MECHANISMS OF WALKING RECOVERY AFTER STROKE (NCT02858349)

UNIVERSITY OF CINCINNATI IRB RESEARCH PROTOCOL 2016-1916

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STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

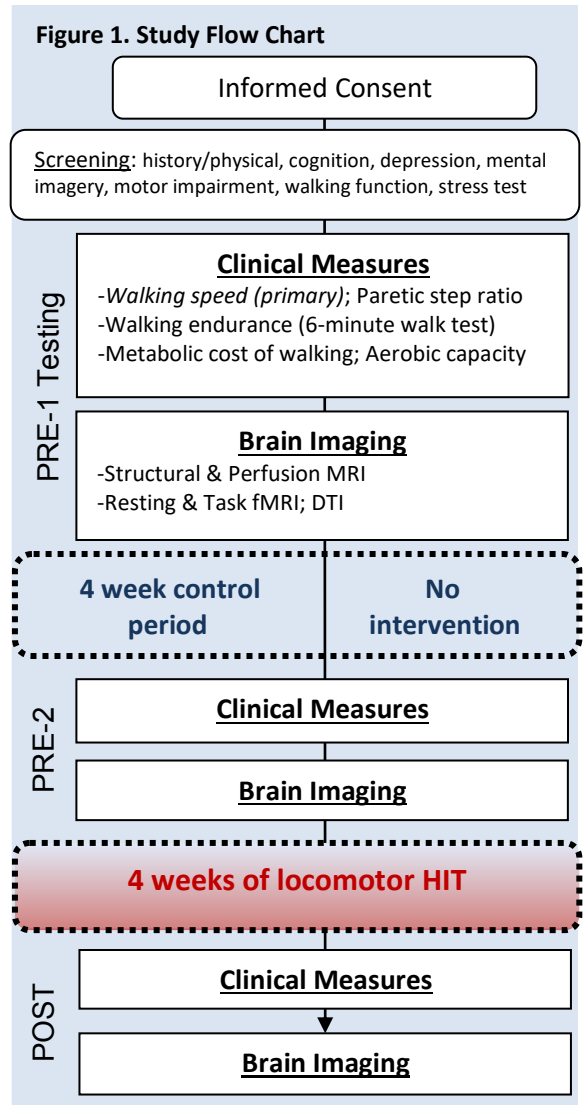# STUDY PROTOCOL

Research Design

This study will use a single-group repeated measures design. Ten subjects with chronic stroke will have clinical walking assessment and brain imaging before and after a 4 week control period and 4 weeks of locomotor high-intensity interval training (Figure 1). The control period will be used to confirm test-retest reliability of the measures and the absence of spontaneous improvements.[1,2]

Recruitment. As in previous studies, we will recruit persons with stroke from the Greater Cincinnati Northern Kentucky area by collaborating with our large referral base of regional therapists, physicians and support groups and by using our existing database of >300 local persons with stroke who are interested in participating in research. Clinician referrals can be done in two ways: 1) the clinicians may provide our name and contact information to the potential subject; 2) if the potential subject verbally approves, the clinician can give us their name and contact information.

For persons interested in participating, we will further explain the study, confirm initial eligibility and perform informed consent. After a research staff member explains the purpose of study and the consent, potential participants will be given at least 24 hours to decide if they want to participate. During this consenting process, the subject will be provided a copy of the consent form. Standardized questions will be asked to ensure that the subject understands the study before consenting. The consent form also includes a HIPAA authorization.

Eligibility Criteria. Based on our research experience, previous studies and American College of Sports Medicine (ACSM) guidelines,[3] we will observe the following eligibility criteria. Inclusion criteria: 1) age 30-90 years; 2) unilateral stroke experienced >6 months prior to enrollment in middle cerebral artery (MCA) territory without complete disruption of the putamen on the lesion side;[4] 3) walking speed $\leq$1.0 m/s on the 10 meter walk test;[5,6] 4) able to walk 10m over ground with assistive devices as needed and no physical assistance.[7] Exclusion criteria: 1) MRI incompatibility (e.g. metallic or electronic implants, severe claustrophobia); 2) inability to perform mental imagery (time dependent motor imagery screening test [TDMI]);[8,9] 3) evidence of significant arrhythmia or myocardial ischemia on treadmill ECG stress test, or significant baseline ECG abnormalities that would make an exercise ECG uninterpretable;[3] 4) recent (<3 months) cardiopulmonary hospitalization; 5) unable to communicate with investigators or correctly answer consent comprehension questions; 6) significant ataxia or neglect (score of 2 on NIH stroke scale item 7 or 11);[10] 7) severe lower extremity (LE) spasticity (Ashworth >2);[11] 8) recent (<3 months) illicit drug or alcohol abuse or significant mental illness; 9) major post-stroke depression (PHQ-9 $\geq$10)[12] in the absence of management of the depression by a health care provider (either anti-depressant medication or psychotherapy); 10) participating in physical therapy or another interventional research study; 11) recent (<3 months) paretic LE botulinum toxin injection; 12) concurrent progressive neurologic disorder or other major medical, orthopedic or peripheral vascular conditions that would limit improvement; 13) pregnancy.

Screening. After informed consent, subjects will undergo a screen including: medical record review, a history and physical, a depression screen (PHQ-9),[12] stroke-specific testing of mental imagery ability (TDMI),[8,9] aphasia screening (Western Aphasia Battery Screening Test[13]), a motor impairment assessment (Fugl-

Figure 1. Study Flow Chart

Informed Consent

Screening: history/physical, cognition, depression, mental imagery, motor impairment, walking function, stress test

PRE-1 Testing

Clinical Measures
- *Walking speed (primary)*; Paretic step ratio
- Walking endurance (6-minute walk test)
- Metabolic cost of walking; Aerobic capacity

Brain Imaging
- Structural & Perfusion MRI
- Resting & Task fMRI; DTI

4 week control period | No intervention

PRE-2

Clinical Measures

Brain Imaging

4 weeks of locomotor HIT

POST

Clinical Measures

Brain Imaging

Meyer[14]), a 10m walk test,[5,15] a resting ECG, a treadmill screening test[15] and a stroke-specific treadmill ECG stress test[16] to confirm eligibility and to obtain baseline characteristics and potential cofactors.

Stress testing will be performed, according to published guidelines,[3,17,18] by the trained, experienced clinical staff of the University Hospital Cardiovascular Stress Laboratory (UH-CSL), with assistance from a licensed physical therapist on the study team. Subjects will wear a harness secured to an overhead support system for safety in case of loss of balance (not for body weight support). ECG and vitals will be monitored according to published guidelines.[3,17,18] Subjects will perform a peak effort, graded treadmill stress test to volitional fatigue, individualized based on the treadmill screening test.[16] Test termination criteria will include subject request to stop at volitional fatigue, severe gait instability, or according to published guidelines.[3,16-18] This initial stress test will be conducted without oxygen uptake (VO2) measurement to maximize subject communication and comfort.[7]

Subjects will be notified about the results of their ECG and stress test. If they are disqualified from further participation in the study based on the results of these tests, they will also be given the option to have the results sent to their physician.

Women of childbearing potential will be asked if there is any possibility that they are pregnant before any study activities take place. As part of the informed consent process, these participants will also be instructed to notify the research staff if the possibility of pregnancy arises at any point while enrolled in the study. In the case of possible pregnancy, study activities will continue only after a urine pregnancy test is done and found to be negative.

The Locomotor HIT Intervention was developed in our pilot work. Subjects will train 45 minutes, 3 times per week for 4 weeks. A harness connected to an overhead support system will be used for fall protection (not weight support) during all treadmill walking and subjects will be closely guarded by a licensed therapist at all times. Each training session will consist of a 3 minute warm up (30-50% HR reserve), 10 minutes of floor HIT, 20 minutes of treadmill HIT, 10 more minutes of floor HIT and a 2 minute cool down. HIT will involve repeated bursts of walking at maximum safe speed, alternated with recovery periods. During each session, treadmill speed will be systematically progressed based on performance. During floor HIT, subjects will be given visual feedback about the distance covered during previous bursts and encouragement to increase distance with each burst. One or more activity monitor(s) (see clinical Outcome Testing below) and a heart rate monitor will be worn during training sessions to characterize and monitor training intensity.

Clinical Outcome Testing will be done before and after the 4 week control period, then again after the locomotor HIT intervention. This testing will be conducted by a licensed physical therapist, with assistance from a research assistant as needed. Each outcome testing session will last approximately 2 hours and may include the following measures:

Walking speed is the gold standard measure of post-stroke walking function that reflects overall mobility[19-21] and health status.[22] It is reliable and valid after stroke.[23,24] Walking speed will be captured with a stopwatch and/or with the GaitRITE, a commercially available 14-ft electronic walkway with 16,128 embedded pressure sensors, which instantaneously processes walking trial data to reliably and validly compute temporal-spatial gait parameters, including walking speed.[25,26] Participants will walk across the hallway and/or GaitRITE, using assistive devices, orthotics and guarding as needed. Each test may be performed twice at comfortable speed and twice as fast as safely possible. Comfortable walking speed will be the primary clinical outcome measure.

The *6-minute walk test* involves walking back and forth around two cones, using assistive devices, orthotics, guarding and rest breaks as needed.[27] The distance that the subject is able to walk in six minutes is recorded.

The NIH Toolbox Standing Balance Test involves holding up to 5 standing positions for 50 seconds each (http://www.nihtoolbox.org/WhatAndWhy/Motor/Balance/Pages/Balance.aspx). The sequence is: eyes

open on a solid surface, eyes closed on solid surface, eyes open on foam surface, eyes closed on foam surface, eyes open in tandem stance. Stopping rules are in place to ensure participant safety with these progressively demanding positions. Postural sway is recorded for each position using an accelerometer that the participant wears at waist level. Based on the postural sway during each attempted position, this test provides raw scores and age adjusted scores using national normative data. Elements of the *NIH Toolbox Cognition Battery* (http://www.nihtoolbox.org/WhatAndWhy/Cognition/Pages/default.aspx) may also be used.

The metabolic cost of gait is assessed using oxygen consumption rate (VO2) measurement during quiet sitting followed by VO2 measurement during treadmill walking at comfortable speed.[28] The metabolic cost of gait is the difference between VO2 at comfortable walking speed and VO2 at rest, normalized to walking speed.[28] VO2 will be measured using the Parvomedics TrueOne 2400 metabolic cart[29] and a facemask interface. The metabolic cost of gait estimates the energy cost of daily mobility,[7] increases with compensatory gait deviations,[28] and is reliable and valid after stroke.[30,31]

Aerobic capacity testing uses a similar protocol to the stress test above. It involves a screening test to determine the fastest speed at which the person can safely walk followed by an individualized peak effort, graded treadmill exercise test to volitional fatigue with VO2 measurement.[16] For the peak effort test, treadmill speed will begin below the subject's individualized fastest safe speed. Increases in speed and/or grade will be used to gradually increase the workload to find each subject's peak exercise capacity.[3] Test termination criteria will include subject request to stop at volitional fatigue, severe gait instability or according to published guidelines.[3,16-18] Peak aerobic capacity is defined as the highest VO2 measurement achieved during the test. After finishing this test and a rest period, subjects may complete a verification phase to determine whether maximum physiologic capacity (a true VO_2-max) was reached.[32] During this verification phase, the subject will be asked to walk as fast as possible for approximately 3 minutes. VO_2 data will be examined for a plateau, which would indicate VO_2-max.[32]

Daily physical activity assessment involves wearing an activity monitor continuously during waking hours for ≥3 days and recording sleep/wake times.[33-36] The monitor(s) will be worn around the non-paretic ankle and/or on the wrist or in a pocket. This monitoring records the number of steps taken and patterns of walking activity, and uploads data to computer software for analysis.

The *Kinesthetic and Visual Imagery Questionnaire (KVIQ-10)* involves having the participant perform 5 different movements followed by mental imagery of each movement. The participant is asked to rate the clarity of the visual imagery and the intensity of the imagined sensations for each movement on separate 5 point scales. The KVIQ-10 has been shown to be reliable and valid for persons with stroke.[37]

The *Stroke and Aphasia Quality of Life Scale* is a reliable and valid self-report quantitative survey that includes up to 53 questions about quality of life related to stroke and was designed to maximize response feasibility for persons with and without aphasia.[38,39]

The Global Rating of Change (GROC)[40] is a questionnaire that assesses overall impressions of change in health status from the perspective of the participant. The GROC is a 15 point ordinal scale with −7 indicating "a very great deal worse," 0 indicating "no change," and +7 indicating "a very great deal better". The GROC is not applicable at baseline testing because it measures change only.

Brain Imaging Procedures

Like clinical outcomes, brain imaging will be performed before and after the 4-week control period and after the locomotor HIT intervention for subjects with stroke. All scans will be performed on a 3.0T MRI system in the Imaging Research Center at CCHMC. Each imaging session will involve approximately one hour of brain scanning. During scanning, subjects will be positioned in a custom scaffold to stabilize the body and control leg movement. Initial alignment scans will be performed, followed by high-resolution anatomical scans, diffusion scans, functional scans and perfusion scans. The functional scans will be focused on the assessment of brain activation during imagined walking,[41,42] knee extension[43,44] and cognitive tasks. These tasks may involve

presentation of visual or auditory stimuli and subjects may be asked to respond by performing an actual or imagined movement, a cognitive task or by button-press. Subjects will be monitored by camera during functional scanning for compliance. Subjects will also practice task conditions prior to brain imaging.

Adverse Event (AE) Monitoring
Each study visit, subject voluntary reporting of AEs will be encouraged and AEs of interest will be specifically queried for subjects with stroke, including: falls, orthopedic injuries, faintness, new/increased pain and muscle soreness. During clinical testing and training sessions, subjects will also have monitoring and post-session questioning to identify any signs or symptoms of cardiorespiratory insufficiency, new/worsening neurological impairments or orthopedic injury.

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STATISTICAL ANALYSIS PLAN

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Clinical Trial Hypotheses. From PRE-2 to POST, subjects will exhibit a significant increase in walking speed (primary hypothesis) and other outcomes (secondary hypotheses).

Statistical Analysis. A mixed effects general linear model will be used with the outcome of interest (e.g. walking speed) as the dependent variable, a fixed (categorical) effect for time (PRE-1, PRE-2, POST) and an unstructured covariance matrix to account for repeated measures within the same participant. Hypotheses will be tested by the significance of the contrast estimate from PRE-2 to POST at the 0.05 significance level. PRE-1 and PRE-2 will also be compared to confirm test-retest reliability and the absence of spontaneous changes during the control period.

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