TITLE: Effects of Functional Electrical Stimulation Cycling versus Cycling Only on Walking Performance and Quality of Life in Individuals with Multiple Sclerosis: A Pilot Study

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Protocol Template Guidance
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A. SPECIFIC AIMS

People with MS (PWMS) receive traditional rehabilitation during the course of their disease but there is a lack of consensus regarding intervention type and exercise dosage.[1] Functional Electrical Stimulation Cycling of the lower extremities (FES-LE) is utilized clinically for PWMS; however, there is a lack of research, which supports its efficacy on gait, endurance, transfers and quality of life (QOL). Previous studies regarding FES-LE cycling for PWMS were conducted on individuals with greater disability levels than those proposed in this study and did not measure the impact of this rehabilitation tool on quality of life.[2,3] Previous studies have methodological weaknesses and lacked a sufficient number of subjects, a comparison group or a standardized progression protocol. This study will seek to determine the benefits that FES-LE cycling has over cycling alone on walking performance and quality of life in PWMS.

AIM 1: To determine if there is a difference between FES cycling and cycling only in PWMS on temporal and spatial components of gait.

Walking speed is a commonly used measure in clinical practice and has been cited in the literature as the "sixth vital sign."[4] Gait speed will be measured using the Timed 25 meter walk test (T25FW) and participants will be instructed to walk at a "fast but safe speed" consistent with a protocol as suggested by Gijbels et al[5] and Bethoux and Bennett.[6] This measure was chosen since it is commonly used as part of the Multiple Sclerosis Functional Composite, its clinical utility, and ease of administration. [7]

Goldman et al examined changes in the T25FW in relation to changes in life roles.[8] A T25FW of 6 to 7.99 seconds is related to a change in occupation, unemployment, walking with a device and/or the need for some help with instrumental activities of daily living (IADL) while walking speeds greater than or equal to 8 seconds are related to the need to use a walker and inability to perform IADLs.[8]

In addition to the T25FW, a wireless inertial sensor (BTS G-Walk) will be used to collect gait and movement data during all physical outcome measures. Evidence supports that body-worn motion sensors provide additional information about gait and balance that standard timed walking tests may not detect.[9]

AIM 2: To determine if there a difference between FES cycling and cycling only in PWMS on quality of life measures.

The MSQOL-54 is a multidimensional self-report quality of life questionnaire that takes 15-30 minutes to complete (permission to use MSQOL-54 received from Barbara Vickry, MD, MPD, via email communication, March 21, 2014).[10] It measures health-related quality of life using both generic and disease specific measures and was constructed by experts in the field. [10] This measure was chosen since it is more comprehensive than other MS disease-specific quality of life scales and is recommended for use amongst international experts who participated in a multidisciplinary consensus meeting.[11]

AIM 3: To determine if there a difference between FES cycling and cycling only in PWMS in the 6 Minute Walk Test.

The 6MWT measures a person's self-paced walking distance over a 6 minute period and is a valid and reliable measure of walking performance in PWMS.[12–14] The 6MWT was found to have excellent test-retest reliability (ICC= .96, 95% CI .87- .99) over a one-week interval in PWMS (EDSS 2.0 – 6.5).[15] Pilutti et al also found there to be a significant difference between the 6MWT performance in PWMS with mild vs. moderate to severe disability (mild= 530.7m, range 292.6 - 782.1m, moderate to severe= 349.8m, range 51.5 – 605.3m, $p < .0001$).[16] It was also found that PWMS (EDSS 2 -6.4, median 4.0) classified as fallers demonstrated a significant difference in the their 6MWT distance compared to a group of non-fallers (fallers= 1288 feet, non-fallers= 1533 feet, t= 2.2, p= .02).[17]

Cadence and stride length have been found to explain difference in 6MWT performance in people with mild vs. moderate and severe MS when controlling for age ($F[2,299\} = 38.17$, $p<.001$, partial $-\eta^2 = .20$; $F[2,299\} = 44.30$, $p<.001$, partial $-\eta^2 = .23$, respectively) but there was no significant difference in cadence between a control group and people with mild MS (p= .06).[16] Using a regression analysis these researchers also found that cadence and stride length explained the difference in the 6MWT between PWMS and controls.[16]

AIM 4: To determine if there is difference between FES cycling and cycling only in PWMS in the 5 Times Sit-to-Stand (5STS).

The 5STS is a timed test that measures how long it takes for an individual to transition from standing to sitting for 5 repetitions. Evidence supports that sit-to-stand tests may be appropriate, time efficient tests to use in the clinical setting to assess LE strength.[18,19] A strong relationship between a 10 times sit-to-stand test and knee extensor and flexor strength was found in a 139 healthy individuals ages 20-62.[18] Currently, there is no data available that demonstrates the reliability or validity of the 5STS in PWMS. The 5STS has been found to be a valid and reliable measure of fall risk in people with PD[20] and the older adult population.[21,22]

B. BACKGROUND AND SIGNIFICANCE

MS is a disabling neurodegenerative disorders that can result in severe disability affecting every facet of an individuals life, creating a financial burden on the individual, family, health care system, and society.[23] It is important for clinicians and people living with MS to have a variety of safe and effective tools to treat individuals with this long-term, progressive disease. Due to the lack of research on the use FES-LE cycling in PWMS, this study will compare the effectiveness of FES-LE cycling to cycling alone, on variety of objective and subjective measures that span the ICF model and are easily applied in contemporary clinical practice.

A common complaint amongst PWMS is gait and balance disturbances including falls.[24] People with MS report a fall incidence of greater than 50% and this incidence increases as individual's age and the disease progress.[17,24]When a large group of PWMS were surveyed the activities where they reported the most frequent falls included transfers, ambulation, standing activities, stairs/curbs, and during exercise/physical activity.[24] Individuals with greater disability in ambulation tend to achieve less than the recommended daily activity levels when compared than those individuals without ambulation limitations.[25]

Exercise and living an active lifestyle are beneficial to PWMS.[26,27] Individuals who exercise often report a decrease in the perception of fatigue.[28] Improvements in fatigue outcome measures have been reported in a variety of exercise types including: high-intensity resistive exercises,[29,30] yoga,[31] and endurance/aerobic exercises.[32] In addition, physically active PWMS monitored by accelerometers reported lower levels of disability, depression, fatigue, and pain.[33]

In a time where healthcare dollars are being stretched and cost containment is on the forefront, therapists need to be efficient with their time, finding interventions that target multiple body structures while addressing activity limitations, participation and QOL. The use of an intervention that combines resistance and aerobic training that provides a repetitive motion may be an effective tool for people with multiple sclerosis (PWMS).

Functional Electrical Stimulation (FES) is a rehabilitation tool that stimulates intact peripheral motor nerves via electrical current evoking muscle contractions for the purpose of functional movement.[34] It has been utilized in patients with paralysis or weakness due to upper motor neuron lesions.[35] The use of FES in rehabilitation dates back to the early 1960's with the use of a heel switch that triggered short bursts of electrical stimulation to the peroneal nerve resulting in ankle dorsiflexion.[36] FES has evolved over the last 50 years and has been used to supplement or replace lost function due to neurological dysfunction. It has been applied to assist individuals with activities such as reaching, grasping, walking, and cycling.[37]

Functional Electrical Stimulation combined with lower extremity (FES-LE) cycling creates patterned movement of the legs and assists individuals with impaired voluntary control of their muscles in completing the cycling task. It has be utilized in a wide variety of patient populations including, but not limited to, spinal cord injury, stroke, traumatic brain injury, parkinson's disease, cerebral palsy and MS. Studies conducted in the stroke and SCI populations have demonstrated improvements in gait velocity, muscle mass, circulation, bone density, and range of motion, as well as a reduction of muscle spasms.[38–42] For PWMS, several studies have documented the use of electrical stimulation (ES) for single muscle groups and few studies have applied it to multiple muscles using a FES-LE cycling training paradigm. [2,43–46]

C. PRELIMINARY STUDIES

Multiple studies report that PWMS benefit in a variety of ways from resistive and aerobic training.[47–49] Exercise equipment that can offer a safe, moderate intensity workout is readily available in the typical gym environment but this may not be the best option for PWMS that demonstrate gait or balance difficulties or need assistance transferring. What makes FES-LE cycling different that other equipment is that once a person is familiar with FES-LE cycling it can be performed in the home environment, therefore offering options to those who do not have time or ability to travel outside the home or who have limited therapy through their insurance.

There are a handful of small studies consisting of case reports and pilot studies that have examined the efficacy and effectiveness on FES cycling for PWMS.[2,3,46,50] A review of the literature yields no randomized control trials or quasi-experimental studies in this specific area of research. Krause, Szecsi, and Straube[46] report a single case study of a non-ambulatory, 46 year-old man with secondary progressive MS with an EDSS score of 7.5. The investigators bilaterally stimulated three muscle groups during cycling: the gluteals, quadriceps, and biceps femoris. This individual was able to tolerate 30 minutes of cycling with short 3-5 minute breaks and did not experience difficulty tolerating the stimulation. They reported he tolerated stimulation amplitudes up to 90mA but did not report the chosen frequency or pulse width for this patient. This individual experienced a reduction in spasticity after each of the two training sessions as measured by the Modified Ashworth Scale (MAS) and the pendulum test. The authors did not measure spasticity reduction hours or days later, therefore no conclusions can be made regarding the long-term effectiveness. In addition, there were no outcomes or subjective descriptions reported that related this reduction of spasticity to gait, functional movement patterns, or quality of life.

Szecsi et al examined the effect of FES-LE cycling on biomechanical and functional outcomes.[3] Eight PWMS completed the FES-LE cycling training 3 times per week, each only 6 minutes long, for 2 weeks while also receiving conventional therapy.[3] No adverse reactions were reported but four subjects dropped out, reasons provided were: change of schedule, change of medications, failure to comply, and difficulty with transfers due to a high degree of disability.[3] Their quadriceps and hamstrings were stimulated in bilateral lower extremities during the stimulation trials.[3] They utilized a fixed frequency of 20 Hz, a maximal amplitude of 127 mA, and a fixed pulse width of 300 μsec.[3] These settings may not be optimal to elicit strong contractions in all PWMS. A frequency of 20 Hz is on the low end of what is recommended for FES-LE cycling and in a study by Eser et al, it was demonstrated in people with motor and sensory incomplete injuries that higher frequencies (50 and 60 Hz) demonstrate larger power outputs when pulse width and amplitude are held constant.[51]

In another study by Szecsi et al the effects of cycling both with and without stimulation within each cycling session was studied.[3] Symmetry of pedaling and power output was examined at various intervals during the study.[3] Subjects with MS were able to achieve greater cycling power and symmetry of pedaling with FES than without FES.[3] Functional outcomes were measured both before and after training and included the 10 MWT, MAS and Manual Muscle Testing (MMT).[3] There were no significant changes in these measures except for a

short-term reduction in spasticity before and after each training session.[3] Subjective feedback from participants revealed reports of increased functional abilities (e.g. transfers, stairs, activities of daily living) and quality of gait, such as improved leg lifting.[3] It is unknown if more functional improvement would have been revealed if the training period were longer and more intense. The training period is in this study was significantly below the exercise recommendations for PWMS.

In a pilot study by Ratchford et al the research team examined the relationship between FES-LE cycling and function.[2] Four individuals with primary or secondary progressive MS completed the study with EDSS ranging from 6.0 to 6.5 inclusive. Individuals performed FES cycling in the home environment using an FES cycle (RT300) for 6 months.[2] In addition to looking at impairments and functional measures at baseline, 3 months, and after the 6 month period, they also examined the relationship between FES cycling and changes in cytokines and growth factors in cerebral spinal fluid (CSF).[2] Participants were trained to use the FES cycle in their home and started with the same initial settings: a symmetric biphasic waveform, phase duration 250 microseconds randomized ± 25%, and a frequency 33 to 45 pulses per seconds.[2] Electrical stimulation was applied to the quadriceps, hamstrings, and gluteal muscles.[2] There were no serious adverse advents but one participant reported an increase in spasticity, which was treated by an increase in their Baclofen dose.[2] Another participant with a history of irritable bowel syndrome reported increased bowel incontinence and this was remedied by adjustments in this individuals bowel program.[2]

The outcomes of the Ratchford et al study were favorable but because of insufficient power, statistical interpretation was limited. Participants were asked to cycle three times per week for one hour sessions.[2] The mean number of sessions per week was 3.8, demonstrating that these individuals were able to tolerate training for the suggested time period.[2] The average power output and mean distance per session over the first two weeks and the last two weeks were 3.2 watts and 9.9 miles and 4.6 watts 10.6 miles, respectively.[2] The improvements in the main neurologic measures, the Two Minute Walk Test (2MWT), Timed 25-foot Walk Test, and the TUG, were 13%, 36%, and 22%, respectively.[2] Investigators also observed improvements in self-selected walking speed, double support time, and step length coefficient of variation, as measured on the instrumented GAITRite walkway.[2] Results showed a decrease in pro-inflammatory cytokines and an increase in nerve-related growth factors in the PWMS who performed FES cycling when compared to healthy controls.[2] These preliminary findings suggest that FES cycling may reduce inflammation and promote neuronal repair along with improvements in clinical outcome measures.[2]

In the largest retrospective study to date Hammond et al reported on 40 individuals who participated in a long-term FES-LE cycling program for 15 months.[52] The sample of subjects had EDSS scores ranging form 2.5 – 7.5 and were distributed across the three main types of MS (RRMS, SPMS, PPMS).[52] Their main outcome measure was the EDSS and the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). The ISNCSCI is an evaluation tool that examines sensory and motor function as well as anal and perianal function, but has yet to be validated in the MS population.[52] Details regarding duration, intensity, stimulation parameters, and muscles stimulated were not published. EDSS and ISNCSCI scores remained stable over the 15 month periods and in those with PPMS and RRMS, there was a slight decrease in EDSS

score, noting improvement in disability, although it was not statistically significant.[52] Based on this study, long-term FES cycling use may help to stabilize or prevent disease progression in PWMS.

The results of the FES-LE cycling MS studies described above stimulated different muscles and utilized a variety of training protocols and stimulation parameters.[2,3,46,50,52] In addition, it does not appear that any of the investigators chose to stimulate the tibialis anterior or gastrocnemius musculature, which are both integral muscles for efficient gait. The anterior tibialis is the primary muscle utilized for clearing the foot during heel strike and swing and the gastrocnemius plays an integral role in the propulsion of gait during swing phase, both of these muscles can be effected in PWMS.[53]

Based on review of research studies, the dosage of FES-LE cycling in this study will be 3 times per week for 8-week duration and will be applied to bilateral LEs and five muscle groups including the gluteals, quadriceps, hamstrings, tibialis anterior and gastrocnemius. A progressive interval-training regime will be employed and each training session will last a total of 45 minutes and participants will be progressed accordingly using a systematic progression protocol.

D. RESEARCH DESIGN AND METHODS

1. Rationale/overview

This study will be a prospective pretest-posttest comparison group design with repeated measures. The purpose of this study will be to assess the immediate and short-term effects of an 8-week LE cycling program on motor function, mobility and QOL for PWMS. The goal of this study is to examine if FES-LE cycling is more effective than cycling alone. Groups will be compared to determine changes in spatiotemporal gait characteristics, quality of life, endurance, and ability to transition from sit to stand following training.

2. Research Site

The study will be conducted at Stony Brook University's (SBU) Rehabilitation Research and Movement Performance (RRAMP) laboratory in Stony Brook, NY. An FES-LE ergometer (RT300, Restorative Therapies, Inc., Baltimore, MD) and a BTS G-Walk system along with BTS G-Studio software (BTG Bioengineering, viale Forlanini 40, 20024 Garbagnate Milanese MI, Italy and 147 Prince Street, Suite 11, Brooklyn, NY) will be utilized in this study.

3. Study sample

Twenty participants with a diagnosis of MS, at least 18 years of age who meet the inclusion/exclusion criteria (Table 1), will participate in this study.

Table 1 Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Medical Diagnosis of MS	Cognitive deficits (score < 22/30 on the Montreal Cognitive Assessment) that would interfere in their ability to sign consent and understand the procedures for the study.
At least 18 years of age, inclusive	History or presence of other neurological pathologies that interfere with movement
Patient-determined Disease Steps (PDDS) score between 3.0 and 6.0 inclusive	Received physical therapy within the last 4 weeks prior to the study
Ability to attend training sessions 3 times per week for an 8-10 week period	History of an acute exacerbation of their MS symptoms within 4 weeks prior to the study
Passing a submaximal exercise tolerance test	Immunosuppressive or steroid therapy within the past 4 weeks
Adequate hip range of motion (at least 110 degrees)	Significant spasticity (Modified Ashworth Score ≥ 3 at the quadriceps and hamstring muscles) in the LE's that interferes with the cycling motion
Adequate knee range of motion (10-90 degrees)	History of congestive heart failure
	Coronary artery disease
	Uncontrolled hypertension
	History of epilepsy or history of seizures
	Cardiac demand pacemaker or implanted defibrillator
	Unhealed fractures in the lower extremities
	Pressure sores or open wounds on the LEs
	Pregnant or trying to conceive.

4. Screening

Potential participants will undergo a phone screening prior to their initial visit. If the participant meets all the inclusion/exclusion criteria, they will be asked to set-up an appointment to meet with the primary investigator at the RRAMP lab. At that time, consent will be obtained and the baseline measures will be gathered and participants will be randomized into either the FES cycle group or the cycling only group. Participants will undergo a subjective and objective evaluation to determine if they meet the inclusion and exclusion criteria that were not able to be determined via phone screening. This evaluation will include an

assessment of cognition using the Montreal Cognitive Assessment (MoCA),[54] joint range of motion using a goniometer, degree of spasticity, presence of spinal reflexes, sensory function, motor function, and functional mobility. Cognitive screening will be performed to screen for participants capacity to provide informed consent, understand basic instructions, and provide feedback during training sessions. There does not appear to be a universally accepted screening measure to determine capacity to give informed consent in research studies but the screening should be related to the risks presented by the research.[55] Although this study presents minimal risk to participants, it will be important for participants to have an understanding of the equipment and protocol being utilized.

The assessment for exercise tolerance will follow the American College of Sports Medicine (ACSM) guidelines.[56,57] ACSM recommends that before beginning an exercise regimen, professionals employ two or more techniques to measure relative intensity.[56] ACSM suggests using submaximal testing[56] as practical approach to testing since most physical therapists do not have the necessary equipment for metabolic testing. To monitor relative intensity, heart rate (HR), blood pressure (BP) and rating of perceived exertion (RPE) will be measured during a graded exercise test.[56] A submaximal clinical exercise tolerance test (SXTT) will be measured on a LE ergometer since it is best to do testing on the piece of equipment that will be used for training.[58]

The ACSM recommendations when performing exercise testing for persons with MS will be followed during this study.[59] These recommendations include:

- testing in the morning if this is the optimal time for the participant
- beginning with a warm-up of unloaded pedaling
- using of a fan for cooling
- using a continuous or discontinuous protocol of 3 to 5 minute stages with an increase of work rate of approximately 12 to 25 Watts (W) per stage
- monitoring heart rate and blood pressure
- using the RPE scale to estimate stress level (Appendix H– RPE Scale).[56]

In this study, the SXTT will be conducted on the RT300 LE ergometer since it is the equipment being utilized during the study. HR and pulse oxygen will be measured in sitting at baseline and then recorded in during the last 5 seconds of each interval during clinical testing.[57] BP will be measured and recorded in sitting at baseline and during the last 45 seconds of each interval.[57] The RPE scale will be explained to participants at rest and recorded during the last 15 seconds of each interval. Data from the SXTT will be recorded on the participant data sheet. Participants will be asked to cycle at a target speed between 35-45 rpm, while the PT systematically increases resistance. The participant will start with unloaded cycling and every 3 minutes the resistance will be increased by 3 Newton-meters (Nm) per stage which is approximately 14 Watts per stage.[59,60] The SXTT will be discontinued when the participant reaches self-reported fatigue or if their vital signs fall outside a safe range. Maximal workload will be defined at the last completed interval before termination.

ACSM's guidelines for discontinuing testing include:[57,60]

- self-reported fatigue- participant expresses they can no longer pedal due to fatigue.
- reaching 70% heart rate reserve which is 85% of age-predicted HR_{max}, (HR_{max} = 220 – age x .85).
- Failing to conform to exercise protocol, which for this study will be defined as falling 10 rpm below the target rpm speed of 35-45 for greater than 10 seconds.
- hypotensive responses- systolic blood pressure drops ≥ 10 mm Hg from baseline.[57]
- hypertensive responses- systolic blood pressure > 250 mm Hg and/or a DBP of > 115mm Hg.[57]
- symptom exacerbation[58,59]- including headache, change in vision, numbness, sudden paralysis, dizziness, vertigo
- chest pain, shortness of breath, wheezing, and leg cramps.[57]

5. Procedures

Outcome measures were selected based on the International Classification of Functioning, Disability, and Health (ICF) model, recommendations from the APTA Neurology Section's Multiple Sclerosis Outcome Measures Taskforce,[61] clinical expertise, and research goals of the current study (Table 3). Members of the taskforce developed specific recommendations for practice environments (entry-level education, research, acute care, inpatient and outpatient) and also rated each outcome on a 4-point ordinal scale (4= highly recommended, the outcome measure has excellent psychometric properties and clinical utility;3= recommended, the outcome measure has good psychometric properties and good clinical utility; 2= unable to recommend at this time, there is insufficient information to support a recommendation of this outcome measure; 1= not recommended, the outcome measure has poor psychometric properties and/or poor clinical utility). All measures that were recommended for research were considered if they were rated a 3 or 4.[62]

The chosen battery of outcome measures for this study will be: 12 Item Multiple Sclerosis Walking Scale (MSWS-12), Modified Fatigue Impact Scale (MFIS), Multiple Sclerosis Quality of Life Inventory (MSQOL 54), Activities Specific Balance Scale (ABC), Godin Leisure-Time Exercise Questionnaire (GLT), Timed Up and Go, 5Times Sit-to-Stand , 6 Minute Walk Test, and Timed 25-Foot Walk.

Selected outcome measures will be performed at the follow four intervals:

- baseline- within one-week prior to the first training session;
- mid-point of training- before training session #13;
- post-training- between 1-3 days after the 24th training session, and
- approximately one-month after the last training session.

Physical tests will be administered in the following order for each participant: 6MWT, T25W, TUG, and 5STS. Participants will be provided at least a five-minute rest period between all physical tests. Safety precautions during testing will include: a quiet area free of distractions, gait belt, guarding and assistance as

needed. In order to measure both temporal and spatial gait parameters, the BTS G-Walk (BTG Bioengineering, viale Forlanini 40, 20024 Garbagnate Milanese MI, Italy and 147 Prince Street- Suite 11, Brooklyn, NY) will be utilized to collect gait data during the 6MWT, TUG, 5STS, and T25FW. The G-Studio software will automatically generates spatio-temporal parameters including: speed, cadence, stride length, step length, gait cycle duration, stance duration, swing duration, and single and double phase duration.

Table 2.

Outcome measures

Outcome Measure	Collection of Data
Godin Leisure-Time Exercise Questionnaire (GLTEQ)[a, p]	• Baseline
12 Item Multiple Sclerosis Walking Scale (MSWS-12)[a]	• Baseline • Post-training • 1 month after training
Modified Fatigue Impact Scale (MFIS)[b, a, p]	• Baseline • Post-training • 1 month after training
Multiple Sclerosis Quality of Life Inventory (MS-QOL 54)[a, p]	• Baseline • Post-training • 1 month after training
Activities Specific Balance Scale (ABC)[p]	• Baseline • Post-training • 1 month after training
Timed Up and Go (TUG)[A]	• Baseline • Mid-point • Post-training • 1 month after training
Five Times Sit-to-Stand (5STS)[A]	• Baseline • Mid-point • Post-training • 1 month after training
6 Minute Walk (6MWT)[A]	• Baseline • Mid-point • Post-training • 1 month after training
Gait Speed[A] Time 25-Foot Walk (T25FW)[A] Cadence, Gait symmetry, Stance duration, Swing duration, Single and double support phase duration, Step length, Stride length, Gait cycle duration[A]	• Baseline • Mid-point • Post-training • 1 month after training

ICF Model Domain: B, Body Structures & Function; A, Activity; P, Participation

Video Recording

This research project may include video recording during any outcome measure testing or cycling sessions for periods of minute or less. Particapants will only be videotaped if they initial the video recording section on the consent form that indicates they give the PI permission to videotape. This video recording will be available to be seen by the researcher, the Internal Review Board (IRB), any granting agencies, my dissertation committee, physical therapists and physical therapy students. If this video is used in papers or talks, we will make sure your face is not visible. We will keep this video in a locked

cabinet in RRAMP lab. You can request not to be videotaped and this will not affect your eligibility or participation in the study.

Training Protocols

Participants will train for 45 minutes, three-days per week, for eight-weeks using an FES-LE cycle (Figure 3; Table 6) (RT300, Restorative Therapies Inc., Baltimore, Maryland, USA). Basic demographic information (age, weight, and diagnosis) will be entered into Restorative Therapies Internet (RTI) Data Link and a random ID number will be generated and subjects will choose their own 4-digit pin number. The participant number will be used as the participant ID number on all paperwork associated with the study.

For FES-LE cycling, stimulated muscles will be standardized and will include the gluteals, hamstrings, quadriceps, anterior tibialis, and gastrocnemius. At the beginning of every session, the skin will be cleaned with alcohol and dried prior to placing the electrodes on the skin. Each participant will have their own set of electrodes that will be labeled with their participant number and will be stored at the research lab. Electrodes will be placed according to the guidelines outlined and participant morphology (Table 5; Figure 7). Before and after each training session, skin will be inspected for erythema, breakdown and/or irritation.

Expirations dates on the electrodes will be checked prior to the commencement of training. The manufacturer of the electrodes recommends that each electrode can be used for a maximum of 10-15 sessions. If an electrode no longer adheres appropriately to the skin, it will be discarded and a new electrode will be utilized. In order to track usage, each participant's package of electrodes will be labeled with the date and participant identification number.

Table 7.

Electrode sizing and placement

Muscle	Electrode Size	Location of placement
Quadriceps	3" X 4"	One will be placed one hand width above the knee centered on the belly of the quad and the second electrode will be placed at least a hand width above the first electrode. For participants with a longer thigh length, it will be placed higher in the middle of the quad belly.
Hamstrings	3" X 4"	Electrodes will be placed directly underneath where the quad electrodes are centered in the middle of the hamstrings.
Gluteals	2" X 3.5"	One electrode will be placed vertically with the top of the electrode parallel to the top gluteal cleft and the second electrode two-finger widths lateral to the first.

Anterior Tibialis	1-2” x 4" and 1- 2” X 3.5”	One electrode will be placed proximally on the muscle belly and the second electrode will be placed distally about 2/3 way down the shin.
Gastrocnemius	1-2” x 4" and 1-2” X 3.5	One electrode will run horizontal across the calf, just below the knee and the second electrode will be a minimum of two-finger widths below the first electrode just distal to the gastrocnemius belly.

*The electrode sizes above are guidelines and will be adjusted for participant morphology. If some is smaller than average, they may require smaller size electrodes in order to avoid overflow to other muscle groups.

Participants will be positioned in a standard waiting room chair and their legs will be positioned on the pedals and secured with Velcro strapping according to the manufactures recommendations. The bike and chair will be positioned to maintain 5-15 degrees of knee flexion when in the fully extended position of cycling. The height of the ergometer will be adjusted so that the rear of the participant’s thigh does not press into the seat cushion as they cycle. A back support may be placed behind the participant as needed. When necessary, adjustments to seat height and depth will be made utilizing cushions in order to optimize positioning and cycling angles.

Setting Initial Stimulation

After all initial measures are obtained, initial stimulation settings will be set during the baseline testing session prior to the training period. Frequency for all participants will be at 43.5Hz for all muscle groups and will not be changed throughout the study. During this baseline session all muscle groups will be turned on at the same time while the participant passively cycles (i.e. motor of the cycle is moving their legs) with the pulse width starting at 250 µsec for all muscle groups. Amplitude will ramp up at 1% per second and the participant will be instructed to tell the investigator to limit the stimulation when the feel any of their muscles reach a point where the stimulation is starting to get uncomfortable. The investigator will then adjust each muscle group individually to its maximal tolerable stimulation while the participant continues to passively cycle. Adjustments in amplitude will be increased in increments of 1mA increments until a participant achieves a maximal but tolerable muscle contraction. If a participant’s tolerance to stimulation is reached before a detectable contraction is palpated pulse width will be decreased by 10µsec increments and amplitude will be adjusted by 1mA increments until a maximal muscle contraction to their tolerance is achieved. The maximum level will be set at the value that has been determined to create a strongest tolerable motor response. If a participant is still unable able to achieve a muscle contraction due to discomfort, the highest stimulation parameters they reached will be used and parameters will be adjusted during training sessions as they accommodate to the stimulation. All initial settings will be automatically saved in RTI Data Link.

FES Training Session Protocol

The participant’s stimulation levels from their previous session will be used as starting parameters for each session. If during training sessions the participant can tolerate more stimulation, amplitude will be

increased in 1 mA increments. If they reach the maximum amplitude level of 140ma and can tolerate more stimulation, pulse width will be increased by 10μsec increments.

Participants will experience a 2-minute warm-up period in which the ergometer's motor provides passive cycling and moves the participants' legs. This will allow for the participant to work out any spasms or stiffness they may be experiencing. The ergometer will then transition into "active mode" in which the electrical stimulation slowly ramps up to allow the individual to accommodate to the stimulation. During this period, the participant will receive stimulation while also using their own muscle power against a set resistance while working to maintain a set target speed of 35-45 rpm. In order to have participants working at a moderate intensity, starting resistance will be set at 60% of the maximal workload from the submaximal clinical exercise tolerance test (SXTT).[58] Workload will then be progressively increased to a maximum of 80% of the workload.[58]

Participants will be encouraged to cycle continuously for at least 45 minutes using an interval training protocol. They will cycle for 5 minutes with stimulation and then 1 minute passively cycle without stimulation. This 5:1 (5 minutes of active cycling with stimulation: 1 minute passive cycling without stimulation) cycle will repeat 7 times during the session. Participants will then receive a 1-minute cool-down at the end where they receive no stimulation and the cycles motor passively moves the lower limbs.

Since individuals in this study will have some degree of volitional control to cycle faster than their control speed, stimulation minimums/maximums will be set to the same level to ensure stimulation does not drop below the therapeutic level for each muscle group, therefore no matter how fast the participant cycles the stimulation will remain on during the 5 minute stimulation period. The RT300 can provide 'motor support" and the ergometer will be set for the participant to receive 'motor support' throughout the cycling period if they are not maintaining their target speed.

If at any time during training a participant reports fatigue and needs to discontinue cycling, stimulation will be discontinued and the participant will continue the rest of their session in passive mode with the motor fully assisting their movement for the remainder of the therapy session (Figure 7). Once a participant can cycle the full 45 minutes using the 5:1 protocol, resistance will be increased by 5% increments every 3 sessions. The following instructions will be used prior to each training session:

> "You will be cycling for 45 minutes. The first 2 minutes are a warm-up period in which the cycle is taking you through the cycling motion, so just relax and let the bike do the work. After the warm-up, start to actively cycle at a moderate effort level. The stimulation will slowly ramp up over a 2-minute period to the stimulation levels we set during the previous session. If at any time the stimulation gets uncomfortable, please let me know and we can adjust the stimulation for each muscle group. You will cycle actively for 5 minutes and then receive a 1-minute break where the cycle will do all the work. This pattern of 5 minutes on, 1 minute off, will repeat 7 times during your training session. If at any time you experience fatigue, please let me know and you can take a break for up to 5 minutes and then continue where you left off. The cycle is set to go into a passive cycling mode if your speed falls 10 rpm below the set target speed of 35-45 mph. The stimulation will be turned off and you will finish the remainder of the session allowing the bike to do all the work. If you feel that you cannot continue with passive cycling, please let me know and we can finish the session at anytime."

Cycling-only Protocol

Participants in this training groups the will be set-up on the RT300 in the same manner as those in the FES training group but they will not receive electrical stimulation nor wear stimulation pads; they will use the RT300 as an ergometer only. During the cycling-only phase, participants will cycle continuously for 45 minutes using an interval training protocol (5 minutes of active cycling: 1 minute passive cycling) at a set target speed of 35-45 rpm. This 5:1 cycle will repeat 7 times and then go into a 1-minute cool-down. Total active cycling time will be 35 minutes. If a participant needs a rest the cycle can go into passive mode and the motor of the cycle will provide full support. Once the participant is able to tolerate 45 minutes of cycling without rests at or above the specified target speed, the resistance will be increased in 5% increments every 3 sessions.

Participants in both groups will receive feedback from the screen on the bike (Figure 8) during and after their treatment sessions, including distance traveled, right to left cycling symmetry, heart rate and oxygen saturation.

The following instructions will be used prior to each training session:

> "You will be cycling for 45 minutes. The first 2 minutes are a warm-up period in which the cycle is taking you through the cycling motion, so just relax and let the bike do the work. After the warm-up, start to actively cycle at a moderate effort level. You will cycle actively for 5 minutes and then receive a 1-minute break where the cycle will do all the work. This pattern of 5 minutes on, 1 minute off, will repeat 7 times during your training session. If at any time you experience fatigue, please let me know and you can take a break for up to 5 minutes and then continue where you left off. The cycle is set to go into a passive cycling mode if your speed falls 10 rpm below the set target speed of 35-45 mph. If that occurs, will finish the remainder of the session allowing the bike to do all the work. If you feel that you cannot continue with passive cycling, please let me know and we can finish the session at anytime."

RT 300 Features

The RT300 has several features that will be utilized during this study. One feature is the "control speed offset." If a participants cycling speed falls below the target speed by a pre-set revolutions per minute (rpm), the ergometer's motor will take over for the remainder of the session and assist the participant. The control speed offset will be set at – 10 rpm for all participants. The target speed for all participants will be 35-45 rpm and if a participant's speed falls below 35 rpm the ergometer's motor will take over and the cycle will finish the session in passive mode.

The SAGE stimulator also monitors electrode adherence and if an electrode falls off the system pauses and ceases stimulation and the motor turns off. An error message will be displayed on the screen telling the user which electrode needs to be checked. Once the electrode is secured, the session can continue.

If at any time a participant feels light-headed, nauseous, or dizzy during the training session or if their parameters fall outside the ACSM exercise guidelines, training will be discontinued for the remainder of the session.

All participants will be continuously monitored by a wireless heart rate and pulse oximeter with set parameters. Target HR goal for each participant will be set at 65% of their age-adjusted max HR (200 - age x .65). The maximum heart rate with set at 85% of age-adjusted max HR (220-age x .85). Participants will be encouraged to keep their HR within a 65% to 85% range. If a participant goes above their maximum heart for greater than 10 seconds, the ergometer and session will be paused and the participant will be given a 3-minute

rest until their HR comes down to their target heart rate. If their HR does not come down into the appropriate range, they will continue the remainder of the session in the passive cycling mode. The minimum heart rate will be set at 5 bpm below the participants resting baseline to allow for normal HR variability that can occur from day-to-day.

If oxygen saturation (SPO_2) falls below 88% the session will be paused and the participant will be instructed to perform deep breathing. Once the participant is back to their baseline SPO_2 saturation, they will be permitted to resume. They will be allowed a maximum of 5 minutes to achieve baseline. If they do not achieve their baseline within 5 minutes, they will continue the remainder of the session in the passive cycling mode.

E. STATISTICS

Data Interpretation

This study will follow an experimental pretest-posttest comparison group design with selected measures at baseline, 4 weeks (half-way through the intervention), 8 weeks (end of the intervention), and one-month after training is completed (follow-up).

Descriptive statistics, including frequency counts for categorical variables and measures of central tendency and dispersion for continuous variables will be calculated. Baseline demographic data will be compared across treatment groups to assess the adequacy of randomization using the Mann-Whitney for continuous data and chi-square tests of independence for categorical data.

The hypotheses of the research study will be examined using the Permutation Test for Paired Replicates with the treatment group (FES cycling vs. Cycling only) as the between participants independent variables and time (baseline and 4 weeks, 8 weeks, and 1 month) as the within subjects independent variable. This non-parametric statistical test was chosen due to the small sample size.

All dropouts, and the reason for dropping out of the study, will be reported. A priori alpha level of 0.05 will be used for all data analysis. Interquartile ranges for all for all outcome measures will be reported.

Data will also be analyzed using a Spearman's rank correlation to see if there is a relationship between GLTEQ scores, which measures pre-training activity levels, and the participants post-training gait speed and 6MW. All data analysis will be performed using IBM SPSS statistics software.

F. FUNDING STATUS, DETAILS

No funding for this study has been secured at this time.

G. HUMAN SUBJECTS RESEARCH PROTECTION FROM RISK

Risk to Subjects

This research protocol and risk to participants is minimal.

Adequacy of Protection Against Risks

Participants will be closely guarded by a trained investigator during all physical outcome measures and will be wearing gait belt, therefore the fall risk is this experiment is comparable to the risk individuals incur during everyday walking. During training, participants will be seated and risk of injury is minimal. Participants may become tired or fatigued during training and rest breaks will be permitted.

Potential Benefits of Proposed Research to the Subjects and Others

The following benefits that occur from exercising regularly may occur as a result of being enrolled in this study. This may include an improvement in: voluntary muscle control, fatigue, endurance and quality of life.

Importance of the Knowledge to be Gained

Previous studies have demonstrated FES-LE cycling is a safe, feasible, and effective exercise modality for non-progressive neurological disorders,[2,42,63,64] but only a few studies have applied this modality to a neurodegenerative disorder, such as MS. These individuals have similar impairments and activity limitations to individuals with non-progressive disorders such as SCI and stroke, yet there is lack of strong evidence to support the use of this modality for PWMS. FES-LE cycling may be an effective way for PWMS to safely exercise while having a positive effect on gait speed, aerobic capacity, function and quality of life (QOL). In addition, the use of this technology may motivate an individual to engage in physical activity because the cycle provides real-time visual feedback. Once a patient is familiar with FES cycling they can perform it as part of a wellness program in the clinical setting or in the privacy of their own home. The cycle being used in this study allows the therapist to monitor progress and change parameters remotely.[65] In a study examining the perceived barriers to exercise, physical exertion and limited access to exercise locations were listed as the greatest barriers to exercise in PWMS.[66] Since cycling is performed in a seated position, it is safe for individuals with balance deficits who are limited due to their inability to perform activities safely in a standing position without supervision. Overtime this treatment paradigm could potentially save money and time not only for PWMS but also the healthcare system. FES cycling is utilized in the home environment and is sometimes fully or partially covered by medical insurance. In the past 10 years, FES home-based cycling has been successfully utilized in patient populations such as SCI[2,67] and CP.[68]The purpose of this study will be to assess the immediate and short-term effects of an 8-week LE cycling program on motor function, mobility and QOL for PWMS. The goal of this study is to examine if FES-LE cycling is more effective than cycling alone.

H. DATA SAFETY MONITORING PLAN (for more than minimal risk studies)

Not applicable

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