# Remote Limb Ischemic Conditioning to Enhance Muscle Power, Dynamic Balance, and Walking Performance in Children with Cerebral Palsy

10/15/2020

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| **Study Objectives** | The objective of this research study is to determine if remote limb ischemic conditioning (RLIC) can enhance quadriceps muscle power, dynamic balance and walking performance in children with cerebral palsy (CP). |
| **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.[1] 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.[2] 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.[3]<br><br>In humans, the cardioprotective effects of RLIC have been demonstrated.[4,5] For example, applying an inflated blood pressure cuff to the upper or lower limb has shown efficacy for protection in people undergoing cardiac surgeries,[4,6] elective surgery to repair abdominal aortic aneurysm,[7] experiencing myocardial infarction,[5] and with symptomatic intracranial arterial stenosis. Subsequent studies have shown RLIC as neuroprotective[8] and improves exercise performance in healthy young adults.[9-12] Based on the promising results of our clinical trials which demonstrated that when paired with training, RLIC improves muscle strength and motor learning in healthy young and older adults respectively.[13,14] Therefore, we postulate that the effects of RLIC might extend in neurological population such as CP.<br><br>Our central hypothesis is that the multifactorial mechanisms of RLIC can be harnessed as a neurorecovery agent to enhance rehabilitation and outcomes in children with CP. This research will focus on improving quadriceps power and dynamic balance since quadriceps weakness and impaired balance performance are often cited as major factors that limit the mobility and walking performance of children with CP.[15-17] The results of our randomized controlled trials have shown that RLIC facilitates motor learning and muscle strength, and retention of these changes in older and young, neurologically intact adults.[13,14] However, these learning and strength effects have only been seen only in healthy population. Hence, the next step is to investigate if RLIC can enhance performance of an ecologically valid motor task such as dynamic balance task, increase skeletal muscle power, and increase walking performance in children with CP. |

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| | This study is important because if eventually effective, RLIC could have profound effect on the rehabilitation and recovery of brain plasticity and muscle performance in children with CP and other neurological population. |
| **Study Design** | Between groups repeated measures design. |
| **Groups** | Group 1: Children with CP receiving RLIC<br><br>Group 2: Children with CP receiving sham conditioning<br><br>Children who qualify and consent will be randomly assigned to either group 1 or 2. Participants will be blinded to the group assignment and the assessor will be blinded to the participant's group assignment. |
| **Number of Subjects & Power Analysis** | Sample size estimates are based on peak knee extension power data from Moreau et al.[18] A total of 24 participants (12 in each group) will provide 80% power to detect an effect size of 0.62 at significance level of 0.05.<br><br>The sample size was calculated based on a two-sided Wald test of regression coefficients in linear mixed effects model adjusting for design effect and correlation of repeated measures from the same subjects.[19] |
| **Inclusion & Exclusion Criteria** | **Inclusion Criteria:**<br>1. Children diagnosed with unilateral or diplegic CP<br>2. Gross Motor Function Classification System (GMFCS) levels I-III<br>3. 6-13 years of age<br><br>**Exclusion Criteria:**<br>1. Children with other developmental disabilities such as autism, developmental coordination disorders, etc.<br>2. Children with cognitive deficits or communication problem<br>3. Children with balance disorders such as vestibular disorders, posterior fossa tumor etc.<br>4. Children with known cardiorespiratory dysfunctions<br>5. Children who are receiving other adjunct therapies such as TMS, tDCS, vagal nerve stimulation etc.<br>6. Presence of lower extremity condition, injury, or surgery which could compromise conditioning and training<br>7. Children with sickle cell disease |
| **RLIC and Sham Conditioning** | Remote limb ischemic conditioning will be achieved via blood pressure cuff inflation to 20 mmHg above resting systolic blood pressure up to 200 mmHg.[20,21] Sham conditioning will be achieved via blood pressure cuff inflation to 25 mmHg on the more involved thigh. 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.** RLIC or sham conditioning will be performed on visits 1-14. |

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| **Behavioral Training** | Three tasks will be used for behavioral training on visits 3-14.<br><br>1) Power training task (20-30 minutes)<br>2) Balance training task (15 minutes; rest breaks as needed)<br>3) Treadmill training (15 minutes)<br><br>**Power Training:** Prior to training and at the beginning of each training week, we will obtain 1 repetition maximum (1 RM) on each leg. 60-80% of the 1 RM will be used as training intensity with progression toward 80% based on that week's 1 RM. Training will involve unilateral and bilateral leg presses (Total Gym GTS, San Diego, CA), 3 times/week for 4 consecutive weeks (12 sessions). Each session will begin with 5 minutes of warm-up exercises. Each participant will perform 6 sets of 5-7 concentric extension contractions with maximum efforts, and with one-three minutes rest after each set.[22]<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.[23] This task was selected because it can be easily modified to the appropriate level of difficulty in accordance with each subject's motor abilities.<br><br>**Treadmill Training:** We will use short burst interval treadmill training. We will use the self-selected and fast walking speeds determined by the 10-meter walk test as the training intensity for the child for each session. Short burst interval training will consist of 30 seconds fast followed by 30 seconds of slow walking. We chose this type of training since it closely resembles the walking performance of a child in the community. |
| **Descriptive measures** | Demographic information, including age, dominant side, gender, ethnicity, race, level of physical activity, height, body weight, school grade, GMFCS level, prenatal, natal, or postnatal history, co-morbidities, current medications, history of any surgery, and current and past rehabilitation will be collected on all subjects on visit 1. Performing all these descriptive measures on visit 1 will allow us to determine the inclusion/exclusion of the participant in the study. |
| **Outcome Measures** | The outcomes measured include-<br><br>Performance on:<br><br>1. Quadriceps power<br><br>2. Electromyography<br><br>3. Balance<br><br>4. Walking |

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| | **Quadriceps power:** will be measured using Humac Norm Isokinetic testing device (Computer Sports Medicine Inc, Stoughton, MA). Quadriceps power over 5 maximal test repetitions at 90̊/sec will then be calculated every 10 ms (velocity x torque).<br><br>**Electromyography (EMG):** The EMG data will be used to quantify the electrical amplitude of quadriceps muscle. Increase in the amplitude of EMG is an indicator of neurophysiological adaptation to strength training.[24,25] We will simultaneously record the EMG activity of quadriceps muscle while performing isokinetic testing. EMG data will be gathered 6-channel EMG system (Delsys Inc, USA) with the sampling frequency set at 1000 Hz). Surface EMG sensors will be placed at the muscle belly in the direction of muscle fibers, according to surface EMG for non-invasive assessment of muscles (SENIAM) guidelines (http://www.seniam.org). EMG data will be processed off-line in MATLAB R2016a (MathWorks, Natick, MA) with custom-written software using cutoff frequencies of 20 and 500 Hz for lower and upper band-pass, respectively and by averaging by averaging the amplitude of the EMG activation during the middle 3000 ms for each trial.<br><br>**Performance on the standing balance task** will be quantified by identifying the number of seconds in a 30-second trial that an individual is able to maintain the platform within ±5° of horizontal.<br><br>**Walking Performance:**<br><br>Walking performance will be measured with:<br><br>1. **Walking speed:** Self-selected and fast walking speeds will be measured using 10-meter walk test. Children will complete three trials at each speed and the average of the respective trials will be considered for analysis. During these tests, children will walk across a GaitRITE digital mat (CIR Systems, Sparta, NJ) and we will quantify walking speed, step length, step width, and cadence.<br><br>2. **Gait analysis:** Lower extremity walking kinetics and kinematics will be measured using a 10-camera motion analysis system (Qualisys Inc., Gothenburg, Sweden) sampling at 200 Hz. Specific kinematic variables are hip, knee, and ankle joint angles at midstance, peak hip extension, peak knee extension, and peak ankle plantarflexion during stance phase. Kinetic dependent variables include peak hip, knee, and ankle sagittal plane joint moments and total support moment, and peak positive and negative hip, knee, and ankle sagittal plane joint power.<br><br>3. **Accelerometry:** Lower extremity activity will be measured using accelerometers worn on bilateral ankles for 24 hours. Specific accelerometry variable will be number of steps. |

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| **Order of Experiment/Study Visits** | This study involves 16 total visits. Participants will be in the study for up to 8 weeks. Please refer to Table 1 for a timeline of study visits.<br><br>**Visit 1:** We will provide informed consent and assent and gather demographic data. Next we will perform baseline assessments for the performance on the quadriceps power, EMG, balance, and walking.<br><br>Then, we will quantify power of bilateral knee extensor by recording peak knee extensors toque and electromyography of bilateral rectus femoris, vastus lateralis, and vastus medialis.<br><br>Next, we will gather measurements on balance task.<br><br>Next, we will assess walking performance using 10-meter walk test, 3-D gait analysis, and accelerometry.<br><br>Subjects will then be randomized to their treatment group. After randomization, subjects will undergo RLIC or sham conditioning (see RLIC and Sham Conditioning for the details). **This visit will take approximately: 3 hours.**<br><br>**Visit 2:** Subjects will undergo RLIC or sham conditioning **This visit will take approximately: 1 hour.**<br><br>**Visit 3-14:** Subjects will undergo RLIC or sham conditioning. Next, behavioral training will commence (power training task and balance training). The order of behavioral training task practice will be randomized. Visits 3-14 will occur every alternate business day. **These visits will take approximately: 2-2.5 hours.**<br><br>**Visit 15:** Subjects will complete post-testing which will include a) quadriceps power; b) EMG; c) balance task, and d) walking performance. Visit 15 will be on the next business day after visit 14. During this visit, participants will <u>not</u> receive RLIC or sham conditioning. **This visit will take approximately: 2 hours.**<br><br>**Visit 16:** Post-test performance assessment on power, EMG, balance, and walking will be performed after 4-weeks from the visit 15. Participants will <u>not</u> receive RLIC or sham conditioning during the follow-up visits. Participants will fill out a survey on the follow-up visit indicating whether they think that they received RLIC or sham treatment. **This visit will take approximately: 2 hour.** |
| **Data Analysis** | Data will be analyzed using a mixed model ANOVA with time (pretest, posttest, and follow-up) 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.<br><br>**Conditioning:** |

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| | The likely risks are:<br><br>1. *Bruising on the conditioning thigh:* To avoid bruising from the pressure cuff, participant's arm will be covered with a folded cotton pillowcase.<br><br>*2. Discomfort:* To avoid discomfort in the conditioning thigh during each conditioning cycle, we will ask the participant about discomfort. If the participant reports discomfort, we will reposition the pressure cuff on the thigh and allow the participant to move the thigh during 5-minutes of deflation cycle.<br><br>*3. Pain or tingling on the conditioning arm*: To avoid pain or tingling in the conditioning thigh during the conditioning cycle, we will ask the participant about pain and tingling. If the participant reports pain or tingling, we will reposition the pressure cuff on the thigh and allow the participant to move the thigh during 5-minutes of deflation cycle.<br><br>**Power Training:**<br><br>The likely risks are<br><br>1. *Knee or thigh pain:* To avoid the knee or thigh pain, participants will perform warm-up exercises for 5 minutes before starting the strengthening.<br>2. *Muscle fatigue and delayed onset muscle soreness*: Power training on every alternate day will allow sufficient time to recover from muscle fatigue and delayed onset muscle soreness.<br><br>**Balance:**<br><br>The less likely risks are<br><br>1. *Falling from the balance board*: To avoid falling from the balance board, participants will be permitted to use a handrail as needed for safety during balance task and up to two research team members will supervise the balance performance. Participants will also wear a gait belt for safety, which will help the research team member to catch the participant if they start to fall.<br><br>**Treadmill:**<br><br>The less likely risks are<br><br>1. *Muscle fatigue and falling from the treadmill:* To avoid falling from the treadmill, participants will be provided sufficient rest. Participants will also be allowed to use a handrail as needed and will also wear a gait belt for safety.<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 <60 bpm or >160 bpm, systolic BP <70 mmHg or >130mmHg, diastolic |

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| | BP <40 or >90 mmHg, $O_2$ saturation <90%, or if pain is >6 on 10-point Likert pain scale. Moreover, during the follow up session, all subjects will be asked questions about any adverse effects that resulted from participation in this study. |
| **Investigators** | PI: Swati Surkar, PhD, PT |
| **Number of Centers** | 1 center: East Carolina University |
| **Key References** | Please see the reference list. |

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Table 1: Order of the 16 study visits. Testing occurs on Study Visits 1, 15, and 16. Conditioning which involves 5 cycles of 5 minutes of lower extremity peripheral ischemia (or sham), alternating by 5 minutes of no ischemia, occurs on Study Visits 1-14. Training occurs on Study Visits 3-14 (Study Visits 4-14 occur every other business day, excluding weekends and holidays) and includes power, balance and treadmill training.

| **Assessments** | | **Visits** | | | | | | | | | | | | | | | |
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| | 1 (D1) | 2 (D2) | 3 (D3) | 4 (D5) | 5 (D7) | 6 (D9) | 7 (D11) | 8 (D13) | 9 (D15) | 10 (D17) | 11 (D19) | 12 (D21) | 13 (D23) | 14 (D25) | 15 (D26) | 16 *(4 weeks from visit 15)* |
| Consent/ Demographic details | ✔ | | | | | | | | | | | | | | | |
| Pre-testing | ✔ | | | | | | | | | | | | | | | |
| Conditioning (RLIC/ Sham) | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | | | | | | | ✔ | | |
| Training | | | ✔ | ✔ | ✔ | ✔ | ✔ | | | | | | | ✔ | | |
| Post-testing | | | | | | | | | | | | | | | ✔ | ✔ |

*D= business day

1. Pre-testing includes: Performance on the- 1) Power task, and 2) balance task, and 3) walking task.
2. Training includes: Training on the- 1) Bilateral Knee Extensor Strengthening, 2) Balancing task on the balance board, and 3) Short burst treadmill training.
3. Post-testing includes: Performance on the- 1) Power task, 2) balance task, and 3) walking task.