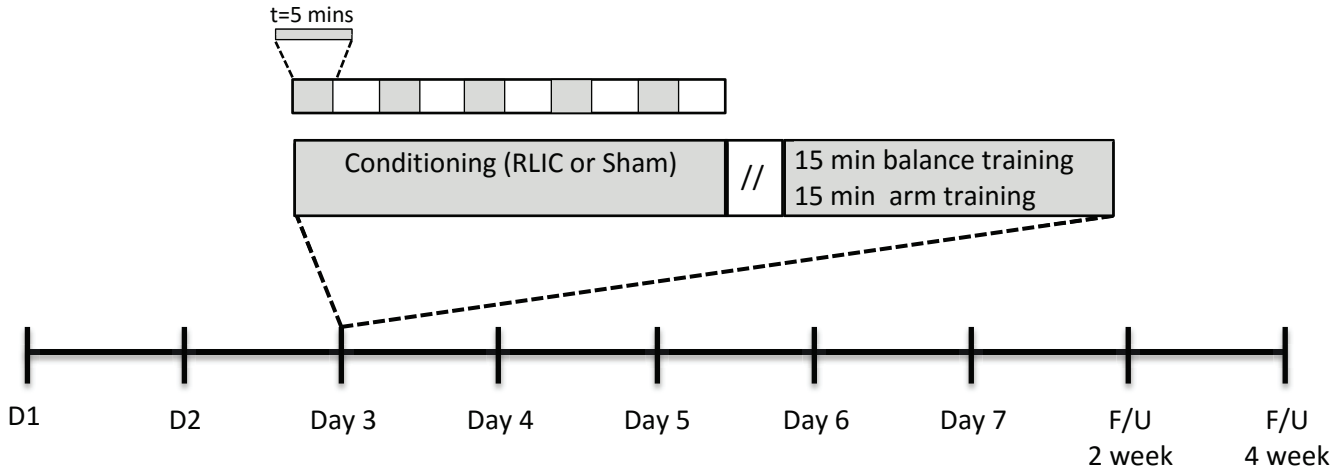

Figure 1 Subjects will participate in 9 total sessions. D1 and D2 are conditioning alone. Remote limb ischemic conditioning (RLIC) involves 5 cycles of 5 minutes of upper extremity peripheral ischemia (induced either by a blood pressure cuff inflated to 20 mmHg >systolic BP), alternating with 5 minutes of no ischemia. For the next 5 consecutive days, subjects receive a combinational intervention of RLIC plus training. On training days, subjects undergo the RLIC and perform 15 minutes of standing balance training and 15 minutes of cognitive training. The final trials of the two training items will serve as posttest measures. Performance on standing balance and associative recognition tasks are measured at BL, at the beginning of training day 1, at the end of training days 1-5, and at each F/U.

1. Lovett-Barr MR, Satriotomo I, Muir GD, et al. Repetitive intermittent hypoxia induces respiratory and somatic motor recovery after chronic cervical spinal injury. *J Neurosci.* Mar 14 2012;32(11):3591-3600.

2. Trumbower RD, Jayaraman A, Mitchell GS, Rymer WZ. Exposure to acute intermittent hypoxia augments somatic motor function in humans with incomplete spinal cord injury. *Neurorehabil Neural Repair.* Feb 2012;26(2):163-172.

3. Fuller DD, Johnson SM, Olson EB, Jr., Mitchell GS. Synaptic pathways to phrenic motoneurons are enhanced by chronic intermittent hypoxia after cervical spinal cord injury. *J Neurosci.* Apr 1 2003;23(7):2993-3000.

4. 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.* Jan 14 2014;82(2):104-113.

5. Oxman T, Arad M, Klein R, Avazov N, Rabinowitz B. Limb ischemia preconditions the heart against reperfusion tachyarrhythmia. *Am J Physiol-Heart C.* Oct 1997;273(4):H1707-H1712.

6. Hausenloy DJ, Mwamure PK, Venugopal V, et al. Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. *Lancet.* Aug 18 2007;370(9587):575-579.

7. Meng R, Asmaro K, Meng L, et al. Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. *Neurology.* Oct 30 2012;79(18):1853-1861.

8. Ali ZA, Callaghan CJ, Lim E, et al. Remote ischemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair - A randomized controlled trial. *Circulation.* Sep 11 2007;116(11):I98-I105.

9. Botker HE, Kharbanda R, Schmidt MR, et al. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet.* Feb 27 2010;375(9716):727-734.

10. Cherry-Allen KM, Gidday JM, Lee JM, Hershey T, Lang CE. Remote limb ischemic conditioning enhances motor learning in healthy humans. *J Neurophysiol.* Jun 1 2015;113(10):3708-3719.

11. Taubert M, Draganski B, Anwander A, et al. Dynamic properties of human brain structure: learning-related changes in cortical areas and associated fiber connections. *J Neurosci.* Sep 1 2010;30(35):11670-11677.

12. Schaefer SY, Patterson CB, Lang CE. Transfer of training between distinct motor tasks after stroke: implications for task-specific approaches to upper-extremity neurorehabilitation. *Neurorehabil Neural Repair.* Sep 2013;27(7):602-612.