Effect of number of remote limb ischemic conditioning cycles of learning enhancement.

NCT03512041

NIHR01HD085930-Aim2

05/19/2017

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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 and cognitive learning. The immediate goal is to test the effect of number of RLIC cycles on motor learning in neurologically intact adults. An additional goal is to determine a physiological marker of the effectiveness of RLIC through collecting blood samples during various time points throughout the study. 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. Cognitive and motor learning guide the adaptation of the central nervous system and are essential components 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 motorneurons, 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 hypoxia 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 the effect of number of RLIC cycles on motor learning in neurologically intact adults and if we can find a physiological blood marker related to effective administration of RLIC. We hypothesize that 3 cycles of RLIC will be sufficient to enhance motor leaning compared to sham conditioning, and that there will be a dose-dependent (number of cycles) response in learning, thus making training more efficient, more effective, and longer-lasting. Determining the number of cycles necessary to elicit the benefits of RLIC is important in developing the most effective and least burdensome treatment for future patients with motor deficits.
Study Design	Between subjects repeated measures design. Please refer to Figure 1.
Groups	Group 1: Neurologically Intact Subjects + 5 cycles of RLIC Group 2: Neurologically Intact Subjects + 4 cycles of RLIC Group 3: Neurologically Intact Subjects + 3 cycles of RLIC Group 4: Neurologically Intact Subjects + 5 cycles of sham conditioning Subjects who qualify and consent will be randomly assigned to either group 1, 2, 3 or 4. Allocation will be concealed from those responsible for assessing patients for eligibility and entry into the study.
Number of Subjects & Power Analysis	Based off of 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. 10 subjects will be enrolled for each of the 4 groups. However, we request permission to enroll 55 subjects total to allow for screen failures and participants who do not complete all study visits. This will give us the ability to detect differences on the balance task of at least 3-4 seconds. Differences less than this (and smaller effect sizes) are unlikely to be clinically-relevant in future target populations. 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 study visits.
Inclusion & Exclusion Criteria	**Inclusion Criteria: ¶** 1)Between the age of 18 and 40 years ¶ ¶ **Exclusion Criteria: ¶** 1)History of neurological condition (i.e. stroke, Alzheimer's disease, Parkinson's disease), 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 (i.e. peripheral vascular disease) which may contraindicate RLIC ¶ 5)Any cognitive, sensory, or communication problem that would prevent completion of the study ¶ 6)Current intensive weight lifting or interval training exercise ¶ 7)Current substance abuse or dependence ¶ 8)Current use of medication with selective serotoninreuptake inhibitors. 9)Unwillingness to travel for all study visits ¶
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 8 total visits. Participants will be in the study for up to 6 weeks. Please refer to Figure 1 for details about study visits. **D1**: Subjects will be asked to avoid food, drink (except water), and vigorous exercise beginning midnight the day of their visit. A trained clinical interviewer will provide informed consent and conduct a structured clinical interview. Eligible individuals will be asked to complete descriptive measures. Next, subjects will have an electrocardiogram (ECG) recording while they sit quietly for 7 minutes. Then, subjects will undergo a blood draw (4 teaspoons). Next, researchers will gather baseline measurements on all primary and secondary outcome measures. Subjects will then be randomized to their treatment group. After randomization, subjects will undergo their assigned dose of RLIC or sham conditioning. After conditioning, subjects will have another 7-minute resting ECG recording and undergo another blood draw (4 teaspoons). **This visit will take approximately: 2.5 hours** **D2**: Subjects will be asked to avoid food, drink (except water), and vigorous exercise beginning midnight the day of their visit. Subjects will undergo a blood draw (4 teaspoons). Then, subjects will undergo their specified dose of RLIC or sham conditioning. **This visit will take approximately: 1 hour** **D3-6**: Subjects will undergo their specified dose of RLIC or sham conditioning. Next, behavioral training will commence (a balance task, arm task, and computer task). The order of behavioral training task practice will be randomized. **These visits will take approximately: 2 hours** **D7:** Subjects will be asked to avoid food, drink (except water), and vigorous exercise beginning midnight the day of their visit. Subjects will undergo a blood draw (4 teaspoons). Then, subjects will undergo their specified dose of RLIC or sham conditioning. Next, subjects will complete behavioral training tasks and post-testing. **This visit will take approximately: 2.5 hours** **F/U**: Post-test performance assessment on the primary and secondary outcome measures will be performed. Participants will <u>not</u> receive RLIC or sham conditioning during the follow-up visits. Participants will fill out a survey indicating whether they think that they received RLIC or sham treatment. **This visit will take approximately: 45 minutes**
RLIC Treatment Parameters	Remote limb ischemic conditioning will be achieved via blood pressure cuff inflation to 20 mmHg above systolic blood pressure on the non-dominant, upper extremity regardless of the assigned number of cycles. Sham conditioning will be achieved via blood pressure cuff inflation to 10 mmHg under diastolic blood pressure on the non-dominant, upper extremity.

	Subjects will be blinded to their group assignment (RLIC or sham conditioning).
Behavioral Training Parameters	Three tasks will be used for behavioral training on D1-D7. 1) Balance training task (15 minutes; rest breaks as needed) 2) Arm training task (10 minutes; rest breaks as needed) 3) Computer training task (10-20 minutes) 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.[10] This is a lab-based test. This 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. The arm task is a cup stacking task. Subjects are asked to stack ten cups in three different arrangements, using bilateral upper extremities. This task should be completed as quickly as possible. The computer training task is a discrete sequence production task. The computer task involves having subjects learn six, 10-element sequences of key presses. Each sequence is uniquely cued before commencement. 5 boxes are shown on the screen and subjects respond by pressing a key on the keyboard with their right hand that corresponds to the position of the boxes on the screen. This particular task was selected because it can improve with practice.[11]
Descriptive measures	Demographic information, including age, dominant side, gender, ethnicity, race, level of physical activity, height, body weight, employment status, education level, co-morbidities, and current medications will be collected on all subjects on D1.
Primary Outcome Measures	The primary outcome measures are: 1) Performance on the standing balance motor task 2) Performance on the arm task 3) Performance on the computer task Performance on the standing 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. Performance on the arm task will be measured by the time to complete the three cup-stacking structures. The measure of performance on the computer task will be the average time to complete each unique sequence in milliseconds. Please refer to Table 1 for a summary of the assessment schedule.
Secondary Outcome Measure	The secondary outcome measure is: 1) Blood draw: probe for levels of serum markers of RLIC The blood draw will be performed by trained members of the Washington University Clinical Research Unit. Blood will be processed the Washington University CORE Laboratory. Please refer to Table 1 for a summary of the assessment schedule.
Data Analysis	Data will be analyzed using a mixed model ANOVA with a within subject factor of time (pretest vs. posttest) and a between subjects factor of conditioning (RLIC vs. sham treatment).
Safety Considerations & Monitoring	The study will be submitted to and approved by the Washington University Human Research Protection Office prior to initiation. 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 training tasks is fatigue. Subjects will be encouraged to take rest breaks 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 lower extremity balance tasks and performance of all tasks will be supervised by a study team member. With regards to the RLIC, rare side effects may occur, including HTN, hippocampal cell death, learning deficits, and metabolic syndrome. However, this protocol involves between 3 and 5 cycles of peripheral ischemia, which is below the dose that has been found to be harmful. This number of RLIC cycles is associated with tolerable pain and does not cause changes in systematic blood pressure or heart rate, and has not resulted in side effects.[9] 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 session 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 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 Co-I: Dr. Jin-Moo Lee, MD, PhD Study Coordinator: Anna Mattlage, PhD
Number of Centers	1 center: Washington University School of Medicine
Key References	Please see the reference list.

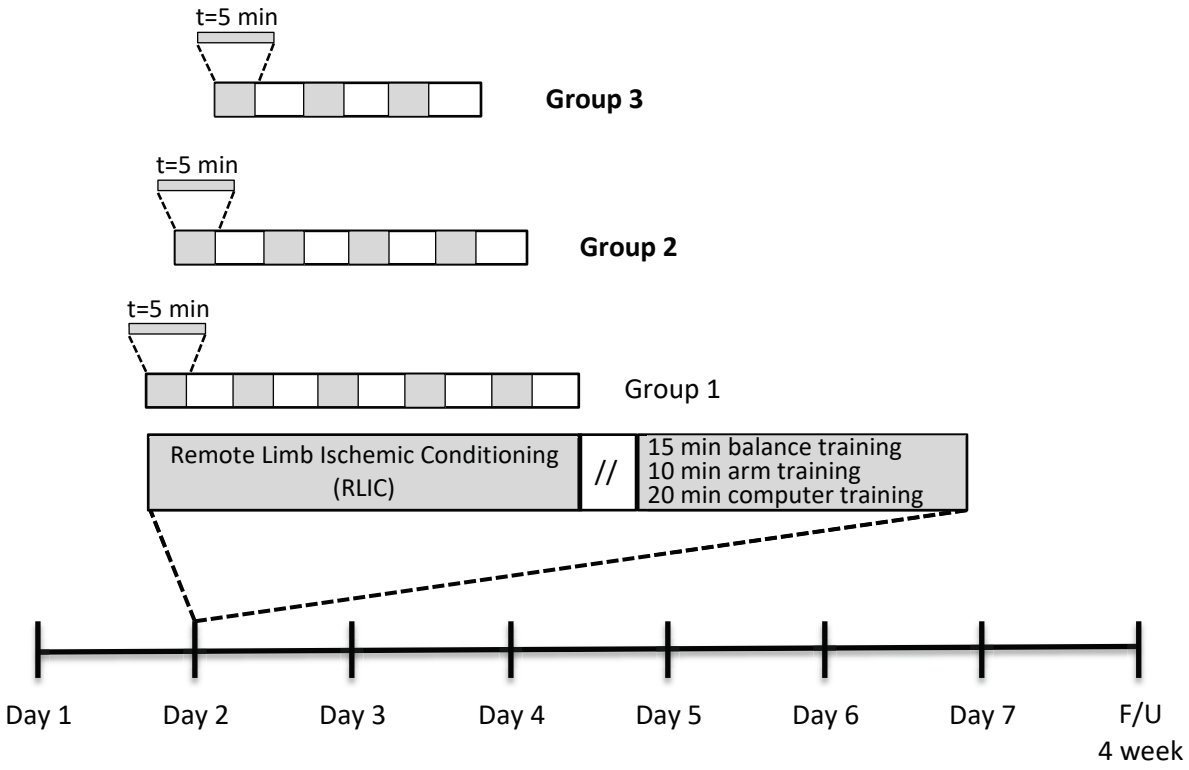

Figure 1. Remote limb ischemic conditioning (RLIC) involves between 3 and 5 cycles (depending on the group randomization) of 5 minutes of upper extremity peripheral ischemia (induced either by a blood pressure cuff inflated to 20 mmHg >systolic BP), alternating with 5 minutes of no ischemia. For 5 consecutive weekdays, subjects receive a combinational intervention of RLIC (or sham) plus training. On training days, subjects undergo the RLIC and perform 15 minutes of balance training, 10 minutes of arm training, and 20 minutes of computer training.

Table 1

Assessments	Time Points							
	Day 1		Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Follow-up
Fast Prior to Visit	X		X					X	
Balance Task	X			X	X	X	X	X	X
Arm Task	X			X	X	X	X	X	X
Computer Task	X			X	X	X	X	X	X
Blood Draw	X	X	X					X	
ECG	X	X							

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