Effects of Functional Electrical Stimulation Cycling on Fatigue and Quality of Life in People with Multiple Sclerosis Who Are Nonambulatory

Deborah Backus, PT, PhD; Marina Moldavskiy, BS; W. Mark Sweatman, PhD, MBA

CME/CNE Information

Activity Available Online: To access the article, post-test, and evaluation online, go to http://www.cmscscholar.org.

Target Audience: The target audience for this activity is physicians, physician assistants, nursing professionals, rehabilitation professionals, and other health care providers involved in the management of patients with multiple sclerosis (MS).

Learning Objectives:

1) Discuss the rationale for functional electrical stimulation (FES) cycling for people with MS who are nonambulatory and use a wheelchair for mobility.
2) Describe an FES protocol that is safe and potentially effective for people with MS who are nonambulatory.

Accreditation Statement:

JOINT ACCREDITATION
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, this activity has been planned and implemented by the Consortium of Multiple Sclerosis Centers (CMSC) and Delaware Media Group. The CMSC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physician Credit: The CMSC designates this journal-based activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurse Credit: The CMSC designates this enduring material for 1.0 contact hour (none in the area of pharmacology).

Disclosures: **Francois Bethoux, MD,** Editor in Chief of the *International Journal of MS Care* (IJMSC), has served as Physician Planner for this activity. He has disclosed relationships with Springer Publishing (royalty), Qr8 (receipt of intellectual property rights/patent holder), Biogen (receipt of intellectual property rights/patent holder, speakers' bureau), GW Pharma (consulting fee), MedRhythms (consulting fee, contracted research), and Adamas Pharmaceuticals (contracted research). **Laurie Scudder, DNP, NP,** has served as Reviewer for this activity. She has disclosed no relevant financial relationships. **Deborah Backus, PT, PhD,** has disclosed no relevant financial relationships. **Marina Moldavskiy, BS,** has disclosed no relevant financial relationships. **W. Mark Sweatman, PhD, MBA,** has disclosed no relevant financial relationships. The peer reviewers for IJMSC have disclosed no relevant financial relationships. The staff at IJMSC, CMSC, and Delaware Media Group who are in a position to influence content have disclosed no relevant financial relationships. Note: Financial relationships may have changed in the interval between listing these disclosures and publication of the article.

Method of Participation:

Release Date: August 1, 2020
Valid for Credit Through: August 1, 2021

In order to receive CME/CNE credit, participants must:

1) Review the continuing education information, including learning objectives and author disclosures.
2) Study the educational content.
3) Complete the post-test and evaluation, which are available at http://www.cmscscholar.org

Statements of Credit are awarded upon successful completion of the post-test with a passing score of >70% and the evaluation. There is no fee to participate in this activity.

Disclosure of Unlabeled Use: This educational activity may contain discussion of published and/or investigational uses of agents that are not approved by the FDA. The CMSC and Delaware Media Group do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the CMSC or Delaware Media Group.

Disclaimer: Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any medications, diagnostic procedures, or treatments discussed in this publication should not be used by clinicians or other health care professionals without first evaluating their patients' conditions, considering possible contraindications or risks, reviewing any applicable manufacturer's product information, and comparing any therapeutic approach with the recommendations of other authorities.

Note: Supplementary material for this article is available at ijmsc.org.

DOI: 10.7224/1537-2073.2019-101

Background: Functional electrical stimulation (FES) cycling provides an exercise opportunity for people with multiple sclerosis (MS) who are nonambulatory. This study evaluated the efficacy of FES cycling for reducing fatigue and improving quality of life in people with MS who are nonambulatory and compared outcomes with those in a control group that did not take part in FES cycling.

Methods: Adults with MS with self-reported Expanded Disability Status Scale scores of 7.0 to 8.5 were randomized into a training group (n = 12) or a control group (n = 9). The training group performed FES cycling for 30 minutes, two to three times a week for 12 weeks. The primary outcome was safety, measured as the number and type of adverse events and any increase in symptoms. Other outcomes collected before and after the intervention were scores on the modified Ashworth Scale, manual muscle test, 5-item Modified Fatigue Impact Scale (MFIS-5), Fatigue Scale for Motor and Cognitive Functions (FSMC), Medical Outcomes Study Pain Effects Scale, Patient Health Questionnaire-9 (PHQ-9), Multiple Sclerosis Quality of Life–54 (MSQOL-54), and Exercise Self-Efficacy Scale.

Results: Twelve participants completed the study and were analyzed. Six participants completed training with no adverse events. The MFIS-5 (Cohen's d = 0.60), FSMC (Cohen's d = 0.37), and PHQ-9 (Cohen's d = 0.67) scores and the physical health composite of the MSQOL-54 (Cohen's d = 1.48) improved for the training group compared with the control group (n = 6).

Conclusions: Functional electrical stimulation cycling is safe for people with MS who are nonambulatory and may reduce fatigue and improve measurements of quality of life. ***Int J MS Care*. 2020;22: 193-200.**

People with multiple sclerosis (MS) who cannot safely ambulate more than household distances (ie, 25-100 feet) generally require a wheelchair or scooter for community mobility. Requiring a wheelchair leads to reduced physical activity, often to a point where it is detrimental to health.[1-5] Thus, people with MS who are nonambulatory can benefit from a means for increasing their physical activity. One way to increase physical activity is to exercise.[6,7] Evidence suggests that exercise is safe for people with MS and that participation in exercise may improve their health.[6,7] The preponderance of studies in people with MS focus on those who retain some ability to ambulate in the community. However, emerging evidence suggests that people with greater levels of disability, including those who use a wheelchair as their primary means of mobility, can safely exercise and, furthermore, may also benefit from increasing their activity.[8-21]

A major challenge for people who use wheelchairs is the barrier to exercise options.[22,23] Weakness, paralysis, spasticity, and fatigue often make it difficult to exercise at an intensity or duration that provides a sufficient exercise stimulus. Often it is difficult to access equipment for exercise due to the limitations of a wheelchair.[23] One intervention that shows promise for helping people with MS with severe mobility challenges achieve exercise is functional electrical stimulation (FES) cycling. This intervention combines the use of surface electrical stimulation with a motor-powered ergometer and is a potential exercise option for people with MS who are nonambulatory (Expanded Disability Status Scale [EDSS] score >6.5).[9,11,13,15,19,21]

Two recent reviews report the potential of FES cycling for reducing symptoms and improving the quality of life (QOL) for people with MS who have substantial mobility impairment.[19,20] However, both reports highlight the heterogeneity of participants in earlier studies (ie, including both those with MS who are ambulatory and nonambulatory), making it difficult to determine the specific effect on people with MS who are nonambulatory. Backus et al[13,15] reported that 14 people with MS, all of whom could not ambulate in the community and used a wheelchair for mobility, who took part in FES cycle training two to three times a week for 4 to 5 weeks (12 sessions total) not only did so without adverse events but also improved their cycling performance. Participants also demonstrated a significant decrease in the physical (P = .02) and psychosocial (P < .01) subscales of the Modified Fatigue Impact Scale (MFIS)[15] and showed improved muscle oxidative

From the Crawford Research Institute, Shepherd Center, Atlanta, GA, USA (DB, MM); and Sociology/Human Development and Aging Services, School of Liberal Arts, Georgia Gwinnett College, Lawrenceville, GA, USA (WMS). *Correspondence:* Deborah Backus, PT, PhD, Crawford Research Institute, Shepherd Center, 2020 Peachtree Rd NW, Atlanta, GA 30309, USA; e-mail: Deborah.backus@shepherd.org.

capacity.[13] Including exclusively nonambulatory people with MS helps us better understand the impact of FES cycling, and exercise in general, for people with MS who use a wheelchair for mobility. What remains unknown from the earlier studies is whether the exercise stimulus was sufficient or whether extended training would facilitate more meaningful effects related to symptoms, function, or QOL. A study with a greater dosage of FES cycling would provide important information related to the potential for FES cycling to induce significant effects in people with MS who are nonambulatory. Fornusek et al[11] reported that people with MS and severe disability could safely perform FES cycling one to two times a week for 10 weeks, suggesting that they can exercise in this way for a longer duration.

Scally et al[19] and Edwards and Pilutti[20] also highlighted the need for randomized controlled trials evaluating the efficacy of FES cycling in people with severe disability. Given that MS is a chronic and progressive condition, a lack of decline in function or no increase in symptoms can be meaningful. For example, being able to exercise without an increase in fatigue is meaningful. An improvement in a symptom such as fatigue, spasticity, or pain after an intervention can be clinically significant if those who do not take part in the intervention either remain unchanged or experience worsening of symptoms. Comparing outcomes between people with MS who are nonambulatory and participate in an FES cycling intervention and those who do not receive the intervention is warranted. The purpose of this study was to evaluate and compare the safety and potential efficacy of 12 weeks of FES cycling for reducing fatigue and improving QOL in people with MS who are nonambulatory (self-reported EDSS scores of 7.0-8.5) and those who did not take part in FES cycle training.

Methods

This was a pilot randomized controlled trial with a pre-post design conducted in the clinical space of a not-for-profit long-term acute care facility. All the procedures were approved by the research review committee of the Shepherd Center (Atlanta, Georgia) before the start of study activities. The principal investigator (D.B.), a licensed physical therapist, oversaw all aspects of the study. A trained and blinded (to group assignment) physical therapist performed all assessments, and two trained exercise staff (M.M. and one other) oversaw all FES cycle training sessions.

Participants

All the participants provided written informed consent before starting study activities. Participants were recruited via flyers, referrals from providers in the MS clinic, and at local MS-related events (eg, National MS Society walks or support group activities). Eligible individuals were at least 18 years of age, physician diagnosed as having MS, nonambulatory (ie, used a wheelchair for indoor and outdoor mobility [EDSS score >6.5]), and experiencing fatigue as indicated on the Fatigue Severity Scale (ie, mean score >2.3, the mean in healthy adults).[24] Participants were excluded if they had any neuromuscular, musculoskeletal, or cardiovascular injury or disease or any condition that prevented them from safely exercising on the FES cycle, such as an existing pacemaker, defibrillator, or other implanted electronic or metallic device (other than a Baclofen pump); had unstable long bone fractures of the lower limb or trunk; had allergy to surface electrodes or conductive gel; or could not tolerate sitting for at least 1 hour. Individuals were also excluded if they had experienced a diagnosed relapse in the past 6 months or if electrical stimulation could not elicit a muscle contraction.

Procedures

Once enrolled in the study, each participant was randomly assigned to either the training group or the control group (Figure S1, which is published in the online version of this article at ijmsc.org). Those in the training group took part in a 12-week FES cycle training intervention as described later herein. Those in the control group completed a 12-week wait period during which they were encouraged to keep their activities and medications constant and completed the same data collection procedures as the training group.

FES Cycle Training Intervention

The training group trained on the RT300 FES cycle (Restorative Therapies Inc, Baltimore, MD) while seated in their wheelchair. Trained exercise staff assisted each participant in applying the surface electrodes over the muscle bellies of the gluteus maximus, hamstrings, and quadriceps bilaterally and safely positioning the participant's lower limbs on the pedals of the RT300 device. Participants cycled volitionally with assistance from the electrical stimulation as needed and with oversight for safety by the exercise staff. The goal was for participants to train three times a week for approximately 12 weeks (36 sessions).

The FES cycling protocol was based on previous research demonstrating that participants can perform cycling with the parameters established, and in some cases demonstrated improvements in FES cycling performance.[13,15] Each session comprised three phases: a 2-minute passive warm-up phase (no volitional cycling or electrical stimulation), followed by a 30-minute active phase (volitional cycling or assisted with electrical stimulation), and ending with a 2-minute passive cycling cool-down phase. During the passive phases, the ergometer propelled the pedals at 35 rpm, and during the active phase, the goal was for the participant to achieve a target cycling speed of 35 to 50 rpm. The stimulation parameters for this study were also predetermined based on an earlier pilot study[13,15]: pulse width of 200 microseconds and frequency of 50 Hz. The stimulation intensity varied based on the par-

ticipant's tolerance and the amount of stimulation required to achieve the target cycling speed.

Once a participant could pedal actively, either volitionally or assisted with stimulation, for 30 minutes at 35 to 50 rpm for three consecutive sessions without defaulting to the passive mode, resistance was added in 0.14-Nm increments. Each participant progressed at their own rate. The exercise staff monitored the participant during and immediately after each session for reports of fatigue, pain, and spasticity, or any other changes in MS symptoms. Data on FES cycling performance, including active time, amount of stimulation, resistance, and distance, were collected throughout the session and analyzed offline.

Outcome Measures

The primary outcome measure was safety, measured by the number and type of adverse events and any increase in symptoms that remained or worsened between sessions. The exercise staff overseeing each FES cycling session documented participant self-report of fatigue, pain, and spasticity at the beginning and end of each session using the visual analog scales for fatigue, pain, and spasticity. Each used a Likert scale to rate the symptom, with 0 meaning absence of the symptom and 10 meaning severe perception of the symptom.

One concern related to the safety of FES cycling for people with MS is that exercise, and specifically using FES in the lower limbs, might lead to an increase in spasticity or a worsening in lower limb muscle function or weakness. Thus, the secondary outcome was detriment in lower extremity function during the study, measured as an increase in spasticity or a decrease in strength in the lower limbs. Within 1 week of the start of and 1 week after the intervention phase, a trained physical therapist performed the modified Ashworth Scale[25] to assess spasticity and a manual muscle test[26] to assess strength in the lower limbs. The physical therapist scored bilateral hip flexors, adductors, and extensors; knee flexors and extensors; and ankle dorsiflexors and plantarflexors each separately (scores from 0 = no increase in resistance to movement to 4 = limb is rigid) and calculated a total modified Ashworth Scale score for each limb. Similarly, the physical therapist assessed the bilateral iliopsoas, gluteus maximus, quadriceps, hamstring, gastrocnemius/soleus, and anterior tibialis anterior muscles for strength; assigned a grade of 0, 1, 2, 3, 4, or 5 to each; and calculated a total for each limb.

Tertiary exploratory outcomes comprised the efficacy of FES cycle training for improving fatigue and QOL, measured using participant-reported outcome measures before training (pretest) and within 1 week after completion of all training sessions (posttest). All participant-reported outcome measures are used with and validated for people with MS.[27,28] Participants completed the five-item MFIS (MFIS-5)[27,28] and the Fatigue Scale for Motor and Cognitive functions (FSMC)[29] to assess fatigue; the Medical Outcomes Study Pain Effects Scale[27,28] to assess pain; the Patient Health Questionnaire-9 (PHQ-9)[30] objectifying depression severity; and the 54-item MS Quality of Life measure (MSQOL-54)[31] to assess QOL. The MSQOL-54 is an MS-specific health-related QOL instrument comprising the 36-item Short Form Health Survey supplemented by 18 MS-specific symptom measures, including fatigue, pain, bladder function, bowel function, emotional status, perceived cognitive function, visual function, sexual satisfaction, and social relationships. Confidence related to exercise was measured using the Exercise Self-Efficacy Scale.[32]

Data Analysis

Statistical analysis was performed using Microsoft Excel (Microsoft Inc. Redmond, WA) and IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY). Descriptive analyses were performed to determine means, change scores, and percentage change for each outcome measure.

Given the size of the sample, inferential statistics were not used. Instead, effect size was determined using Cohen's *d* formula for dependent, single-group, and pre-post change.[33,34] An effect size of 0.2 is considered small; 0.5, medium; and 0.8, large. An effect size below 0.2 is considered not meaningful.

Results

Participants

Of 84 people with MS screened for eligibility, 21 met the inclusion criteria and were enrolled in the study; 12 were randomized to the training group and nine to the control group (Figure S1). Twelve of 21 participants completed the study, six participants each in the training group and control group. All the participants indicated some level of fatigue on the Fatigue Severity Scale (mean ± SD score, 4.44 ± 1.34). See Table 1 for demographic characteristics of participants who completed the trial.

FES Cycling Performance

Table S1 presents a summary of the FES cycling performance outcomes. Two of the six participants started the training able to actively cycle 30 minutes, either volitionally or with assistance from FES. One participant could cycle only approximately 21 minutes at the beginning of the intervention, and another could cycle only approximately 8 minutes, but both increased their time to 30 minutes of active cycling by the end of the intervention. The other two participants remained the same in their cycling time (<3 minutes). Those who could cycle for 30 minutes by the end of training increased their average resistance by approximately 116% and distance cycled by approximately 108%. Those who could not cycle 30 minutes did not receive resistance and did not increase their distance cycled.

All but one participant completed 36 (100%) of the required training sessions. There was one protocol deviation for a participant who completed 37 training sessions because of an error in scheduling.

***Table 1.* Participant demographic characteristics**

Characteristic	Total (N = 12)	Training group (n = 6)	Control group (n = 6)
Sex, No. (%)			
Male	5 (42)	3 (50)	2 (33)
Female	7 (58)	3 (50)	4 (67)
Age, y			
Mean ± SD	55.42 ± 10.33	56.17 ± 10.01	54.67 ± 11.55
Range	39-70	46-70	39-65
Race, No.			
White	5	2	3
Black	7	4	3
Type of MS, No.			
Relapsing-remitting	3	2	1
Secondary progressive	4	3	1
Not specified	5	1	4
Fatigue Severity Scale score			
Mean ± SD	4.44 ± 1.34	3.90 ± 0.98	4.98 ± 1.51
Range	2.4-6.6	2.9-5.6	2.4-6.6
ESES score			
Mean ± SD	28.92 ± 6.01	29.00 ± 5.02	28.83 ± 7.36
Range	17-37	21-35	17-37
MOS Pain Effects Scale score			
Mean ± SD	13.42 ± 6.50	12.17 ± 8.23	14.67 ± 4.63
Range	6-25	6-25	6-18
EDSS score, No.			
7.0	6	3	3
7.5	3	2	1
8.0	1	1	0
8.5	2	0	2
EDSS score median	7.2	7	7.5

Abbreviations: EDSS, Expanded Disability Status Scale; ESES, Exercise Self-Efficacy Scale; MOS, Medical Outcomes Study; MS, multiple sclerosis.

Primary Outcome: Safety

Six adverse events occurred during the study, five in the training group and one in the control group; none of these adverse events were related to the intervention. Two adverse events in the training group occurred in the same participant and were due to a preexisting leg decubitus that reopened during the intervention phase of the study. Shortly after her first enrollment the participant attended her FES cycle session after a weekend without training and the exercise staff noted the opening of the wound when setting the participant up on the FES cycle. Training was ceased and the participant was referred to the wound care specialist. This participant was re-enrolled during the second year of the trial after receiving clearance from the wound specialist and the physician. The wound reopened and the participant was subsequently dropped from the study. The study team as well as the medical team concluded that the wound did not result from the study protocol because it was sustained before the study, the support straps for the FES cycle pedals were neither on top of nor near the wound site, and the wound was not undergoing stress with the cycling motion.

The other three adverse events in the training group included a small wound on the bottom of a participant's foot, a knee injury sustained at home while playing with a child, and pseudo-relapse that occurred when the participant was not training over the holidays and that seemed to be related to a urinary tract infection and other medical issues. The adverse event in the control group was a relapse. All adverse events resulted in the participants being withdrawn from the study (Figure S1).

For participants who completed the intervention (n = 6), there was minimal change in mean ± SD visual analog scale scores for fatigue (–0.01 ± 1.10), pain (0.40 ± 0.68), or spasticity (0.51 ± 0.84) over the 12 weeks.

Secondary Outcome: Lower Limb Function

There was minimal change in mean ± SD modified Ashworth Scale scores (left = –0.50 ± 5.06; right = –0.80 ± 5.83) and mean ± SD manual muscle test scores (left = –0.10 ± 1.20; right = 1.10 ± 1.85) after the intervention phase.

Tertiary and Exploratory Outcomes: Participant-Reported Outcomes

Table 2 presents fatigue, pain, and depression scores. Four of the six training group participants and three of the six control group participants experienced a decrease in fatigue on the MFIS-5. One participant in each group

***Table 2.* Participant-reported outcomes: change scores for training and control groups**

Outcome measure	Change score, mean ± SD		Effect size
	Training group (n = 6)	Control group (n = 6)	
5-Item MFIS score	–2.50 ± 4.55	0.17 ± 4.36	0.60
FSMC			
Total score	–4.67 ± 4.13	–2.17 ± 8.54	0.37
Cognitive score	–2.50 ± 3.39	–1.50 ± 3.39	0.29
Motor score	–2.17 ± 3.54	–0.67 ± 5.82	0.31
MOS Pain Effects Scale score	–0.50 ± 6.28	–1.00 ± 2.53	0.10
PHQ-9 score	0.33 ± 2.42	–2.50 ± 5.47	0.67

Abbreviations: FSMC, Fatigue Scale of Motor and Cognitive Functions; MFIS, Modified Fatigue Impact Scale; MOS, Medical Outcomes Study; PHQ-9, Patient Health Questionnaire-9.

experienced an increase, and the others had no change. Overall, there was a moderate effect size between the two groups for change in fatigue as measured using the MFIS-5 (Cohen's d = 0.60). There was no meaningful difference between the groups on the FSMC total (Cohen's d = 0.37) or cognitive (Cohen's d = 0.29) and motor (Cohen's d = 0.31) subscores. Five of the six participants in the training group had a decrease in FMSC total scores, and one had no change. Four of the six participants in the control group had a decrease in FMSC total scores, and two an increase.

There also was no meaningful difference between the groups on the Pain Effects Scale (Cohen's d = 0.10); on average, the scores for both groups decreased.

Higher scores on the PHQ-9 indicate greater depression. Nine of the 12 participants reported depression at the start of the study. Four had scores in the minimal range (≤5) and three in the mild range (5-9) that did not change outside of this range after the intervention. Two participants, one in each group, indicated moderate depression, with a PHQ-9 score of 13 before the intervention. Both reported a decrease after the intervention; the one in the training group decreased to the moderate range (score, 9), and the participant in the control group decreased to no depression. Overall, there was a moderate effect size (Cohen's d = 0.67) between groups, with the control group decreasing by an average of 2.5 points, changing from mild to minimum depression. This change in the control group seemed to be largely driven by the one control participant who had a 13-point change in the PHQ-9 score after the intervention. When calculated without that participant, there was no effect of group (Cohen's d = 0.03).

The MSQOL-54 subscores and physical and health composite scores are shown in Table S2. There was a large effect on the physical health (Cohen's d = 0.85), health perception (Cohen's d = 1.12), health distress (Cohen's d = 1.22), and physical health composite (Cohen's d = 1.48), with the training group improving and the control group declining. Similarly, there was a large effect of training on the physical composite of the PHQ-9 (Cohen's d = 0.76), with the training group increasing a mean ± SD of 2.57 ± 5.71 and the control group decreasing 1.07 ± 3.72. There was no effect on the mental composite scores of the PHQ-9.

There was a medium effect (Cohen's d = 0.46) of training on participants' reports of exercise self-efficacy, with a greater increase in mean ± SD Exercise Self-Efficacy Scale scores for the training group (1.67 ± 1.94) than the control group (0.33 ± 2.94).

Discussion

To our knowledge, this is the first randomized controlled trial evaluating the impact of FES cycling exclusively in people with MS who are nonambulatory. This is important because previous FES cycle trials have included people who can walk community distances, and the findings for people with severe weakness or paralysis are likely to be entirely different. Understanding the unique needs of people with MS who are nonambulatory will more likely lead to developing and implementing interventions and exercise options to meet their specific needs. For example, people who can walk typically can access exercise interventions and do not require specialized equipment to meet the minimum suggested guidelines for physical activity.[35] Notably, similar to earlier studies, there were no adverse events associated with FES cycle training in this study, and no increase in MS-related spasticity, fatigue, or pain.[18,19] Similar to earlier studies of FES cycling in people with MS who primarily use a wheelchair for mobility,[10,13,15] most participants in the training group (four of six) improved in their FES cycling performance, suggesting that they have the capacity for change in neuromuscular conditioning and control.

Participants in the training group did not have an increase in fatigue during or after a training session, suggesting that the intervention is tolerable as delivered for these participants. That they also experienced a decrease in fatigue at the end of the intervention phase is similar to our earlier findings that participants who completed FES cycle training experienced a reduction in fatigue.[13,15] Participants in the control group experienced an increase in fatigue on the MFIS-5 at the end of the 12-week wait period and only a slight reduction on the FSMC score. These findings suggest that FES cycling may reduce fatigue in people with MS who are nonambulatory and, therefore, might be a beneficial intervention for those who are experiencing fatigue. This requires further study to understand the extent of the benefit and the potential mechanism of this fatigue in people with MS who are nonambulatory.

The large difference in the QOL scores between the groups, with the training group having an increase in physical composite scores on both the MSQOL-54 and the PHQ-9 and the control group having a decrease, is meaningful but in contrast to earlier FES cycling

studies.[15,19] This discrepancy could be due to the use of different outcome measures or due to the dosing and parameters of FES cycle training in these studies. Nonetheless, these findings suggest that FES cycling may improve physical measures of QOL in people with MS who are nonambulatory and requires further study.

The findings from this study are similar to others showing that people with severe disability due to MS can exercise safely and can experience a reduction in symptoms and an improvement in their QOL when they exercise safely.[20] For instance, people with EDSS scores of 7.0 to 8.0 who exercise via aerobic exercise training[12] or total-body recumbent stepping[14] experience a reduction in fatigue and improvements in QOL. These findings taken together provide compelling evidence that people with MS who are nonambulatory can not only exercise without detriment but also experience improvements in symptoms and QOL. Although the findings reported herein may not be specific to FES cycling, it is important to consider that FES cycling is an intervention that provides a way for people with severe weakness or paralysis to exercise who otherwise might not be able to do so. Comparing the impact of other interventions, such as electrical stimulation alone, upper extremity exercise, resistance training, or bodyweight-supported treadmill training, with FES cycling outcomes in this population would be useful for understanding what is required for people with MS who are nonambulatory to benefit from exercise interventions.

Some limitations of this study should be considered when interpreting the findings. The size of the trial is small (n = 12). However, the findings support those from other studies and provide evidence that warrants further investigation in a larger randomized or pragmatic trial. There was also considerable dropout from this trial. Although a concern, it is notable that the dropout was not due to the training itself. Specifically, participants did not drop out of the study because of a lack of desire to train. The reasons for dropout are those common to people with chronic disabling conditions such as MS, eg, comorbidities and medication changes and requiring special transportation because of using a wheelchair for mobility. This highlights the importance of finding accessible exercise interventions for people with MS who are nonambulatory.[36] Furthermore, these exercise options need to be available in settings closer to, or even in, the person's home to overcome the barrier of transportation. Also notable is that the participants who stayed in the trial attended all the sessions. Thus, retention was high in participants who did not experience the complications of MS and disability. This also suggests that participation in this trial was meaningful to participants.

In conclusion, FES cycling is a safe and potentially beneficial intervention for exercise and increasing physical activity, as well as reducing fatigue and improving some measures of QOL, in people with MS who are nonambulatory. Further research will provide insights into how to best use this intervention to optimize outcomes in people who otherwise are limited in their ability to access interventions to improve function, health, and overall QOL. □

PRACTICE POINTS

- Individuals with MS who are nonambulatory and train on a functional electrical stimulation cycle can experience less fatigue and improvements in quality-of-life measurements.
- People with MS who use wheelchairs for mobility can meet recommendations for exercise using a functional electrical stimulation cycle to train two to three times a week.

Financial Disclosures: The authors declare no conflicts of interest.

Funding/Support: Funding for this project was provided by the National Multiple Sclerosis Society and supplemented by private donations to the Shepherd Center.

References

1. Gulick EE, Goodman S. Physical activity among people with multiple sclerosis. *Int J MS Care*. 2006;8:121-129.
2. Vanner EA, Block P, Christodoulou CC, Horowitz BP, Krupp LB. Pilot study exploring quality of life and barriers to leisure-time physical activity in persons with moderate to severe multiple sclerosis. *Disabil Health J*. 2008;1:58-65.
3. Motl RW. Physical activity and irreversible disability in multiple sclerosis. *Exerc Sport Sci Rev*. 2010;38:186-191.
4. Beckerman H, de Groot V, Scholten MA, Kempen JC, Lankhorst GJ. Physical activity behavior of people with multiple sclerosis: understanding how they can become more physically active. *Phys Ther*. 2010;90:1001-1013.
5. Klaren RE, Motl RW, Dlugonski D, Sandroff BM, Pilutti LA. Objectively quantified physical activity in persons with multiple sclerosis. *Arch Phys Med Rehabil*. 2013;94:2342-2348.
6. Motl RW, Pilutti LA. The benefits of exercise training in multiple sclerosis. *Nat Rev Neurol*. 2012;8:487-497.
7. Vollmer T, Benedict R, Bennett S, et al. Exercise as prescriptive therapy in multiple sclerosis: a consensus conference white paper. *Int J MS Care*. 2012;14:2-14.
8. Giesser B, Beres-Jones J, Budovitch A, Herlihy E, Harkema S. Locomotor training using body weight support on a treadmill improves mobility in persons with multiple sclerosis: a pilot study. *Mult Scler*. 2007;13:224-231.
9. Szecsi J, Schlick C, Schiller M, Pöllmann W, Koenig N, Straube A. Functional electrical stimulation-assisted cycling of patients with multiple

sclerosis: biomechanical and functional outcome: a pilot study. *J Rehabil Med*. 2009;41:674-680.
10. Pilutti LA, Lelli DA, Paulseth JE, et al. Effects of 12 weeks of supported treadmill training on functional ability and quality of life in progressive multiple sclerosis: a pilot study. *Arch Phys Med Rehabil*. 2011;92:31-36.
11. Fornusek C, Hoang P. Neuromuscular electrical stimulation cycling exercise for persons with advanced multiple sclerosis. *J Rehabil Med*. 2014;46:698-702.
12. Skjerbæk AG, Næsby M, Lützen, K, et al. Endurance training is feasible in severely disabled patients with progressive multiple sclerosis. *Mult Scler*. 2014;20:627-630.
13. Reynolds M, McCully K, Burdett B, Manella C, Hawkins L, Backus D. Pilot study: evaluation of the effect of functional electrical stimulation cycling on muscle metabolism in nonambulatory people with multiple sclerosis. *Arch Phys Med Rehabil*. 2015;96:627-632.
14. Pilutti LA, Paulseth JE, Dove C, Jiang S, Rathbone MP, Hicks AL. Exercise training in progressive multiple sclerosis: a comparison of recumbent stepping and body weight–supported treadmill training. *Int J MS Care*. 2016;18:221-229.
15. Backus D, Burdett B, Hawkins L, Manella C, McCully K, Sweatman M. Outcomes after functional electrical stimulation cycle training in individuals with multiple sclerosis who are nonambulatory: a pilot study. *Int J MS Care*. 2017;19:113-121.
16. Edwards T, Motl RW, Sebastião E, Pilutti LA. Pilot randomized controlled trial of functional electrical stimulation cycling exercise in people with multiple sclerosis with mobility disability. *Mult Scler Relat Disord*. 2018;26:103-111.
17. Pilutti LA, Edwards T, Motl RW, Sebastião E. Functional electrical stimulation cycling exercise in people with multiple sclerosis: secondary effects on cognition, symptoms, and quality of life. *Int J MS Care*. 2019;21:258-264.
18. Pilutti LA, Motl RW. Functional electrical stimulation cycling exercise for people with multiple sclerosis. *Curr Treat Options Neurol*. 2019;21:54.
19. Scally JB, Baker JS, Rankin J, Renfrew L, Sculthorpe N. Evaluating functional electrical stimulation (FES) cycling on cardiovascular, musculoskeletal and functional outcomes in adults with multiple sclerosis and mobility impairment: a systematic review. *Mult Scler Relat Disord*. 2020;37:101485.
20. Edwards T, Pilutti LA. The effect of exercise training in adults with multiple sclerosis with severe mobility disability: a systematic review and future research directions. *Mult Scler Relat Disord*. 2017;16:31-39.
21. Williams J, Moldavskiy M, Bauer K, et al. Safety and feasibility of various functional electrical stimulation cycling protocols in individuals with multiple sclerosis who are non-ambulatory. *Arch Rehabil Res Clin Transl*. 2020;2:100045.
22. Learmonth YC, Rice IM, Ostler T, Rice LA, Motl RW. Perspectives on physical activity among people with multiple sclerosis who are wheelchair users: informing the design of future interventions. *Int J MS Care*. 2015;17:109-119.
23. Rimmer JH, Riley B, Wang E, Rauworth A, Jurkowski J. Physical activity participation among persons with disabilities: barriers and facilitators. *Am J Prev Med* 2004;26:419-425.
24. Grace J, Mendelsohn A, Friedman JH. A comparison of fatigue measures in Parkinson's disease. *Parkinsonism Relat Disord*. 2007;13:443-445.
25. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther*. 1987;67:206-207.
26. Kendall FP, McCreary EK, Provance PG, Rodgers MM, Romani WA. *Muscle Testing and Function with Posture and Pain*. 5th ed. Lippincott Williams & Wilkins; 2005.
27. Ritvo P, Fischer JS, Miller DM, Andrews H, Paty DW, LaRocca NG. *MSQLI—Multiple Sclerosis Quality of Life Inventory: A User's Manual*. National Multiple Sclerosis Society; 1997.
28. Rudick R, Antel J, Confavreux C, et al. Recommendations from the National Multiple Sclerosis Society clinical outcomes assessment task force. *Ann Neurol*. 1997;42:379-382.
29. Penner IK, Raselli C, Stocklin M, Opwis K, Kappos L, Calabrese P. The Fatigue Scale for Motor and Cognitive Function (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler*. 2009;15:1509-1517.
30. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire (PHQ-9): validity of a brief depression severity measure. *J Gen Int Med*. 2001;16:606-613.
31. Vickrey B. *MSQOL-54-Multiple Sclerosis Quality of Life Instrument*. National Multiple Sclerosis Society; 1995.
32. McAuley E. Self-efficacy and the maintenance of exercise participation in older adults. *J Behav Med*. 1993;16:103-113.
33. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Academic Press; 1988.
34. Durlak J. How to select, calculate, and interpret effect sizes. *J Pediatr Psychol*. 2009;34:917-928.
35. Latimer-Cheung AE, Ginis KA, Hicks AL, et al. Development of evidence-informed physical activity guidelines for adults with multiple sclerosis. *Arch Phys Med Rehabil*. 2013;94:1829-1836.
36. Backus D. Increasing physical activity and participation in people with multiple sclerosis: a review. *Arch Phys Med Rehabil*. 2016;97:S210-S217.