Aerobic Training to Improve Energy Utilization and Antioxidant Capacity in Stroke
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Fifteen to 30% of stroke survivors are disabled permanently, resulting in functional dependence and a sedentary lifestyle following stroke. Hemiparetic gait, a common disability after stroke, elevates the energy cost of ambulatory activity by 1.5-2 fold, but it is currently unknown how chronic stroke affects total daily energy expenditure and dietary intake. Altered energy balance following a stroke (expenditure ≠ intake) may result in impaired substrate utilization (fat versus carbohydrate oxidation), the production of oxidative stress and ultimately decreased cardiovascular and muscular endurance leading to increased fatigue.

This project will compare the effects of chronic treadmill training plus "heart healthy" nutrition modification versus whole body stretching plus nutrition on energy balance (dietary intake, resting metabolic rate, and exercise and non-exercise energy expenditure) and substrate utilization (measured during an acute exercise bout) in older chronic stroke survivors. Furthermore, to examine mechanisms of change, we measured changes in markers of oxidative stress before and after the interventions.

Aim 1: To assess the effects of six months of TM+N versus ST+N on total daily energy expenditure (primary outcome) and substrate oxidation in chronic stroke survivors.
Aim 2: To examine the effects of six months of TM+N versus ST+N on systemic oxidative stress in chronic stroke survivors.

Experimental Design
Overview: This project is designed to determine whether treadmill training plus nutrition (TM+N) versus stretching plus nutrition (ST+N) (control) will 1) improve energy expenditure and substrate oxidation and 2) reduce systemic oxidative stress. We will study men and women with chronic stroke and stable neurological deficits.
Eligibility criteria include:

- Age >20 years
- BMI 20-50 kg/m^2
- History of stroke at least 6 months prior
- Adequate language and neurocognitive function to safely participate in informed consent, and exercise testing and training
- Completion of all conventional inpatient and outpatient physical therapy
- Capable of walking 3 consecutive minutes on a treadmill at 0.1 MPH with handrail support
- Under the care of a primary care medical provider
- Written consent from their doctor that it is safe for them to participant in physical activity.

Exclusions: Exclusion criteria include:

- Medical History: a) recent hospitalization (less than 3 months prior to study entry) for severe medical disease, b) peripheral arterial disease with vascular claudication, c) orthopedic or chronic pain condition restricting exercise, d) pulmonary or renal failure, e) active cancer, f) untreated poorly controlled hypertension measured on at least 2 occasions (greater than 160/100) g) type I diabetes mellitus, untreated and / or poorly controlled diabetes with fasting blood glucose of greater than 200 and HbA1c greater than 10.0, i) currently pregnant
- Neurological history: a) dementia by clinical evaluation b) severe receptive or global aphasia which confounds testing and training, operationally defined as unable to follow 2 point commands, c) neurologic disorder restricting exercise, such as Parkinson's Syndrome, d) untreated major depression
- Increased alcohol consumption defined as greater than 2 oz. liquor or 2 times 4 oz. glasses of wine or 2 x 12 oz. cans of beer per day
- Treatment with hormone replacement therapy
- Cardiac history of: a) unstable angina, b) recent (less than 3 months prior to study entry) myocardial infarction, congestive heart failure (NYHA category II-IV); c) hemodynamically significant valvular dysfunction

Subjects will be randomized to TM+N or ST+N (1:1 allocation). Groups will be matched for sex and race. All subjects will be studied at baseline and after 6 months of TM+N or ST+N. This design will allow us to determine total daily energy expenditure, nutritional intake, and substrate oxidation following six months of TM+N and ST+N in older stroke survivors. Further, the design will enable us to determine the effects of TM+N and ST+N on systemic oxidative stress.

Metabolic Test by Phase

The experimental design of this study involves 7 phases, completed over 9-10 months (**Table 1**). *Phase 1* involves screening and enrollment. *Phase 2* involves baseline testing. Volunteers then will be randomly assigned to TM+N or ST+N (control) (*Phase 3*). *Phase 4* consists of 2 weeks of weight and dietary stabilization prior to baseline research testing. *Phase 5* consists of 2 week testing (post heart healthy). *Phase 6* consists of 6 months of TM+N or ST+N. After the intervention, subjects will undergo final research testing (*Phase 7*).

Subject Screening and Enrollment (Phase 1)

a) Screening Visits: Eligible volunteers will have the study explained and provide informed consent according to the guidelines of the local Institutional Review Board for Human Research. A fasting blood profile for lipids, liver, renal and hematological function will be drawn. A 12-lead resting electrocardiogram (EKG) will be obtained and a medical history and physical examination performed. Height and weight will be measured using a standard physician's scale. Seated blood pressures will be measured in duplicate. Information on demographics and family medical history will be recorded. Subjects will complete the Mini Mental State Exam (MMSE) (60) and Center for Epidemiologic Studies Depression Scale (CES-D) questionnaires. Volunteers also will have a screening VO_2peak treadmill test as described below.

Table 1: Research Design

	Time Duration	Research Activity
Phase 1	3 weeks	Screening & Enrollment
Phase 2	1 week	Baseline Testing
Phase 3	1 day	Randomization
Phase 4	2 weeks	Weight & Dietary Stabilization
Phase 5	1-2 months	Metabolic Pre Testing
Phase 6	6 months	TM+N or ST+N
Phase 7	1-2 months	Metabolic Post Testing

Baseline Testing (Phase 2): During this phase, subject will undergo a submaximal treadmill test, blood draw, and resting metabolic rate (RMR), as described below.

Randomization (Phase 3): Subjects are randomly assigned to either progressive 6 month treadmill aerobic exercise training 3 times per week plus nutritional modification or the reference control of education and stretch 2 times per week for 6 months plus nutritional modification.

Weight and Dietary Stabilization (Phase 4): Subjects will meet with a Registered Dietitian 2-3 times weekly for 2 weeks to learn "heart healthy" dietary patterns and ensure weight stabilization before metabolic testing. Details of the diet are described below. Prior to metabolic testing, subjects are asked to remain weight stable.

Metabolic Testing (Phase 5): This testing phase will occur over a period of 1-2 months for each individual. A VO_2peak treadmill test, body composition (anthropometrics, DXA, CT) tests, questionnaire completion, and functional and strength measures will occur during this phase. Subjects will be weight stabilized throughout the metabolic testing.

Treadmill Training plus Nutritional Modification versus Stretch Control plus Nutritional Modification (Phase 6):

<u>Treadmill Training</u>

Training programs will be individualized based on each participant's gait capacity and defined by peak heart rate (HR max) achieved during a baseline treadmill test. Training will be gradually progressed to a target of 50 minutes of exercise at 75-85% of HRR as tolerated by the subject. To assess treatment fidelity, staff will monitor progression weekly. A program of home walking equivalent in intensity and duration (3 days/week) to the current treadmill intensity and duration (3 days/week) will be recommended. Safety during treadmill training will be assured with a parachute style safety harnesses in non-weight bearing mode to support truncal balance, if necessary, to reduce the risk of fall. Participants may also use light handrail support. After stroke, the paretic arm is often less effective for support.

Stretch Controls:
Stretch controls will be enrolled in supervised stretching program for 2 days/week for 1 hour sessions. The stretch program will focus on basic mobility skills, including balance, sit-to-stand, weight shifting, and leg strength. Exercises will be performed in standing, seated, and lying positions. The stretching group will serve as an attention control.

Nutritional Modification: All participants will undergo up to 2 weeks nutritional modification counseling in Phase 4. These nutritional sessions will instruct participants how to consume an isocaloric, "heart healthy" diet with adequate protein (<30% of calories as fat, <10% as saturated fat, <2,400 mg sodium, 25 g/d of fiber, and 1.0-1.2 g/kg/d of lean protein) with a registered dietitian (RD). The RD will collect 24-hour or 3-5 day food records during the counseling session to ensure understanding of the dietary prescription. Additionally, compliance will be assessed throughout the remainder of the study in Phases 5-7 by periodic food records as deemed necessary on an individual basis. Weight will be monitored throughout the study to ensure weight stability. Additional dietary instruction will be provided to adjust caloric intake if weight fluctuates ±2%.

Post Intervention Metabolic Testing (Phase 7): Body weight must be stable ± 0.25 kg over the two week period prior to post-testing. Subjects will repeat tests outlined in Phase 5. Metabolic assessments will be performed ~36 hrs after the last bout of exercise or stretching and participants will continue to train or stretch during the post-testing period, respectively.

Study Procedures
1. Screening and Baseline Evaluations: Questionnaires to screen for depression and dementia will be administered to determine eligibility. Credentialed study staff evaluate all participants to determine whether their basic rehabilitation needs have been addressed before study entry. Participants will undergo standard medical and neurological examinations to establish medical eligibility and to characterize neurological deficits. Structured neurological evaluations may include range of motion tests, manual motor testing, and sensory examinations.

2. Blood and Urine Analyses: We will measure heart disease risk factors, CBC, comprehensive metabolic panel, lipid profile, glucose, insulin, free fatty acids, cytokines, oxidative stress, antioxidant capacity, triglycerides, lipoprotein lipids, leptin, and adiponectin. A urine pregnancy test is performed prior to the DXA and CT scans, if the participant is a woman with child bearing potential.

3. Mobility Function and Motor Control:
These tests will be administered in Phase 5 and Phase 7.
30 meter walks: Self-selected and fastest-comfortable floor walking velocity will be determined from 30 meter walks with subjects using the same assistive device and/or orthosis as normally used to "walk across the room at home." For the 30 meter walks and all walking tests described below, staff will walk beside and spot subjects to minimize risk of falls. Walks will be initiated from standing, with completion across an end line 2 meters beyond the 30 meter point, to avoid confounding from end of walk slow down. Subjects will be timed during both the self-selected and fastest comfortable paces.
6 min walk: Subjects will use the same assistive device and/or orthoses typically used and will be instructed to cover as much distance as they can in six minutes over a flat walking surface.
Timed Up and Go (TUG): Subjects are observed and timed while they rise from a chair, walk 3 meters, turn around, walk back, and sit down. A series of 3 TUGs will be performed to assess economy of this simulated ADL. An assistive device and/or orthoses may be used.

4. Treadmill Tests:
Peak: Treadmill tests will start at a self-selected pace, and will be advanced by adequate increments according to tolerance, perceived exertion, and medically credentialed clinician rating of gait stability. This clinically supervised test will determine treadmill gait safety, functional eligibility to participate (must walk 3 minutes at 0.1 MPH with handrail support), cardiopulmonary response to strenuous exertion defining exercise tolerance and safety, and allow us to pre-select testing parameters for subsequent constant velocity peak effort graded treadmill testing. Belt safety harness will be worn with a spotter behind the subject, and handrail support will be used at all times. Peak exercise tests will evaluate the cardiopulmonary response to exertion, under clinician supervision with continuous vital signs and EKG monitoring. Tests will be terminated at the subject's request, and based on American College of Sports Medicine criterion. Baseline peak test is reviewed by a cardiologist as part of our quality assurance program. The peak fitness test will be completed during Phase 1, Phase 5, and Phase 7.

Submaximal Treadmill Test: After a 12 hour fast, economy of hemiparetic gait will be measured using open circuit spirometry during a standard constant load submaximal effort treadmill walking task at a pre-established gait velocity (60-80% of self-selected floor walking velocity). This slower walking velocity is selected because untrained subjects with stroke usually cannot maintain their self-selected walking pace, precluding steady state measures of oxygen consumption that defines gait economy. The mean rate of VO_2 will be calculated based on the final 3 minutes of a 10-minute walk under steady state oxygen consumption conditions. Subjects not achieving a plateau in VO_2 will be re-tested at a lower velocity on a different date to eliminate potential confounding effects of fatigue on testing. This test will be completed before (Phase 3) and after (Phase 5) the Dietary Education (Phase 4), as well as in Phase 7 after the 6-month exercise or stretching interventions.

5. Energy Expenditure
Resting Metabolic Rate (RMR) will be measured using the ventilated hood technique while subjects lie quietly in bed for 30-45 mins under a clear plastic hood with expired air collected through a one-way valve (Weir JB deV. RMR will be measured at rest in Phase 3, 5 and 7.

Activity Monitoring: Subjects will answer activity questionnaires. They will wear an accelerometer activity monitor on their belt for 5 to 7 days to determine caloric expenditure in daily activities in Phase 5 and Phase 7.

6. Dietary Intake Assessment: A Registered Dietitian will instruct subjects on how to complete a 3-5-day food record or collect 24 hour dietary recalls that will be analyzed and used as measures of dietary habits. Dietary assessment will occur in at the beginning and end of Phase 4, as well as in Phase 7 following the 6-month interventions.

Statistical Analysis and Expected Results: Data from the study will be entered into a data set and validated by the study PI. Initially, analyses will be adjusted for site to determine whether site is a significant covariate to our outcomes of interest; however, if site is not significant, it will be dropped from further analyses. Descriptive statistics will be calculated for all variables using SAS version 9.3 (SAS Institute, Cary, N.C.) and the R statistical package. Exploratory data analyses will be performed to check the data for extreme values and to determine the distribution of values. Extreme values will be verified against original source documents. When necessary, data will be transformed to normality using appropriate transforms. A two-tailed $P < 0.05$ will considered indicative of a significant result. In addition to P values, 95% confidence intervals will be reported. The primary variable of interest to test the main hypotheses includes: 1) total daily energy expenditure measured by RMR (indirect calorimetry) + energy expenditure during activity (accelerometry). Secondary variables include substrate oxidation measured as fat and glucose oxidation during submaximal exercise, systemic (plasma) oxidative stress, VO_2peak.

Statistical Analysis Plan
Primary Aim: To assess the effects of six months of TM+N versus ST+N on total daily energy expenditure (primary outcome) and substrate oxidation in chronic stroke survivors.

Expected Results: We anticipate that TM+N will result in significant changes in RMR and energy expenditure during activity, as well as greater reliance on fat at resting and an improved ability to switch from fat to carbohydrate utilization during submaximal exercise and after a mixed meal challenge.

Aim 2: To examine the effects of six months of TM+N versus ST+N on systemic and tissue inflammation and oxidative stress and antioxidant capacity in chronic stroke survivors.

Expected Results: We expect that TM+N will result in decreased oxidative stress in the circulation.

The change (post-pre) value of the energy expenditure and substrate oxidation outcomes, along with measures of oxidative stress and antioxidant capacity will be the dependent (outcome) variables in a series of ANOVAs (one for each outcome variable). Independent variables will include the initial value of the outcome variable, group assignment, along with the subject's age and BMI, and if needed (i.e. if there are differences between the exercise and stretching subjects) medications and medical conditions other than presence of stroke. Baseline dietary intake will be treated as covariates. These analyses will tell us if there is a differential effect of exercise versus stretch control with nutritional modification on the outcome measures.

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