ACUTE METABOLIC RESPONSE TO FUNCTIONAL ELECTRICAL STIMULATION CYCLING IN PEOPLE WITH MS WITH SEVERE MOBILITY IMPAIRMENTS

BY

THOMAS EDWARDS

THESIS

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Advisor:

Adjunct Professor Lara A. Pilutti

ABSTRACT

Persons with multiple sclerosis (MS) with severe mobility impairment have low levels of cardiorespiratory fitness (CRF). Exercise training is one strategy for improving CRF, however there are limited modalities for safely and effectively increasing CRF in individuals with MS with severe disability. In this thesis a systematic review of literature pertaining to exercise training and individuals with MS with severe disability was conducted. This review evaluated the effectiveness of said interventions for improving physical fitness and improving physical function. After this systematic review, a cross sectional analysis was done in order to characterize the acute metabolic demand associated with functional electrical stimulation (FES) cycling. Eleven participants with MS that required assistance for ambulation completed a session of either FES cycling or passive leg cycling. Oxygen consumption (VO_2), heart rate (HR), and work rate (WR) were recorded during the session. It was determined that FES cycling elicited had acute metabolic demand that corresponded with moderate-to-vigorous exercise intensity and this response was significantly more intense than passive leg cycling alone. This suggests that FES cycling can elicit a sufficient cardiorespiratory stimulus for improving CRF in people with severe MS.

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Chapter 1

Review of Current Literature

1.1 INTRODUCTION

Multiple sclerosis (MS) is the most prevalent demyelinating, neurological disease and is the most common non-traumatic cause of neurological disability in young adults[1]. The disease is characterized by chronic inflammation, demyelination and neurodegeneration within the central nervous system (CNS) resulting in lesion development[2]. The initial stage of MS involves inflammatory attacks which target the neurons of the CNS, resulting in damage to the myelin sheath and surrounding oligodendrocytes. The intact myelin sheath accelerates interneuron electrical impulses, optimizing neurotransmission. Oligodendrocytes are responsible for the development and repair of the myelin sheath.[2] As inflammatory attacks persist, damage to these neurological structures become seemingly irreversible[2]. The location and extent of damage to these structures manifests in neurological and functional impairments, including walking dysfunction, muscle weakness, spasticity, fatigability, balance dysfunction, impaired cognition, and depression[3–7]. As the disease progresses, the inflammatory attacks on neurological structures become less frequent. However, immune cells continue to deteriorate myelin resulting in chronic elevated neurological inflammation. Indeed, in the later stages of MS there is often a shift in pathology from an inflammatory disease (characterized clinically by acute exacerbations or relapses) to more a neurodegenerative disease (characterized clinically by progressive worsening of neurological symptoms)[2]. This is particularly important as the progressive deterioration of neurological structures is the underlying disease mechanism that contributes to irreversible damage and loss of neurons, resulting in greater impairment and disability[2,8].

The prevalence of MS varies considerably with geography, with the greatest prevalence observed in the northern hemisphere. Indeed, the highest prevalence of MS is found in North America and Europe (>100/100,000 inhabitants) while in Eastern Asia and sub-Saharan Africa the prevalence is much lower (2/100,000 inhabitants)[9]. These discrepancies suggest that environmental factors potentially influence the development of MS. Decreased levels of vitamin D with increasing latitude has been suggested as one explanation for the increased prevalence of MS in northern countries. It is thought that individuals living in northern countries experience less exposure to sunlight based vitamin D[10]. However, it is important to note that the prevalence of MS in geographical areas in the southern hemisphere are lower than higher locations in the northern hemisphere, despite comparable sunlight exposure[10]. Other proposed environmental risk factors for developing MS are infection and smoking, however, these factors require further invesgation[9].

In addition to environmental risk factors there are important genetic risk factors that influence MS. Firstly, sex is an important risk factor related to the development of MS with a ratio of 2.3-3.5 women being diagnosed for every male diagnoses, potentially a result of different genetic expression of men and women[11]. Ethnicity is another genetic risk factor that influences the development of MS. A higher prevalence of MS has been observed in non-Hispanic whites compared to other ethnic groups[9], but this has been disputed by other studies suggesting a higher prevalence in African Americans[12]. Furthermore, numerous genes have been identified as MS susceptibility genes, that are thought to predispose certain individuals to develop MS[13].

1.2 CLASSIFICATION

The pathogenesis of the disease is classified into four types of MS: relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), primary-progressive MS (PPMS) and progressive-relapsing MS (PRMS)[2]. The most common type of MS is RRMS, which accounts for roughly 85% of initial diagnoses[14]. RRMS is characterized by episodic inflammatory attacks (commonly referred to as relapses), and periods between relapses (commonly referred to as remissions)[15]. During a relapse, an individual typically experiences an exacerbation of symptoms in addition to a new, unexplained neurologic symptom for more than 24 hours[15]. Unfortunately, a relapse can cause permanent damage to the neurological structures, resulting in increased symptom severity. However, as the disease progresses the disease course may change and most individuals diagnosed with RRMS eventually transition to SPMS. Importantly, SPMS differs from RRMS as relapses and increased inflammation become less prevalent and disease progression becomes more gradual, resulting in ongoing, progressive neurodegeneration. This neurodegeneration manifests as greater functional impairment, more severe disability and worsening symptology[16,17]. PPMS involves a similar disease course as SPMS, except the gradual disease progression at diagnosis[17]. Indeed, individuals with PPMS experience continuous disease progression and symptom accumulation, instead of the relapse-remission pattern overserved in RRMS. Furthermore, damage and lesions are also more common in the spinal cord in PPMS compared to with RRMS[17]. According to the National Multiple Sclerosis Society, roughly 10% of persons with MS have PPMS at diagnosis[14]. The least prevalent form of MS (~5% of diagnoses) is PRMS. The disease course of PRMS is similar to PPMS, as individuals with PRMS experience gradual disease progression and disability accumulation, while also experiencing periodic exacerbations of symptoms (relapses)[17].

1.3 DISABILITY MEASUREMENT

The most common measure of clinical disability for individuals with MS is the Expanded Disability Status Scale (EDSS)[18]. The EDSS is a scale designed to quantify neurological disability experienced by individuals with MS through assessments of seven functional systems (FS) including visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, and cerebral, and ambulatory ability. The scale ranges from 0 (no disability) to 10 (death). Typically, 0.0-3.0 on the EDSS is indicative of minimal (mild) disability and patients in this EDSS range have minimal physical impairments, but may experience other symptoms associated with MS (e.g. fatigue, vision, sensation impairment). EDSS scores of 3.0-5.5 can be considered moderate and individuals experience ambulatory impairment and compromised gait, but no assistive device is necessary for ambulation. Additionally, symptoms experienced have a greater impact on the individual. Lastly, the range of 6.0-9.5 can be considered severe disability, and scores in this range are highly dependent on ambulation and the use of assistive devices characterized as unilateral assistance (6.0), bilateral assistance (6.5), or wheelchair dependent (7.0). Scores greater than 7.0 are associated with immobility and bed rest[18].

1.4 PHYSICAL FITNESS

Physical fitness is defined as a set of attributes or characteristics that a person has or has achieved that relates to the ability to perform physically activity. Health-related fitness is comprised of three main components: muscular fitness, cardiorespiratory fitness, and body composition[19]. Muscular fitness (MF) is the ability to generate and maintain muscular force using skeletal muscle contractions and has been associated with health and participatory outcomes[20–22]. Indeed, it has been reported that low MF is related to mortality and increased risk for metabolic syndrome, osteoporosis, diabetes, and cardiovascular disease in healthy and clinical populations[21,23–25]. Furthermore, MF has been shown to be lower in individuals with MS compared to healthy controls[22]. Cardiorespiratory fitness (CRF) refers to the delivery, extraction, and use of oxygen for prolonged aerobic exercise. Similar to MF, CRF is an important indicator of health status for both clinical and nonclinical populations. Low CRF has been associated with increased risk for morbidity and it has been reported that persons with MS have significantly lower CRF levels compared to matched controls[26,27]. Importantly, CRF has been associated with neurological disability, brain structure, walking performance, cognitive function, body composition, symptoms, and quality of life in persons with MS [22,28–33]. Lastly, body composition refers to the proportion of fat and fat-free (muscle) mass that makes up an individual's body[19]. Unfortunately, individuals with MS often experience loss of muscle mass (atrophy) and decreased bone mineral density, while also experiencing increases in fat mass[3]. This shift in body composition can result in increased risk of coronary heart disease, non-insulin dependent diabetes mellitus, and lipid abnormalities[34]. For the purpose of this thesis, there will be a primary focus on the MF and CRF components of physical fitness.

1.5 EXERCISE TRAINING AND MULTIPLE SCLEROSIS

As physical fitness is related to numerous health- and disease-related outcomes in the general populations and in people with MS, it is important to develop strategies for improving physical fitness. One such strategy is exercise training. Exercise training is defined as, "planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness"[19,35]. A systematic review of 54 studies examining exercise training in people with MS reported that performing exercise two times a week at a moderate intensity is effective for improving physical fitness (MF and CRF) for individuals with mild-moderate disability[36]. Additionally, it was reported that exercise training may be beneficial for improving mobility, fatigue, and health-related quality of life (HRQOL)[36]. These results were supported by a recent meta-analysis of 20 randomized control trials that reported exercise training was associated with an overall small change in MF (ES=.27) and moderate change in CRF (ES=.47)[37].

There are established benefits of improving MF and CRF in both clinical and non-clinical populations. Improvements in MF are particularly beneficial for those with MS as they have been associated with improved walking speed, walking endurance, gait, and fatigue[29,36,37]. Furthermore, improvements in CRF are particularly important for individuals with MS for maintaining mobility, cardiovascular health, body composition, and physical function [28,29,31]. Considering the benefits associated with improved physical fitness, exercise training should be a fundamental component of a multidisciplinary approach for managing disability in those with MS.

1.6 FITNESS AND SEVERE MULTIPLE SLCEROSIS

As MS progresses, individuals experience increased symptom severity and decreased functionality. Unsurprisingly, as disease severity increases, physical fitness (both MF and CRF) decrease. This was exemplified in one study that examined physical fitness across the disability spectrum in people with MS[22]. With regards to MF, it was found that individual with MS with severe disability (based on criteria of EDSS≥6.0/need of assistance device for walking[18]) had a mean knee extensor strength of 90.6 Newton-meters (Nm), considerably lower than those with MS with mild/moderate disability (163.3 & 137.7 Nm, respectively)[22]. Individuals with MS with severe disability also had a mean knee flexor strength of 18.4 Nm compared to 42.9 Nm and 50.6

Nm measured in individuals with mild and moderate disability, respectively,[22]. In addition to lower levels of MF, it has been reported that individuals with MS with severe disability have lower levels of CRF compared to individuals with mild-moderate disability[22,27]. One study reported that individuals with MS with severe disability had a mean VO_{2peak} of 14.7 ml/kg/min, considerably lower than individuals with mild-moderate disability (25.2 & 18.8 ml/kg/min, respectively)[22].

Low fitness levels in people with MS with high disability likely reflect physiological deconditioning due to low levels of physical activity[38] as well as the impact of the disease itself on mobility and physiological function. Indeed, individuals with MS have low levels of physical activity compared to the general population and these levels decrease as disability becomes more severe[38]. Low physical fitness contributes to functional impairment and a vicious cycle is established as physical activity participation becomes more difficult with increasing disability, ultimately leading to further deconditioning and functional loss. Fortunately, exercise training can be implemented to disrupt this cycle, to increase physical activity levels, physiological fitness, and potentially physical function[36,37].

1.7 PURPOSE AND RATIONALE

As previously discussed, there is evidence supporting exercise training for improving walking performance, fitness, cognition, fatigue, anxiety, and depressive symptoms in persons with MS[5,31,37,39,40]. However, much of the current literature pertaining to exercise training in people with MS has focused on individuals with mild-to-moderate disability. Furthermore, the exercise approaches that have been effective in persons with mild-to-moderate disability may not be physically accessible for individuals with MS with severe disability. It is for these reasons that adapted exercise training modalities should be considered when prescribing exercise training for individuals with MS with severe disability. An adapted exercise modality is a type of exercise training equipment that is specifically designed to be used by all individuals, regardless of ambulatory ability[41].

One adapted exercise training modality that has been proposed for individual with MS with severe disability is functional electrical stimulation (FES) cycling. FES cycling uses a combination of neuromuscular stimulation and a motor-controlled cycle ergometer. Self-adhering surface electrodes are placed over muscle groups of the lower extremities and a small amount of electrical stimulation is used to supplement muscular contractions while cycling[42]. The electrodes are connected to a microprocessor in the cycle ergometer with a specialized cable and the microprocessor generates an activation pattern of the leg muscles that results in a cycling motion[42]. This assistive stimulation can improve muscle recruitment during cycling and promote greater physiological adaptations to exercise training for individuals with MS with severe disability[43,44].

Despite the promise of FES cycling as an exercise training modality for individuals with MS with severe disability, few studies have examined this modality in people with MS, including the acute metabolic demand of FES cycling. It is imperative to characterize the acute metabolic response of FES cycling to understand the exercise intensity that can potentially be achieved using this modality. Indeed, if FES cycling results in an exercise intensity corresponding to moderate-to-vigorous physical activity (MVPA) it could represent a viable aerobic exercise training stimulus for improving CRF and managing physiological deconditioning for persons with MS who have severe disability.

To date, the acute metabolic demand of FES cycling has not been characterized in persons with MS. Herein, the purpose of this thesis was twofold: (i) to evaluate and summarize the current literature investigating the effects of exercise training for people with MS with severe disability and evaluate the exercise training modalities and approaches applied; and (ii) to characterize the acute metabolic demand of a single bout of FES cycling in people with MS with severe mobility impairment and compare this to a single bout of passive leg cycling matched for exercise duration. Examining the current literature pertaining to exercise training and severe MS will provide a critical evaluation of the exercise interventions that have been used in this population. This evaluation will provide a summary of the potential physiological, functional and psychosocial benefits associated with specific exercise training modalities in this population. This will provide researchers and clinicians direction on the potential benefits of exercise training for this population and the specific modalities that have been most efficacious. This will further highlight future specific avenues and next steps for researchers to move the body of literature on exercise training in people with severe MS forward using high-quality methodologies. This review will provide necessary background and rationale for evaluating the acute metabolic demands of FES cycling.

The metabolic demand associated with an acute session FES cycling is an important aspect of this exercise modality that has yet to be characterized in people with MS. Such an investigation will determine if FES cycling provides a sufficient exercise stimulus to promote improvements in CRF. Indeed, if FES cycling results in an exercise intensity that could improve CRF it could be considered a viable exercise training modality for individuals with MS with severe mobility impairment. This is particularly important as this exercise modality is an adapted exercise training approach and can be used by individuals with severe mobility impairment (individuals with MS with severe disability) in the home and community settings.

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Chapter 2

Exercise Training and Severe Multiple Sclerosis: A Systematic Review

2.1 INTRODUCTION

Multiple sclerosis (MS) is a chronic, neurological disease that affects 1 in 1000 people in the United States making it the most common non-traumatic cause of neurological disability in young adults[1]. The disease is characterized by inflammation, demyelination and neurodegeneration within the central nervous system (CNS), and this damage results in functional impairments and symptomatic experiences. Unfortunately, these impairments and symptoms worsen as neurological disability increases [2].

An EDSS score of 6.0[3] is a commonly reported benchmark of disease progression and disability [4,5]. It is well documented that individuals with MS with an EDSS score of ≥6.0 have greater impairments in muscular fitness, aerobic fitness, mobility, and balance compared to individuals with lower disability scores [2,6–10]. Additionally, symptoms of fatigue, spasticity, depression and cognitive impairment become more severe with increasing disability[10–15]. Physiological deconditioning induced by lower levels of physical activity likely contributes to these impairments with disability progression[16]. Indeed, lower levels of physical activity have also been reported in individuals with MS with higher disability scores[17].

Current disease-modifying agents have limited efficacy in preventing the accumulation of long-term disability in MS[5]. Consequently, alternative strategies for disease management in persons with MS with severe mobility disability should be considered. One potential strategy is exercise training. There is evidence for the benefits of exercise training for improving walking performance, fitness, cognition, fatigue, anxiety, and depressive symptoms in persons with MS[18–20,15,21]. Despite these benefits, much of the current literature pertaining to exercise training in people with MS has focused on individuals with mild-to-moderate disability (i.e., EDSS scores 1.0-5.5)[22]. This is problematic as individuals with MS with severe mobility disability are often excluded from studies of exercise training, limiting the evidence to those with mild-to-moderate MS disability. Furthermore, the exercise approaches that have been effective in persons with mild-to-moderate disability may not be physically accessible for individuals with MS with severe mobility limitations. Therefore, there is a demand for a comprehensive review of exercise training strategies that have been implemented for managing disability for people with MS with severe mobility disability.

Herein, we conducted a systematic review of exercise training interventions in persons with MS with severe mobility disability (EDSS $\geq$6.0) to: (i) evaluate and summarize the current evidence for the effects of exercise training on disability, physical fitness, physical function, symptoms, and participatory outcomes; (ii) evaluate the exercise training modalities and approaches applied; and (iii) identify current limitations and future research directions for exercise training in persons with MS with severe mobility disability. This review will provide a summary of the potential benefits of exercise training in persons with MS with severe mobility disability, and a future research agenda for developing effective strategies for managing disability through exercise training.

2.2 METHODS

2.2.1 Article Inclusion Criteria and Search Strategy

This review focused on English-language studies that examined the effect of exercise training on disability, physical fitness, physical function, symptoms, and participatory outcomes in individuals with MS with severe mobility disability. Exercise training is defined as “planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness" [23]. We conducted a search of four electronic databases (PubMed, EMBASE, OvidMEDLINE, and PsychINFO) using the search terms "multiple sclerosis" AND "exercise" OR "physical activity" OR "fitness" AND "advanced disability" OR "severe mobility disability " OR "progressive" OR "robot". This search was supplemented by an additional hand-search of the authors' personal databases and relevant reviews and meta-analyses involving exercise training in persons with MS.

The inclusion criteria involved full-text articles that: (i) included participants with a diagnosis of MS; (ii) included primarily participants with a reported EDSS score ≥6.0 and/or definitively described disability consistent with this level of neurological impairment (e.g., use of an assistive device for ambulation); and (iii) implemented a prospective, structured exercise intervention per the definition of exercise previously described. For the purpose of this review, we selected an EDSS score of ≥6.0 as this is considered a robust disability landmark characterized by the need for assistance in ambulation (e.g., cane, walker)[3,4]. We included randomized and nonrandomized controlled trials, and pre-post intervention designs based on the limited evidence. Relevant data was extracted by one of the member of the research team (TAE), and verified by a second researcher (LAP).

2.2.2 Article Quality Assessment

The quality of each article was determined using the Physiotherapy Evidence Database (PEDro)[24] scale for randomized control trials (RCTs) and the Downs and Black scale for non-RCTs [25]. The PEDro scale has a maximum possible score of 11 points, while the Downs and Black scale has a maximum possible score of 28 points. For both scales, a higher score is indicative of better methodological quality. Articles were independently evaluated by each of the authors. Scoring discrepancies between the authors were resolved by re-examining the articles and through discussion. The level of evidence of each article was categorized using the Spinal Cord Injury Rehabilitation Evidence (SCIRE) system[26], a 5-level system that distinguishes between studies of differing quality and incorporates the types of research designs commonly used in rehabilitation research (Table 1). These scales have been used in several published systematic reviews and meta-analyses of exercise training in persons with MS[18–20,22].

2.3 RESULTS

Figure 1 illustrates the literature search and screening process. The electronic database search initially retrieved 1157 articles and eight additional articles were retrieved from other sources. After removal of duplicate articles, 531 articles remained. In total, 512 articles did not meet the specific inclusion criteria, leaving 19 articles from 18 studies in the review. Specific reasons for article exclusion are presented in Figure 1.

The findings from the studies reviewed have been categorized and summarized by the type of exercise training modality, as either conventional or adapted exercise training. Table 2 summarizes the participant and exercise training characteristics for each of the 18 studies reviewed grouped by exercise training modality. Five articles examined conventional exercise training (aerobic and resistance training), eight articles from seven studies examined body-weight support treadmill training (BWSTT), one article examined total-body recumbent stepper training (TBRST), and five articles examined electrical stimulation cycling (ESAC). Table 3 summarizes the effect of exercise training for each study grouped by outcome type (i.e., disability, physical fitness, physical function, symptoms and participation. Overall, there was considerable variability in the number and type of outcomes reported in the studies. Six studies reported on disability assessed using the EDSS and MSFC. Ten studies reported on physical fitness using a variety of aerobic and muscular fitness outcomes. There were 16 studies that included measures of physical function captured by tests of walking, gait, agility, balance, spasticity, and upper extremity function. Finally, 12 studies reported on symptoms and participatory outcomes assessed most commonly as fatigue and QOL. Considering the limited number of studies that were retrieved, and the variability in the outcomes included across studies, we did not attempt a meta-analytic approach, but rather evaluated and synthesized the effects of each exercise modality using a descriptive approach.

2.3.1 Conventional Exercise Training

Three studies involved conventional aerobic exercise training, one was an RCT with level 1 evidence and the other two were level four evidence[27–29]. Overall, there were no significant improvements reported on the outcomes included in these three studies. Non-significant improvements were noted in cardiorespiratory fitness (VO_{2peak}), some physical function tasks (balance, gait, agility, walking speed, and upper extremity function), fatigue, depression, and QOL.

Two level four evidence studies examined conventional resistance exercise training[30,31]. Significant improvements in muscular strength were reported in both studies. One of the studies also reported significant improvements in muscle endurance, balance, fatigue symptoms, and QOL in response to progressive resistance training combined with neuromuscular electrical stimulation[30].

2.3.2 Adapted Exercise Training

For this review, we considered adapted exercise training as the use of specialized exercise training equipment that is designed to accommodate individuals with mobility disability. The adapted exercise modalities reviewed were BWSTT, TBRST, and ESAC. A detailed summary of these adapted exercise modalities has been published elsewhere[32].

Bodyweight Support Treadmill Training (BWSTT)

Of the eight studies retrieved involving BWSTT, four studies were level one evidence RCTs and four were level four evidence[33–39]. Two studies reported a significant decrease (i.e., improvement) in EDSS score; however, two other studies reported no change in disability status. A significant improvement in knee extensor strength was reported in only one study. With regards to physical function, both significant and non-significant improvements were noted in several studies for walking endurance, walking speed, gait kinematics, balance, and agility. Several studies reported reduced fatigue (n=4) and improved QOL (n=5) following BWSTT, and some of these changes were statistically significant.

Total Body Recumbent Stepper Training

We retrieved only one level four study involving TBRST in persons with MS with severe mobility disability[40]. There was no change in disability or physical function reported in this study. Symptoms of fatigue were significantly reduced after the intervention, and non-significant, small-to-moderate effects of exercise training on QOL were reported.

Electrical Stimulation Assisted Cycling

We have identified two forms of ESAC: functional electrical stimulation (FES) and neuromuscular electrical stimulation (NMES) cycling[41–45]. All five studies involving ESAC included level four evidence. Only one study reported on disability status and did not observe a change in response to ESAC. Two studies reported significant improvements in physical fitness assessed as thigh circumference and muscle oxygen consumption (mVO_2). None of the studies reported significant improvements in physical function. One study reported a significant reduction in fatigue and pain symptoms following ESAC. There was mixed evidence for the effects of ESAC on spasticity, walking speed, and other participatory outcomes.

2.4 DISCUSSION

The purpose of this review was to examine and evaluate the current body of literature involving to exercise training in persons with MS with severe mobility disability. Eighteen studies with 290 participants were retrieved and reviewed. Overall, the evidence supports some benefit of conventional exercise training for physical fitness, and potential benefits of adapted exercise training on physical function, fatigue, and QOL. Herein, we further evaluate each method of exercise training and provide direction to advance the body of literature pertaining to exercise training in individuals with MS with severe mobility disability.

2.4.1 Conventional Exercise Training

Aerobic Exercise Training

There may be potential benefits of conventional aerobic exercise training for people with MS with mobility disability; however, considering the limited number of studies and mixed findings we are cautious in the interpretation these results. The three studies involving aerobic exercise training in people with MS with severe mobility disability reported some improvements in aerobic fitness and physical function after exercise training. These improvements are consistent with the larger research base that reports improvements aerobic fitness and mobility after aerobic exercise training in persons with mild-moderate MS[20,46]. Furthermore, these studies demonstrated that aerobic exercise training is feasible for individuals with severe mobility disability based on low dropout rates, few adverse events, and high exercise compliance[27–29]. This is notable as conventional aerobic exercise can be effective for managing physical deconditioning, a significant problem for individuals with MS with severe mobility disability[17]. Additionally, there are several advantages of conventional aerobic exercise modalities such as ease of use and availability. Conventional aerobic exercise modalities are also inexpensive compared to other adapted exercise equipment, and in some cases, can be used in the home-setting.

Resistance Exercise Training

Conventional resistance exercise training might have benefits for muscle strength, physical function, and fatigue in people with MS with severe mobility disability[30,31]. This is consistent with the current body of literature involving progressive resistance exercise training in persons with mild-moderate MS, as improvements in strength, fatigue, balance, and mood have all been reported[20,47]. Improvements in physical fitness (e.g., strength) would be particularly beneficial to those with severe mobility disability as these changes might further translate into improvements in physical function (e.g., walking performance). There are several advantages of conventional resistance training that might be particularly appropriate for individuals with MS with mobility impairment. Resistance training can be performed with free-weights, weightmachines, resistance bands or an individual's body weight. This allows for variation in exercise prescription and adaptability for all individuals. Resistance exercises can also be performed in a seated position, reducing the risk for falls and making it accessible to those who are wheelchair-dependent. Despite these advantages, there are some limitations such as the need for instruction in appropriate technique and prescription.

2.4.2 Adapted Exercise Training

Bodyweight Support Treadmill Training

Of the modalities reviewed, the effects of exercise training were most consistent for BWSTT, likely due to the number of studies on this modality. Significant improvements were noted for physical function, symptoms, and QOL. Similar improvements have been reported in other clinical populations after BWSTT (e.g., stroke, spinal cord injury) [48–52]. The main advantage of BWSTT is the task-specific nature of the training modality as a tool for walking and gait rehabilitation[32]. The potential to improve walking performance is particularly relevant for individuals with MS, as impaired walking is one of the most prevalent and debilitating symptom experienced[1,4,53]. BWSTT is also safe for individuals of all disability levels as the harness minimizes risk of falling and is accessible for all individuals regardless of disability level.

Despite the benefits of BWSTT, there are still important drawbacks such as the high cost and subsequent low availability of the exercise equipment. A typical BWSTT session will require assistance from several therapists, further increasing the cost to users. The high costs may restrict the availability of BWSTT in community setting, limiting its use to specialized rehabilitation centers. Further, it has been suggested that restricting gait kinematics (via therapist or robotic assistance) may limit opportunities to self-correct gait, which may be detrimental when attempting to improve walking and gait kinematics[54]. The contribution from therapists or robotic assistance may result in less active contribution from the individual, potentially limiting adaptations in physiological fitness[32].

Total Body Recumbent Stepper Training

One study has evaluated TBRST and reported a reduction in symptoms of fatigue and improvements in QOL[40]. Furthermore, it was reported that TBRST was safe, well tolerated, and enjoyable for those with MS with severe mobility disability. Improvements in VO_{2peak} and walking performance has been observed in individuals with stroke after TBRST [55]. One distinct advantage of TBRST is the full-body training stimulus involving both upper and lower extremity exercise. This full-body exercise can result in improvements in aerobic and muscular fitness, and this could translate into improvements in physical function[32,50,54]. Furthermore, the self-driven nature of TBRST allows for all work to be done by the exerciser, rather than assistance from therapists or a robotic orthosis. Another advantage of the TBRST is the simplicity of the exercise modality compared to other adapted exercise equipment. TBRST does not require extensive setup or preparation and it is a viable modality for community and/or home setting. Unfortunately, the efficacy of TBRST is currently unknown as only one study has examined this modality in those with MS.

Electrical Stimulation Assisted Cycling

The evidence supporting ESAC was mixed, likely owing to the low quality of the studies reviewed (i.e., no RCT, all level 4). There was some evidence for the benefits of ESAC on physical fitness, although there was mixed evidence for the effect of ESAC on physical function, symptoms, and participatory outcomes. Studies examining ESAC in other clinical populations have reported improvements in walking performance, muscular fitness, fatigue, pain, muscle spasticity and HRQOL. There are potential advantages of combined electrical stimulation and volitional exercise such that the added stimulation allows for greater recruitment and activation of weakened muscles, potentially increasing the adaptations to exercise training. These adaptations could translate into improvements in physiological function such as muscle strength, aerobic capacity, and fatigue resistance. This is particularly advantageous for those with MS with severe mobility disability due to physiological deconditioning of the lower extremity musculature[56]. Another advantage of ESAC is the accessibility of the exercise modality as many protocols allow individuals to exercise while remaining seated in their own personal wheelchair. There are still inherent limitations of ESAC. First, the set-up can be cumbersome and complicated, and may be more challenging for individuals with cognitive impairment. Often assistance is required to set-up an ESAC modality, potentially limiting self-administration. Further, the electrical stimulation excites both motor and sensory nerves which may cause pain for individuals with spared sensation, potentially discouraging individuals from using this modality.

2.5 LIMITATIONS

2.5.1 Limitations of the Literature

When reviewing this literature, it became apparent that there were clear limitations. First, many of the studies had small sample sizes. Indeed, all studies included in this review have small samples with the largest sample including 49 participants. Many of the studies included did not involve appropriate control conditions. Furthermore, the studies included heterogeneous MS samples with respect to demographic and other clinical characteristics. Another limitation of the literature is the lack of a consistent cut-point or grouping for participants with MS with severe mobility disability. This makes it difficult to apply the findings to all people with MS with severe mobility impairment, as there may be considerable variability in disability level of these individuals. Another limitation is the inconsistency of exercise prescription in the studies reviewed as there was considerable variability in the modality, duration, frequency and/or intensity of exercise training. Lastly, outcomes were measured and reported immediately after the exercise intervention, and few studies reported follow-up measurements, thus the long-term effect of exercise training is difficult to determine. Additionally, there were inconsistencies in the outcome measures applied, making it difficult to draw meaningful conclusions considering the limited evidence.

2.5.2 Limitations of the Review

In addition to the limitations of the literature, there are also limitations of the review itself. We used a descriptive systematic approach for study selection and review. Due to the limited evidence and diverse outcomes included in the studies reviewed, we chose not to perform a meta-analysis at this stage, but rather summarized the potential benefits of each exercise approach. The descriptive systematic review approach allowed a detailed evaluation of the exercise training modalities that were implemented. The studies reviewed were selected by two members of the research team and were therefore subject to selection bias. Additionally, we only included articles that were published in English academic journals, subjecting our review to publication bias. We also chose to only include studies that implemented a structured exercise training program and excluded studies that involved various types of rehabilitation (e.g., physiotherapy, occupational therapy, etc.). Lastly, our classification of severe mobility disability (EDSS score ≥6.0 and/or disability consistent with this level of impairment) may have resulted in the exclusion of studies with other pertinent information.

2.6 FUTURE DIRECTIONS

There are promising preliminary benefits of exercise training in persons with MS with severe mobility disability, however, the current literature on this topic is quite limited. There are significant gaps in the literature that should be addressed to provide a comprehensive examination of the benefits of exercise training for this population. First, a thorough investigation of the most effective prescription of exercise training with respect to duration, intensity, frequency, and modality is warranted using high quality, randomized controlled trial designs. There are various modes of exercise training that have received minimal attention (e.g., recumbent stepper) or have not been evaluated at all in persons with MS with severe mobility disability (e.g., combined arm and leg ergometer). Attention to the disability level of the sample should also be considered. Perhaps different prescriptions of exercise training are needed based on ambulatory ability (e.g., unilateral and bilateral support vs. wheelchair dependent). Few studies have exclusively examined exercise training approaches for persons with MS who are wheelchair dependent, and this should be a focus of future research to improve the health of all individuals with MS. The mechanisms of delivery of exercise training also require consideration, particularly given limitations in transportation and accessibility for those with severe mobility disability. The efficacy of home-based or telerehabilitation approaches (e.g., Internet-delivered) should be evaluated and compared with supervised exercise training in future investigations.

Finally, the selection and evaluation of appropriate and comprehensive outcomes of exercise training interventions in persons with severe mobility disability should be evaluated and reported, including detailed metrics of safety, feasibility, and patient-reported experiences of exercise training.

2.7 CONCLUSIONS

There is limited evidence on the role of exercise training in persons with MS with severe mobility disability, and we summarize this literature based on conventional and adapted exercise training approaches. Preliminary data suggest that conventional exercise training might improve physical fitness in persons with MS with severe mobility disability. Adapted exercise training may have benefits for physical function, fatigue, and QOL. There are potential advantages of adapted exercise training modalities (BWSTT, TBRST, and ESAC) in that they can be more physically accessible and task-specific. However, adapted exercise modalities are often expensive and only available in specialized settings. Considering the limited evidence, further research is necessary to determine the most efficacious and effective exercise approaches for individuals with MS with severe mobility disability.

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Chapter 3

Acute Metabolic Demands of Functional Electrical Stimulation Cycling

3.1 INTRODUCTION

Cardiorespiratory fitness (CRF) is an important indicator of health for both clinical and nonclinical populations, and low CRF is associated with increased risk for morbidity and mortality [1,2]. Persons with multiple sclerosis (MS) have markedly lower CRF levels compared to controls without MS [2–6], and CRF decreases as a function of increasing disability in individuals with MS [4,6]. Indeed, persons with severe disability have been reported to have a 52.6% lower peak oxygen uptake (VO_{2peak}) compared to individuals with mild disability [4]. Lower physical activity levels reported in individuals with mobility disability are likely an important contributor to physiological deconditioning [7]. Importantly, CRF has been associated with neurological disability, walking performance, brain structure, cognitive function, body composition, symptoms, and quality of life in persons with MS [2,4–6,8–10]. Consequently, intervention strategies that target and improve CRF in people with MS who have severe disability are of the utmost importance.

One approach that has been effective for improving CRF in persons with MS is exercise training. One meta-analysis reported that exercise training was associated with a moderate improvement (g=.47) in CRF in people with MS [11]. However, most studies of exercise training have been limited to individuals with MS who have mild-to-moderate disability, often excluding those individuals with significant mobility impairment (Expanded Disability Status Scale [EDSS] ≥5.5). These individuals potentially have the most to benefit from exercise training, yet many conventional exercise modalities are physically inaccessible [12]. Alternative and accessible exercise approaches are needed to ensure that individuals with MS who have mobility disability have the opportunity to improve CRF and benefit from exercise training.

One exercise modality that has been developed for individuals with mobility impairment is functional electrical stimulation (FES) cycling. FES cycling uses surface electrodes and mild electrical stimulation to evoke involuntary muscle contractions. These contractions are sequenced with a motorized cycle ergometer, simulating a cycling cadence [13,14]. The superficial stimulation allows for greater recruitment of weakened muscles fibers, theoretically increasing overall oxygen consumption and the potential for adaptations with exercise training. Previous research has reported a 52% and 194% increase in HR and VO_2, respectively, from resting levels in response to acute FES cycling in individuals with spinal cord injury (SCI) [15]. Consequently, improvements in CRF have been observed in people with SCI after habitual FES cycling training [16,17].

The American College of Sport Medicine (ACSM) recommends an exercise intensity of 40-85% of VO_{2peak} or 70-90% of HR_{peak} (moderate-to-vigorous physical activity [MVPA]) for improving CRF in adults [18,19]. Physical activity guidelines for adults with mild-to-moderate MS recommend 30 minutes of moderate intensity aerobic activity, twice weekly [20]. Indeed, if FES cycling results in an exercise intensity corresponding to MVPA it could represent a viable aerobic exercise training modality for improving CRF and managing physiological deconditioning, in addition to other important outcomes, in persons with MS who have severe mobility impairment.

To date, the acute metabolic demand of FES cycling has not been characterized in persons with MS. Herein, the purpose of this study was twofold: (i) to characterize the acute metabolic demand of a single bout of FES cycling in people with MS with severe mobility impairment; and (ii) to compare the metabolic demands of FES cycling to a single bout of passive leg cycling matched for exercise duration. Determining the exercise intensity of acute FES cycling (i.e., stress response) has important implications for the prescription of exercise training and the potential for improving CRF in individuals with MS with severe mobility impairment (i.e., adaptation).

3.2 METHODS

3.2.1 Participants

Eleven participants from an ongoing trial of supervised FES cycling exercise were recruited to participate [13]. Participants were part of a six-month exercise training intervention evaluating the efficacy of FES cycling for improving walking ability, physiological fitness, and symptoms in individuals with severe MS disability [13]. The participants were randomly allocated into one of two leg cycling conditions: (i) FES cycling or (ii) passive leg cycling (PLC). Criteria for inclusion were: (i) between the ages of 18-64; (ii) a confirmed diagnosis of MS; (iii) use of unilateral or bilateral assistance for ambulation (EDSS score of 5.5-6.5); (iv) no history of a relapse within the past 30 days; (v) not currently participating in exercise on two or more days per week; (vi) asymptomatic (no known cardiovascular, pulmonary, or metabolic disease or symptoms suggestive of these conditions based on the Physical Activity Readiness Questionnaire[21]); (vii) not currently pregnant or plans to become pregnant during the trial; (viii) no contraindications for FES cycling (epilepsy, pacemaker, implanted defibrillator, fracture, or implanted screws/pins); (ix) physician approval for exercise testing and training.

3.2.2 Outcome Measures

Clinical and Demographic Characteristics

Height and weight were measured in the laboratory to the nearest 0.1cm or kg, respectively, using a scale with a stadiometer (Detecto, Webb City, MO). Disability status was determined through a clinically-administered EDSS [22] examination by a Neurostatus-certified assessor. Clinical and demographic characteristics were collected using a self-report questionnaire.

Peak Cardiorespiratory Fitness

Peak CRF was assessed using a symptom-limited incremental exercise protocol performed on a recumbent stepper (Nustep T5^{XR} recumbent stepper, Nustep Inc., Ann Arbor, MI) [4]. The test began with a 1-minute warm-up at 15W and the resistance was gradually increased by 5W per minute until volitional fatigue [4]. Expired gases were collected continuously using a two-way, non-rebreathable valve (Hans Rudolph Inc., Shawnee, KS) connected with an open circuit spirometry system (TrueOne 2400, Parvo Medics, Sandy, UT). Heart rate (HR; Polar Electro Oy, Kempele, Finland) and ratings of perceived exertion (RPE)[23] were recorded every minute during the test. Peak power output was recorded from the recumbent stepper and expressed in Watts (W). Peak cardiorespiratory capacity (VO_{2peak}) was determined when at least one of the following criteria were recorded: (i) respiratory exchange ratio (RER) $\geq$1.10; (ii) HR_{peak} within 10 bpm of age-predicted maximum (i.e., 220-age); or (iii) RPE $\geq$17 [4].

Acute Cycling Session

The acute cycling session was conducted on an RT300 cycle ergometer (Restorative Therapies Inc, Baltimore, MD). The participants in the FES cycling group received electrical stimulation during voluntary leg cycling via self-adhering surface electrodes placed over muscle groups of the lower extremities (quadriceps, hamstrings, and gluteals). The stimulation parameters were as follows: waveform symmetric biphasic, phase duration of 250ms, and pulse rate of 50 pulses per second. The intensity of leg muscle stimulation was adjusted per muscle group according to each participant's sensory tolerance. Participants were instructed to maintain a cycling cadence of ~50 rpm during the acute cycling session and pedaling resistance was automatically adjusted by the RT300 to maintain this cycling cadence. The participants in the passive cycling condition did not wear the electrodes and did not receive electrical stimulation. A pedaling cadence of ~50 rpm was generated entirely by the electric motor of the cycle ergometer. Continuous gas exchange and HR were measured during the entire session using the same system as for the peak CRF test. RPE was recorded every minute by a member of the research team [23]. Lastly, work rate (WR) (expressed in Watts [W]), cycling resistance (expressed in Newton meters [Nm]), and the percentage of stimulation received, relative to maximum stimulation tolerated by each participant (%MaxStim), were recorded continuously by the RT300 cycle ergometer and reported for describing the cycling session parameters.

3.2.3 Protocol

All procedures were approved by a University Institutional Review Board and participants provided written informed consent. The participants were informed of the possible risks and benefits during the informed consent process. Participants completed two testing sessions separate by approximately one week. At the first testing session, participants reported to the laboratory and completed the symptom-limited cardiopulmonary exercise test. This enabled the intensity of the acute session to be expressed as a percentage of peak values. At the second session, participants completed the acute cycling protocol (i.e., FES or passive leg cycling). The acute exercise protocol consisted of four phases: (i) a five-minute period of monitored rest with no physical exertion (RE); (ii) a one minute transition/warmup period (WU); (iii) a 15-minute period of active cycling (AC); and (iv) a five-minute cool down period (CD). The acute exercise protocol is graphically presented in Figure 3.

3.2.4 Data Analysis

Data analysis was performed using IBM SPSS Statistics (Version 22.0, IBM Corp., Armonk, NY). Descriptive statistics were used to summarize the demographic, clinical, peak and acute cardiorespiratory response variables. The acute response variables were averaged per minute across the entire session and expressed as mean values for the RE, AC, and CD phases per cycling condition. The acute response was further expressed as a percentage of peak values obtained from the cardiopulmonary exercise test for VO_2, HR and WR, as these variables are commonly used indicators of exercise intensity. Comparisons between the FES cycling and passive cycling groups were made using independent samples *t*-tests, *chi*-square tests, and one-way analysis of variance (ANOVA) with *post-hoc* Bonferroni corrections. Statistical significance was set at $p<.05$.

3.3 RESULTS

3.3.1 Characteristics of the Participants

The characteristics of the participants in the FES and passive cycling conditions are reported in Table 4. There were no significant differences in height, weight, disability, or disease duration between the two conditions. There was a significant difference in age between the FES cycling and passive cycling condition, such that the FES cycling group was older than the passive cycling group (*p*=.03). Consequently, analysis of covariance (ANCOVA) were performed using age as a covariate in all subsequent comparisons by condition. There were no significant differences in the peak cardiorespiratory response between the FES cycling and passive leg cycling condition (all $p>.05$).

3.3.2 Acute Metabolic Response to FES Cycling

Figure 4 provides a graphical presentation of the mean physiological response variables for the FES cycling group per minute across the acute session. Mean oxygen consumption (VO_2) increased by 190% from 3.0±0.6 ml/kg/min during RE to 8.7±1.8 ml/kg/min (63.5% of VO_{2peak}) during AC. VO_2 then returned to 5.9±1.3 ml/kg/min during the CD. Mean HR increased by 50% from 68±12.1 bpm during RE to 102±9.7 bpm (76.4% of HR_{peak}) during AC, then decreased to 91±14.3 bpm in CD. During the AC phase, mean WR was 27.0W (57.3% WR_{peak}), and median RPE reported was 13.5 (IQR=5.5). Mean resistance on the cycle was 4.7±0.2 Nm, and the mean percentage of stimulation received was 35.3±26.6%.

3.3.3 FES Cycling vs Passive Leg Cycling Response

The mean physiological responses recorded during the AC phase of FES cycling and passive leg cycling are presented in Table 5. There was a significant difference in mean VO_2 (p=.001), HR (p=.002), WR (p<.001), and RPE (p<.003), such that mean values were higher during FES cycling compared to passive cycling based on ANCOVA. The mean RER recorded during FES cycling was greater than during passive cycling; however, this difference was not statistically significant (p=.08).

When examining group differences based on the percentage of peak cardiorespiratory test values, the FES cycling condition achieved a significantly higher relative mean VO_2, compared to the passive leg cycling group (p=.007). Mean HR was higher in response to FES cycling compared to the passive leg cycling; however, this difference was not statistically significant (p=.07). Lastly, The FES cycling group achieved a significantly higher mean WR expressed as a percentage of peak values, compared to the passive leg cycling group (both p<.001).

3.4 DISCUSSION

We conducted the first study to characterize the acute metabolic demands of FES cycling in people with MS with severe mobility impairment, and furthered compared this response to passive leg cycling. This is important for identifying if FES cycling represents a potent enough stimulus (i.e., stressor) for yielding changes in CRF (i.e., adaptations) over time with training. Considering traditional indicators of exercise intensity, FES cycling exercise corresponded to an intensity of 63.5%, 76.4%, and 57.3% of VO_{2peak}, HR_{peak}, and WR_{peak}, respectively, and as expected FES cycling was more intense than passive leg cycling. Overall, these findings suggest that FES cycling exercise is capable of providing a sufficient stimulus for improving CRF, and should be considered as an aerobic exercise training modality for managing physiological deconditioning in people with MS who have severe mobility impairment.

Participation in moderate-to-vigorous intensity physical activity (40%-85% of VO_{2peak} and/or 70%-90% of HR_{peak}) is associated with improvements in CRF [18]. In response to FES cycling, the participants in the current study satisfied the common criteria for attaining MVPA, suggesting that FES cycling can provide an adequate stimulus for improving CRF in people with severe MS. Individuals with low CRF (VO_{2peak}<40 ml/kg/min), such as those with severe MS, can experience improvements in CRF at even lower exercise intensities (~30% VO_{2peak}) [18,19]. This is particularly important for individuals with MS at the upper end of the disability spectrum who experience significant physiological deconditioning. Of note, the exercise intensity achieved in response to FES cycling in the current study is consistent with intensities reported in previously aerobic exercise training studies in people with MS [20]. This suggests that people with MS with mobility disability are capable of achieving similar intensities of aerobic exercise training as individuals with mild-to-moderate MS, and importantly, this intensity of exercise training is sufficient for improving CRF.

As expected, the cardiorespiratory response to FES cycling was significantly more intense than that observed in response to passive cycling alone, suggesting an important contribution of voluntary leg cycling, added electrical stimulation, or the combination of both components. Interestingly, the mean exercising WR achieved in response to FES cycling was 27.0 W, or 57.3% of WR_{peak}. This is noticeably higher than previously reported WR values attained during FES cycling protocols in people with MS who have severe disability. One study reported a mean WR of 5.2W during a single FES cycling session [24]. Another study reported a mean WR of 4.45W during an FES cycling session with a minimum duration of 30 minutes [25]. It is important to note that both of these exercise protocols instructed participants not to cycle voluntarily during the FES session and were to rely completely on the neuromuscular stimulation to produce the cycling movement. This is likely the cause of the discrepancy in WR between the current study and the previous research. The combination of voluntary leg cycling exercise with supplementary stimulation can enable greater exercise intensities and longer durations of exercise to be achieved [24]. This approach is ideal for individuals with MS with severe disability as it would maximize the volume of exercise that can be accomplished, thus promoting greater physiological improvements.

The supplementary neuromuscular stimulation provided from FES cycling further has important benefits for people with MS with severe disability. It has been reported that individuals with MS have compromised muscular strength and motor-unit recruitment compared to healthy controls, despite similar muscle cross sectional area [26]. This impairment becomes more severe as disability increases [4,26]. Such impairments in muscular function may be overcome by using neuromuscular stimulation in combination with leg cycling exercise to increasing overall muscle activation, allowing for greater motor-unit recruitment, muscle mass involvement, and force production [26]. This supports the use of FES cycling a potentially valuable exercise training modality for individuals with severe MS disability.

Another aspect of FES cycling that should be considered is the metabolic efficiency. To date, few studies have examined the acute metabolic demands of FES cycling. One study compared the metabolic efficiency (caloric equivalent of work performed/aerobic expenditure x 100) of FES cycling performed by participants with SCI to voluntary leg cycling in able bodied (AB) controls [27]. That study demonstrated that participants with SCI had cycling efficiencies ranging from 2-14%, while AB participants had efficiencies ranging from 4-34%. That study demonstrated that VO_2 was higher during FES cycling compared to voluntary cycling, despite an equivalent WR. Another study compared the metabolic efficiency of FES cycling to voluntary cycling within a group of AB individuals [28]. That study demonstrated that FES cycling caused an increase in VO_2 during exercise and determined that FES cycling was roughly half as metabolically efficient as voluntary cycling.[28] These reported inefficiencies are likely a result of suboptimal biomechanics that occurs with FES cycling. External neuromuscular stimulation causes crude recruitment of the muscle groups, lack of synergistic and antagonistic joint control, mixed muscle fiber recruitment, and adverse muscle activation timing, all of which contribute to reduced metabolic/biomechanical efficiency during cycling [29–31]. This apparent inefficiency may be beneficial in that it increases the energetic demand associated with this task, ultimately contributing to a more intense exercise stimulus and promoting physiological adaptations [27].

3.5 LIMITATIONS

There are several important limitations of this study that must be considered. The sample size of the study was relatively small which may limit the applicability of the findings. Another limitation is the evaluation of a single exercise modality (RT 300 leg cycle). It would be valuable to compare the acute cardiorespiratory response using a variety of different adapted exercise modalities with and without FES, as well as through the modulation of voluntary and passive conditions. This would allow for a greater understanding of the contribution of the neuromuscular stimulation and the voluntary exercise components. Finally, the peak cardiorespiratory exercise test and the acute metabolic session were performed on two different exercise modalities. This could limit the accuracy of the physiological response expressed as a percentage of peak values.

3.6 CONCLUSIONS

We determined that FES cycling elicits a metabolic stimulus that corresponds to MVPA and that FES cycling is more intense than passive leg cycling. The combination of voluntary leg cycling and supplementary neuromuscular stimulation can assist individuals with severe MS to achieve higher exercise training intensities, and consequently, could improve physiological fitness (i.e., CRF). FES cycling is an accessible, adapted exercise modality that can be used by people with MS with severe disability in the home or community setting, and should be considered as an option for aerobic exercise training in this population.

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Chapter 4

Discussion and Reflection

4.1 INTRODUCTION

This thesis characterized the acute metabolic demand associated with a single bout of functional electrical stimulation (FES) cycling in individuals with MS with severe mobility disability. First, a systematic review was conducted to examine and evaluate the current literature pertaining to exercise training in individuals with MS with severe disability. The purpose of this systematic review was to examine and evaluate the exercise modalities/strategies used for improving disability, physical fitness, physical function, symptoms, and participatory outcomes. The evidence reviewed suggested potential benefits of conventional exercise training for improving physical fitness. Importantly, this review showed that adapted exercise training modalities have the potential to improve physical function, fatigue, and quality of life, and this might be particularly beneficial as adapted exercise modalities are physically accessible for people with MS with severe disability. However, this review revealed significant gaps in the literature that should be addressed to provide a comprehensive examination of the benefits of exercise training in this population. One such gap is the limited understanding of the physiological response associated with different adapted exercise training modalities. A greater understanding of this physiological response would help to optimize exercise prescription in this population.

Considering this important limitation, we characterized the acute metabolic demand of FES cycling in people with MS with severe disability, and further compared this response to passive leg cycling. A greater understanding of this metabolic demand (i.e., exercise intensity) has important implications for the potential benefits associated with this exercise modality. The

American College of Sport Medicine (ACSM) recommends regular, moderate-to-vigorous physical activity (MVPA) for improving cardiorespiratory fitness (CRF) in adults[1,2]. Indeed the acute metabolic demand of a bout of FES cycling corresponded to MVPA based on accepted indicators of exercise intensity (VO_2 and HR). This is important as it indicates that FES cycling could be a viable exercise training modality for improving CRF and managing physiological deconditioning for individuals with MS with severe disability. This characterization warrants a more vigorous investigation of FES cycling, as well as other adapted exercise modalities, in order to optimize exercise prescription for this population. Furthermore, this knowledge has important clinical implications as it demonstrates that FES cycling is a viable strategy for improving CRF, which may in turn improve physical function and disease symptoms[3–6].

4.2 SYSTEMATIC REVIEW

The systematic review examined 19 studies with 290 participants. The quality of each article was determined using the Physiotherapy Evidence Database (PEDro)[7] scale for randomized control trials (RCTs) and the Downs and Black scale for non-RCTs[8]. Most of the studies included were identified as having level four quality evidence (i.e., uncontrolled, pre-post trials), while the remaining studies were identified as having level one quality evidence (i.e., RCTs). Furthermore, all studies included in the review were categorized as either conventional exercise training or adapted exercise training. Although the literature pertaining to conventional exercise training in persons with severe MS is very limited (n=5), the results suggest preliminary efficacy for improving CRF, muscular fitness (MF), mobility, and balance[9–13]. Fourteen studies involving adapted exercise training were reviewed and improvements in MF, walking performance, mobility, balance, and HRQOL were reported. Furthermore, spasticity, symptoms of fatigue and pain, and neurological disability also decreased after adapted exercise training [14–26].

4.2.1 Conventional Exercise Training

Three studies were retrieved that examined conventional aerobic exercise training in people with severe MS and improvements in CRF, walking performance, mobility, and balance were reported. Furthermore, both studies determined that aerobic exercise training is feasible for individuals with severe disability based on low dropout rates, minimal adverse events, and high compliance with the exercise program [9,11]. Improvements in CRF are particularly important for maintaining mobility, cardiovascular health, body composition, and physical function[3–5]. Two studies examined conventional resistance training in people with MS with severe disability and reported improvements in walking performance, mobility, MF, balance, and fatigue [12,13]. These preliminary results suggest promise for conventional resistance exercise training for improving muscular health and physical function. Increases in MF (more specifically strength) would be particularly beneficial to those with severe MS as these improvements would reasonably translate to improvements in functional outcomes (e.g., walking performance). Furthermore, resistance exercises can also be performed in a seated position, reducing the risk of falling and making it accessible to those with compromised mobility.

4.2.2 Adapted Exercise Training

There were eight studies that evaluated body-weight support treadmill training (BWSTT) and reported improvements in walking performance, mobility, MF, balance, spasticity, fatigue, HRQOL, and neurological disability [14–21]. The main advantage of BWSTT is the task-specific nature of the training modality as a tool for the rehabilitation of walking performance [28]. The potential to improve walking performance is particularly relevant for individuals with MS, as impaired walking is the most prevalent and debilitating symptom associated with the disease [29–31]. Furthermore, BWSTT is an accessible exercise modality which allows anyone to utilize it regardless of disability level. However, it is important to note that BWSTT is expensive and limited to clinical rehabilitation settings[28].

One study evaluated total body recumbent stepper training (TBRST) and reported a reduction in symptoms of fatigue and improvements in HRQOL[22]. Furthermore, it was reported that TBRST was safe, well tolerated, and enjoyable for those with MS with severe disability [32]. This full-body exercise modality could result in greater improvements of both CRF and MF, and this could translate into improvements in functional outcomes [28,33,34].

Five studies examined electrical stimulation assisted cycling (ESAC) and reported improvements in MF, walking performance, mobility, muscle spasticity, fatigue, pain, and HRQOL[35,23,26,24,25]. Unfortunately, none of these studies were RCTs and all had level four evidence. There are potential advantages associated with combining electrical stimulation and exercise training such that the added stimulation allows for greater recruitment and activation of weakened muscles, potentially increasing the adaptations to exercise training. These adaptations could translate into improvements in physiological function such as muscle strength, aerobic capacity, and fatigue resistance. This is particularly advantageous to those with severe MS due to physiological deconditioning of the lower extremity musculature [36]. Another major advantage of ESAC is the accessibility nature of the exercise modality. Many ESAC protocols allow individuals to exercise while remaining seated or in their own personal wheelchair. This not only increases the accessibility of the modality, but also greatly improves the safety of exercise training.

4.3 ACUTE METABOLIC DEMAND

Characterizing the acute metabolic demand of FES cycling is important for determining if this modality provides a sufficient exercise stimulus to promote changes in CRF. Considering accepted indicators of exercise intensity, FES cycling exercise corresponded to an intensity of 63.5%, 76.4%, and 57.3% of VO_{2peak}, HR_{peak}, and WR_{peak}, respectively, during the exercise session. As expected, FES cycling was more intense than passive leg cycling alone. Overall, these findings suggest that FES cycling exercise can provide a sufficient stimulus for improving CRF, and should be considered as an aerobic exercise training modality for managing physiological deconditioning in people with MS who have severe mobility impairment.

Participation in MVPA (40%-85% of VO_{2peak} and/or 70%-90% of HR_{peak}) has been associated with improvements in CRF[1] and the participants in this study satisfied the criteria for MVPA. This is important as it indicates that FES cycling can provide an adequate stimulus for improving CRF in people with severe MS. Furthermore, individuals with low CRF (VO_{2peak}<40 ml/kg/min), such as those with MS with severe disability, can experience improvements in CRF at even lower exercise intensities (~30% VO_{2peak})[1,2]. This is particularly beneficial for individuals with MS at the upper end of the disability spectrum who typically have low CRF levels and experience significant physiological deconditioning.

The cardiorespiratory response to FES cycling was significantly more intense than passive cycling alone based on many accepted indicators of exercise intensity. This indicates that the contribution of voluntary leg cycling and/or added electrical stimulation are important determinants of exercise intensity. The combination of voluntary leg cycling exercise with supplementary stimulation enables people with MS with severe disability to exercise at a greater intensities and for longer durations[26]. This approach is ideal for individuals with MS with severe disability as it could maximize the volume of exercise training that can be accomplished, thus optimizing physiological improvements.

The supplementary neuromuscular stimulation provided might have important benefits for people with MS with severe disability. Individuals with MS have compromised muscular strength and motor-unit recruitment compared to healthy controls, despite similar muscle cross sectional area[37]. Unsurprisingly, this impairment becomes more severe as disability increases[37,38]. These impairments may be overcome by using neuromuscular stimulation in combination with leg cycling exercise to increasing overall muscle activation. This would allow greater motor-unit recruitment, muscle mass involvement, and force production[25]. Another aspect of FES cycling that should be considered is the metabolic efficiency. Some studies have reported that FES cycling is generally less metabolically efficient than voluntary leg cycling[39,40]. These inefficiencies are most likely a result of suboptimal biomechanics associated with FES cycling[40] and may contribute to a more intense exercise stimulus, thus promoting physiological adaptations[39].

4.4 LIMITATIONS OF THESIS

Overall, there are limitations to this thesis that must be considered. First, the sample size of the study was relatively small which may limit the applicability of the findings. It is important to note that this thesis only evaluated one single exercise modality as opposed to examining multiple exercise modalities individually or in combination. It would be valuable to compare the acute cardiorespiratory response using a variety of different adapted exercise modalities with and without FES. This would allow for a greater understanding of the contribution of the neuromuscular stimulation and the voluntary exercise components. Second, we only examined the acute metabolic demands of FES cycling and although participants were capable of training at a moderate-vigorous intensity, we cannot assume that this will translate into adaptations in CRF long-term. RCTs of FES cycling training are necessary to determine the potential adaptations to this modality with exercise training. Third, this thesis examined a specific group of people with MS (i.e., severe mobility impairment). While it is important to examine this subgroup of people with MS, it may also limit the generalizability of the results. Finally, the peak cardiorespiratory exercise test and the acute metabolic session were performed on two different exercise modalities. This could limit the accuracy of the physiological response expressed as a percentage of peak values.

There are important limitations of the systematic review portion of this thesis that must be considered. First, we used a descriptive systematic approach for study selection, rather than a meta-analysis. Due to the limited evidence and diverse outcomes measured in the studies reviewed, we did not examine effect sizes nor the effects of exercise training on specific outcomes, but instead elected to evaluate the exercise modalities implemented and summarize their potential benefits. The descriptive systematic review approach allowed a detailed assessment of the exercise training modalities that were implemented. The studies reviewed were selected by two members of the research team and were therefore subject to selection bias. Additionally, we only included articles that were published in English academic journals, subjecting our review to publication bias. A decision was made to only include studies that implemented a structured exercise training program and exclude studies that examined the effects of various types of rehabilitation. Last, our classification of severe MS disability (EDSS score ≥6.0 and/or disability consistent with this level of impairment) may have resulted in the exclusion of studies with other pertinent information.

4.5 FUTURE DIRECTIONS

As the systematic review indicated, there are promising preliminary benefits of exercise training in persons with severe MS. However, the current literature on this topic is quite limited and there are significant gaps that must be addressed to provide a comprehensive understanding of the benefits of exercise training in this population. There is a demand for investigation of the most effective exercise prescription with respect to duration, intensity, frequency, and specifically, modality. In order to determine the most effective exercise prescription, high quality, RCT designs must be conducted. There are various exercise training modalities that have received minimal attention in persons with severe MS (e.g., FES cycling, TBRST) which require further examination. Attention to the disability level of the sample should also be considered and different prescriptions of exercise training might be needed based on ambulatory ability. The delivery mechanisms of exercise training also require further consideration, particularly given limitations associated with transportation and accessibility for those with MS with severe disability. For example, further research should be conducted evaluating the feasibility of home-based, Internet-delivered, and telerehabilitation training programs as these mechanisms of exercise delivery may be more desirable for an individual with MS with severe disability. It would be beneficial to compare the acute metabolic demand of FES cycling to other exercise modalities (both with and without FES). For example, it would be beneficial to compare FES cycling to voluntary leg cycling as this comparison would allow for a greater understanding of the potential benefits of supplementary FES during exercise training.

4.6 CONCLUSIONS

This thesis aimed to evaluate the current literature pertaining to exercise training for individuals with MS with severe disability and to characterize the acute metabolic response of a bout of FES cycling in this population. The preliminary benefits of exercise training for individuals with MS with severe disability were highlighted, but there were also evident gaps in literature that need to be addressed. One such gap was the limited examination of the acute exercise response associated with adapted exercise modalities. It is because of this that we characterized and evaluated the metabolic response of individuals with MS with severe disability to an acute session of FES cycling. This thesis determined that the acute metabolic demand of FES cycling corresponded to MVPA, an exercise intensity that is associated with improvements in CRF. This has important clinical implications as conventional exercise modalities may not be physically accessible for this population. FES cycling is an adapted exercise modality that could be used for improving CRF and managing physiological deconditioning, in turn improving physical function and decreasing symptoms[3–6]. Despite this, further investigation of FES cycling is necessary in order to optimize exercise prescription for this population and fully understanding the potential benefits associated with this promising exercise modality.

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Chapter 5
Figures and Tables

Figure 1: PRISMA (The preferred reporting items for systematic reviews and meta-analyses) flow diagram of the literature review process

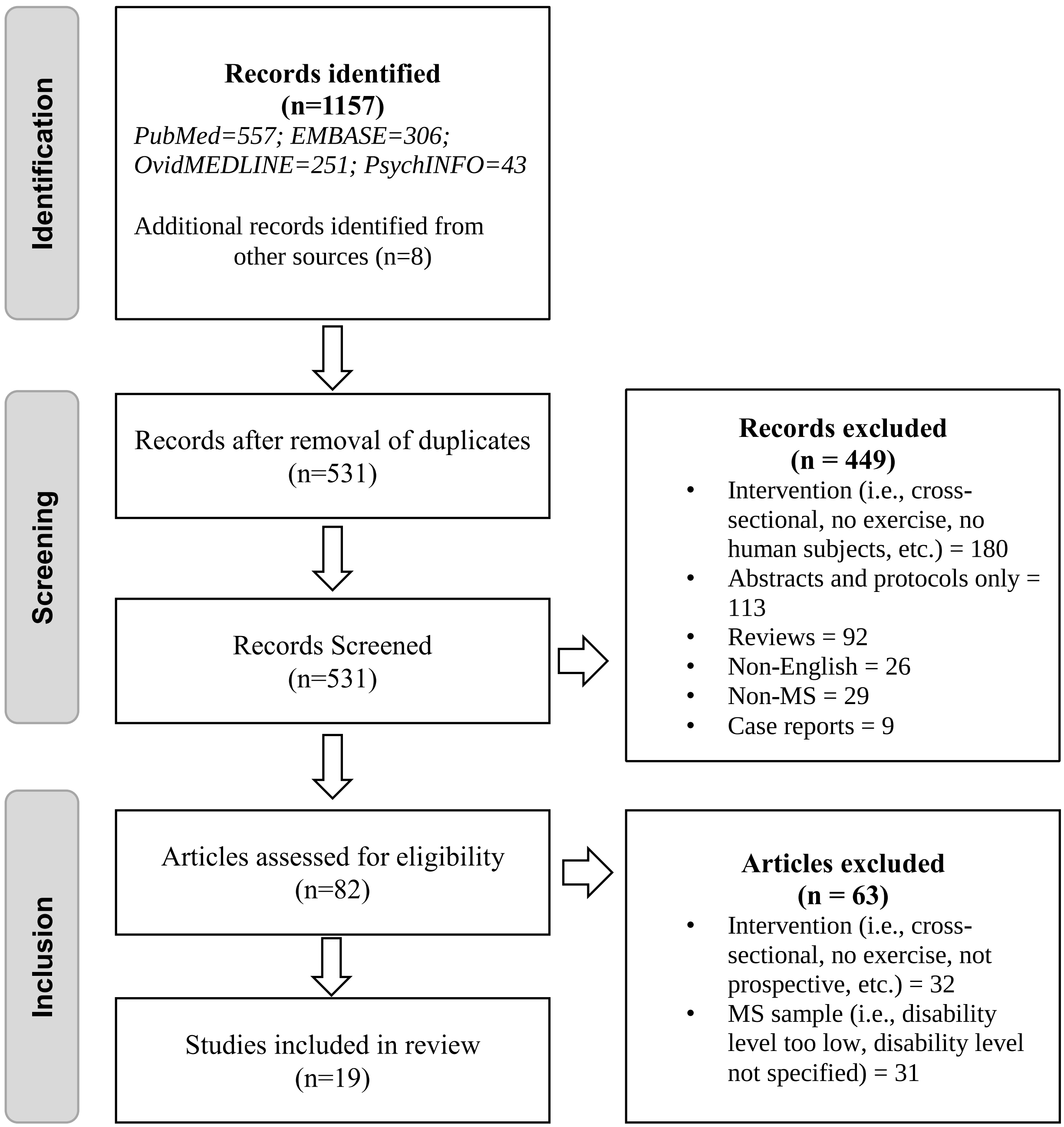

Figure 2: Graphical representation of the exercise protocol.

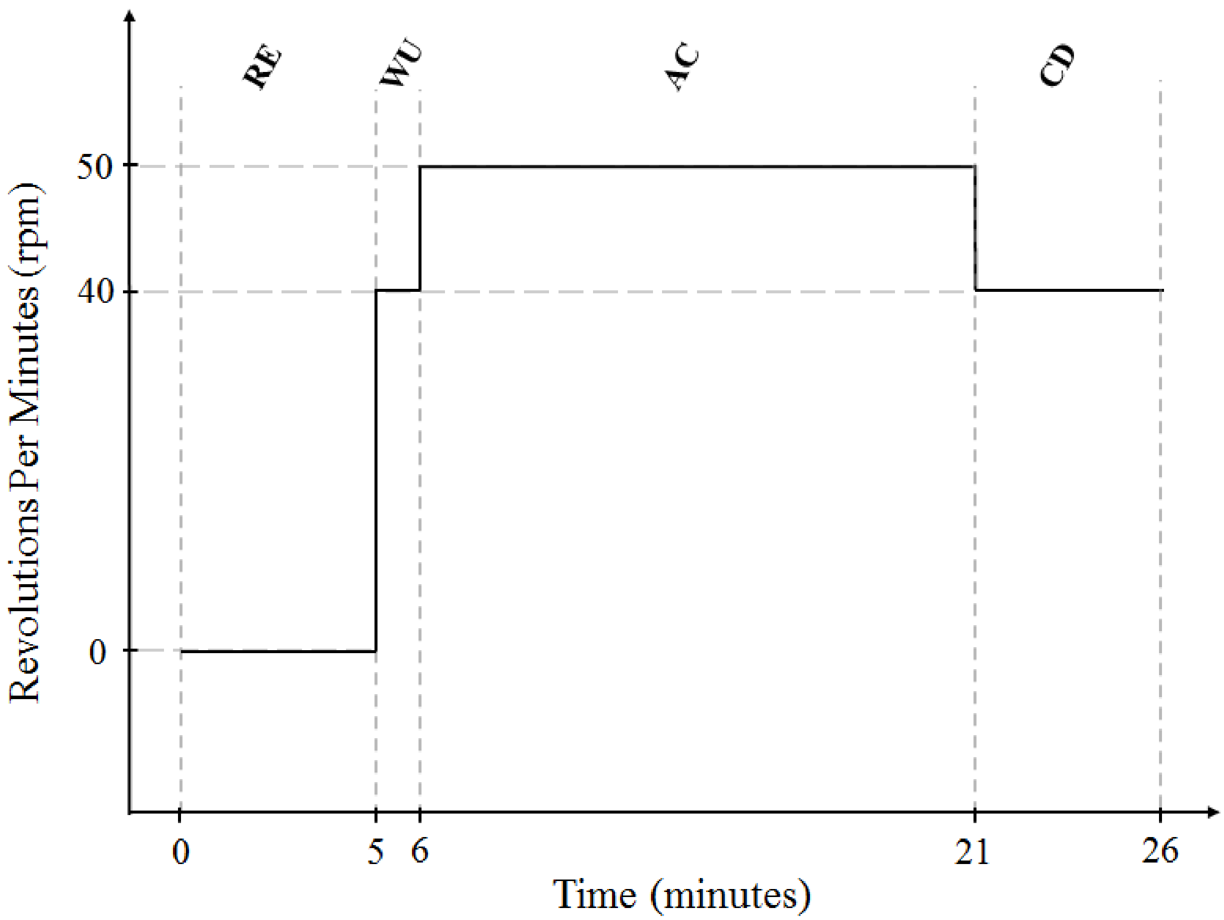

Figure 3: Graphical representation of the continuous physiological response of the FES group during the acute exercise session.

Abbreviations: RE, resting phase; WU, Warmup phase; AC, Active cycling phase; CD cooldown phase.

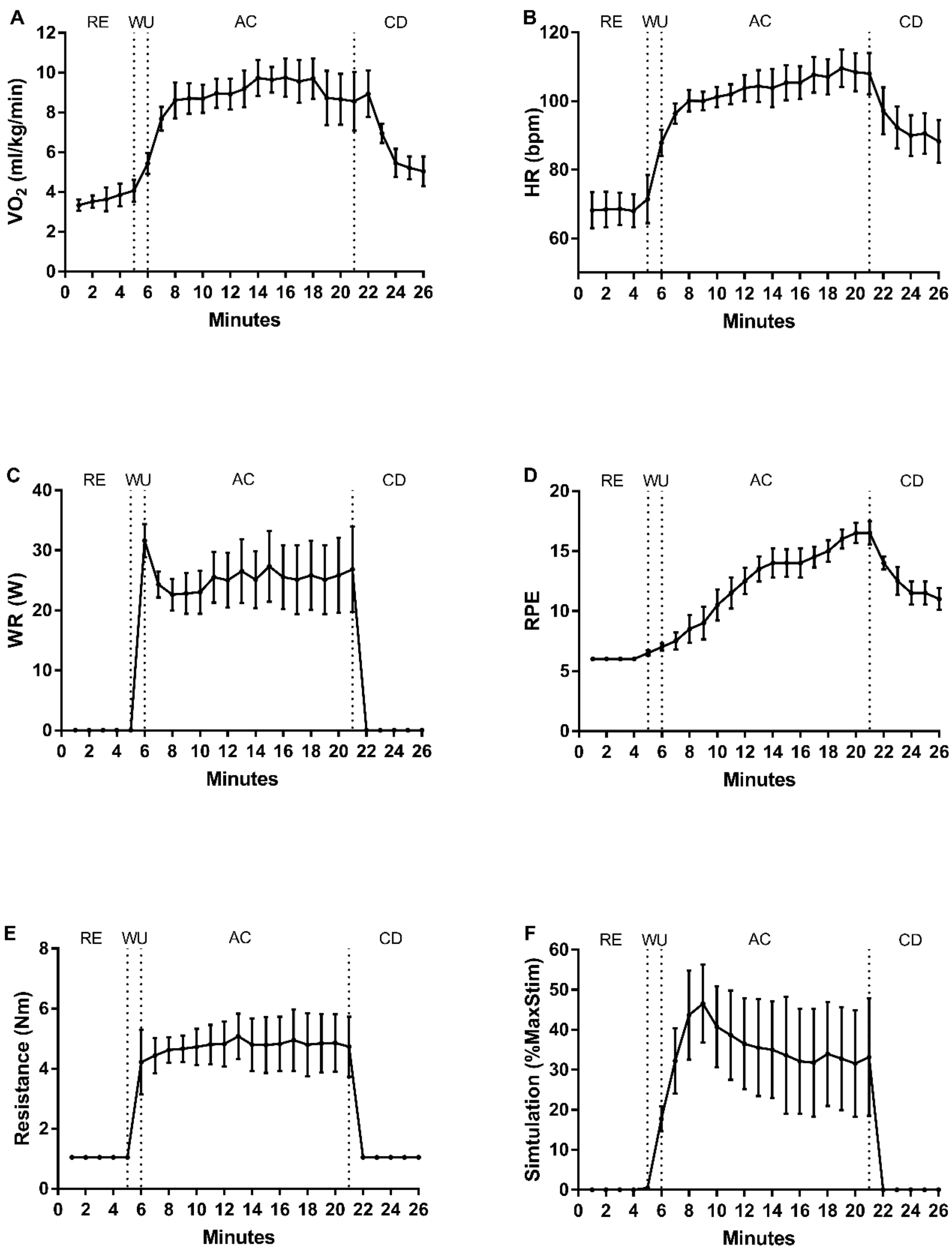

Table 1: Level of evidence and criteria applied to studies included in the review based on the Spinal Cord Injury Rehabilitation Evidence (SCIRE) system.

Level of Evidence	Criteria
Level 1 (*n*=5)	• **RCT:** PEDro Score >6. Includes cross over design with randomized experimental conditions and within-subjects comparison.
Level 2 (*n*=0)	• **RCT:** PEDro Score ≤6. • **Prospective controlled trial:** non-randomized. • **Cohort:** longitudinal study using two (minimally) similar groups with one group being exposed to a condition.
Level 3 (*n*=0)	• **Case-control studies:** retrospective study comparing controls conditions.
Level 4 (*n*=13)	• **Pre-post:** trial with a baseline measure, intervention and a post-test using a single group of subjects. • **Post-test**: post-test with 2 or more groups using a single group (intervention followed by a post-test with no retest or baseline assessment).
Level 5 (*n*=0)	•**Observational**: study using cross sectional analysis to interpret relations.

Table 2: Participant and training characteristics of the 18 articles reviewed, grouped by modality as conventional or adapted exercise training

Study Characteristics			Participant Characteristics			Training Characteristics			
Reference (Quality)	**n**	**Exercise Modality**	**EDSS Range**	**Disease Duration(y) Mean ±SD**	**Age (y) Mean ±SD**	**Duration (weeks)**	**Frequency (x/week)**	**Time (min)**	**Intensity**
CONVENTIONAL EXERCISE TRAINING									
Aerobic Exercise Training (*n*=3)									
Jackson et al 2012a D&B = 16	2	KICK	6.0–6.5	NR	58±4.2	8	2	30-40	≤75% HRR or ≤5 RPE
Jackson et al 2012b D&B = 17	5	KICK	6.0-6.5	10.6±4.9	55.6±5.4	5	3	60	≤75% HRR or ≤5 RPE
Skjerbaek et al 2013 PEDro = 7	6 5	ARM/LEG CON	6.5–8.0 6.5-8.0	NR NR	62.0±5.9 55.2±8.2	4	10 sessions	23	65%–75% VO_{2peak}
Resistance Exercise Training (*n*=2)									
Coote et al 2015 D&B = 20	10 15	PRT PRT + NMES	NR[a] NR[a]	12.2±4.0 11.8±5.5	51.8±12.1 51.8±12.6	12 12	2-3 2-3	NR NR	1-3 sets of 12 repetitions 1-3 sets of 12 repetitions
Filipi et al 2011 D&B = 17	23 17	PRT PRT	5.0–7.0 7.0–8.0	NR NR	NR NR	24 24	2 2	50 50	2–3 sets of 10 repetitions 2–3 sets of 10 repetitions
ADAPTED EXERCISE TRAINING									
Body Weight Support Treadmill Training (BWSTT) (*n*=8)									
Beer et al 2007 PEDro= 8	19 16	RBWS CON	6.0–7.5 6.0–7.5	15.0±8.0 15.0±9.0	49.7±11.0 51.0±15.5	3	5	30	1–2.8 km/h
Giesser et al 2006 D&B= 14	4	TBWS	7.0–7.5	NR	47.0±5.3	~20	2	60	.85-1.03 m/s
Lo & Triche 2008/ Wier et al 2011 D&B= 16/15	6 7	RBWS TBWS	3.5-7.0 3.5-7.0	NR NR	50.2±11.4 49.6±11.8	3	2	40	30%-40% BWS 2.2-2.5 km/h
Pilutti et al 2011 D&B= 19	6	TBWS	6.0–8.0	11.5±6.6	48.2±9.3	12	3	30	1.1-1.6 km/h 77.9%-51.7% BWS
Schwartz et al 2012 PEDro= 8	15 17	RBWS CON	5.0–7.0 5.5–7.0	11.3±6.7 14.9±8.1	46.8±11.5 50.5±11.5	4	2-3	30	40%–20% BWS
Straudi et al 2013 PEDro = 7	8 8	RBWS CON	4.5–6.5 4.5–6.5	17.1±12.0 18.6±10.8	49.6±12.0 61.0±8.8	6	2	30	3km/h, 100%-0% BWS

Table 2 (Cont.)

Vaney et al 2012 PEDro = 7	26 23	RBWS CON	3.0–6.5 3.0–6.5	NR NR	58.2±9.4 54.2±11.3	3	NR	30	50% BWS (gradually decreased)
Total Body Recumbent Stepper Training (TBRST) (*n*=1)									
Pilutti et al 2016 D&B= 18	5 5	TBRST BWSTT	7.0(mdn) 7.0(mdn)	15.2±8.9 12.7±11.2	58.8±3.0 48.2±4.3	12 12	3 3	30 30	3.8–4.6 RPE 2.8–4.5 RPE
Electrical Stimulation Assisted Cycling (ESAC) (*n*=5)									
Backus et al 2016 D&B=20	14	FES	NR[b]	15.3±7.4	55.4±11.0	4	2-3	30	35-50rpm
Fornusek & Hoang 2014 D&B=18	7	NMES	6.5–8.5	NR	48.0±9.0	10	~1.8	40	35-50rpm
Ratchford et al 2010 D&B=18	5	FES	6.0–6.5	13	50 (mdn)	24	3	60	NR
Reynolds et al 2015 D&B=20	8	FES	>6.0	16.8±6.9	54.5±13.9	4	3	30	50rpm
Szecsi et al 2009 D&B = 20	8	FES	4.0–8.0	13.3±8.0	52.1±7.5	2	3	20–30	NR

Abbreviations: PEDro, physiotherapy evidence database scale; D&B, Downs and Black scale; KICK, kickboxing training; ARM, arm ergometry; LEG, leg ergometry; CON, control group; BWS, body weight support; RBWS, Robot-assisted body weight support; TBWS; therapist-assisted body weight support; FES, functional electrical stimulation; NMES, neuromuscular electrical stimulation; NR, Not reported; AT, aerobic threshold; rpm, revolution per minute.

NR[a]= EDSS score not-reported. Participants used assistive devices for ambulation.
NR[b]=EDSS score not-reported. Participants were described as non-ambulatory; unable to ambulate outside the home without assistance.

Table 3: Summary of the outcomes reported in the 19 articles reviewed involving exercise training in severe MS.

	Outcomes			
Reference	**Disability**	**Physical Fitness**	**Physical Function**	**Symptoms & Participation**
CONVENTIONAL EXERCISE TRAINING				
Aerobic Exercise Training (*n*=3)				
Jackson et al 2012a	-	-	↓ABC, ↑BBS, ↑DGI, ↓TUG, ↔Walking speed	-
Jackson et al 2012b	-	-	↑ABC, ↑Mini-BESTest	-
Skjerbaek et al 2013	-	↑VO_{2peak}, ↔HR_{peak} ↔Grip strength	↓9HPT, ↔Box and Block, ↔6-min wheelchair test	↔Fatigue, ↓MDI, ↑QOL
Resistance Exercise Training (*n*=2)				
Coote et al 2015	-	PRT: ↔Muscular endurance (KE), ↑Strength* (hip extensors), ↑Strength (KE) PRT+NMES: ↑Muscular endurance* (KE), ↑Strength* (hip extensors), ↑Strength (KE)	PRT: ↑BBS, ↓MSWS-12, ↔Spasticity, ↔TUG PRT+NMES: ↑BBS**, ↓MSWS-12, ↓Spasticity, ↔TUG	PRT: ↔Fatigue, ↔QOL PRT+NMES: ↓Fatigue*, ↑QOL*(physical), ↔QOL(psychological)
Filipi et al 2011	-	↑1-RM*(leg extension, shoulder press, back row, lat pulldown, chest press)	-	-
ADAPTED EXERCISE TRAINING				
Body Weight Support Treadmill Training (BWSTT) (*n*=8)				

Table 3 (Cont.)

Beer et al 2007	-	↑Strength** (KE)	↑6MW**, ↔Stride length ↑Walking speed**	-
Giesser et al 2006	↔EDSS	↑Strength (combined MMT of hip abductors/flexors/extensors, KE/KF, and dorsiflexors/plantarflexors)	↑6MW, ↑BBS, ↓Spasticity, ↑Walking speed	↑QOL
Lo & Triche 2008/ Wier et al 2011	↓EDSS**	-	↑6MW**, ↓Double support time**, ↔Step length ratio, ↑T25FW**	↔Bladder/bowel control ↓Fatigue*, ↓Fatigue, ↑Life satisfaction*, ↑MHI, ↓Pain*, ↓Perceived deficits*, ↑QOL*, ↑QOL, ↔Sexual satisfaction, ↔Social support, ↔Visual impairment impact
Pilutti et al 2011	↔EDSS, ↓MSFC	-	↔9HPT, ↑Walking speed	↓Fatigue, ↑QOL*
Schwartz et al 2012	↓EDSS*	-	↑6MW, ↑BBS*, ↓TUG* ↔Walking speed	↑FIM**, ↑QOL
Straudi et al 2013	-	-	↑6MW*, ↑Gait kinematics*/**, ↓TUG, ↑Walking speed*	↓Fatigue
Vaney et al 2012	-	-	↑BBS, ↔RMI, ↔Spasticity ↔Walking speed	↓Fatigue, ↔PA, ↔Pain, ↑QOL
Total Body Recumbent Stepper Training (TBRST) (*n*=1)				
Pilutti et al 2016	↔MSFC	-	↔9HPT, ↔Walking speed	↓Fatigue*, ↑QOL
Electrical Stimulation Assisted Cycling (ESAC) (*n*=5)				
Backus et al 2016	-	↔Strength (combined MMT of hip flexors, KE/KF, dorsiflexors)	↔Spasticity	↔Bladder/bowel control ↓Fatigue*, ↓Fatigue, ↔MHI, ↓Pain*, ↔Perceived deficits,

Table 3 (Cont.)

				↔QOL, ↔Sexual satisfaction, ↔Social support, ↔Visual impairment impact
Fornusek & Hoang 2014	-	↑Thigh circumference**	↓Spasticity (self-reported)	↑Circulation, ↑Transfer ability (self-reported)
Ratchford et al 2010	↔EDSS	↑ Strength (hip extensors, KE/KF) ↓Strength (hip flexors, dorsiflexors)	↑2MW, ↓9HPT (dominant), ↑T25FW, ↑Gait kinematics, ↓TUG, ↑Walking speed ↔Spasticity	↑QOL, ↔SCL-90
Reynolds et al 2015	-	↑mVO_2*	-	-
Szecsi et al 2009	-	↔Strength (KE/KF)	↓Spasticity (acute), ↔Spasticity (long-term), ↔Walking speed	-

↑ Indicates increase in outcome measure; ↓ Indicates decrease in outcome measure, ↔ Indicates no increase or decrease in outcome. *Indicates statistically significant difference, $p<.05$; **Indicates statistically significant difference, $p<.001$.

Abbreviations: 1-RM, 1-repetition maximum; 2MW, 2-minute walk test; 6MW, 6-minute walk test; 9HPT, 9-hole peg test; ABC, activities-specific balance confidence scale; BBS, Berg Balance Scale; DGI, Dynamic Gait Index; EDSS, Expanded Disability Status Scale; FIM, functional independence measure; KE, knee extensors; KF, knee flexors; MDI, Major Depression Inventory; MHI, Mental Health Inventory; Mini-BESTest, Mini-Balance Evaluation Systems Test; MMT, Manual Muscle Test; MSFC, Multiple Sclerosis Functional Composite; MSWS-12, 12-item Multiple Sclerosis Walking Scale; mVO_2, muscle oxygen consumption; PA, physical activity; QOL, quality of life; RMI, Rivermead Mobility Index; SCL-90, Symptom Checklist-90; T25FW, timed 25-foot walk test; TUG, Timed Up-and-Go test; VO_{2peak}, peak oxygen consumption. Outcome variables are presented in alphabetical order within each category.

Table 4: The demographic, clinical and peak cardiorespiratory fitness variables for the FES cycling and passive leg cycling groups.

Variable	**FES Cycling (*n*=6)**	**Passive Cycling (*n*=5)**	***p*-value**
Demographic and Clinical			
Age (years)	58 (6.0)	47.8 (7.4)	.03*
Height (cm)	160.8 (9.8)	165.4 (14.1)	.54
Weight (kg)	68.8 (17.1)	95.5 (42.7)	.19
EDSS, mdn (IQR)	6.25 (.63)	6.0 (.75)	.80
MS duration (years)	20.8 (7.8)	21.0 (7.3)	.97
Peak Cardiopulmonary Exercise Response			
VO_{2peak}	13.9 (3.6)	14.1 (6.7)	.89
HR_{peak}	135.7 (24.9)	144.2 (26.3)	.48
WR_{peak}	46.7 (11.3)	80.0 (49.6)	.38
RER_{peak}	1.2 (0.4)	1.1 (0.1)	.54
RPE_{peak}, mdn (IQR)	17.0 (4.25)	15.0 (5.5)	.78

Values are reported as means (SD), unless specified otherwise.
Abbreviations: VO2, volume of oxygen consumption; HR, heart rate; WR, work rate; RER, respiratory exchange ratio; RPE, rating of perceived exertion.
*Indicates significant difference between groups at the $p<.05$ level.

Table 5: The average physiological response during the active cycling phase of the acute exercise session for the FES cycling and passive leg cycling groups. Values are reported as mean (SD) unless specified otherwise.

Variable	**FES Cycling (*n*=6)**	**Passive Cycling (*n*=5)**	***p*-value**
Training Variables			
VO_2 (ml/kg/min)	8.7 (1.8)	3.1 (.58)	.001*
HR (bpm)	102.0 (9.7)	77.6 (5.6)	.002*
WR (W)	27.0 (9.2)	.34 (.63)	<.001*
RER	.93 (0.1)	.85 (0.1)	.08
RPE, mdn (IQR)	13.5 (5.5)	6.0 (1.5)	0.03*
Percentage of Peak Variable			
$\%VO_{2peak}$	63.5 (9.7)	26.9 (13.1)	.007*
$\%HR_{peak}$	76.4 (9.7)	55.5 (12.9)	.07
$\%WR_{peak}$	57.3 (12.9)	.43 (.74)	<.001*

Abbreviations: VO2, volume of oxygen consumption; HR, heart rate; WR, work rate; RER, respiratory exchange ratio; RPE, rating of perceived exertion.

*Indicates significant difference between groups at the $p<.05$ level.