**Remote limb ischemic conditioning to enhance learning and muscle strength in healthy, young adults**

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| Remote Limb Ischemic Conditioning to Enhance Performance, Learning And Muscle Strength | |
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| **Study Objectives** | The objective of this research study is to determine if remote limb ischemic conditioning (RLIC) can enhance learning of an ecologically valid, complex cognitive-motor (driving) task and increase skeletal muscle strength in neurologically intact young adults. |
| **Background & Rationale** | Ischemic conditioning is an endogenous phenomenon in which exposing a target organ or tissue to one or more brief episodes of ischemia results in protection of that organ against subsequent ischemia (Gidday, 2006). The effects of ischemic conditioning are not confined within an organ but can be can be transferred from one organ to another, a technique called remote ischemic conditioning (Saxena et al., 2010). A clinically feasible method for this is remote limb ischemic conditioning (RLIC), where episodes of ischemia and perfusion are induced with a blood pressure cuff placed on the arm (Kharbanda et al., 2009).<br><br>In humans, the cardioprotective effects of RLIC have been demonstrated (Hausenloy et al., 2007; Botker et al., 2010). For example, applying an inflated blood pressure cuff to the upper or lower limb has shown efficacy for protection in people undergoing cardiac surgeries (Hausenloy et al., 2007; Meng et al., 2012), elective surgery to repair abdominal aortic aneurysm (Ali, Callaghan et al. 2007), experiencing myocardial infarction (Botker et al., 2010), and with symptomatic intracranial arterial stenosis (Meng, Asmaro et al. 2012). Although the cardioprotective effects of RLIC have been well established, the neuroprotective effects are just beginning to be evaluated (Meng et al., 2012). Moreover, the effects of RLIC on skeletal muscle is largely unknown. Only a single study so far has shown that RLIC decreases depletion of ATPs, decreases lactate accumulation and increases myeloperoxidase, which helps in reducing inflammation and apoptosis in skeletal muscles of rats (Addison et al., 2003).<br><br>The proposed study is a part of larger study that is investigating if the effects of RLIC might extend beyond cardio- and neuroprotection and into plasticity, learning and recovery. The preliminary results of the proof-of-concept study from our lab has shown that RLIC robustly facilitates motor learning and retention in young, neurologically intact adults (Cherry-Allen et al., 2015). However, these learning effects have been seen in a lab controlled motor task. Hence, the next step is to investigate if RLIC can enhance performance of real world, ecologically valid complex cognitive-motor task such as driving in a simulated environment and increase skeletal muscle strength in healthy young adults.<br><br>This study is important because if eventually effective, RLIC could have profound effect on the rehabilitation and recovery of cognitive-motor function and muscle strength 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. |
| **Study Design** | Between groups repeated measures design. |

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| **Groups** | Group 1: Neurologically Intact Subjects + 5 cycles of RLIC<br>Group 2: Neurologically Intact Subjects + 5 cycles of sham conditioning<br><br>Subjects who qualify and consent will be randomly assigned to either group 1 or 2. Allocation will be concealed from those responsible for assessing participants for eligibility and entry into the study. |
| **Number of Subjects & Power Analysis** | Based on our pilot data for the balance task training, we will need 20 participants in each group (total 40) to achieve atleast 80% power to detect mean differences of 3 seconds of change scores (posttest - pretest) between 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. We request permission to enroll 55 subjects total to allow for screen failures and subjects those who do not complete all study visits.<br><br>Based off of the earlier study on strength training (Christie and Kamen, 2010), 20 participants in each group (40 total) will give 98% power to detect mean difference of 17 % change in the muscle strength (posttest – pretest) after 2-weeks strength training based on a two-sample t-test at a significance level of 0.05. The standard deviations for change scores are assumed to be 10.81 lbs and 12.2 lbs for pre- and post-strength training respectively. |
| **Inclusion & Exclusion Criteria** | **Inclusion Criteria:**<br>1) Healthy adults between the age of 18 and 40 years<br><br>**Exclusion Criteria:**<br>1) History of neurological condition (i.e. stroke, Alzheimer's disease, Parkinson's disease), ADD, ADHD, depression, bipolar disorder, balance impairment, or vestibular disorder<br>2) History of motion sickness, moderate to severe motion sickness on nausea or oculo-motor components of Simulator sickness questionnaire (Appendix 1) (Kennedy et al., 1993), inability to ride a car, boat, train or airplane, and impaired vision, and visual acuity below state guidelines for driving<br>3) Recent wrist, hand or forearm injury that would prevent ability to lift weights<br>4) History of lower extremity condition, injury, or surgery which could compromise performance on motor training task<br>5) Any extremity soft tissue, orthopedic, or vascular injury (i.e. peripheral vascular disease) which may contraindicate RLIC<br>6) Any cognitive, sensory, or communication problem that would prevent completion of the study<br>7) History of sleep apnea<br>8) Current intensive weight lifting or interval training exercise<br>9) Current substance abuse or dependence<br>10) Unwillingness to travel for all study visits |

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| **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 (Cherry-Allen et al.; 2017). Sham conditioning will be achieved via blood pressure cuff inflation to 10 mmHg under diastolic blood pressure on the non-dominant, upper extremity. Conditioning will involve 5 cycles of 5 minutes blood pressure cuff inflation followed by alternating 5 minutes of cuff deflation. Subjects will be blinded to their group assignment (RLIC or sham conditioning). **Conditioning requires 45 minutes.** |
| **Behavioral Training** | Three tasks will be used for behavioral training on visit 3-8.<br><br>1) Driving task (15-20 minutes)<br>2) Strengthening task (20-30 minutes)<br>3) Balance training task (15 minutes; rest breaks as needed)<br><br>**Driving task:** The driving task requires the subject to drive in a simulated environment of STISIM M300WS (Systems Technology, Inc.), which presents a realistic driving experience through controlled, complex tasks related to vehicle dynamics, natural pedal and steering wheel controls, and a wide field of view display. Participants are asked to drive through increasingly complex scenario over mixed roadways (complex urban, suburban, rural, and construction zone). Hazards, maneuvers and basic rules of the road are presented to the participant during the scenarios. Performance will be quantified on a weighted composite score for time to scenario completion, pedestrian hitting, collisions, center lane crossing, off road accidents, stop sign and traffic light rules, and other driving errors.<br><br>**Strengthening task:** Strengthening of wrist extensor muscles was chosen because wrist extensor strength is a key characteristic for participation in many upper extremity rehabilitation interventions (Hakkennes, and Keating, 2005). For training and testing, participants will sit with shoulder and forearm supported so motion is isolated to the wrist. A single column wall-mounted pulley with stackable weights of 2.5 lbs will be used. Prior to training and testing, participant will be guided through a warm-up to avoid injury and maximize performance. The warm-up exercises will include 2 sets (30 seconds each) of wrist oscillations, 3 sets of each 10-seconds isometric contraction of wrist extensors, and 6-8 repetitions of 50% of 1 RM weight with the wrist extensors. Training will be initially set at 6 sets of 6-8 repetitions at 80% of 1 RM, which would be required high intensity to achieve training effects (Jenkins et al., 2017). The load will be increased if the subjects performs 4 sets of 6-8 repetitions with 80% of 1 RM. Training will be progressed by increasing the resistance if 8 repetitions are achieved on 4 of 6 sets. We will provide 3-minutes of rest after each set to prevent muscle fatigue and soreness.<br><br>**Balance Task:** 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 (Taubert, Draganski et al. 2010). 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 |

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| | 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, height, body weight, employment status, education level, co-morbidities, and current medications will be collected on all subjects on visit 1. |
| **Primary Outcome Measures** | The primary outcome measures are:<br>1. Performance on the driving task<br>2. Performance on the strengthening task<br>3. Performance on the standing balance task<br><br>**Performance on the driving task:** It will be measured by composite score.<br><br>Composite score= Time x Errors<br>• Time=time to completion of entire driving scenario<br>• Errors= number of pedestrian hitting, collisions, center lane crossing, off road accidents, stop sign and traffic light rules, and other driving errors.<br><br>*Lower score would indicate better performance.<br><br>**Performance on the strengthening task** will be assessed by-<br>a. One repetition maximum (1RM) of wrist extensors: Maximum amount of force (lbs) that can be generated in one contraction (Shimano et al., 2006). It will be quantified as the maximum amount of weight (lbs) that participant can lift in one repetition.<br>b. MVIC of wrist extensors: Maximum amount of isometric force (lbs) exerted by wrist extensor muscles against the dynamometer (Meldrum et al., 2007). It is a standardized method for measurement of muscle strength using dynamometry.<br>c. Amplitude of EDC: EMG data will be used to quantify the amplitude of EDC. Increase in the amplitude of EMG is an indicator of neurophysiological adaptation to strength training (Carroll et al., 2011; Christie and Kamen, 2010).<br><br>**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. |
| **Order of Experiment/Study Visits** | This study involves 10 total visits. Participants will be in the study for up to 6 weeks. Please refer to Figure 1 for details about study visits.<br><br>**Visit 1:** 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 15-20 min driving test in a simulated environment of a STISIM M300WS (Systems Technology, Inc.) driving simulator to quantify driving performance. |

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| | Then, we will quantify muscle strength of the non-dominant wrist extensors by recording 1 RM. We will record the maximum amount of weight (lbs) that the participant will lift while performing wrist extension as 1 RM. Next, we will measure maximum voluntary isometric contraction (MVIC). We will ask the participant to produce maximum wrist extension force by pushing against the dynamometer placed on the dorsum of the wrist for three maximal-effort contractions lasting 5 seconds each with 2 minutes rest between each contraction. The average of three contractions will be considered as MVIC for wrist extensor muscles. We will also simultaneously record the electromyographic (EMG) activity of extensor digitorum communis (EDC) muscle while performing MVIC. EMG data will be gathered using 2-channel EMG system (Noraxon Inc, USA).The active electrodes will be placed on the belly of EDC. Two active electrodes will be separated with 2 centimeters distance and the ground electrode will be placed on the bony prominence (lateral epicondyle) of the elbow.<br>Next, we will gather baseline measurements on balance task.<br>Subjects will then be randomized to their treatment group. After randomization, subjects will undergo RLIC or sham conditioning. **This visit will take approximately: 2.5 hours.**<br><br>**Visit 2:** Subjects will undergo RLIC or sham conditioning. **This visit will take approximately: 1 hour.**<br><br>**Visit 3-8:** Subjects will undergo RLIC or sham conditioning. Next, behavioral training will commence (driving task, strengthening task, and balance training). The order of behavioral training task practice will be randomized. Visits 3-8 will occur every alternate day. **These visits will take approximately: 2 hours.**<br><br>**Visit 9:** Subjects will complete post-testing which will include a) 15-20 min driving test; b) 1 RM and MVIC of the wrist extensor muscles on the training arm; c) EMG of the EDC muscle on the training arm, and d) balance testing. Visit 9 will be on the next day after visit 8. **This visit will take approximately: 1 hour.**<br><br>**Visit 10:** Post-test performance assessment on driving test, 1 RM and MVIC and EMG of the EDC muscle on the training arm, and balance testing will be performed after 4-weeks from the visit 9. Participants will <u>not</u> receive RLIC or sham conditioning during the follow-up visits. Participants will fill out a survey on the second follow-up visit indicating whether they think that they received RLIC or sham treatment. **This visit will take approximately: 1 hour.** |
| **Data Analysis** | Data will be analyzed using a mixed model ANOVA with time (pretest vs. posttest) as within subject factor and group (RLIC vs. sham treatment) as between subject factor. |
| **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 likely risks are- |

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| | 1. **Conditioning:** *bruising, discomfort, pain or tingling on the conditioning arm.*<br>To avoid bruising from the pressure cuff, participant's arm will be covered with a piece of cotton cloth. During each conditioning cycle, we will ask the participant about discomfort, pain or tingling in the conditioning arm. If the participant reports pain or tingling, we will reposition the pressure cuff on the arm and allow the participant to move the arm during 5-minutes of deflation cycle.<br>2. **Driving:** *motion sickness that can result in dizziness, nausea, yawning, perspiration, excessive blinking, vertigo, headache and general discomfort. There may be some anxiety while performing a simulated driving task.*<br>To avoid motion sickness, the temperature of the driving simulation room will be regulated; we will keep the room cool and turn the fan on to maintain ventilation. We will also closely visually monitor early signs of motion sickness. Moreover, if the participant reports motion sickness during the training, we will immediately stop the simulator and will ask the participant to relax in the simulator chair until the symptoms subside. However, if motion sickness persists, participant will not resume the simulated driving training on that day and we will ask the participant to monitor the symptoms until before the start of the next visit. If motion sickness persists until next visit, we will discontinue participation from driving training. To reduce anxiety, we will reassure the participants that their performance will not impact their ability to drive on road.<br>3. **Strengthening:** *minor risk of injury to wrist muscles, wrist pain, muscle fatigue and delayed onset muscle soreness.*<br>To avoid musculoskeletal injury, participants will perform warm-up exercises (gentle stretching of wrist muscles, wrist oscillations, isometric muscle contractions of the wrist muscle, and 1 set of low-intensity weight lifting) for 5 minutes before starting the strengthening. Strength training on every alternate day should allow sufficient time to recover from muscle fatigue and delayed onset muscle soreness.<br>4. **Balance:** *small risk of falling from the balance board.*<br>Subjects will be permitted to use a handrail as needed for safety during balance task and two research team members will supervise the balance performance.<br><br>In order to monitor for further overall safety, we will continuously monitor lightheadedness, 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, diastolic BP <40 or >100 mm Hg 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<br>Study Coordinator: Swati Surkar, PhD, PT |

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| **Number of Centers** | 1 center: Washington University School of Medicine |
| **Key References** | Please see the reference list. |

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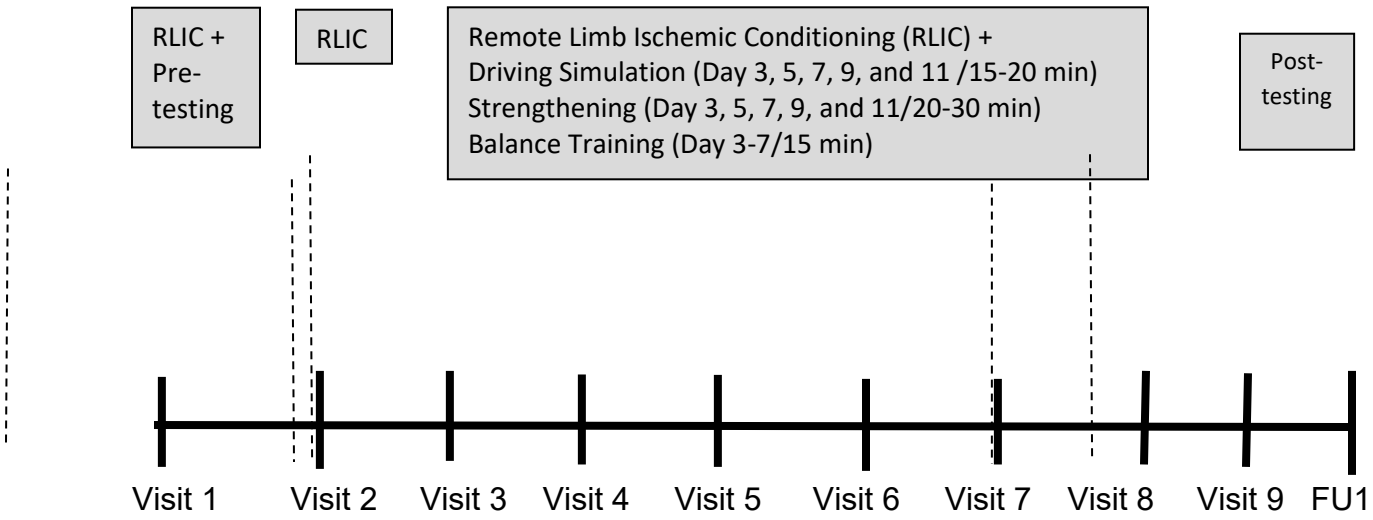


Figure 1. Remote limb ischemic conditioning (RLIC) involves 5 cycles of 5 minutes of upper extremity peripheral ischemia (induced by a blood pressure cuff inflated to 20 mmHg >systolic BP), alternating by 5 minutes of no ischemia. For 6 sessions (visit 3-8 for every alternate day), subjects receive a combinational intervention of RLIC (or sham) plus training. On training days, subjects undergo the RLIC and perform 15-20 minutes driving simulation, strengthening for 20-30 minutes and15 minutes of balance training.

## Appendix 1

No._____ Date_____

**SIMULATOR SICKNESS QUESTIONNAIRE**

**Kennedy, Lane, Berbaum, & Lilienthal (1993)*****

Instructions : Circle how much each symptom below is affecting you right now.

| | | | | |
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| 1. General discomfort | None | Slight | Moderate | Severe |
| 2. Fatigue | None | Slight | Moderate | Severe |
| 3. Headache | None | Slight | Moderate | Severe |
| 4. Eye strain | None | Slight | Moderate | Severe |
| 5. Difficulty focusing | None | Slight | Moderate | Severe |
| 6. Salivation increasing | None | Slight | Moderate | Severe |
| 7. Sweating | None | Slight | Moderate | Severe |
| 8. Nausea | None | Slight | Moderate | Severe |
| 9. Difficulty concentrating | None | Slight | Moderate | Severe |
| 10. Fullness of the Head | None | Slight | Moderate | Severe |
| 11. Blurred vision | None | Slight | Moderate | Severe |
| 12. Dizziness with eyes open | None | Slight | Moderate | Severe |
| 13. Dizziness with eyes closed | None | Slight | Moderate | Severe |
| 14. *Vertigo | None | Slight | Moderate | Severe |
| 15. **Stomach awareness | None | Slight | Moderate | Severe |
| 16. Burping | None | Slight | Moderate | Severe |

Total: items 1 to 16 (scale of 0 to 3).

Nausea: items 1 + 6 + 7 + 8 + 12 + 13 + 14 + 15 + 16.

Oculo-motor: items 2 + 3 + 4 + 5 + 9 + 10 + 11.

* Vertigo is experienced as loss of orientation with respect to vertical upright.

** Stomach awareness is usually used to indicate a feeling of discomfort which is just short of nausea.

Last version : March 2013 ***Original version : Kennedy, R.S., Lane, N.E., Berbaum, K.S., & Lilienthal, M.G. (1993). Simulator Sickness Questionnaire: An enhanced method for quantifying simulator sickness. International Journal of Aviation Psychology, 3(3), 203-220