Protocol #: 20-0695
Project Title: Low Load Resistance Training Using Blood Flow Restriction for People with Multiple Sclerosis
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I. Hypotheses and Specific Aims:

Specific Aim 1: Determine the feasibility of BFR by assessing recruitment rate, retention, adherence, satisfaction, and safety.

Hypothesis: Feasibility will be demonstrated by: 1) enrolling 20 participants in 8 months, 2) retaining at least 16 (80%) participants, 3) 80% adherence to intervention, 4) 90% satisfaction with intervention, and 5) no serious adverse events related to the intervention.

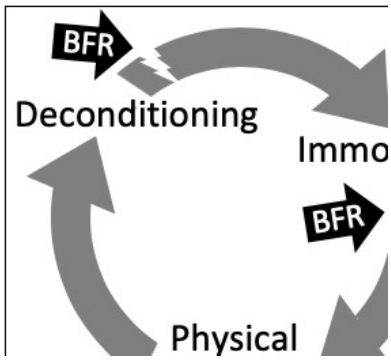
Specific Aim 2: Determine changes in knee and hip extension, hip abduction, and ankle plantarflexion muscle strength after the 8-week intervention.

Hypothesis: Following intervention there will be clinically important within-group strength changes that correspond to established minimal detectable change values and which can be characterized as having at least a moderate effect size as defined by Cohen's *d*.

Exploratory Aim: Explore changes in functional mobility (30-Second Sit-to-Stand, Berg Balance Scale, Timed 25-Foot Walk. 10-day average activity level) and self-report measures (12-Item MS Walking Scale, Modified Fatigue Impact Scale, MS Impact Scale-29, and Patient-Specific Functional Scale) after the 8-week intervention.

II. Background and Significance:

Few exercise studies enroll people with MS who have advanced disability (EDSS ≥ 6).[1–3] In people with MS and mild-to-moderate disability (EDSS < 6.0) exercise improves functional mobility.[4–6] However, these same interventions are not always feasible for those with advanced disability who have difficulty with independent walking and even standing.[1] Severe mobility limitations put people with MS and advanced disability at high risk for entering a negative cycle of deconditioning and decreased physical activity (Fig 1) which can worsen quality of life and health.[7–15] Therefore, exercise interventions to improve deconditioning and mobility designed specifically for people with MS who have advanced disability are crucially important.



An intervention that has not been studied fully in people with MS and advanced disability is resistance training.[1] Muscle weakness is highly prevalent in people with MS,[16] contributes to immobility,[17] and worsens as disability advances.[10,18] In people with MS and mild-to-moderate disability, moderate-to-high intensity resistance training improves weakness and functional mobility.[3–5,19,20] However, there is limited evidence evaluating the impact of resistance training in those with advanced disability.[21–23] These individuals may need unique exercise approaches due to 1) limitations in physical access to equipment and facilities, and 2) inability to tolerate

higher intensities due to more severe MS-related symptoms such as fatigue.[1,24,25]

Blood flow restriction (BFR) training is a potentially feasible way to improve strength in people with MS and advanced disability, while addressing access barriers and fatigue. BFR uses an external cuff to partially occlude blood flow of an exercising limb, causing muscle hypoxia and metabolic stress.[26,27] Under these conditions, low intensity resistance training (20-30% of 1-repetition max [1RM]) has been shown to be as effective at increasing strength as high intensity training without BFR (70-80% of 1RM) in people with a variety of orthopedic conditions.[26–28] With BFR, resistance training can be effective using simple exercise equipment such as resistance bands (or even just active range of motion or isometrics), and in accessible settings such as the clinic or home.[26] Finally, because of lower loads, resistance training with BFR puts less stress on muscles, connective tissues, and joints, which may increase tolerance due to less delayed onset muscle soreness and fatigue.[26]

The primary objective of this pilot study is to determine the feasibility of low-load resistance training using blood flow restriction (BFR) in people with multiple sclerosis (MS) and advanced disability (Expanded Disability Status Scale [EDDS] 6.0-7.0).

III. Preliminary Studies/Progress Report:

There are early data supporting the safety of BFR in people with MS, yet to our knowledge, **no study has examined BFR with resistance training.** A recent small study reported that BFR during a walking program improved walking speed in people with MS EDSS 5.5-6.5.[29] This study did not measure strength outcomes, but there were no adverse events or discontinued treatments over 132 total sessions.[29] **We used BFR with resistance training for 12 weeks in one patient with MS (EDSS 3.0) without adverse events**.[30] This individual improved strength (hand-held dynamometry), and self-reported walking (12-Item MS Walking Scale [MSWS-12]) and fatigue (Fatigue Severity Scale [FSS]).[30] Of note, improvements were comparable to minimal detectable change (MDC) values in people with MS (Table 1).[18,31,32] These early trial[29] and case report[30] data are promising. However, to inform clinical use and efficacy trials, more study is needed to determine the feasibility of resistance training with BFR in people with MS and advanced disability.

Table 1. Case data	12 Week Change	MDC[18]
L Hip Abduction	+56.6%	29.3%
R Hip Abduction	+87.6%	
L Hip Extension	+49.7%	42.2%
R Hip Extension	+69.2%	
L Knee Extension	31.9%	26.9%
R Knee Extension	20.0%	
L Ankle Plantarflexion	14.7%	N/A
R Ankle Plantarflexion	15.3%	
MSWS-12	-19	-22
FSS	-1.8	-1.9

IV. Research Methods

A. Outcome Measure(s):

Table 2. Outcome measures and time points of assessment.

Outcome Measures	Baseline	Every session	Week 8
Expanded Disability Status scale and descriptive data	X		
Muscle Strength: Handheld Dynamometer and clinical assessments	X		X
Functional mobility: T25FW, 30STS, BBS, Wrist and waist mounted Actigraphs	X		X
Patient-reported outcomes: MSWS-12, MFIS, PSFS MSIS-29, PASIPD	X		X
Pain: Numeric Pain Rating Scale	X	X	X
Fatigability: Numeric fatigue rating scale	X	X	X
Vitals: BP, HR	X	X	X
Adherence: Patient Log, Unit Compliance		X	X
Satisfaction: Satisfaction Survey and semi-structured interview			X
Safety: Patient report and Medical Record		X	X

Abbreviations: T25FW: Timed 25-Foot Walk Test; 30STS: 30-second Sit-to-Stand Test; BBS: Berg Balance Test; MSWS-12: 12-Item Multiple Sclerosis Walking Scale; MFIS: Modified Fatigue Impact Scale; PSFS: Patient-Specific Functional Scale; MSIS-29: Multiple Sclerosis Impact Scale; PASIPD: Physical Activity Scale for Individuals with Physical Disabilities;

Description of Outcome Measures

Feasibility (Aim 1) will be determined by recruitment rate, percent retention, adherence to exercises and sessions, satisfaction measured on a 7-point Likert scale and during an exit interview, and safety as measured by adverse events. Adverse events related to the program will be documented at all clinic and testing sessions and reported per COMIRB procedures.

The exit interview will be a semi-structured qualitative interview and will be conducted by an outcome assessor trained in qualitative interviewing methodology via Zoom to gather qualitative data about the participant's perceptions of their experiences with the intervention at the end of study intervention period. All interviews will be conducted over a secure Zoom link, but participants will be asked to turn off video when recording so that only audio is recorded.

Muscle strength (Aim 2) will be assessed by hand-held dynamometry for knee extension (seated), and hip abduction (supine), and ankle plantarflexion (supine) reported in kg, and normalized to BMI.[18] Ankle plantarflexion will also be measured using a heel raise protocol in standing,[18] and hip abduction will be assessing in standing using the Trendelenburg test.[33] We have demonstrated the reliability and validity of these strength assessments in people with MS, and also published minimal detectable change values.[18]

Exploratory Aim**:**

Functional mobility will be measured by the 30-second Sit-to-Stand test (30STS), Berg Balance Scale (BBS), and Timed 25-Foot Walk (T25FW). 30STS counts the number of times a patient can transfer from sitting to standing in 30 seconds, and is an important marker of functional independence.[34] BBS will assess task-specific balance and ADL function.[35] The T25FW is the standard measure of gait speed in MS and correlates with disability and function.[36] Participants will be allowed to use their usual assistive devices and/or orthotics during functional mobility

assessments and will use the same assistive device/orthotic for both baseline and follow-up assessments.

Functional mobility will also be measured by ActiGraph accelerometer-based activity monitors (ActiGraph Inc. Pensacola FL), which are reliable[37] and valid[38] in people with MS. Actigraph monitors will be provided at the initial screening visit and follow-up assessments, and worn for 10 days. Measuring physical activity counts using ActiGraph requires a waist-mounted version for people who are ambulating and a wrist-mounted version for those using a manual wheelchair. As there will be a range of participants who are primarily ambulators or wheelchair users and the potential for some participants to go between a wheelchair and ambulation within a given day, all participants will be asked to wear both a wrist-mounted and waist-mounted Actigraph for 10 days at baseline and follow-up assessments.

Self-reported function and fatigue will be assessed by the 12-Item MS Walking Scale (MSWS-12)[39] and the Modified Fatigue Impact Scale (MFIS),[40] respectively. The Patient-Specific Functional Scale (PSFS) will evaluate patient achievement of individual goals related to the intervention.[41] The Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) will be used to assess physical activity in participants. The Multiple Sclerosis Impact Scale (MSIS-29) is a validated scale that assess quality of life and disability in people with MS.[42] The PASPID is a unique scale that is validated to assesse physical activity in people who have walking disability or use a wheelchair for mobility.[43]

Other outcomes taken before and after each session will include pain and performance fatigue measured on visual analog scales, and vital signs (HR, RR, BP).

Sample characteristics will include EDSS, age, sex, height, weight, time since diagnosis, and 3-month fall history. Dr. Mañago, who has training in EDSS assessment, will perform all EDSS assessments.

B. Description of Population to be Enrolled:

Twenty subjects will be recruited primarily through the Rocky Mountain Multiple Sclerosis Center (RMMSC), which has over 600 monthly visits from patients with MS. The trial will be shared on the RMMSC website (>8 million annual views) and newsletter (published 17 times a year, circulation > 2,000 in Colorado), and through targeted emails sent to patients who have already expressed an interest in research. In addition, a recruitment specialist will be trained to recruit, pre-screen, and schedule participants who express interest in the study. In addition, advertisements will be placed in University of Colorado Hospital outpatient physical therapy clinics.

Inclusion Criteria

- Adults ages 18-65
- Neurologist-confirmed diagnosis of multiple sclerosis
- Expanded Disability Status Scale (EDSS) 6.0 to 7.0
    - EDSS 6.0: unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting
    - EDSS 6.5: Bilateral assistance (cane or crutch) required to walk at least 20 meters with or without resting
    - EDSS 7.0: unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day

Exclusion Criteria

- EDSS 7.5 or greater: Restricted to wheelchair for all mobility, unable to walk more than a few steps, even with walking aid
- EDSS 5.5 or less: Able to walk more than 100 meters without walking aid or rest
- Unable to provide consent or follow simple directions

- Prior history of Deep Venous Thrombosis/ Pulmonary Embolism
- History of peripheral vascular disease, thrombophilia or other clotting disorders
- Patient report of easy bruising
- Any comorbid conditions or pain that substantially affects physical function or would interfere with the participant's ability to safely complete rehabilitation (e.g. neurologic, vascular, cardiac problems, orthopedic, or ongoing medical treatments) as determined by a neurologist of physical therapist
- Severe lower extremity spasticity as defined as Modified Ashworth scale > 2
- Currently undergoing supervised resistance training with a physical therapist or other exercise professional
- Use of Blood Flow Restriction currently or in the previous 3 months prior to enrollment
- MS-related exacerbation or changes to their disease-modifying drug therapy in the month prior to enrollment
- Inability to tolerate pressure cuff during baseline assessment

C. Study Design and Research Methods

Eligible participants will be consented and assessed on baseline measurements 0-14 days prior to their surgery. Subjects will be oriented to the use of BFR at this baseline visit. As a small percent of individuals may not tolerate the sensations associated with BFR, subjects that do not tolerate BFR (up 80% limb occlusion pressure) during this orientation will not be enrolled in the study. These cases would be documented and inform future trial design. In addition, this baseline screening allows for orientation to the intervention which would aide overall feasibility of following through with the intervention. Following baseline, all subjects will receive intervention (below) and then be assessed at and 8-weeks (end of intervention). Recruitment will target at least 5 participants from each EDSS level 6.0, 6.5, and 7.0.

Intervention

Dr. Mañago will deliver intervention to all participants. An FDA-cleared BFR system, the Delfi PTSII (Delfi Medical Innovations, Vancouver, BC), will be used to deliver the intervention. The system allows for rapid inflation and deflation, precise control of pressure throughout training, and automatic shut offs for safety. The cuff allows for automatic determination of limb occlusion pressure (LOP), the pressure at which all arterial and venous blood flow is fully restricted. The device has advanced pressure leak detection that monitors the tourniquet cuff, tubing, and connectors for air leaks and safely alerts staff to hazards or follow-up actions required. The device has visual and audio alarms for over and under pressure and elapsed time as well as a large, easily visible display of tourniquet pressure and elapsed time. The Delfi PTS II for BFR calibrates and self-tests on startup. It has a safety interlock that limits the normal maximum pressure and integrated tourniquet cuff testing as recommended in current AORN Standards and Recommended Practices.

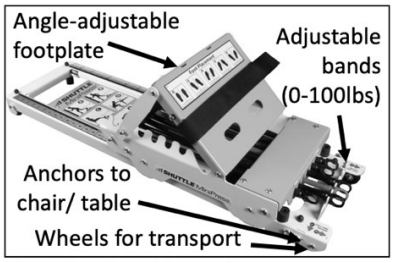


Fig 2. Shuttle Mini-Press®

All participants will begin each treatment session by performing 5 minutes of a low-intensity warm-up exercise (e.g. lower leg ergometer). Following that, the pressure cuff will be placed at the most proximal portion of the leg and dosed following standard BFR guidelines: 1 set of 30 reps, then 3 sets of 15 reps at 20-30% 1RM with up to 80% limb occlusion.[26,27] Exercises will target bilateral 1) knee and hip extension, 2) hip abduction, and 3) ankle plantarflexion, as these muscles are important for functional mobility in people with MS.[17,44,45] Exercises will be individualized for each participant from a standardized exercise set and dosed based on 1RM. Progression will be based on 1) body position (supine, sidelying, seated, standing), and 2) presence and/or degree of resistance (gravity

eliminated, isometric, to active and resisted range of motion). Resistance will be provided by the Shuttle Mini-Press (Shuttle Systems, Bellingham, WA, Fig. 2), a portable resistance trainer that allows for precise dosing but is also adaptable to people with mobility limitations.[46] Dosing will be re-assessed every 2 weeks and progressed as able.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

There are risks associated with exercise in people with MS such as fatigue, musculoskeletal pain, delayed onset muscle soreness, and even falls. All exercise will be supervised by the PI, a physical therapist with 15 years' experience treating people with MS. Most exercises can be completed in sitting or lying down, and Dr. Mañago will supervise and closely guard all transfers and transitions. If participants progress to standing exercises, where risk of falling is greatest, they will also be allowed to hold on to a rail, chair, table, counter or other stable surface in order to maintain balance and prevent falls.

Participants will undergo muscle testing which in rare cases might cause temporary muscle or joint pain and/ or fatigue. Muscle testing is part of a routine physical therapy exam. People with pain that limits ability to give a maximal contraction will be excluded from the study. We have evaluated HHD in our clinical practice and in COMIRB 15-0420 assessed 72 people with MS using HHD, and have not observed any adverse events. Three subjects reported minor discomfort with the procedure in COMIRB 15-0420. Participants will be able to withdraw from the study at any time or stop the testing procedure if they are ever uncomfortable. If pain is limits the baseline assessment testing procedure, the participant will be excluded from the study and recorded as a screen failure.

The people with MS in this study will have difficulty walking. During performance testing of their mobility outcomes, there is a risk of loss of balance resulting in an injurious fall. All participants, however, will be supervised and closely guarded by a trained outcome assessor who has experience working with people who have mobility limitations. They can also use their preferred assistive device during assessment. Therefore, while some participants may lose their balance, the risk of a fall is very low. The risk of falling or lose of balance is no greater than during a routine physical therapy assessment and intervention.

There is a potential risk of injury with the utilization of BFR. The most common side effects are transient in nature. These include muscle soreness at the area of the tourniquet cuff, numbness distal to the cuff during the treatment and mild delayed onset muscle soreness within 24-72 hours after the treatment. Nakajima et al[48] retrospectively reported on the side effects of nearly 13,000 individuals (age range 20-80 yrs old) who had engaged in BFR exercise. Reported side effects venous thrombosis 0.055%, pulmonary embolism 0.008%, and rhabdomyolysis 0.008%. Temporary side effects included subcutaneous hemorrhage 13.1%, numbness 1.297% and cold feeling 0.127%. Some of these side effects may be attributable to the lack of a standardized tourniquet system and safe limb occlusion pressure. There is a wide range of variability in the tourniquets historically used for this training, from elastic bands to blood pressure cuffs. In this study a surgical tourniquet with a cuff designed specifically for the thigh will be utilized (Delfi Gen II System). This system maintains a continuous and even pressure in the cuff, even while the limb is moving. Additionally, limb occlusion pressure will be standardized at 80% of the subjects' arterial occlusion pressure. At this pressure, there will be diminished venous outflow to induce a metabolic effect while still allowing for arterial flow.

Another risk to the participants is unauthorized access or use of personal health information. All reasonable steps will be taken to protect the patient's privacy. Health records will only be accessed electronically through EPIC on a University of Colorado computer. Patients will have to already have a clinical relationship with the investigators, so all health information accessed will have already been recorded as part of their routine medical care. A unique identifier will be given to each participant so that identifying information is not stored as part of the data. Paper data forms used during the testing procedures will be stored in a locked file cabinet.

Finally, given the current COVID-19 Pandemic, there is an increased risk of exposure when leaving the home. While MS does not increase risk of contracting or dying from COVID-19, those with advanced disability are recommended to minimize their exposure.[47] Our lab is currently authorized to conduct in-person study visits and we are in compliance with institutional and CDC protocols for screening, cleaning, social distancing, and personal protective equipment use. Exposure will be further minimized as our lab space allows for isolated treatments and assessments, and participants will only interact with Dr. Mañago for intervention and the outcomes assessor for assessment.

Potential benefits to the subject include improvements in strength and function following the intervention. However, they might achieve similar benefit from routine physical therapy treatment. Finally, knowledge gained from the study could potentially benefit patients in the future.

E. Potential Scientific Problems:

As with any study that involves recruitment, there is a potential problem of not reaching the needed number of subjects in a timely manner. In the past we have successfully recruited people with MS for rehabilitation studies through our clinical practice at the University of Colorado Hospital (UCH). Additionally, we will collaborate with the Rocky Mountain Multiple Sclerosis Center (RMMSC), to target advertising via an email newsletter and in-person contact at outreach events. The study only requires 20 participants and we are confident in our sample size calculation based on our clinic data. Reaching our estimated sample should give us the needed power to test our hypotheses and provide data necessary to develop a larger randomized trial.

The lack of control group could be seen as a design limitation, however our goal is to assess feasibility, and an underpowered randomized control trial could result in inaccurate effect size estimates and misinform future trial design.[48]

Missing Data. All participants with outcome measurements will be included in the intent-to-treat analysis. Although we will encourage participants to be fully compliant to their assigned treatment regimen and testing sessions, they will not be dropped from follow-up measurements for lack of compliance. The importance of complete follow-up will be stressed during enrollment and consent, and repeated during study participation. Participants will be contacted repeatedly if they miss follow-up visits, and all efforts will be made to get participants to return for scheduled follow-up visits. Although statistical methods can be used to 'adjust' for missing data, these methods rely on the untestable assumption that data are "missing at random" so that the effect of the missingness can be removed through statistical modeling. We will instead focus on preventing missed follow-up visits for this feasibility study.

F. Data Analysis Plan:

Aim 1**:** Feasibility will be met by enrolling 20 participants in 8 months, retaining 16 participants, adherence to at least 80% of exercises and sessions, at least 90% reporting being at least "satisfied" with intervention on the Likert scale (≥5/7), and no serious adverse events associated with the intervention. Aim 2**:** Strength changes will be compared to published minimal detectable change values in people with MS for knee extension (29.4%), hip extension (42.2%), hip abduction (26.9%), and ankle plantarflexion (8 repetitions).[18] Finally, Cohen's *d* will be used to determine strength and mobility effect sizes, and will be characterized as trivial (0-0.19), small (0.20-0.49), moderate (0.50-0.79), or large (≥0.80).[49] Exploratory Aim**:** Changes in functional mobility (30STS, BBS, T25FW) and self-reported outcomes (MSWS-12, MFIS, PSFS) will be compared to published values on important change[31,34,41,50–52] and further characterized by Cohen's *d* as in Aim 2.

Qualitative data from the semi-structured interview and participant satisfaction survey will be utilized to examine patient perceptions of barriers and facilitators to adherence and factors related

to satisfaction with the training program. The qualitative analysis will focus on *what* participants said to inform potential modifications of the training program. Analysis will consist of four distinct phases (decontextualization, recontextualization, categorization, and compilation) and be conducted by two investigators. The two investigators will independently complete the analysis and discuss findings to obtain consensus. Analysis by two independent investigators will increase trustworthiness and validity of the qualitative findings.

Calculation of Sample Size:
The study is designed to determine feasibility, therefore, a control group is not included,[48,53] and sample size was determined in order to inform future study design.

G. Summarize Knowledge to be Gained:

Testing the feasibility of BFR is the first step in the development of this intervention.[22,48] The next steps would be a randomized trial to assess the efficacy of BFR in people with MS and EDSS ≥ 6, and exploring the feasibility of BFR for in-home use. We plan to submit future grants to foundation (NMSS) and agency (DOD, NIH) awards mechanisms.

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