Intensive Aerobic Cycling Is Feasible and Elicits Improvements in Gait Velocity in Individuals With Multiple Sclerosis: A Preliminary Study

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ABSTRACT

BACKGROUND: Aerobic exercise (AEx) has many potential benefits; however, it is unknown whether individuals with multiple sclerosis (MS) can attain the optimal intensity and duration to harness its effects. Forced-rate exercise (FE) is a novel paradigm in which the voluntary pedaling rate during cycling is supplemented to achieve a higher exercise intensity. The aim of this pilot trial was to investigate the feasibility and initial efficacy of a 12-week FE or voluntary exercise (VE) cycling intervention for individuals with MS.

METHODS: Twenty-two participants with MS (Expanded Disability Severity Scale [EDSS] 2.0-6.5) were randomly assigned to FE (n = 12) or VE (n = 10), each with twice weekly 45-minute sessions at a prescribed intensity of 60% to 80% of maximum heart rate (HR).

RESULTS: Eighteen individuals (FE = 11; VE = 7) completed the intervention, however, adaptations were required in both groups to overcome barriers to cycling. Overall, participants exercised for an average of 42.2 ± 2.3 minutes at an aerobic intensity of 65% ± 7% of maximum HR and a pedaling cadence of 67.3 ± 13.3 RPM. Cycling led to improved treadmill walking speed (0.61 to 0.68 m/sec, $P = .010$), with somewhat greater improvement with FE compared to VE (increase of 0.09 vs 0.03 m/s, respectively, $P = .17$) post intervention. Notably, the participant with the highest disability level (EDSS 6.5) tolerated FE but not VE.

CONCLUSIONS: Aerobic exercise is feasible for individuals with MS, although those with increased disability may require novel paradigms such as FE to achieve targeted intensity. Further trials are warranted to investigate the effects of FE across the MS disability spectrum.

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Multiple sclerosis (MS), a relapsing and/or progressive disease characterized by autoimmune inflammation, demyelination, and neurodegeneration in the brain and/or spinal cord, affects 2.8 million people worldwide.[1] Disease-modifying treatments (DMTs) prevent relapses caused by inflammation; however, they have limited ability to prevent or reverse disability accumulation caused by disease progression, demonstrating the need for therapies beyond the established immunological landscape.[2] Based on animal studies, aerobic exercise (AEx) has the potential to alter central nervous system (CNS) function by diminishing neuroinflammation, enhancing neuroplasticity, and facilitating myelin repair.[3-6] Initial studies on the ability of AEx to influence CNS function in individuals with MS are limited. Recently, Langeskov-Christensen et al showed that high-intensity AEx improved fitness and lowered relapse rates, but had no effect on the primary outcome of total brain atrophy in individuals with MS.[7] Interestingly, there was a trend towards improvement in gray matter parenchymal fraction in the AEx group, which correlated with improved cardiovascular fitness.

Despite unclear CNS mechanisms for neural protection and repair, AEx can improve symptoms in individuals with MS, including fatigue, mood, mobility, and balance.[2] However, fewer than 20% of individuals with MS engage in the recommended amounts of moderate-to-vigorous physical activity, as compared to 40% of neurologically healthy peers.[8] Rather than disinterest in exercise, common clinical features of MS, including debilitating fatigue, weakness, and spasticity, are likely contributors to low levels of physical activity.[8,9] Given these limitations to sustained exercise, it is unknown if individuals with MS, particularly those with higher levels of disability, can engage in the intensity and duration of AEx that is required to induce positive CNS effects.[5,9]

Forced-rate exercise (FE) is a novel mode of training in which a semirecumbent cycle ergometer is custom-engineered

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with a motor that facilitates pedaling at a greater speed and intensity than the rate that individuals can achieve on their own, which is thought to alter the CNS.[10-13] It is important to note that the efforts of the individual are supplemented, but not replaced; heart rate (HR) is continuously monitored to ensure that the participant is contributing to the activity. Animal models have shown that high-rate FE protocols are superior in altering neurotrophins and synaptic structures compared to voluntary exercise (VE) paradigms, leading to the hypothesis that FE, with its high rate and consistent pattern of exercise, facilitates a neuroplastic response within the CNS.[5,14] When tested in people with Parkinson disease (PD) and in individuals post stroke, the higher rate associated with FE resulted in improved motor function,[10,13,15,16] quality of life (QOL),[17] aerobic capacity,[18,19] walking function,[11,12,20] and improved connectivity within the CNS.[21-23] We theorized that, similar to individuals with PD and stroke, FE could be used to overcome barriers to intensive AEx in individuals with MS and to promote improvements in their motor function.

The primary aim of this pilot randomized clinical trial (RCT) was to investigate the feasibility of a 12-week FE or VE aerobic cycling intervention in individuals with MS. Our secondary aim was to investigate the preliminary effects of FE versus VE on gait. We hypothesized that FE would facilitate exercise of greater intensity and duration, resulting in improved functional outcomes when compared to VE.

METHODS

Participants

In the 2-armed clinical trial Therapeutic effects of forced aerobic exercise in multiple sclerosis (ClinicalTrials.gov identifier: NCT04906057), individuals who met the following criteria were recruited to participate: (1) neurologist-confirmed diagnosis of MS with Expanded Disability Status Scale (EDSS) score of 2.0 to 6.5, (2) 18 to 75 years of age, (3) minimal risk for cardiovascular event using American College of Sports Medicine Exercise Criteria,[24] (4) stable dose of spasticity/fatigue medications for 2 months. Exclusion criteria were (1) myocardial infarction, heart failure, or heart surgery within 3 the past months, (2) cardiac arrhythmia, (3) hypertrophic cardiomyopathy, (4) severe aortic stenosis, (5) pulmonary embolus, (6) concurrent physical therapy, (7) significant contractures, (8) inability to hydrate, and (9) other contraindication to exercise. All potential participants received physician approval for participation and were screened using the American College of Sports Medicine Exercise Preparticipation Health Screening algorithm.[24] The study was approved by the Cleveland Clinic Institutional Review Board and all participants provided informed consent.

Participants completed 2 baseline testing sessions 1 month apart evaluating gait velocity and walking capacity. The purpose of 2 baselines was to allow for familiarization of gait assessments and to determine stability of measures that may be influenced by learning effect or fluctuations in day-to-day performance. Following baseline testing, participants were randomly assigned to undergo FE or VE. Randomization was stratified based on EDSS level (2.0-4.0 vs 4.5-6.5) to facilitate comparable levels of disability across groups.

Intervention

The FE protocol was based on methodology from our previous studies in stroke and PD, and involved a 45-minute session of supervised exercise on a custom-engineered stationary semirecumbent cycle ergometer.[10,11,13,15,16] The cycle was equipped with a motor programmed to respond to the voluntary effort of the participant to maintain a target cadence. The VE session was identical, but participants cycled without assistance from the motor. Participants in both groups attended sessions twice a week for 12 weeks. Aerobic intensity for both groups was monitored continuously using a Wahoo chest strap (Wahoo) synchronized via Bluetooth to an Apple iPad (Apple, Inc) allowing both the participant and the therapist to monitor HR and encourage exercise within the prescribed HR zone. The target HR zone for all participants was set at 60% to 80% of age-predicted maximum HR. Participants were instructed to exercise within their target HR zone during the 35-minute main exercise set, occurring between 5-minute warm- up and cool-down phases. Clip-in cycling shoes were used to ensure a secure interaction between the individual's feet and the pedals. Additional adaptations were made on an individual basis to accommodate neuromuscular impairments to ensure optimal biomechanical alignment during cycling. Intervention sessions were overseen by a physical therapist or exercise physiologist certified in Basic Life Support by the American Heart Association.

Outcomes

Exercise Variables

The following data measuring response to exercise were obtained during each session and recorded in REDCap: average HR during warm-up, main exercise set, and cooldown; blood pressure at baseline, every 10 minutes, and after exercise; and rating of perceived exertion every 5 minutes. Additionally, the following variables measuring exercise intensity were obtained for each session: average pedaling cadence (revolutions per minute [RPM]) and power output (watts) during warm-up, main exercise set, and cooldown; and total active exercise duration.

Gait Velocity

Gait data were collected during treadmill walking using the Computer Assisted Rehabilitation ENvironment (CAREN) (Motekforce Link) system and overground using the Zeno Walkway Gait Analysis System (ProtoKinetics) at both baseline time points, end of treatment (EOT), and 1 month after EOT (EOT+1). The primary efficacy outcome, comfortable gait velocity, was determined during a practice trial by gradually increasing treadmill speed on the CAREN system until the participant verbalized that they were at a comfortable pace, at which time treadmill speed was fixed and two 2-minute trials were completed. Overground gait velocity was measured using the Zeno instrumented walkway and included 2 self-paced and 2 fast-paced trials. Participants were permitted to use the handrails during treadmill trials and used preferred walking aides for overground walking trials.

Six-Minute Walk Test

The 6-minute walk test (6MWT) was used to assess overground walking capacity. Participants were asked to self-select a brisk but safe walking speed to cover their greatest distance along a 300-foot (91 meter) path in 6 minutes. Total distance traveled was obtained using a measuring wheel. For all overground walking assessments (Zeno and 6MWT), orthoses and walking aides were used according to the participant's preference for community mobility, remaining consistent across testing time points.

Statistical Analysis

Data from participants who completed the 12-week intervention were included in the analysis. Demographics, patient characteristics, exercise parameters, and gait outcomes were summarized by mean and standard deviation or median and interquartile range for continuous variables and count with percentage for categorical variables. Baseline 1 and baseline 2 outcomes were compared using paired sample *t* tests. As no statistically significant difference was observed between baseline values, baseline 2 values were used for subsequent analyses. To assess the effects of aerobic cycling on gait outcomes, values from baseline 2 to EOT were examined using paired sample *t* tests with groups collapsed. Outcomes measured at EOT were compared between groups in linear regression models; baseline values of outcomes were adjusted for in the models. Group differences in changes in exercise cadence over sessions were examined via mixed-effect models, where independent variables included session, group, and interaction between session and group; patient random effect was included in the model. Given that the results of this study were exploratory and hypothesis-generating, there were no adjustments for multiple comparisons; *P* values less than .05 were considered statistically significant, however, the preliminary focus was on the direction and magnitude of effect.

RESULTS

Enrollment and Tolerability

A total of 23 participants were enrolled in the study and 18 completed the intervention. Refer to the CONSORT diagram in **FIGURE S1** for details. Prior to randomization, 1 individual withdrew, citing excessive time commitment. Initial random assignment placed 12 participants in the FE cohort and 10 participants in the VE group. Given that the primary aim of this study was feasibility, accommodations related to group allocation were made for 2 participants. One individual (with EDSS 6.5) started in the VE group but did not have sufficient leg strength to continue and was reallocated to FE. Another participant who was initially assigned to FE was unable to tolerate the recumbent style of the bike due to ongoing radicular lower back pain and was reallocated to the VE intervention and used an upright cycle. Following these accommodations, 12 participants were still in the FE group and 10 were still in the VE group. Four individuals withdrew prior to completing the intervention, so 18 total (11 FE and 7 VE) participants completed EOT testing and were included in the analysis.

TABLE 1. Participant Demographics and Exercise Parameters

	Total (N = 18)	FE (n = 11)	VE (n = 7)	*P* value
Age	54.9 ± 10.6	53.6 ± 12.2	56.9 ± 7.9	
Sex				
Male	8 (44.4)	5 (45.5)	3 (42.9)	
Female	10 (55.6)	6 (54.5)	4 (57.1)	
Multiple sclerosis type				
Relapsing-remitting	10 (55.6)	6 (54.5)	4 (57.1)	
Primary progressive	1 (5.6)	0 (0)	1 (14.3)	
Secondary progressive with disease activity	3 (16.7)	2 (18.2)	1 (14.3)	
Secondary progressive without disease activity	4 (22.2)	3 (27.3)	1 (14.3)	
Expanded Disability Severity Scale	4.0 [3.5, 6.0]	4.0 [3.5, 6.0]	3.5 [3.0, 4.0]	
Average exercise duration	42.2 ± 2.3	42.2 ± 2.4	42.2 ± 2.4	.96
Average exercise cadence	67.3 ± 13.3	69.1 ± 11.1	64.5 ± 16.7	.50
Average percent of max heart rate	65 ± 7%	63 ± 7%	70 ± 5%	**.034**

Statistics presented as mean ± SD, median [Q1, Q3], N (%). P values based on 2-sample *t* test. Bold text denotes statistical significance at $P \leq .05$ based on paired *t* test.

Participant Demographics and Characteristics

TABLE 1 depicts participant demographics, characteristics, and exercise parameters stratified by group. Participants were, on average, 54.9 years of age; 44.4% were male; 55.6% presented with relapsing-remitting MS and 44.4% had progressive forms of MS. None of these patient characteristics (ie, age, sex, MS type) differed meaningfully across groups. The EDSS scores for participants ranged from 2.0 (indicates minimal disability) to 6.5 (indicates the requirement of constant bilateral assistance), with an overall median EDSS of 4.0. Of note, the FE group had slightly higher EDSS scores, with a median EDSS of 4.0 (75th percentile of 6.0) compared with a median EDSS of 3.5 (75th percentile of 4.0) in the VE group.

Exercise Parameters

Average session duration across all participants was 42.2 minutes (Table 1). The mean exercise session duration increased similarly from the 1st to the 24th session in both groups (**FIGURE S2A**). Importantly, on average, both groups

TABLE 2. Change in Motor Outcomes From Baseline to End of Treatment

Variable	n	Baseline	EOT	Mean difference (EOT-baseline)	SE	*P* value
Treadmill gait velocity (m/s)	17	0.61 (0.26)	0.68 (0.30)	0.07	0.03	**.010**
Overground gait velocity, SP (m/s)	17	0.91 (0.23)	0.93 (0.24)	0.02	0.03	.50
Overground gait velocity, FP (m/s)	14	1.25 (0.17)	1.32 (0.22)	0.07	0.04	.14
6MWT (m)	18	341.7 (115.2)	352.0 (116.1)	10.3	11.05	.37

6MWT, 6-minute walk test; EOT, end of treatment; FP, fast-paced velocity; SP, self-paced velocity.
Bold text denotes statistical significance at $P \leq .05$ based on paired *t* test.

met aerobic intensity goals of 60% to 80% of maximum HR, although the average percentage of maximum HR was higher in the VE group compared with the FE group (70 ± 5% vs 63 ± 7%, respectively; *P* = .034; Table 1). Although average exercise cadence across all 24 sessions was only slightly higher in the FE group compared with VE group (69.1 ± 11.1 RPM for FE and 64.5 ± 16.7 RPM for VE, *P* = .50, Table 1), the FE group increased their exercise cadence across the 24 sessions to a greater extent than the VE group (**FIGURE S2B**) (14.6 RPM total increase for FE vs 4.1 RPM increase for VE, *P* <.001).

Gait Outcomes

Mean treadmill walking speed increased significantly across the 12-week cycling intervention, from 0.61 meters per second (m/s) at baseline to 0.68 m/s at EOT, (*P* = .01, **TABLE 2**). Subsequent analysis showed somewhat greater improvement in treadmill walking speed in the FE group compared with the VE group (increase of 0.10 ± 0.10 vs 0.03 ± 0.11 m/s, respectively; *P* = .17), although baseline treadmill walking speed was somewhat lower in the FE group compared to the VE group (0.52m/s ± 0.08 vs 0.69 ± 0.13 m/s, respectively; *P* = .25). Notably, improvements in treadmill gait velocity remained relatively stable 4 weeks after the intervention (**FIGURE S3A**). After the intervention, all other gait outcomes (overground self-paced velocity, overground fast-paced velocity, and 6MWT distance) showed slight improvements from the baseline, although these improvements were not statistically significant (Table 1 and **FIGURES S3B-S3D**).

DISCUSSION

The primary aim of this pilot study was to assess the feasibility of applying intensive AEx in the form of FE and VE cycling as a therapeutic intervention for individuals with MS. The clinical symptoms of MS (eg, spasticity, weakness, fatigue, impaired balance) have been reported as barriers to physical activity, and, specifically, to intensive AEx. However, stationary cycling may provide a safe method of maintaining high levels of physical activity, particularly for individuals with compromised walking ability or postural instability. In our pilot trial, AEx was tolerated by participants who exercised at an average aerobic intensity of 65% of maximum HR, and no serious adverse events related to the intervention were reported. Furthermore, no relapses were reported throughout the study period, similar to previous findings that high-intensity exercise reduces MS disease activity.[7] Some participants reported transient weakness or fatigue lasting 1 to 2 hours after exercise sessions but noted rapid resolution of symptoms. Importantly, these transient symptoms did not impact their ability to complete routine instrumental activities of daily living, did not worsen mobility, and did not result in falls. Additionally, while the staff was prepared with cooling vests to manage episodic overheating due to the Uhthoff phenomenon, this was not experienced by any of the participants.

For this pilot clinical trial, one-on-one supervision was provided, and exercise parameters were progressed on an individual basis. Multiple study participants in both groups had initial difficulty maintaining neutral biomechanical leg alignment during cycling but worked with a physical therapist on accommodations, often using straps or elastic bandages to maintain proper leg alignment. Others experienced clonus or spasms, necessitating stretching prior to exercise sessions. These situations highlight the important role that rehabilitation therapists play when implementing exercise programs for people with complex neurologic impairments. After working through various barriers, participants successfully completed the intervention.

Critical lessons were learned regarding the application of FE or VE to individuals who present with varying levels of disability and comorbidities. For example, 1 individual who presented at an EDSS of 6.5 and was randomly assigned to the VE group was not able to generate sufficient volitional muscle action to pedal independently; this necessitated physical assistance from the therapist. Given our primary aim of feasibility, the participant, who was discouraged by the inability to fully participate, was reallocated to the FE group after 7 VE sessions. The individual was quickly able to tolerate full 45-minute sessions of FE, achieving an average aerobic intensity of 60% of maximum heart rate. Notably, the individual later acknowledged that they were going to withdraw from the study after the eighth VE session. However, after switching to FE, the participant reported considerable improvements in fatigue and homebased mobility by the end of the study, and they strongly advocated for continued FE as a therapeutic component for long-term symptom management. Future studies that include VE as an intervention arm could enroll individuals up to an EDSS of 6.0 to ensure the ability to participate in the randomized intervention.

In another instance of feasibility, a participant who was randomly assigned to FE and who presented with chronic radicular lower back pain was not able to tolerate the recumbent style of the FE bike. After 4 sessions, this individual was switched to VE, which was administered on an upright cycle ergometer (rather than recumbent); this participant tolerated the remainder of the sessions. Furthermore, the participant's average aerobic intensity during 4 sessions on the FE bike was 55.6% of max HR, and it increased to 66.1% during the remaining 20 sessions on the upright VE bike. Comfort and lack of radicular back pain were cited as the main reasons that this individual was able to exercise at a greater intensity when using the upright cycle. Of note, the participant purchased an identical upright cycle upon completion of the study, acknowledging self-observed benefits to sustained exercise. While these 2 instances compromised scientific rigor with respect to elucidating the differential effects of FE versus VE on gait outcomes, they provided valuable insight into variables that influence the tolerability of FE and VE interventions and will inform methods for future studies.

An unexpected complication in the trial was a high incidence of community-acquired COVID-19 infection among participants. During the December 2021 to February 2022 surge related to the Omicron variant, Cuyahoga County experienced the highest rates of COVID-19 in the country. At the time, data were just emerging that demonstrated that individuals with MS on DMTs had a less robust immune response to SARS-CoV-2 vaccines, resulting in breakthrough cases.[25] While not a requirement for participation, all enrolled participants were on DMTs and all had been vaccinated. Four participants (2 in each group) contracted COVID-19 during this surge and while enrolled in the study, which may have ultimately influenced efficacy outcomes. One FE participant was able to resume the study following the required isolation period; however, 2 VE participants withdrew citing considerable worsening of fatigue after the infection. The fourth (in the FE group) contracted the infection during the follow-up period, attending EOT+1 testing but presenting with worse function and symptoms compared to baseline, citing increased fatigue and pain after infection. The study duration (12 weeks) was too short to allow time for recovery and re-enrollment after infection, and in hindsight, enrollment targets were too low to overcome the impact of COVID-19 infections among participants. Future protocols should be designed to accommodate illness or other conditions that arise, allowing participants to recover and resume interventions in a more pragmatic manner.

CONCLUSIONS

As outlined above, FE (but not VE) was well tolerated by the participant with an EDSS of 6.5, and the recumbent bike position was not well tolerated in another individual with lumbar radicular pain. However, once accommodations based on these participant-specific issues were made (ie, allowing 2 randomized participants to switch groups), participants in both protocols tolerated intervention intensity, and exercise duration increased significantly over the course of the study in both groups. Likewise, both groups demonstrated increases in cycling cadence over the course of the study, although to a significantly greater extent in FE participants, which was expected given the motor assistance and programmed cadence targeting high-rate exercise. Similar to our previous studies employing FE in other disease populations, individuals with MS actively contributed to the exercise, achieving moderate-intensity aerobic training; thus, pedaling was not passive. Participants in both groups achieved the targeted aerobic intensity of 60% to 80% of maximum HR, but those in the VE group achieved a higher aerobic intensity of 70% compared to 63% by FE participants. The FE group presented with slightly higher levels of disability as measured by the EDSS, which may have contributed to the differences observed in aerobic intensity. Aerobic intensity remained relatively stable across the 24 sessions, indicating that individuals with MS can achieve moderate-intensity exercise relatively quickly, but training over 8 to 10 sessions was required for individuals to attain the targeted 45-minute exercise duration.

A significant improvement in the primary efficacy outcome, gait velocity, was observed across all participants during treadmill walking, with a nonsignificant trend toward greater improvements in the FE group compared with the VE group. This may be related to the somewhat lower baseline walking speeds (and higher EDSS levels) in the FE group and should be investigated further in future, appropriately powered studies.

While task specificity is considered important in motor learning, a transfer of training can occur between distinct motor tasks, with improvements in the performance of untrained tasks following the repetitive training of a different task with similar kinematic and spatiotemporal requirements.[26] Although cycling and walking are different motor tasks, both require the rapid reciprocal activation and relaxation of lower

PRACTICE POINTS

Individuals with multiple sclerosis across a wide disability range can exercise at a moderate-high intensity, although this may require novel paradigms (eg, forced-rate exercise) for individuals with higher levels of disability.

Skilled therapists play a key role in facilitating aerobic exercise for individuals with multiple sclerosis by customizing accommodations for individual impairments (eg, spasticity, incoordination, weakness) that may initially present as barriers.

extremity muscles in a synergistic, cyclical, and rhythmic manner.[26] In individuals with MS, diminished power, spasticity, and abnormal timing and coordination of muscle agonists and antagonists disrupt the modulation of phasic muscle activity, resulting in inefficient movement patterns during gait.[27] High cadence cycling may train muscles to work synergistically, ensuring smooth intra- and interlimb reciprocal activation, similar to activation patterns used to coordinate joint angle accelerations and decelerations during gait.[28,29]

The findings of our study are limited by the small sample that was unbalanced between groups. While this study was designed as an RCT with the intent to identify differential effects of FE and VE, the attrition rate was higher than expected due to COVID-19–related infections. Additionally, to obtain data on our primary outcome of feasibility, 2 participants were reassigned because both were motivated to continue the intervention but did not tolerate their original group allocations. This was seen as an opportunity to learn about how this intervention is feasible for individuals with MS who present with varying levels of disability, disease progression, disease type, and comorbidities that need to be considered for adoption in the real world. Lessons learned will be incorporated into future study designs; namely, (1) participants with EDSS scores greater than or equal to 6.5 cannot be expected to tolerate VE interventions, (2) improved screening to detect musculoskeletal comorbidities that may impact an individual's ability to participate is warranted, (3) studies with longer duration and more frequent interventions (3-5 times weekly for ≥ 6 months) are needed to test whether aerobic cycling can impact behavioral outcomes, and (4) mechanistic studies are needed to better understand how AEx impacts the CNS, which will lead to more targeted exercise prescription. ■

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