<u>Study Submission Protocol for: Heart-Brain Retraining: Forced Aerobic Exercise for Stroke Rehabilitation</u>

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Specific Aims

Stroke is the leading cause of disability in the United States with approximately 795,000 new or recurrent strokes per year[1]. An estimated 25-50% of patients post-stroke remain disabled after rehabilitation[2]. Repetitive task practice (RTP) and constraint-induced movement therapy (CIMT)[3, 4], which focus on retraining motor function, have been shown to be effective in stroke recovery. However, these promising approaches are time-intensive and have not been fully embraced clinically. The development of an adjunctive intervention capable of facilitating neuromotor recovery, while simultaneously decreasing cardiovascular risk factors, would be valuable to current stroke rehabilitation approaches. Forced aerobic exercise (FE) may be this promising intervention. Animal studies using a FE paradigm, in which the rodent is exercised on a motorized treadmill at a rate greater than its voluntary rate, indicate an endogenous increase in neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF)[5]. These neurotrophic factors are thought to underlie neuroplasticity and motor (re)learning[6-8]. Previous studies have shown aerobic exercise can improve cardiovascular fitness post-stroke; however, these studies have not systematically examined the impact of exercise on motor recovery[9-12]. **It is hypothesized that patients with stroke, due to decreased motor cortical output[13], cannot sustain high rates of voluntary exercise[14] necessary to trigger the endogenous release of neurotrophic factors which underlie neuroplasticity and recovery; therefore, forced-exercise is necessary to augment their voluntary efforts and will be superior to voluntary exercise in facilitating motor recovery.** We have developed a safe and effective method of delivering forced-exercise to Parkinson's disease (PD) patients (NIH R21HD056316). Clinical and imaging data with PD patients indicate forced-exercise, but not voluntary exercise, triggers a neurophysiologic response in the CNS resulting in global improvements in motor and non-motor functioning and increased cortical and subcortical activation[15, 16]. **The aim of this project is to conduct a preliminary trial to compare the effects of forced to voluntary exercise in promoting the recovery of motor function in patients with stroke.**

A preliminary single-center, parallel-group, rater-blind study is proposed. A total of 30 chronic (6-12 mos. post) stroke patients with residual hemiparesis will be randomized to one of three groups: combined forced-exercise and repetitive task practice (FE+RTP), combined voluntary exercise and RTP (VE+RTP) or a dose-matched RTP only (RTP only) group. All three groups will receive an identical dose of rehabilitation time over a course of 8 weeks (3X per week); however, the combination groups will perform forced or voluntary exercise for 50% of the session and RTP for the remaining 50% of the session. The RTP only group will engage in RTP exclusively. Outcomes will be gathered at baseline, mid-treatment and end of treatment (EOT).

Aim 1: To compare the effects of FE+RTP, VE+RTP, and RTP only on the recovery of upper extremity motor function. The primary outcome is the change in the Wolf Motor Function Test (WMFT) from baseline to EOT. Secondary outcomes include changes in the Fugl-Meyer Assessment and biomechanical variables quantifying bimanual dexterity[16, 17].

<u>Hypothesis 1:</u> The FE+RTP group will demonstrate greater improvements in upper extremity motor function compared to VE+RTP and dose-matched RTP.

Aim 2: To compare the effects of FE+RTP, VE+RTP, and RTP only on non-motor function. The primary outcome is the change in the Beck Depression Inventory while secondary outcomes include the Stroke Impact Scale and the Trail Making Test A and B.

<u>Hypothesis 2</u>: The FE+RTP group will demonstrate greater improvements in non-motor function compared to VE+RTP and dose-matched RTP.

Aim 3: To compare the effects of FE+RTP, VE+RTP, and RTP only on aerobic capacity. The primary outcome is the change in $VO_{2\,max}$ from baseline to EOT. The 6-minute walk test will serve as the clinical outcome.

<u>Hypothesis 3</u>: Both exercise groups (FE+RTP and VE+RTP) will demonstrate significant improvements in aerobic capacity compared to dose-matched RTP.

BACKGROUND AND SIGNIFICANCE

Stroke, one of the endpoints of cardiovascular disease, is the leading cause of severe, long-term disability among older adults in the United States. The prevalence of stroke survivors with residual neurological deficits is approximately 5.8 million[18]. Despite advances in rehabilitation, six months after stroke, nearly two thirds of patients cannot incorporate the more affected hand into daily activities[19]. Rehabilitation therapies that incorporate principles of motor learning, such as constraint-induced movement therapy (CIMT) and repetitive task practice (RTP) have been found to be effective in facilitating cortical reorganization[20]. The translation of these interventions into clinical practice has been limited by required minimal movement criteria and reliance on intensive therapist-directed treatment[21]. The latter makes these approaches unrealistic in a managed care environment.

In addition to compromised motor function, patients post-stroke experience significant cardiovascular deconditioning, which limits their participation in activities of daily living (ADL's)[9]. For these patients, the performance of simple ADL's result in a significant increase, into the anaerobic heart rate range, in cardiovascular output[9]. Despite the potential value of aerobic exercise in rehabilitation[9-12, 22], typical stroke interventions are of relatively low aerobic intensity as patients' heart rates are in the aerobic zone for less than three minutes[10]. Furthermore, studies investigating the value of aerobic exercise post-stroke have focused on cardiovascular endpoints, neglecting to systematically identify the potential neurophysiologic benefits evident in animal studies[23]. <u>The identification of a safe, cost-effective approach, such as forced aerobic exercise, may have the potential to prime the CNS to augment the recovery of function while simultaneously improving cardiovascular health and fitness. This preliminary project will assess the potential for two approaches of exercise training and task practice to improve motor and non-motor functioning in patients with stroke.</u>

Aerobic exercise and brain function: Although the cardiovascular benefits of aerobic exercise have been well documented, only recently have investigations been conducted to determine the global effects of aerobic exercise, particularly as they relate to improving brain function[24-27]. A recent systematic review found that acute aerobic exercise transiently increased basal peripheral concentrations of brain-derived neurotrophic factor (BDNF) in healthy young adults[6]. This increase in BDNF was only evident with acute aerobic exercise, not strength training, suggesting a relationship between cardiovascular exertion during exercise and BDNF response. The release of BDNF into the bloodstream and subsequently into tissues is thought to be responsible for a cascade of neuroprotective and neuroplastic mechanisms, possibly facilitating neuromotor recovery[6]. Increased concentrations of endogenous neurotrophins have also been implicated as the mechanism for improved cognition, learning, and memory in healthy older adults[28-30]. Animal data have shown enhanced motor training and behavioral recovery with high-intensity aerobic exercise, resulting in lasting neuronal changes within the brain[6, 30, 31]. <u>To date, the role of aerobic exercise, forced or voluntary, in stroke recovery has not been systematically examined[7, 22]. This project will, for the first time, examine the relationship between aerobic exercise and neuromotor recovery following stroke.</u>

Innovation

Applying the forced aerobic exercise model to patients with stroke

Significant pathophysiologic and logistical barriers prevent patients with stroke from obtaining the potential global neurologic and cardiovascular benefits of aerobic exercise training. Cellular changes in skeletal muscle post-stroke include alterations in fiber-type proportions, fiber atrophy, and reduced oxidative capacity[9, 11, 12]. These changes, combined with profound cardiovascular deconditioning, result in diminished motor output, preventing stroke patients from achieving the intensity of exercise necessary to reach the aerobic threshold. In addition to the physiological barriers, endurance training has not been a standard component of stroke rehabilitation as rehabilitation clinicians traditionally focus on motor learning or compensatory strategies to improve basic mobility and ADL skills[12, 32]. When aerobic exercise is included as a part of stroke rehabilitation, the most common method currently being used is treadmill training. Due to safety concerns and diminished motor function, however, patients are either harnessed using a partial body-weight support system or require the direct assistance of the therapist to complete the training intervention. The personnel and equipment requirements associated with treadmill training limit its scalability, especially in those patients with chronic stroke as they are unable to continue this exercise protocol long-term, leading to greater declines in cardiovascular fitness due to physical inactivity[11]. As stated by Macko and colleagues, “Novel exercise interventions are needed to realize the potential for long-term functional recovery and cardiovascular health in the chronic hemiparetic condition”[9]. The forced aerobic exercise intervention developed in our lab, initially for PD patients, is a novel exercise intervention that augments the voluntary efforts of patients[15, 16]. This intervention facilitates neurologic changes and produces cardiovascular benefits of aerobic exercise in a safe and cost-effective manner. The promising results from our PD studies, briefly outlined below, provide rationale for extending this intervention to patients with stroke as a means to prime the CNS for recovery.

Forced-exercise improves global motor function in Parkinson’s disease: Fifty-four patients with idiopathic Parkinson’s disease have completed a preliminary randomized clinical trial comparing the effects of forced (FE) versus voluntary aerobic exercise (VE) on motor and non-motor function. As part of this project, we developed a motor-driven cycle to safely deliver a forced exercise intervention by mechanically augmenting pedaling rate beyond the voluntary efforts of the patient. This cycle will be used in our upcoming NIH R01 project (NIH R01NS073717; Alberts, PI). It is important to note that the participants are actively contributing to the exercise; they are not being moved passively through the pedaling action. Thus, exercise intensity, from an aerobic perspective, is identical across groups. However, the FE group’s pedaling rate is significantly (35%) faster than the VE group.

The Unified Parkinson’s disease Rating Scale-III (UPDRS-III) Motor assessment was the primary clinical outcome. Rater-blinded UPDRS-III scores improved more than a 25% for those in the FE group while improving 11% in the VE group at end of treatment (EOT). Clinical ratings for the FE group were still improved by 14% at EOT + 8 weeks compared to baseline. Despite the comparable gains in aerobic fitness between the two groups, only the FE group demonstrated these relatively long-term gains in motor function, suggesting that exercise rate may be critical in altering brain function.

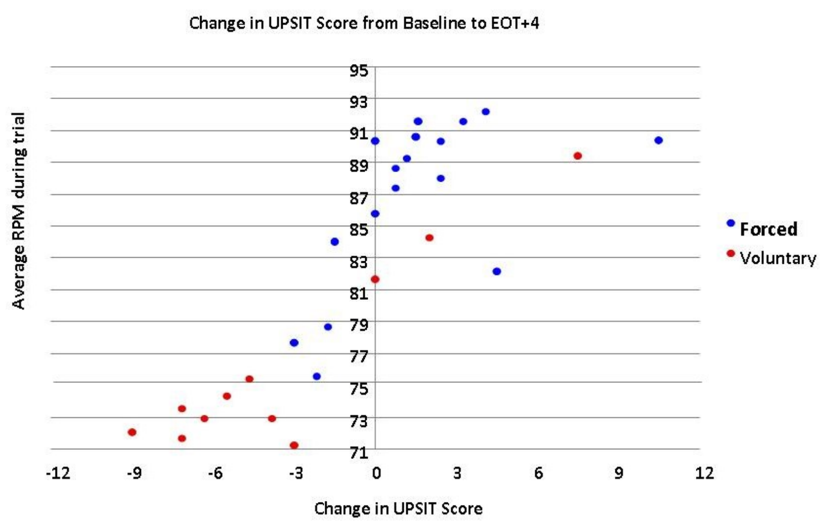

Figure 1: *Improvements in olfaction are present relative to increased pedaling rate.*

In addition to improvements in motor function, gains in non-motor function were also present, primarily in the FE group, suggesting a global CNS response to high-rate exercise. Anosmia has been identified as an early indicator of PD and there are no data suggesting medication or surgical interventions can improve or alter anosmia levels[33]. The University of Pennsylvania Smell Identification Test (UPSIT) was used to assess level of anosmia[34]. Patients completed the UPSIT on three occasions: Baseline, end of treatment (EOT) and four weeks after EOT (EOT+4). Patients did not exercise during this four-week follow up period. Figure 1 illustrates the change in UPSIT score from Baseline to EOT+4 for PD patients in our current trial as a function of pedaling rate (RPMs) over the course of the trial. These initial data suggest that anosmia levels can be maintained or improved (higher scores are better) in individuals who are typically pedaling at relatively high rates, between 80-90 RPMs. It is important to note that two of the PD patients in the voluntary group that pedaled within this range did exhibit improvements in anosmia. Overall, these data suggest that improvements in anosmia or CNS functioning may be rate-dependent, implying that rate may be an important variable to control or monitor in the prescription of effective exercise. From a stroke perspective, these data provide further evidence that high rate aerobic exercise can alter brain function and could be a reasonable adjunct to traditional rehabilitation approaches. The effects of acute FE on brain activation patterns were studied in 10 mild to moderate PD patients using an MRI protocol including whole brain T1-weighted anatomic images and a set of fMRI scans. Subjects were scanned under three conditions: 1) off meds, 2) on meds and 3) following forced-exercise while <u>off</u> meds. Figure 2 shows activation maps averaged across subjects for two axial slices (showing sub-cortical regions) in Talairach space, displayed on averaged T1 anatomic image. In all regions of interest, significant correlations were observed, indicating a similar change in BOLD MRI response for FE and medication. These results indicate forced-exercise and medication utilize similar pathways to produce symptomatic relief. We are unaware of any other data that demonstrates exercise in PD leads to an increase in cortical and subcortical activation.

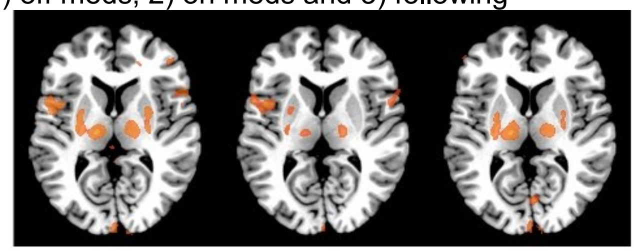

Figure 2: *Forced-exercise produces a similar subcortical response as medication in PD.*

Rationale to translate the Forced-Aerobic Exercise Paradigm to Patients Post-Stroke

Our FE and PD studies indicate that FE enhances brain function and possibly plasticity. Based on animal studies, the mechanism underlying global changes in motor function is likely increased neurotrophic factors as a result of FE. Models of stroke provide a theoretical framework for using FE in stroke rehabilitation, as stroke patients, similar to PD patients have decreased cortical output[13, 35]. This impairs patients with stroke from sustaining high rates of voluntary exercise[14] which appear necessary to trigger the endogenous release of neurotrophic factors. Collectively, the promising results from both animal and human data, in addition to our preliminary results in patients with PD, suggest that high-rate (forced) aerobic exercise has the potential to alter brain function and may promote neuroplasticity. Incorporating forced aerobic exercise into rehabilitation practice to prime the CNS and improve cardiovascular health would be a clinically-relevant, cost-effective adjunct to current models of neurorehabilitation. It is important to note that our approach is different from animal models testing the efficacy of FE and stroke recovery. Recent evidence from animal literature has suggested that FE results in lower BDNF, higher serum corticosterone levels, and decreased behavioral learning than VE[36]. However, the FE intervention in these models was introduced *24-hours* after lesioning, a critical time during which the metabolic demands and diminished homeostasis in the brain are too significant to foster an environment conducive to recovery[36, 37]. A similar negative behavioral effect, presumably due to excitotoxicity,[38-40] has been reported in animal and human models in which intensive CIMT was introduced in the *acute* phase of stroke recovery. However, the same intensive intervention, when applied to individuals ≥ three months post-stroke, resulted in significant motor recovery and fMRI evidence of neural reorganization. We propose to enroll patients 6-12 months post-infarct, well after neurophysiologic homeostasis has been restored, and an optimal environment for neuroplastic recovery is present. With appropriate cardiopulmonary screening, testing and monitoring, patients post-stroke have been shown to safely tolerate aerobic exercise and improve cardiovascular fitness[9, 11, 12, 32, 41-43].The goal of this project is to compare the effectiveness of two modes of aerobic exercise, forced and voluntary, in augmenting recovery of function in patients with stroke.

Research Design and Methods

Experimental Overview: A preliminary single-center, parallel-group, rater-blind study will be completed over two years. A total of 30 chronic (6-12 mos. post) stroke patients with residual hemiparesis will be randomized to one of three groups: 1) forced-exercise and RTP (FE+RTP), 2) voluntary exercise and RTP (VE+RTP) or 3) dose-matched RTP only. All groups will receive an identical dose of rehabilitation time (36 hours) over a course of 8 weeks (3X per week). The combination groups will perform FE on a motor-driven cycle or VE on a recumbent cycle for 50% of the time, followed by RTP for the remaining 50% of the session, while the RTP only group will engage in RTP only. Outcomes will be gathered at baseline, mid-treatment and EOT. A schematic of the study flow is provided in Figure 3.

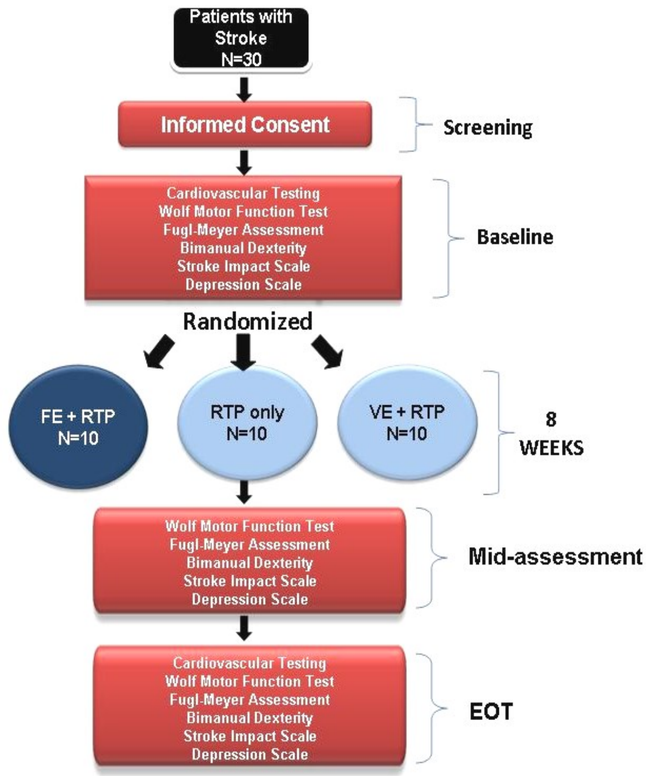

Figure 3: ***Study flow diagram***

<u>Recruitment and Sample:</u> In collaboration with Dr. Fred Frost, Department Chair, Physical Medicine and Rehabilitation, 30 patients from the Cleveland Clinic Health System (CCHS) with chronic stroke will be recruited to participate in this study. An initial chart review indicates that over the past year approximately 600 patients CCHS would meet study criteria. The targeted population represents a collective cohort in whom spontaneous recovery is typically no longer occurring and substantial potential exists to optimally engage neuronal structures promoting plasticity toward functional improvement. Primary inclusion criteria include: 1) 6-12 months post single ischemic or hemorrhagic stroke confirmed by neuroimaging; 2) Approval from patient's primary care physician; 3) Upper extremity Fugl-Meyer Motor Score 19-55. Primary exclusion criteria include: 1) Hospitalization for myocardial infarction, congestive heart failure, or heart surgery (CABG or valve replacement) during the past 3 months; 2) Serious cardiac arrhythmias; 3) Hypertrophic cardiomyopathy; 4) Severe aortic stenosis; 5) Pulmonary embolus[32, 43]. Prior to randomization, all subjects satisfying initial screening criteria for participation will undergo complete cardiopulmonary exercise (CPX) testing. A 12 lead electrocardiogram will be assessed prior to exercise and monitored continuously throughout exercise and recovery. A continuous incremental protocol starting at 25 Watts (W) and increasing in 10W stages every two minutes will be employed. Peak VO_2 will be determined for each subject as the highest 30 sec average of VO_2 during the test. If the test is terminated due to electrocardiographic findings, the subject will be managed medically, referred for further care, and will be excluded from participation in the trial. <u>Dr. Blackburn, Director of Cardiac Rehab, will conduct and interpret the results of the CPX testing to ensure the participant safety.</u>

Experimental Groups

Forced Aerobic Exercise and Repetitive Task Practice (FE+RTP): Subjects in the FE+RTP group (N=10) will use the motor-driven cycle to augment their pedaling rate 35% greater than their voluntary rate, determined from the baseline CPX. The rationale for a 35% rate increase is based on the positive preliminary studies with PD patients[15, 16]. Target heart rate zone will be calculated using the Karvonen formula and will be set to 60-80%. Each training session will last approximately 1.5-2 hours; 45 minute exercise session followed by 45 minutes of RTP. The exercise session will consist of a 5 minute warm-up, 35 minute main exercise set, and 5 minute cool down. For those patients who may be deconditioned upon study enrollment, the 35 minute main exercise set will include 'on the cycle' rest breaks of 2 minutes, every 10 minutes if necessary. If any patient exhibits signs of cardiac distress or hemodynamic compromise as determined by therapist or patient, the session will be stopped immediately and the on-call physician will be paged to the laboratory. Hemodynamic response to exercise will be monitored via blood pressure measurements prior to initiating the exercise protocol, every 10 minutes during exercise, and immediately following exercise cessation, in addition to continuous heart rate monitoring. All exercise training will be supervised by an exercise physiologist or physical therapist certified in Basic Cardiac Life Support.

A 45-minute session of upper extremity RTP will occur within ~15 minutes of exercise session completion. RTP is the considered the current standard of care for upper extremity stroke rehabilitation[44, 45]. Tasks performed with the more impaired upper extremity will be selected from a battery of over 60 activities developed for the EXCITE trial[35] and currently being used as part of our ongoing stroke study. All RTP will be completed with the guidance of a neurologic PT or OT experienced in stroke rehabilitation.

Voluntary Aerobic Exercise and Repetitive Task Practice (VE+RTP): Subjects in the VE+RTP group (N=10) will complete a 45-minute exercise session consisting of a 5 minute warm-up, 35 minute main exercise set, and 5 minute cool down using a recumbent stationary bike, exercising at their self-selected rate. All exercise training will occur under the supervision of an exercise physiologist or PT who will adjust resistance on the cycle to ensure that the subject is exercising within his/her target heart rate zone during the main exercise set (60-80% range using the Karvonen formula, based on ACSM recommendations for older adults). Rest breaks and hemodynamic response monitoring will be conducted in an identical manner by the same personnel as described above with forced-exercise. A 45-minute session of upper extremity RTP will occur within ~15 minutes of exercise session completion in an identical manner as described above with the forced-exercise group.

Repetitive Task Practice only (RTP): Subjects in the RTP only group (N=10) will complete 2 45-minute sessions of RTP as described above separated by a 15-minute rest break, under the guidance of the same neurologic physical or occupational therapist overseeing RTP for the combination groups. This dosage of RTP is feasible, common in current clinical practice, and has been found to be efficacious[46]

Aim 1: To compare the effects of FE+RTP, VE+RTP, and RTP only on the recovery of upper extremity motor function. The primary outcome is the change in the Wolf Motor Function Test[47] (WMFT) from baseline to EOT. Secondary outcomes include change in the Fugl-Meyer Assessment and biomechanical variables quantifying bimanual dexterity used in our previous work[17].

Expected results and interpretation: It is hypothesized that the FE+RTP group will demonstrate greater improvements in upper extremity motor function compared to VE+RTP or dose-matched RTP only. Animal and human studies suggest that high-rate aerobic exercise facilitates the release of neurotrophins in the brain which may serve to prime the CNS in promoting neuroplasticity[6, 8]. Our initial studies in PD patients demonstrated increased cortical and subcortical activation on fMRI following FE[15]. The FE paradigm will allow stroke patients to attain and sustain the high rate of exercise necessary to trigger this neuroplastic response, creating an environment in which motor learning is optimized.

Aim 2: To compare the effects of FE+RTP, VE+RTP, and RTP only on non-motor function. The primary outcome is the change in the Beck Depression Inventory (BDI), Stroke Impact Scale (SIS), and the Trail Making Test A and B (TMT).

Expected results and interpretation: It is hypothesized that the FE+RTP group will demonstrate greater improvements on the BDI, SIS and TMT compared to VE+RTP or dose-matched RTP. Human studies on healthy older adults, adults with dementia, and individuals with PD have all demonstrated improvements in mood, cognition, and quality of life following high-rate aerobic exercise[24-27]. Forced aerobic exercise will facilitate this same response in stroke patients previously not seen with voluntary rate exercise, possibly through increased concentrations of neurotrophic factors.

Aim 3: To compare the effects of FE+RTP, VE+RTP, and RTP only on aerobic capacity. The primary outcome is the change in $VO_{2\,max}$ from baseline to EOT. The 6-minute walk test will serve as the secondary outcome.

Expected results and interpretation: It is hypothesized that both the FE+RTP and VE+RTP groups will demonstrate comparable improvements in aerobic capacity and ambulatory efficiency compared to dose-matched RTP. Numerous studies have demonstrated the positive effects of aerobic exercise training in patients post-stroke on cardiovascular fitness[9, 11, 12, 41-43]. Because patients in both combination groups will be exercising at comparable target heart rates, improvements in cardiovascular fitness are expected to be similar. The RTP only group is not expected to show significant gains in cardiovascular fitness. Improved cardiovascular fitness in both exercise groups, but greater improvements in motor functioning in the FE group will provide evidence for the concept that aerobic exercise alone is not sufficient, in this neurological population, to impact brain function in a manner that leads to improved motor recovery, but that FE is necessary to prime the CNS for remodeling after stroke.

Statistical Analysis and Design: Subjects in all three groups will be compared descriptively on potentially confounding baseline variables (i.e., age, fitness, co-morbidities, degree of hemiplegia, location/type of stroke, side of lesion) to assess the extent of any imbalance across groups. The FE+RTP, VE+RTP, and RTP only groups will be compared on each primary outcome using repeated measures analysis of covariance. The effects of group, time, and the group-by-time interaction will be assessed. In the case of a significant interaction, the groups will be compared at each time point. In addition to p-values, the estimated treatment effect and its 95% confidence interval will be of interest as these data will be used for sample size calculation for a subsequent clinical trial.

Implications: An unmet clinical need remains in identifying effective and efficient rehabilitation approaches that drive neuroplasticity and optimize recovery post-stroke. Determining the interactions between aerobic exercise and motor recovery following stroke can address this unmet need. The promising results from both animal and human studies, in addition to our preliminary results in PD patients, suggest that high-rate (forced) aerobic exercise has the potential to alter physiology in the CNS leading to improvements in function. This approach merits testing in patients with stroke.

Limitations: Previous animal data suggest that the effectiveness of FE is due to an increase in the release of neurotrophic factors[23]. Based on these data, we hypothesize that the same mechanism may be operating in humans. It is fully acknowledged, however, that the accurate measurement of neurotrophic factors is not feasible in this population. The most reliable method of measuring neurotrophic factors within the brain is through tissue sampling, which is obviously not feasible in human studies. An alternative method is via jugular blood draws[8]; for a preliminary study this very invasive procedure is not practical. To address this limitation, objective measures of upper extremity and non-motor performance will serve as proxy for CNS function.

Future Directions: The preliminary data gathered from this project will be used for the submission of a larger NIH R01 randomized clinical trial to determine the precise role of exercise in stroke rehabilitation and whether improved cardiovascular fitness can decrease the risk for recurrent stroke. Furthermore, fMRI will be used to provide insight into the potential mechanism(s) that may underlie greater recovery of function associated with FE.

Protection of Human Subjects

Risks to the Subject:

Human Subjects Involvement and Characteristics

A total of 30 subjects who meet inclusion criteria outlined in this section will be selected for study participation. Males and females from any racial or ethnic background will be eligible. Individuals will be recruited from the Rehabilitation Institute at the Cleveland Clinic, in collaboration with Dr. Fred Frost, department chair. Patients will be screened by a neurologic physical therapist to ensure eligibility. Patients selected for the study protocol will meet the following inclusion and exclusion criteria:

Inclusion Criteria:

a. Able to provide informed consent
b. Within 6-12 months of diagnosis of single ischemic or hemorrhagic stroke, confirmed with neuroimaging
c. Fugl-Meyer Motor Score 19-55 in involved upper extremity
d. Approval from patient's primary care physician
e. Age between 18 and 80 years

Exclusion Criteria:

a. Hospitalization for myocardial infarction, congestive heart failure, or heart surgery (CABG or valve replacement) within 3 months of study enrollment
b. Serious cardiac arrhythmia
c. Hypertrophic cardiomyopathy
d. Severe aortic stenosis
e. Cardiac pacemaker
f. Pulmonary embolus
g. Other medical or musculoskeletal contraindication to exercise
h. Significant cognitive impairment (MMSE <24) or major psychiatric disorder (major depression, generalized anxiety) that will cause difficulty in study participation
i. Anti-spasticity injection (botox) in upper extremity within 3 months of study enrollment
j. Pregnancy

Sources of Material:

Clinical assessment will serve as a measure of degree of impairment and therapeutic efficacy. Patients will receive three clinical and motor assessments over the course of the study. Data will be obtained from subjects specifically for research purposes. Existing records or data will not be used. The identity of individual subjects will not be disclosed in any report of the results of this study. The data collected during this study will remain under the control of the investigators. Confidentiality of medical records and other forms of data will be maintained, with the exception that all such information will be subject to review by representatives of CCF.

Potential Risks:

There are potential risks and discomforts associated with any exercise intervention study. Every effort will be made to minimize these risks using information from the pre-exercise medical evaluation and cardiopulmonary stress test. A defibrillator is located within the exercise area, and a full crash cart readily available within an adjacent clinical area. All research staff that will be supervising exercise sessions is trained in BCLS including emergency resuscitation and life-sustaining measures. A cardiac arrest and resuscitation team is available 24 hours a day within the hospital and can respond immediately to any medical emergency. The intensity of the exercise and exertion it requires may be physically taxing, however, patients will be permitted to rest at any time during the 45-minute exercise session. The appropriate exercise intensity will be personalized to the age, general activity, and medical condition of each individual. Although the exercise bicycle is stationary and sturdy, there is a risk of injury while mounting and dismounting the cycle. The exercise trainer will assist the patient when mounting or dismounting the cycle. If patients experience any sensation that appears to be unusual or uncomfortable, they will be advised to stop the exercise and inform the research staff immediately. Generalized fatigue or muscle soreness may occur as a result of the exercise or repetitive task practice intervention, comparable to what is anticipated during traditionally rehabilitation post-stroke. There may be other risks as of yet unknown. No adverse events or effects occurred using this exercise intervention with Parkinson's disease patients.

Adequacy of Protection Against Risks:

Recruitment and Informed Consent: Patients will be asked to read and sign a consent form that describes the nature and goals of the study, methods to be used, and potential risks and benefits of procedures. CCF IRB will have approved the consent form and experimental protocol. Originals will be retained in a secure location and photocopies will be given to the subject.

Protection Against Risk: Strict adherence to the outlined inclusion and exclusion criteria, in addition to thorough interpretation of the pre-intervention cardiopulmonary stress test will serve to rule out candidates unsafe for the study protocol. Hemodynamic response to exercise will be monitored via blood pressure measurements prior to initiating the exercise protocol, every 10 minutes during exercise, and immediately following exercise cessation, in addition to continuous heart rate monitoring. Previous studies have found that patients post-stroke can safely participate in an intensive aerobic exercise intervention with similar screening and monitoring procedures in place. If a subject experiences any of the risks previously described, they will be asked to report it immediately to the research team. Injuries will be assessed, and if necessary, will be either treated by the medical staff or another referring physician. Any events will be reported to the IRB by the PI's. Dr. Linder will assume the responsibility of monitoring, ensuring the safety and confidentiality of the data. The research team will meet regularly to discuss issues related to this project; especially issues regarding safety and data security.

Potential Benefits of the Proposed Research to Subjects and Others:

Cardiovascular fitness is likely to improve over the course of the study for those randomized to either of the two exercise groups and upper extremity function is likely to improve for all three groups. Improvements in cardiovascular fitness post-stroke often lead to increases in ambulatory efficiency and decreased risk for future cardiovascular events or recurrent stroke. In general, society may benefit from a clearer understanding of the role of aerobic exercise, and particularly, forced aerobic exercise in the recovery of function post-stroke. This could lead to improved rehabilitation outcomes for patients after stroke. Given the low risks involved and potential substantial benefits, we feel that the risk/benefit ratio is strongly in favor of proceeding with the study proposed in the present application.

Importance of the Knowledge to be Gained: The proposed research is intended to provide information about the effects of forced versus voluntary-rate aerobic exercise on the recovery of upper extremity function and cardiovascular fitness post-stroke. Furthermore, identifying an aerobic exercise intervention that patients with stroke can safely participate in, would serve to fulfill an unmet need in this chronically disabled population. This information will help guide the direction of stroke rehabilitation in optimizing neurorecovery, while simultaneously addressing the cardiovascular co-morbidities frequently seen post-stroke.

Data and Safety Monitoring Plan: A five-member panel will be assembled to protect the safety of the participants and ensure the integrity of this study. This committee will consist of Staff within the Cleveland Clinic or outside institutions from the departments of cardiovascular medicine, neurology, rehabilitation medicine, biomedical engineering and bio-statistics. The primary role of this committee will be to: advise the investigators on matters related to safety, project execution, project cessation, adverse events or other activities deemed appropriate by the investigators or NIH. These members will have no direct involvement in the study and will serve as independent monitors.

Inclusion of Women and Minorities:

Women grater than or equal to 18 years of age will be included in this trial. We are targeting a 50% female enrollment in the trial. Based on the 2000 census figures, the racial distribution of the Cleveland metro area is 67.4% White, 27.4% African American, 1.8% Asian, 0.2% American Indian/Alaskan Native, 0.0% Native Hawaiian /Other Pacific Islander, and 3.2% multiracial. The ethnic distribution is 3.4% Hispanic or Latino. Therefore, members of minority groups and their subpopulations will be included in this trial. In our current stroke clinical trial, women comprise 33.3% of our enrollment; African-Americans 50%; Asians 16.7%; and of Hispanic ethnicity, 16.7%. Drs. Alberts and Linder frequently participate in patient education meetings and support groups throughout the Cleveland metropolitan region. As these groups are representative of the population of the Cleveland area, we anticipate recruitment distribution of women and minorities to reflect the Cleveland metropolitan population. All persons meeting eligibility criteria will be afforded the opportunity to participate in the trial. Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic groups (without requiring high statistical power for each subgroup) will occur following completion of the study.

Targeted/Planned Enrollment Table

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	14	14	28
Ethnic Category: Total of All Subjects	15	15	30
Racial Categories			
American Indian/Alaskan Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African-American	4	4	8
White	10	10	20

Racial Categories: Total of All Subjects	15	15	30

<u>Inclusion of Children</u>

The proposed research will not utilize children as stroke does not typically occur in children and those under the age of 18.

REFERENCES

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