Characterizing change in locomotor control following aerobic cycling interventions in

individuals with neurological deficit due to stroke and Parkinson's disease

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Characterizing Change in Locomotor Control Following Aerobic Cycling Interventions

in Individuals with Neurological Deficit due to Stroke and Parkinson's Disease

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ABSTRACT

Gait dysfunction is a common clinical feature of neurological conditions including stroke and Parkinson's disease (PD), contributing significantly to decreased independence with activities of daily living, diminished quality of life, and increased risk of falls. Given this impact on disability, considerable emphasis is placed on rehabilitation strategies to improve gait. The current clinical standard of care for gait rehabilitation involves motor learning-based approaches with an emphasis on task-specific gait training and the management of impairments that lead to gait dysfunction. Over the past decade, we have investigated the role of aerobic cycling to mitigate symptoms of PD and to improve recovery post-stroke. While our primary outcomes involved upper limb motor function, we observed improvements in walking capacity and postural stability in both conditions following the 8-week cycling intervention. These improvements occurred in the absence of task-specific gait training, indicating that cycling either induced a transfer of training effect or that a central mechanism associated with the aerobic nature of the intervention facilitated walking recovery. To further investigate these observed changes in walking, biomechanical gait analysis was conducted in a subset of participants from the Cyclical Lower Extremity for Exercise (CYCLE) Trial and from a study investigating the effects of forced rate aerobic exercise on stroke recovery. The overarching aim was to investigate the biomechanical mechanisms associated with change in gait velocity following the aerobic cycling intervention. We hypothesized that aerobic cycling would induce improvements in locomotor control. Our findings support our hypothesis as increased gait velocity following the 8-week aerobic cycling intervention was accompanied by improved gait biomechanics in individuals with PD and stroke.

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PREFACE

Twenty-nine years ago, I graduated with my bachelor's degree in physical therapy from Cleveland State University and obtained my license to practice on August 23, 1993. I vividly recall being encouraged by our faculty to embrace the concept of lifelong learning and to keep abreast of the literature, as complacency in any medical profession was simply unacceptable. I am proud to have lived up to that promise and I am honored to contribute to the literature that drives our clinical practice and aims to improve the quality of life of the patients we serve.

My accomplishments would not have been possible without the influence of mentors, colleagues, patients, and my family. I would like to thank my dissertation committee for their support and guidance: Dr. Ken Learman, my committee chair and dissertation advisor, for his support and commitment to our profession that we hold ourselves to a high standard in the science of physical therapy. To Dr. Jay Alberts, for challenging me and others who have come after me to persevere in our scientific endeavors, continue to innovate, and to always put in a good day's work, because "there are no shortcuts to the top". To Dr. Debbie Espy, a respected fellow neurological therapist and mentor, for serving as my role model in neurorehabilitation research and higher education. To Dr. Mandy Miller Koop, for sharing her engineering knowledge and expertise which shaped my dissertation, and for her genuine friendship. I am grateful for the leadership in the Neurological Institute at the Cleveland Clinic; specifically, Dr. Andre Machado, Institute Chair, and Dr. Francois Bethoux, Department Chair, for their support in my academic pursuits and for recognizing the potential in me that wasn't always apparent to me. I could not have accomplished my work over the last twelve years

1   BACKGROUND

1.1   Stroke Pathophysiology

Stroke is defined as "a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage."[2] An endpoint of cardiovascular disease, stroke is the second highest cause of long-term disability in the United States (US), following only mental health disorders.[3] There are an estimated 5.8 million survivors of stroke in the US living with residual neurological deficit resulting in a significant economic burden, with direct costs estimated at $38 billion and indirect costs approaching $30 billion annually.[4-6]

Of the estimated 795,000 strokes that occur each year in the United States, 610,000 are new while 185,000 are recurrent.[3] Eighty-seven percent of all strokes are ischemic, 10% are due to intracranial hemorrhage, and the remaining 3% caused by subarachnoid hemorrage.[3] Regardless of mechanism, the loss of body functions and structures associated with stroke are among the most disabling, characterized by hemiplegia or hemiparesis, and/or loss of sensory function resulting in diminished motor control.[7] Deficits in motor control result in activity limitations, including difficulty with functional mobility tasks, postural stability, walking, and the performance of activities of daily living (ADLs).[7] Ultimately, sensorimotor deficits and activity limitations have a profound negative impact on participation, restricting the individual's ability to work, participate in life roles, and fully reintegrate into the community.

While survival rates have improved over the last several decades with advancements in acute stroke care, nearly two-thirds of individuals do not recover full

use of their affected upper extremity (UE) and three-fourths do not regain full use of their lower extremities (LE).[8-10] Limitations in walking contribute significantly to disability, resulting in increased risk for falls, fractures, and decreased confidence in upright mobility.[10-12] Increasing gait velocity is a primary goal for gait rehabilitation post-stroke, as walking speed has been shown to be a predictor of disability.[13-15]

1.1.1 Gait Dysfunction Post-Stroke

Neural control of human gait requires the rapid and precise timing, activation, and coordination of muscles spatiotemporally to allow for the appropriate balance of stability and mobility of each body segment rhythmically throughout the gait cycle.[16] Individuals with hemiplegia due to stroke present with a broad range of impairments from muscle weakness, spasticity, and motor control deficits, resulting in the abnormal activation of muscle synergies.[17] A hallmark of hemiplegic gait is the presence of asymmetry affecting the paretic and non-paretic limbs in addition to the trunk, impacting both stance and swing phase biomechanics.[18] Asymmetries associated with post-stroke impairments affect the spatiotemporal, kinematic, and kinetic characteristics of gait which are difficult to quantify using clinical measures. Therefore, biomechanical gait analysis is used to quantify asymmetries and abnormalities in hemiplegic gait.

Spatiotemporal characteristics of gait include velocity, cadence, step/stride length, step width, swing time, stance time, and the percentage of single and double limb support time. While individuals present with a broad spectrum of spatiotemporal deficits post-stroke, diminished locomotor control typically results in decreased velocity, decreased cadence, decreased and asymmetrical step length, and decreased and asymmetrical time spent in single limb support.[19] As it relates to step length, asymmetries have been

measured in both directions, with the hemiparetic limb presenting with a disproportionately shorter or a longer step length.[9,18] Longer hemiparetic limb step lengths often result in a "step-to" gait pattern, with inadequate stance stability resulting in decreased propulsion of the center of mass past the hemiparetic limb.[20,21] Disproportionately shorter step length of the hemiparetic limb is often due to inadequate strength of the hip flexors or poor positioning of the hemiparetic limb in terminal stance (ie: decreased hip extension).[21] While changes in spatiotemporal gait parameters are often compared at various gait velocities, the variables are highly correlated, making it difficult to ascertain what is responsible mechanistically for changes in gait velocity.[22] Therefore, examining changes in gait kinematics and kinetics, in addition to change in spatiotemporal variables, allows for the most comprehensive assessment when determining biomechanical mechanisms associated with change in gait velocity.[16,23,24]

Altered gait kinematics post-stroke are due to muscle weakness, spasticity, contractures/adaptive muscle shortening, or a combination of all three impairments. Impairments at one joint often impact the kinematic chain proximally or distally, compensating for abnormal biomechanics.[25,26] During stance phase, the primary action of the limb is that of hip extension, which, together with passive ankle dorsiflexion, transports the trunk from posterior to anterior of the stance foot.[20] Weakness of the hip extensors, knee extensors, and/or adaptive shortening of the ankle plantarflexors or hip flexors results in decreased hip extension at terminal stance.[20] The role of the knee is to provide for dynamic stability to allow for weight acceptance, absorbing the shock from initial contact. Common stance phase deficits at the knee include diminished dynamic control from loading response to mid-stance characterized by knee extension or

hyperextension.[20] In terminal stance, spasticity combined with the inability to rapidly

alternate from extension to flexion results in decreased knee flexion. In normal human

gait, the ankle rapidly plantarflexes from ~8 degrees of dorsiflexion terminal stance to

~18 degrees of plantarflexion at pre-swing to propel the body forward onto the

contralateral stance leg.[16] This rapid propulsion is often absent in hemiplegic gait due to

paresis, adaptive shortening of the plantarflexors, or a combination of both.[24,25]

Additionally, one must consider the effect of bracing, as ankle-foot orthoses meant to

compensate for dropfoot also impact stance phase kinematics by limiting dorsiflexion

and/or hip extension at terminal stance.[27]

Swing phase, responsible for ~40 percent of the gait cycle, requires the lower

limb to shorten to allow for adequate clearance during limb advancement.[21] Common

compensatory strategies to provide sufficient clearance include circumduction often

accompanied by hip hiking. This strategy is employed due to hip flexion weakness, the

inability to sufficiently flex the knee, and diminished ankle dorsiflexion power causing

foot drop.[21] Additionally, excessive extensor spasticity and adaptive muscle shortening

can also contribute to these compensatory strategies. The resultant kinematic

characteristics include decreased peak hip flexion, decreased peak knee flexion,

decreased knee extension prior to initial contact, and decreased ankle dorsiflexion

throughout swing phase.[21]

Gait kinetics describe the mechanics of walking as it relates to forces, work, power,

and moments.[28,29] Diminished muscle power due to the hemiparetic condition results in

decreased joint moments in the paretic limb and reduced ground reaction forces

throughout stance phase, particularly evident during peak propulsive forces at terminal

stance.[17] Ankle plantarflexion and hip extension are the two main generators of propulsive forces in human gait. The use of ankle-foot orthoses to control foot drop perpetuates the loss of propulsion as the brace itself inhibits activation of the plantarflexors throughout stance. As shown in Figure 1.1a, vertical ground reaction forces in normal human gait follow an M-shaped curve, with a peak occurring at loading response, a slight decrease during mid-stance due to the propulsive forces from the contralateral limb, and a second peak at terminal stance with limb propulsion. This characteristic M-shaped curve is often reduced or parabolic in persons post-stroke as shown in Figure 1.1b, due to decreased gait velocity, diminished propulsion, and a resultant decrease in momentum-driven weight transfer between the paretic and non-paretic limbs.[29]
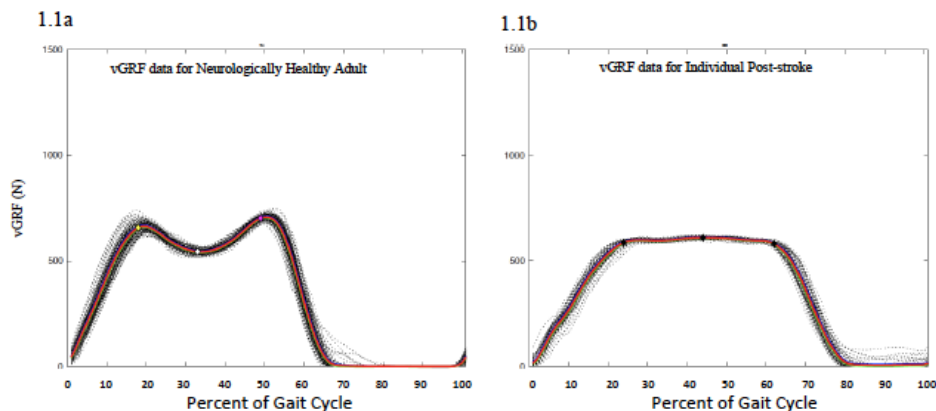
Figure 1.1   Vertical ground reaction force (vGRF) data from a neurologically healthy individual in shown in Figure 1.1a depicting a normal "M-shaped" curve indicative of a peak in force with weight acceptance (yellow-shaded diamond) and push off (pink-shaped diamond), and a valley at mid-stance, when knee extension displaces the center of mass upwardly, reducing the vGRF typically to less than the individual's body weight. In individuals with neurological disorders such as stroke, momentum inherent to human gait is disrupted as evidenced by a parabolic-shaped or flattened curve shown in

1.2   Principles of Motor Learning Applied in Neurorehabilitation

The recovery of motor function post-stroke is mediated by neuroplasticity, thought to be achieved via motor learning. An important concept in stroke rehabilitation

is differentiating recovery from compensation. Recovery involves the formation of new neural connections from undamaged regions of the brain to muscles originally innervated by regions damaged from the stroke.[30,31] Compensation, on the other hand, involves the use of alternative muscles or movement patterns to accomplish a motor task.[30] While learning is required for true recovery and compensation, recovery involves cortical reorganization of the undamaged motor cortex through behavioral task training which is experience-dependent.[30,31]

Motor learning principles originally investigated in neurologically healthy individuals from the early 1900's have been adopted to guide neurorehabilitation in individuals with stroke with the assumption that motor recovery is facilitated by the repetitive practice of movements or motor tasks.[30] Neuroscientists and rehabilitation clinicians have capitalized on the tenet that the brain is capable of remodeling its neural circuitry based on experiences to drive behavioral change.[30,31] Thus, neuroplasticity is driven by motor, sensory, and cognitive experiences, and is considered the key to neural reorganization of the damaged brain.[8,30-32] Acknowledging that the damaged brain may learn differently than a healthy brain, neurorehabilitation scientists continue to investigate how to adapt principles of motor learning to optimize recovery of individuals with stroke.

While motor learning principles have been applied in neurorehabilitation since the 1980's, optimal approaches to drive neuroplasticity of the damaged brain and mechanisms of recovery are not well understood, despite technologies such as high-resolution neuroimaging. Furthermore, the investigation of traditional motor learning principles such as the dose-response relationship and the effects of timing on recovery has yielded mixed results in clinical trials.[10,33-36] Despite these inconsistencies, there is

overwhelming evidence demonstrating the effectiveness of applying motor learning principles to improve function in individuals with stroke, and several key principles of motor learning remain a part of standard clinical practice.

1.2.1 Practice

The recovery of motor function following stroke is thought to be experience-dependent, driven primarily through repetitive practice.[31,37] While repetition is considered a critical factor in facilitating neuroplasticity, the optimal dose for skill acquisition varies tremendously based on numerous factors including lesion severity, stroke chronicity, the difficulty of the skill, novelty versus task familiarity, how motor task practice is administered, and the ability of the individual to engage actively in practice.[31,37] Meta-analyses of human studies investigating dose-response relationships have in general, shown a positive relationship, with greater amounts of practice yielding greater improvements in function.[38] However, the relationship is not linear and considerable variability and heterogeneity are common across studies.[38] Based originally on animal models, it has been theorized that 300-800 repetitions of motor task practice are needed to regain functional tasks for the upper limb.[39,40] Lang and colleagues developed protocols for repetitive upper limb motor task practice with the intent of achieving a minimum of 300 repetitions per one-hour session. An initial proof-of-concept study found clinically significant improvements in upper limb motor function following 18 sessions administered over a course of 6 weeks.[39] However, in a subsequent landmark phase II trial investigating four doses of upper limb motor task practice (3200, 6400, 9600 or individual maximum repetitions administered over thirty-two 1-hour sessions), they found no evidence of a dose-response relationship and relatively small treatment

effects overall.[33] The results of this study left doubt and confusion in stroke rehabilitation clinicians, as long-standing dose-response hypotheses were refuted.

1.2.2 Specificity, Transfer of Task, and Interference

In motor learning, skill acquisition is accompanied by changes in neural connectivity in the motor cortex and cerebellum characterized in part by synaptogenesis and dendritic growth.[31] Following stroke, cortical reorganization occurs specific to the brain region responsible for the newly acquired or reacquired motor task. For example, functional neuroimaging has shown that the repetitive practice of upper limb reaching, grasping, or manipulation results in increased synaptic density in motor map topography of the hand and digits.[41] Given the multitude of tasks that must be learned initially during human development and relearned in the presence of brain injury, it has been suggested that a transfer of training may occur between distinct motor tasks, with improvements in the performance of untrained tasks following the repetitive training of a different task.[42] Transfer of training is hypothesized to occur when the kinematic and spatiotemporal requirements of the tasks are similar. For example, grasping cylindrical-shaped cups of various diameters may result in transfer of training as it relates to the ability to open the hand and maintain sufficient force to grasp and lift the cup. However, motor control requirements differ as it relates to the modulation of forces when grasping a Styrofoam cup versus a glass tumbler. Practicing grasping both types of materials may be necessary for skill acquisition to occur. However, repeated practice of a cylindrical grasp may not transfer to a precision grasp such as holding a pencil. Similarly in human gait, walking is a cyclical movement pattern, characterized by the rapid activation and relaxation of lower extremity extensors and flexors in a synergistic manner during stance and swing phases

of gait. Running is also cyclical but is more demanding from a motor control perspective

due to the more rapid nature of transitions between extensors and flexors, in addition to

the need for increased shock absorption with loading response and increased propulsion

at terminal stance. Therefore, while some degree of transfer of training is expected to

occur between walking and running, task-specific training is needed to proficiently learn

the more complex task of running. Interference refers to one skill impeding the ability to

learn a novel skill within the same neural circuitry. For example, swinging a golf club

and baseball bat are similar from a gross motor function perspective, but must follow

different paths to be effective and proficient. The repeated practice of one may impede

the skill acquisition of the other, as the similarities may make it difficult to learn the

subtleties that are unique to each task.

1.3   Evidence of Gait Recovery Post-Stroke

In recent years, principles of motor learning have guided the design of clinical

trials in stroke, in attempts to provide clarity regarding the type, dose, and intensity of

practice needed to optimize locomotor recovery. Tenets of neurorehabilitation have been

tested including hypotheses related to task specificity, timing of rehab, and dose-response

relationships. Given evidence in motor learning literature that specificity, amount, and

intensity of practice are paramount in influencing neuromuscular adaptations that impact

motor skill acquisition,[43] a recently published clinical guideline was designed to delineate

the evidence of rehabilitation strategies that have been shown to improve locomotor

function post-stroke.[44] The authors cited Level I-II evidence supporting the use of

moderate- to high-intensity walking training to improve walking speed and distance.

Similarly, Level I-II evidence was cited demonstrating the effectiveness of virtual reality

walking training. In contrast, the clinical guideline cited weak evidence supporting the

use of cycling interventions to improve locomotor function in individuals post-stroke,

noting, however, that training occurring at high intensity aerobic levels may show

efficacy more so than low intensity training. There was also weak evidence cited

supporting the use of body weight supported treadmill training, owing to the higher costs

associated with equipment and personnel compared to overground gait training.[10] Lastly,

gait training using robotic assistance was not recommended as several clinical trials

reported results favoring nonrobotic walking groups.[45,46] The recommendations from the

clinical guideline highlight the shifts that have occurred over the past two decades in

clinical rehabilitation practice, and that additional research using high-resolution

outcomes is needed to obtain a more precise understanding about how to facilitate

improvements in locomotor control.

1.4 Parkinson's Disease Pathophysiology

Parkinson's disease (PD) is progressive neurodegenerative disease affecting just

over one million individuals in the United States and is manifested by motor and

nonmotor symptoms.[47] The pathophysiology of PD involves the depigmentation of the

substantia nigra and locus coeruleus resulting in the loss of dopaminergic pathways.[47]

The cardinal motor symptoms associated with PD include resting tremor, bradykinesia,

postural instability, and rigidity. Nonmotor symptoms of PD include cognitive

impairment, depression, anxiety, autonomic nervous system dysfunction, and sleep

disturbance.[47] Pharmacological treatments target dopaminergic neurons to produce more

dopamine and are introduced when symptoms begin to impact the individual's quality of

life. The therapeutic benefits of medications such as Levodopa reduce over time, and can

cause serious side effects including dyskinesias, hallucinations, delusions, somnolence, and dystonia.[47] When pharmacological treatments are no longer effective, deep brain stimulation becomes a viable option most effective at managing resting tremor associated with PD.[47] Supportive therapies including physical, occupational, and speech therapy, are recommended to manage motor symptoms that impact function including walking, balance, freezing of gait, fine motor dexterity to complete activities of daily living, vocalization and swallowing.[48]

1.4.1 Gait Dysfunction in Parkinson's Disease

Gait dysfunction is among the most disabling features of PD, impacted by the cardinal signs of bradykinesia, rigidity, and postural instability, in addition to the diminished amplitude of movement.[49] Collectively, these neurological symptoms result in decreased gait velocity, reduced step length, increased rigidity through the trunk, and impairments in the rhythmic nature of human gait.[49] Gait dysfunction worsens with disease progression, commonly characterized by episodes of freezing of gait, which is the sudden inability to continue walking despite the intent to do so.[49] Dopaminergic medications are successful in mitigating certain aspects of gait dysfunction including velocity and step length, but fail to improve freezing of gait or postural instability. Therefore, when possible, it is helpful to assess individuals off medications to best understand the true impact of the disease on gait and to observe function when the effects of medications wear off.[49]

Deficits in spatiotemporal, kinematic, and kinetic components of gait are observed in persons with PD, with symptoms initially presenting unilaterally and eventually progressing to bilateral involvement.[49] The symptoms of PD which include diminished

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power and rigidity contribute to reduced forward propulsion, which from a spatiotemporal perspective, results in decreased gait velocity, reduced step length, impaired cadence, and increased double limb support percentage.[49,50] The kinematic deficits are characterized by decreased sagittal plane range of motion at the hip, knee, and ankle, in addition to truncal rigidity and diminished arm swing.[47] Altered gait kinetics in persons with PD are primarily associated with changes in ground reaction force (GRF) data, and are often more pronounced than gait kinematics.[51] When evaluating gait kinetics in persons with PD compared to healthy, age-matched controls, Oh and colleagues reported reduced vGRF data, abnormal shape of the vGRF curve, and diminished AP propulsive forces.[51] These kinetic findings support the clinical observations that PD symptoms such as bradykinesia and rigidity negatively impact the momentum-driven and propulsive activity inherent to human gait.

1.4.2   Gait Rehabilitation in Parkinson's Disease

Although the course of PD is progressive, rehabilitation has been found effective in improving impairments which contribute to gait dysfunction and postural instability.[52] The rehabilitation management of gait dysfunction is paramount in PD, as deficits in walking are a significant source of disability and negatively affect participation and quality of life.[52] Rehabilitation is optimal when introduced early after diagnosis, as the course of the disease is somewhat predictive, and early intervention can reduce the complications associated with PD and secondary impairments such as stiffness and loss of range of motion. Furthermore, education and the appropriate timing for the introduction of compensatory strategies and/or assistive devices can serve to reduce fall risk. Approaches to improve gait and postural stability are tailored to address active PD-

related impairments and to prevent or delay anticipated impairments common with disease progression.[48] A recently published clinical practice guideline summarized the evidence as it relates to rehabilitation approaches that have been shown effective in improving gait in persons with PD.[48] A summary of the findings and recommendations is provided in Table 1.1.[48]

Table 1.1 Recommendations to Improve Gait in People with PD

Intervention	Mode	Gait-Related Outcomes
Aerobic Exercise[53]	Moderate intensity (60-75% of max HR) to high-intensity (75-85% of max HR) aerobic exercise on treadmill or stationary bike	Improved Six-Minute Walk Test (6MWT) performance
Resistance Training[54,55]	Progressive resistance exercises	Improved Timed Up and Go (TUG), 2-minute sit to stand, gait velocity and 10-meter walk test
Balance Training[56,57]	Multi-modal balance training	Improved gait velocity, Functional Gait Assessment (FGA), Freezing of Gait, and Spatiotemporal characteristics of gait (stride and step length)
External Cueing[58]	Rhythmic auditory stimulation, metronome-based cueing, proprioceptive stimuli applied through feet, and visual cues	Improved gait velocity, spatiotemporal parameters of gait (step length, cadence), TUG, dual-task TUG, 6MWT, and freezing of gait
Gait Training[59,60]	Overground gait training, partial weight-supported treadmill training, robotic-assisted gait training, virtual reality treadmill training, circular treadmill training, downhill treadmill training, forward and backward treadmill training	Improved gait velocity, step length, cadence, 6MWT, two-minute walk test (2MWT), TUG, FGA, and freezing of gait
Task-Specific Training[61]	Mental imagery, turning training, fall	Improved 6MWT, TUG, 30-second chair stand test, Mini BESTest, TUG

	prevention training, dual task training, multi-modal training	dual task, 360-degree turn, FGA, 10MWT, freezing of gait
Behavior-Change Approach[62]	Application of behavioral change theories with physical therapy or exercise interventions	Improved 6MWT performance

1.5 Aerobic Exercise Training

Public health experts in the US have placed considerable emphasis on highlighting the benefits of aerobic exercise training as it relates to cardiovascular health. However, only recently have scientists investigated the effects of aerobic exercise training on brain function.[63] Aerobic exercise has been shown to increase cerebral blood flow, promote angiogenesis, and is associated with increased levels of dopamine, brain-derived neurotrophic factor (BDNF), and insulin-like growth factor-1 (IGF-1), all of which have been implicated in neuroplasticity and enhanced motor learning.[64-75] Increased concentrations of endogenous neurotrophins are known to facilitate neuronal growth, differentiation, and adaptation, and have been implicated as the mechanism by which exercise improves cognition, learning, and memory in healthy older adults.[69,73] Importantly, exercise intensity appears to be a critical variable to trigger the neurophysiological responses thought to enhance brain function. A systematic review by Knaepen and colleagues found that aerobic exercise training induced a greater upregulation of basal levels of BDNF compared with strength training.[67] While a moderate- to high-intensity training regimen was necessary to increase levels of BDNF in healthy adults, low- to moderate-intensity aerobic exercise training was sufficient to induce a response in people with chronic disease or disability. The response, however, in

both healthy individuals and in people with chronic disease or disability appears to be transient. Nonetheless, transient elevations of circulating BDNF can provide an opportunity to harness its neuroplastic effects, as aerobic exercise may prime the CNS to optimize neural repair and recovery.[76]

Given the substantial scientific rationale demonstrating the potential for aerobic exercise to enhance brain function, exercise studies in humans and animal models have been undertaken to determine behavioral changes and mechanistic responses associated with aerobic exercise training.[66,76-80] In stroke, it is theorized that the upregulation of neurotrophic growth factors including BDNF, IGF-1, and neurotrophin-3 facilitates long-term potentiation, mediating neuroplastic responses within the CNS. Aerobic exercise training also increases levels of neurotransmitters including Dopamine and Seratonin, which can improve learning, memory, and attention. Additionally aerobic exercise training results in increased cerebral blood flow. Collectively, these responses can serve to prime the CNS,[81] increasing the motor learning effects associated with motor task practice. Therefore, in individuals with stroke, rehabilitation clinicians can potentially exploit the effects of aerobic exercise training by pairing it closely in time with motor retraining therapies.[66,76,78]

In Parkinson's disease, the neurophysiological effects of aerobic exercise training are hypothesized to occur on a cellular and molecular level to promote neuroprotection, slow degeneration, and improve neuronal survival and neuroplasticity.[68,73,82-89] Neurobiologically, aerobic exercise modulates the substrates associated with neuroplasticity through neurogenesis, upregulation of neurotrophins, increasing levels of neurotransmitters, reducing oxidative stress, and reducing inflammation.[43,68] A reduction

in motor symptoms has been reported after studies employing high-intensity aerobic exercise training, suggesting that exercise can reduce the degradation of dopaminergic neurons, increase levels of dopamine, or a combination of both.[67,88] In our own study, the effects of exercise on CNS function in ten persons with PD were evaluated using functional MRI and resting state functional connectivity.[90,91] After a forced-rate aerobic cycling session, imaging data indicated altered CNS patterns of activation in the primary motor cortex, supplementary motor area, thalamus, globus pallidus, and putamen, similar to activation patterns seen after levodopa.[90,91] These data complement numerous studies demonstrating that a central mechanism can explain the reduction of motor symptoms associated with PD following intensive aerobic exercise training.

1.5.1 Forced Exercise

The term "forced exercise" originates from animal models in which the experimental set-up allows for exercise intensity to be manipulated by increasing the rate, speed, or duration of exercise, beyond the animal's voluntary intensity.[72] In rodent models, a motorized running wheel or the presentation of a noxious stimulus is used to ensure that the animal maintains a pre-determined exercise intensity.[68,92] Animal studies conducted over the last two decades have investigated the neuroplastic, neurorestorative, and neuroprotective effects of forced versus voluntary exercise on behavioral outcomes, symptoms, and neurophysiological (mechanistic) outcomes. While the optimal dose, rate, and timing of intensive aerobic exercise varies across disease condition and across outcomes of interest, in general, it has been shown that moderate- to high-intensity aerobic exercise is needed to induce a positive effect on neurological function.[68,72]

In humans with neurological conditions such as stroke and Parkinson's disease, impairments in strength, motor control, and the neurological symptoms inherent to each condition such as spasticity, rigidity, and bradykinesia can preclude individuals from achieving and maintaining aerobic activity of sufficient intensity to trigger the proposed neurophysiological response needed to induce neuroplasticity, neurorestoration, or neuroprotection.[76] Recognizing that forced exercise (FE) may be a viable approach to bridge this gap, Dr. Jay Alberts developed a FE aerobic cycling intervention originally using a tandem stationary cycle.[93,94] The tandem cycle allowed for a trainer to assist the participant in maintaining a consistent cadence and power output throughout the session. Heart rate (HR) was monitored continuously to ensure that the patient was contributing to the output and exercised within his/her target HR zone. The FE model evolved after the initial pilot study in PD to be administered on a custom-designed motorized stationary semi-recumbent cycle ergometer

Figure 1.2 Participant from a pilot stroke study completing a forced exercise cycling session under the supervision of the study exercise physiologist.

shown in Figure 1.2 designed to supplement the participant's voluntary efforts. The control system monitors pedaling rate continuously and scales the amount of torque provided to ensure that exercise cadence is maintained at the pre-determined rate. As with the stationary tandem approach, HR is monitored continuously to ensure that the participant is contributing to the exercise and achieving his/her target aerobic intensity. The custom-engineered motorized cycle has been used in all stroke and PD trials following the initial pilot study in PD.[95-100]

1.6   Biomechanical Gait Analysis

The effects of rehabilitation interventions on changes in gait are frequently

measured using clinical assessments in which the time to walk a given distance (e.g.:

timed 10-meter walk) or the distance walked over a given period of time (e.g.: 6MWT) is

measured. These measures can be converted to provide rudimentary measures such as

gait velocity or metrics of walking capacity. However, they lack resolution to inform

clinicians regarding changes in motor control associated with interventions or disease

progression. Biomechanical gait analysis systems that use force plates and motion capture

cameras provide a three-dimensional analysis of joint kinetics and kinematics, in addition

to precise spatio-temporal metrics that can quantify locomotor function.[16]

1.6.1   The Human Body Model for Biomechanical Gait Analysis

The projects described in this dissertation involved biomechanical gait analysis

obtained using the Computer-Assisted Rehabilitation ENvironment (CAREN) system

(Motek Medical, Amsterdam, The Netherlands). Briefly, the CAREN system, depicted in
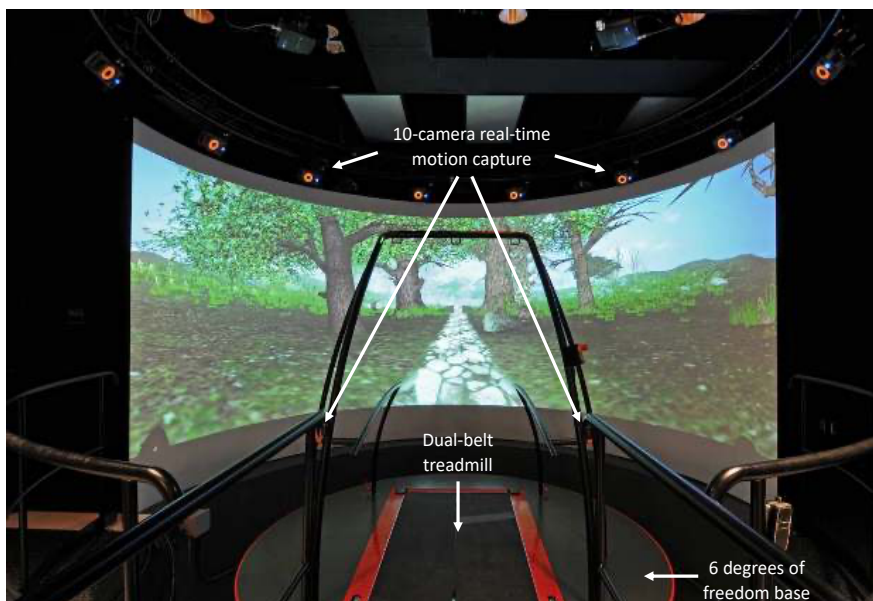
Figure 1.3   The Computer Assisted Rehabilitation ENvironment (CAREN) system

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Figure 1.3, includes a 6 degrees of freedom motion base on which sits a 3-meter diameter

platform with a dual belt instrumented treadmill; a 10-camera real-time motion capture

system; a 120-degree cylindrical screen projection system with surround sound; wireless

EMG and 3 high-speed cameras. The CAREN system creates an immersive virtual

environment with real-time feedback loop, causing the system to respond to subject

motion. Gait data are sampled at 100 Hz and continuously recorded and analyzed offline

using The Human Body Model 2 (HBM2). The HBM2 uses the 3D position of twenty-

five 14.00 mm retroreflective markers as depicted in Figure 1.4a to calculate

biomechanical gait parameters.

A skeleton model is used for biomechanical gait analysis which includes all lower

extremity kinematic degrees of freedom that are controlled by muscles. In all, nine

segments with a total of 21 degrees of freedom are included in the skeleton model, shown
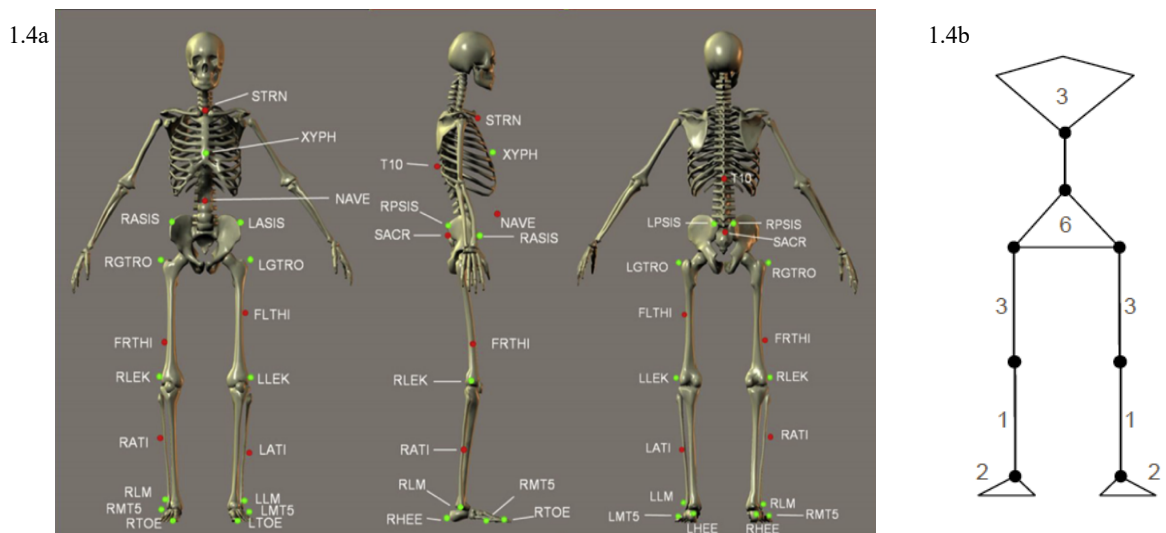
Figure 1.4 The Human Body Model 2 demonstrating anatomical placement of retroreflective motion capture markers used for biomechanical gait analysis (1.4a) and the resultant skeleton model depicting 9 segments comprising a total of 21 kinematic degrees of freedom.

in Figure 1.4b. Each degree of freedom has a kinematic variable associated with it and is

actuated with a force (for translational degrees of freedom) or moment (for rotational

degrees of freedom)[101]

1.6.2 Spatiotemporal Parameters of Gait

The HBM2 computes the following spatial and temporal parameters of gait:

1) Walking speed – calculated from the average horizontal displacement of the markers on the pelvis.

2) Step and stride length – step length is calculated from heel strike to the next consecutive contralateral heel strike, while stride length is the sum of two consecutive step lengths.

3) Step time and stride time – step time is the time from one heel strike to the next consecutive contralateral heel strike while stride time is the time from one heel strike to the next ipsilateral heel strike.

4) Step width – the difference in the mediolateral position of the right and left heel markers during consecutive contralateral heel strikes.

5) Stance and swing time and percentage – stance time is defined as the time between initial contact and the initiation of swing while swing time is from initial swing up to initial contact. Stance and swing time percentage are calculated as the time for stance or swing divided by the sum of stance and swing time.

6) Foot progression angle – the angle of the foot relative to the direction of walking

1.6.3 Kinematic Parameters of Gait

The HBM computes the following kinematic parameters using methods developed by van den Bogert[102] based on marker positions using segment reference frames obtained during calibration:

1) Pelvis: X-, Y-, and Z-plane movement; pelvic tilt, obliquity, and rotation.

2) Trunk: Tilt, flexion, and rotation.

3) Hip: Flexion/extension, abduction/adduction, and internal/external rotation for right and left sides.

4) Knee: Flexion/extension for right and left sides.

5) Ankle: Dorsi- and plantarflexion, pronation/supination for right and left sides.

Marker positions are tracked to provide joint angles in real time throughout the gait cycle in addition to providing the total range of motion throughout the gait cycle.

1.6.4   Kinetic Parameters of Gait

Kinetics involve the relationship between movement and forces acting upon the body.[28] As such, kinetic data in the context of abnormal gait mechanics provides information about abnormal patterns of movement and underlying muscle and joint dysfunction that contribute.[28] The analysis of gait kinetics involve ground reaction forces, joint moments and power. Of note, electromyography (EMG) is also a component of gait kinetics, used to identify patterns of muscle activation during various phases of the gait cycle. While the CAREN system and HBM2 have the capability to include EMG, the studies described in this dissertation did not include this outcome variable.

Ground reaction forces (GRF) measured by the CAREN system are obtained using force plates situated beneath the split-belt treadmill. During gait, GRF are used to describe the forces imposed onto the foot and can be divided into one vertical (vGRF) and two horizontal shear components occurring in the anterior-posterior (AP GRF) and mediolateral planes (ML GRF). Raw GRF data from a neurologically healthy individual are shown in Figure 1.5.[29] The vGRF curve typically presents as an "M" shape, with peaks occurring with weight acceptance and with propulsion at terminal stance. A valley is observed between the peaks during mid-stance, as knee extension displaces the center

of mass upwardly, reducing the vGRF typically to less than the individual's body weight.[29] The AP GRF curve depicts deceleration that occurs with loading response and propulsion that is observed at terminal stance with the plantarflexors propelling the center of mass anteriorly onto the contralateral limb.[29] Lastly, the ML GRF curve is characterized by an initial lateral shear force with loading response, followed by two peaks of medial shear forces at the beginning of mid-stance and at terminal stance.[29]
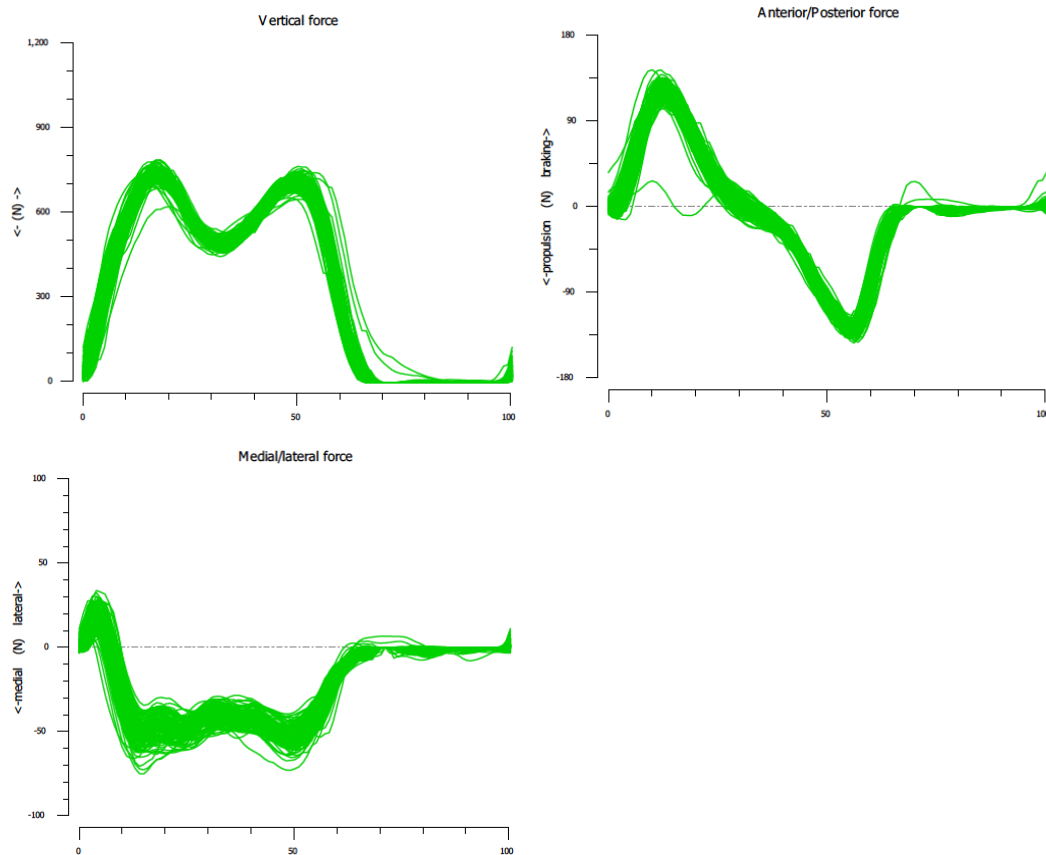
Figure 1.5   Raw vertical, anterior-posterior and mediolateral ground reaction force data from a neurologically healthy individual depicting normal shaped curves indicative of the momentum-driven activity inherent to human gait.

Joint moments quantify the sum of moments imposed by structures including muscles, ligaments, and bones.[28] Joint powers quantify the amount of energy generated and dissipated around a joint.[28] The HBM2 computes both using inverse dynamics and a

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link-segment model.[102,103] Inputs for the model include GRF (magnitude and orientation), joint center and segment locations, and acceleration (linear and angular) of the segments.[28,104] The clinical interpretation of GRF, joint moments, and power collectively allow for the analysis of biomechanical mechanisms associated with abnormal movement.[28]

2   Manuscript 1: Increased comfortable gait speed is associated with improved gait biomechanics in persons with chronic stroke completing an 8-week forced-rate aerobic cycling intervention

2.1   Introduction

A recently published clinical guideline did not support the use of cycling to improve locomotor function in individuals with hemiparesis due to stroke. In a pilot study, we found that individuals demonstrated significant improvements in walking capacity following an 8-week aerobic cycling intervention. However, our primary outcome was change in distance walked during the six-minute walk test, which did not provide information regarding gait biomechanics. Thus, it was unknown if the improvements in walking capacity and comfortable gait speed were accompanied by normalization of gait biomechanics or if individuals exaggerated existing compensatory strategies to walk faster and further. The current chapter addresses this question, as an interim analysis was conducted on individuals (N=14) participating in an 8-week forced rate aerobic cycling intervention who underwent biomechanical gait assessment at baseline and end of treatment.

Increased comfortable gait speed is associated with improved gait biomechanics in persons with chronic stroke completing an 8-week forced-rate aerobic cycling intervention

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ABSTRACT

Objectives: To determine the effects of an 8-week forced rate aerobic exercise (FE) intervention on gait velocity and locomotor control in individuals with chronic stroke.

Design: Cohort study

Setting: Research laboratory

Participants: Individuals with chronic stroke (N=14)

Interventions: Participants underwent FE 3 times per week for 8 weeks, exercising at a targeted aerobic intensity of 60-80% of their heart rate reserve.

Main Outcome Measures: Change in comfortable walking speed in addition to spatiotemporal, kinematic, and kinetic variables were measured using 3D motion capture. Change in walking capacity overground measured by the six-minute walk test (6MWT) was also obtained. To determine the biomechanical mechanisms associated with increased walking speed, change in spatiotemporal, kinematic, and kinetic variables were analyzed separately for those who met the minimal clinically important difference (MCID) for change in gait velocity compared with those who did not.

Results: Significant increases were observed in gait velocity from 0.61 to 0.70 m/s (P=0.004). and 6MWT distance from 272.1 to 325.1 meters (P<0.001). Overall, increased gait velocity was accompanied by normalization of gait biomechanics. Those who met the MCID value for change in gait velocity demonstrated significantly greater improvements in spatiotemporal parameters (P=0.041), ground reaction forces (P=0.047), and power generation (P=0.007) compared to those who did not meet the MCID.

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Conclusions: Individuals with chronic stroke demonstrated significant improvements in gait velocity and walking capacity following 8-weeks of FE, accompanied by improvements in gait biomechanics, indicating improvements in locomotor control and that individuals did not exaggerate existing compensatory strategies to walk faster.

MeSH Key Words: gait, stroke, exercise, biomechanics

Abbreviations: Six-minute walk test (6MWT); three-dimensional (3D); forced rate aerobic exercise (FE); end of treatment (EOT); upper extremity (UE); Computer Assisted Rehabilitation ENvironment (CAREN); ground reaction force (GRF); anterior-posterior (AP); minimal clinically important difference (MCID); multivariate analysis of variance (MANOVA); range of motion (ROM); revolutions per minute (RPM); medial-lateral (ML); vertical ground reaction force (vGRF)

INTRODUCTION

Stroke is a leading cause of severe, long-term disability among older adults.[105] Stroke survivors report walking is a primary factor for optimizing quality of life.[106] Considerable effort is put toward the recovery of gait post-stroke, with particular emphasis on walking speed, because it predicts level of disability.[5] Despite advances in rehabilitation, nearly 75% of individuals do not regain full use of their hemiparetic lower extremities, resulting in residual deficits in locomotion, increased fall risk, and decreased community reintegration.[2–4] Body-weight supported treadmill training and robotic-assisted training are modes of task-specific gait training extensively studied over the past two decades.[107] However, a recently published clinical practice guideline (CPG) cited strong evidence that neither is efficacious in improving locomotion.[108]

We recently reported that two modes of moderate- to high-intensity aerobic cycling improved walking capacity compared to a non-aerobic exercise control group in individuals with chronic hemiparesis[100] contrasting the recent CPG.[108] Following stroke, diminished muscle power and abnormal timing and coordination of muscle agonists and antagonists disrupt the modulation of phasic muscle activity, resulting in inefficient movement patterns during gait.[109] Phasic muscle activity comparable to what is observed during gait is induced in individuals during cycling training.[110-113] High-rate cycling has also been shown to improve rate-dependent mobility.[114] Additionally, neuroimaging studies have shown cortical, subcortical, and cerebellar patterns of activation on imaging during cycling tasks, spatially comparable to a lower limb reciprocal tapping task.[115] Thus, high intensity cycling may elicit a transfer of training to improve locomotor control in persons with stroke.

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Our primary outcome measuring change in walking capacity has been the six-minute walk test (6MWT).[100,116] The 6MWT provided valuable information regarding an individual's walking capacity but provided no insight into whether increases in gait velocity represented improvements in locomotor control. The current study used three-dimensional (3D) motion capture to provide a biomechanical analysis of gait to provide insight into whether increases in gait velocity were associated with improvements in motor control or if individuals sacrificed gait mechanics to walk faster.

The aims of this project were to determine the effects of an 8-week forced rate aerobic exercise (FE) intervention on gait velocity and locomotor control using 3D motion capture in individuals with chronic stroke. Forced exercise is a mode of training in which the voluntary efforts of individuals are supplemented with a motor, allowing them to achieve and sustain a greater exercise rate and intensity.[94,96,97,100,117] It was hypothesized that individuals completing FE would demonstrate increases in gait velocity accompanied by normalization of gait biomechanics from baseline to end of treatment (EOT).

METHODS

A cohort study was conducted to determine the effects of an 8-week FE intervention on locomotor control quantified using biomechanical gait data in individuals >6 months post-stroke (K01HD092556, clinicaltrials.gov registration number NCT03819764). The study was approved by the Cleveland Clinic Institutional Review Board and all participants completed the informed consent process.

Participants

Individuals with a single, unilateral stroke with residual upper extremity (UE) hemiparesis were recruited, as the primary aim of the study was to determine the priming effects of FE on UE recovery. Inclusion criteria were: 1) ≥ 6 months post-stroke, 2) UE Fugl-Meyer motor score 19-55, 3) Ambulatory ≥20 meters, and 4) 18-85 years of age. Exclusion criteria were: 1) hospitalization for myocardial infarction, heart failure or heart surgery within 3 months, 2) cardiac arrhythmia, 3) hypertrophic cardiomyopathy, 4) severe aortic stenosis, 5) pulmonary embolus, 6) contractures, and 7) other contraindication to exercise. All participants underwent a metabolic exercise stress test to ensure safe cardiopulmonary response to maximal exercise.

Forced Exercise Intervention

The FE protocol was based on methodology from our previous studies[94,96,97,100,117] and involved supervised exercise on a custom-engineered stationary semi-recumbent cycle ergometer for 45-minute sessions. The FE cycle motor supplemented pedaling rate 30% greater than the participant's voluntary rate achieved during their exercise stress test. The target heart rate zone (60-80%) was determined for each participant using the Karvonen formula.[118] Participants were instructed by the research therapist to exercise within their target heart rate zone during the 35-minute period between a 5-minute warm-up and 5-minute cool-down phase. Heart rate was continuously displayed using a Wahoo chest strap (Wahoo, Atlanta, GA) synchronized via Bluetooth to an Apple iPad (Apple, Inc, Cupertino, CA) for monitoring purposes. Clip-in cycling shoes were used and individuals completed FE sessions without the use of ankle foot orthoses.

Gait Analysis

Biomechanical gait data were collected using the Computer Assisted

Rehabilitation ENvironment (CAREN) (Motekforce Link, Amsterdam, Netherlands)

system at baseline and following the 8-week FE intervention. The CAREN system

engineer, blinded to group allocation, was responsible for all aspects of gait data

collection. The CAREN system consists of a 10-camera 3D motion capture system

(Vicon Inc., Oxford, UK), D-Flow control software (Motekforce Link), 180° curved

projection screen, and a six degree of freedom motion platform (Moog Inc., Elma, New

York) with an instrumented treadmill (Bertec Corp., Columbus, Ohio). Twenty-six

retroreflective markers were placed on anatomic landmarks as defined by the Human

Body Model 2 to characterize gait function.[103,119]

The primary outcome was change in comfortable gait velocity from baseline to

EOT. An initial walk was conducted to determine comfortable velocity followed by two

2-minute trials at a fixed speed. The initial walk and first 2-minute trial were used to

acclimatize participants to the gait analysis setup. Data from the second trial were

analyzed.

Secondary outcomes included spatiotemporal, kinematic, and kinetic gait

parameters computed using the Human Body Model 2 and the Gait Offline Analysis Tool

(GOAT; version 4.1, Motekforce Link, Amsterdam, Netherlands) and custom MATLAB

code (MathWorks, Natick, MA). Spatiotemporal variables included gait cadence and

paretic and non-paretic values for: step length, stance time, swing time, and single limb

support percentage. Two symmetry ratios were computed. Step symmetry was calculated

as the ratio of paretic limb step length to the stride length, with 0.50 indicating perfect

symmetry.[120] Temporal symmetry was determined by calculating the ratio of swing time

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to stance time for each limb and dividing the paretic limb ratio by the non-paretic limb ratio with 1.0 indicative of perfect symmetry. Kinematics included sagittal plane range of motion of the hip, knee, and ankle. Kinetic data included peak vertical GRF (vGRF), peak anterior-posterior (AP) breaking and propulsion forces, and peak lateral GRF. To quantify the shape of the vGRF curve, ratios between mid-stance and peak values at loading response and terminal stance were computed according to methods described by Takahashi and colleagues.[1] Total power generation for the hip, knee, and ankle were computed as the positive area under the curve.[121] Peak hip and knee extension and ankle plantarflexion moments during stance phase were obtained.

Six-minute Walk Test

A blinded evaluator administered the six-minute walk test (6MWT) to assess overground walking capacity, recording total distance walked.[116]

Statistical Analysis

Descriptive statistics were computed to describe demographic and exercise variables for the overall sample and for the dichotomized groups separating participants who met the minimal clinical important difference (Group$_{MCID}$) value for change in gait velocity versus those who did not (Group$_b$). Groups were compared on demographics and exercise variables using ANOVA for normally distributed variables, Mann-Whitney U tests for non-normally distributed continuous variables, or Chi-square tests for categorical variables. Normality of data was determined using visual inspection of histograms and normal Q-Q plots, along with the Shapiro-Wilk test. Change in comfortable gait velocity and 6MWT performance from baseline to EOT were analyzed using separate paired t-tests with an alpha of 0.05. The remaining spatiotemporal, kinematic and kinetic

Table 2.1 Participant Demographics and Exercise Characteristics

	Overall (n=14)	≥ MCID (n=5)	< MCID (n=9)	P-value
Age (years)	63.6 ± 13.4	65.2 ± 19.3	62.7 ± 10.3	0.36
Male sex (versus female), n	11 (78%)	5 (100%)	6 (67%)	**0.05***
Dominant Side Affected, n	6 (43%)	2 (40%)	6 (67%)	0.69
Time Since Stroke (months)	39 [14, 80]	38 [14, 104]	40 [12, 83]	1.00
Exercise characteristics				
Cadence (RPM)	75.3 ± 7.1	78.9 ± 7.6	73.2 ± 6.4	0.36
Percentage of HRR	59 ± 10%	60 ± 7%	59 ± 11%	0.80
Power (watts)	70.3 [9.5, 113.9]	100.3 [-0.5, 117.6]	65.5 [13.2, 101.7]	0.90
Session Duration, min	44.7 ± 0.5	44.8 ± 0.3	44.7 ± 0.6	1.00
Summary statistics presented as mean ± standard deviation, median [Q1, Q3], or n (%) for categorical data; MCID – minimal clinically important difference for change in gait velocity; RPM- revolutions per minute; HRR- heart rate reserve				

variables were analyzed using separate 2-way multivariate analysis of variance (MANOVA) models (Pillai's trace), with the fixed factor variable representing the Group$_{MCID}$. If the MANOVA was significant, post-hoc comparisons were conducted using separate linear models.

RESULTS

Fourteen participants were included in this cohort study. Demographics, baseline characteristics, and exercise variables are summarized in Table 2.1.

Spatiotemporal characteristics of gait

Changes in spatiotemporal parameters of gait from pre- to post-intervention are shown in Table 2.2. Change in gait velocity for each participant is shown in Figure 2.1. Gait velocity improved from 0.61±0.34 m/s to 0.70±0.32 m/s, *P* = 0.004 (Fig 2.2a). The MANOVA revealed a significant effect for change in spatio-temporal gait variables

favoring Group$_{MCID}$, V = 0.84, F(7, 6) = 4.72, P = 0.041. Separate univariate analyses

revealed significant effects favoring Group$_{MCID}$ for change in cadence, F(1, 12) = 37.69,

P < 0.001; change in paretic limb step length, F(1, 12) = 5.82, P = 0.033; and change in

single limb support percentage for the non-paretic limb, F(1, 12) = 5.13, P = 0.043.

Spaghetti plots for all spatiotemporal variables dichotomized by group are depicted in

Supplemental Figure 2.1.

Kinematic parameters of gait

Average sagittal plane range of motion (ROM) for the hip, knee, and ankle

showed a modest increase at EOT (Table 2.2). The MANOVA did not reveal a

significant between group effect for change in kinematic gait variables, V = 0.47, F(6, 7)

= 1.02, P = 0.482.
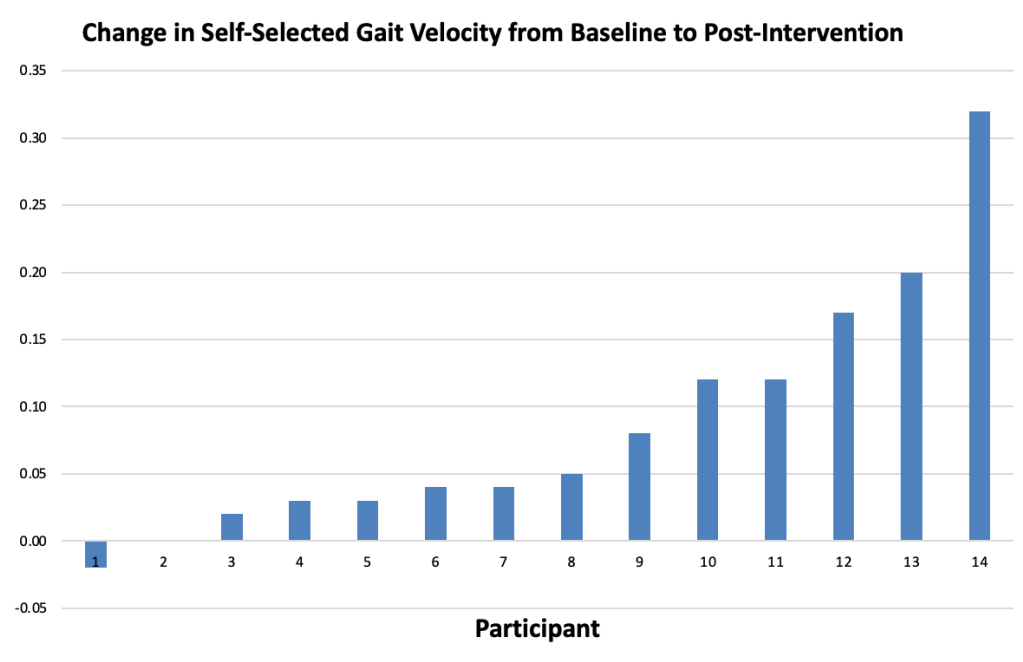
Figure 2.1   Change in gait velocity from baseline to post-intervention for each forced exercise
    cipant revealing all but two demonstrating improvements and five exceeding the minimal
    ally important difference of 0.1 m/sec.

Gait Velocity at Baseline and EOT

Six-Minute Walk Test at Baseline and EOT
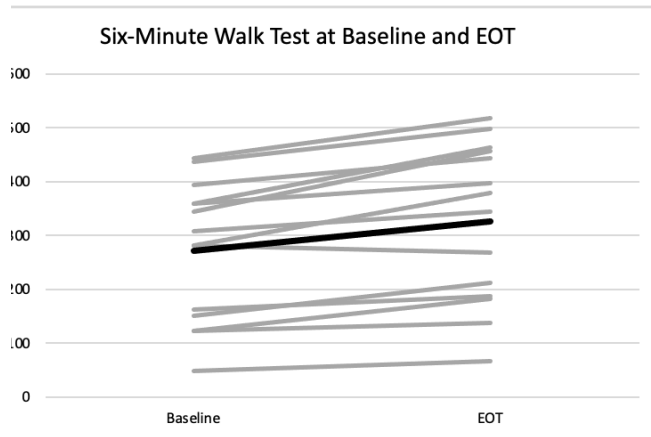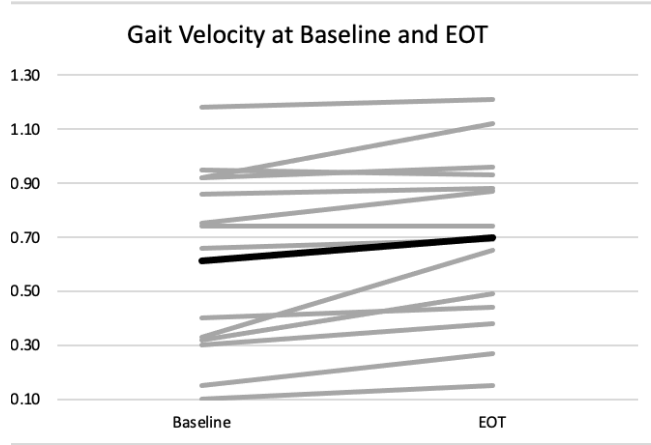
Figure 2.2 Spaghetti plots depicting gait velocity (2.2a) and Six-Minute Walk Test performance (2.2b
ch participant (gray lines) and the cohort (black bold-faced line) at baseline and EOT. Significan
vements were observed in both metrics from baseline to EOT, denoted with an asterisk.

	Limb	Baseline	EOT	Difference
ep Symmetry Ratio eviation from 0.50)	*N/A*	0.04 ± 0.04	0.03 ± 0.03	0.01
ance Time (sec)	*Paretic*	1.09 ± 0.51	0.98 ± 0.34	-0.11 ± 0.20

		Baseline	EOT	Difference
Swing Time (sec)	*Paretic*	0.44 ± 0.06	0.43 ± 0.08	-0.01 ± 0.03
	Non-paretic	0.39 ± 0.05	0.38 ± 0.06	0.00 ± 0.03
Single Support Time (%)	*Paretic*	26.7 ± 4.8	28.2 ± 3.5	1.5 ± 1.6
	***Non-paretic*c**	**29.7 ± 5.8**	**30.6 ± 4.9**	**0.9 ± 2.1**
Kinematic Variable				
Hip ROM, flex/ext, degrees	*Paretic*	32.5 ± 10.6	34.8 ± 10.8	2.2 ± 3.1
	Non-paretic	37.8 ± 10.0	41.7 ± 10.9	3.9 ± 3.6
Knee ROM, flex/ext, degrees	*Paretic*	39.7 ± 15.4	42.5 ± 15.8	2.8 ± 4.4
	Non-paretic	51.2 ± 14.3	52.2 ± 13.1	1.1 ± 2.6
Ankle ROM, dorsi-/plantarflexion, degrees	*Paretic*	17.7 ± 5.6	19.4 ± 5.3	1.8 ± 2.6
	Non-paretic	21.6 ± 7.7	23.8 ± 7.9	2.1 ± 2.9
Clinical Walking Test				
Six-Minute Walk Test (m)*a	*N/A*	**272.1 ± 128.4**	**325.1 ± 147.6**	**53.0 ± 36.4**
Kinetic Variables for Paretic Limb				
	Variable	**Baseline**	**EOT**	**Difference**
Ground Reaction Force (N)*b	*Peak vGRF*	789.8 ± 176.8	798 ± 195	7.8 ± 38.5
	Peak lateral GRF	-28.3 ± 23.6	-30.8 ± 24.7	-2.6 ± 11.1
	Peak AP GRF$_{breaking}$	70.4 ± 44.7	75.0 ± 44.9	4.6 ± 18.8
	Peak AP GRF$_{propulsion}$	-57.2 ± 37.5	-67.1 ± 38.8	-9.9 ± 13.2
Vertical GRF ratios	*vGRF$_{MS}$: vGRF$_{LR}$*	.93 ± .21	.87 ± .13	-.06 ± .15
	vGRF$_{MS}$: vGRF$_{TS}$	.94 ± .11	.91 ± .11	-.02 ± .06
Joint Moment (Nm/kg)	*Hip extension*	0.22 ± 0.17	0.29 ± 0.21	0.07 ± 0.13
	Knee extension	0.54 ± 0.24	0.50 ± 0.29	-0.04 ± 0.33
	Ankle plantarflexion	0.94 ± 0.40	1.06 ± 0.34	0.12 ± 0.28
Total Power Generation (w)*b	***Hip*c**	**8.8 ± 6.4**	**11.3 ± 7.7**	**2.5 ± 5.6**
	Knee	9.8 ± 7.5	10.4 ± 9.1	0.7 ± 5.1
	Ankle	9.4 ± 9.4	11.6 ± 9.8	2.2 ± 4.3
ROM: range of motion; flex/ext: flexion/extension; GRF: ground reaction force; MS: mid-stance; LR: loading response; TS: terminal stance.				

P ≤ 0.05 results denoted in bold

a: Results of ANCOVA

b: Results of MANOVA

c: Univariate post-hoc analysis

Kinetic parameters of gait

Average values for GRF, joint moment, and power data indicating normalization

of gait kinetics are shown in Table 2.2. The MANOVA revealed a significant effect

favoring Group$_{MCID}$ for change in GRF (V = 0.624, F(4, 9) = 3.73, P = 0.047). Separate

analyses revealed no group * time interaction effect for peak vGRF (F(1, 12) = 3.58, P =

0.083), AP breaking forces (F(1, 12) = 2.06, P = 0.176), AP propulsion forces (F(1, 12) =

2.08, P = 0.174), or stance phase lateral GRF (F(1, 12) = 3.50, P = 0.086).
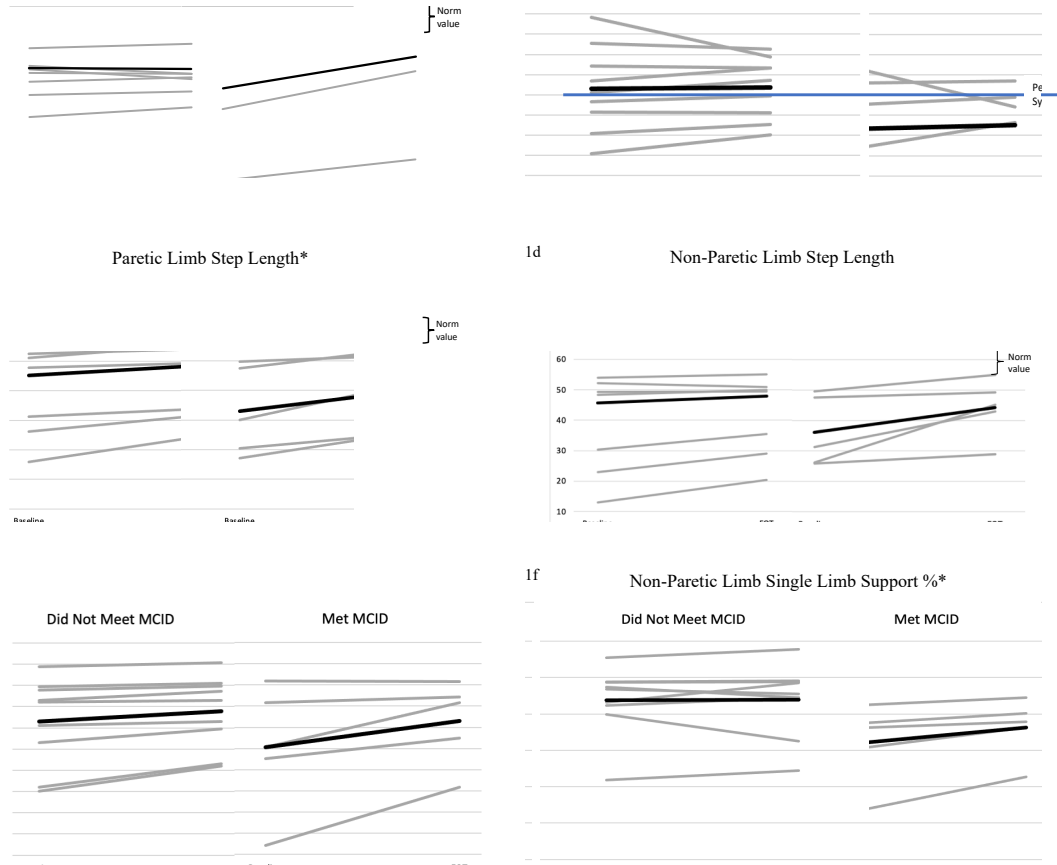
Supplemental Figure 2.1 1Spaghetti plots of select spatiotemporal and kinetic gait variables depicting results for individuals who did not meet the MCID value for change in gait velocity compared to those who met the MCID value. Variables significant in the MANOVA models are depicted with an asterisk. Values for each participant (gray lines) and the cohort (black bold-faced line) are shown at baseline and EOT for the following variables: gait cadence (S2.1a); step symmetry ratio (S2.1b); paretic (S2.1c) and non-paretic (S2.1d) limb step length; paretic (S2.1.e) and non-paretic (S2.1f) single limb support percentage; paretic hip extension moment (S2.1g), and total paretic hip extension power generation (S2.1h).

Increased total hip, knee, and ankle power were also observed as shown in Table 2.2. The MANOVA revealed a significant effect favoring $Group_{MCID}$ for change in joint power (V = 0.686, F(3, 10) = 7.27, P = 0.007). Post-hoc univariate analysis suggests that only total hip power generation (F(1, 12) = 11.39, P = 0.006) had a group * time interaction effect.

Increased joint moments were primarily observed with hip extension and ankle plantarflexion (Table 2.2). The MANOVA did not reveal a significant between group effect for change in joint moment (V = 0.433, F(3, 10) = 2.55, P = 0.115).

Walking capacity

Walking capacity measured by the 6MWT (Fig 2.2b) improved significantly from 272.1±128.4 meters to 325.1±247.6 meters (P < 0.001).[122]

DISCUSSION

Our results suggest an 8-week FE cycling intervention contributed to a significant improvement in gait velocity, accompanied by improvements in spatiotemporal, kinematic, and kinetic gait characteristics. These biomechanical gait changes indicate a training effect resulting in improved locomotor control. Importantly, participants' compensatory strategies did not worsen in order to walk faster. While gait was measured during treadmill walking, improvements in overground walking were also observed, with significant improvements on the 6MWT, exceeding the MCID value of 34.4 meters.[122] Our novel findings may have considerable clinical relevance, as moderate- to high-intensity cycling may be a viable and efficacious option to improve locomotor function in individuals with chronic stroke.[108]

While task-specificity has been considered important in motor learning, a transfer of training has been shown to occur between distinct motor tasks, particularly when the kinematic and spatiotemporal requirements of the tasks are similar.[42] Although cycling and walking are different tasks, both require the rapid reciprocal activation and relaxation of lower extremity muscles synergistically.[111,112,123-127] Thus, high-rate cycling associated with FE, combined with the consistent rhythmic motion induced by the motorized bike, may have elicited a transfer of training resulting in improved locomotor control.

Improvements in Spatiotemporal Gait Parameters Following FE

Participants demonstrated significant improvements in comfortable gait speed; however, this alone does not provide insight into whether compensatory strategies were exaggerated or if gait biomechanics were normalized to facilitate this improvement. Three-dimensional motion capture provided insight into the biomechanical mechanisms associated with increased gait velocity. When considering spatiotemporal characteristics of gait, individuals post-stroke typically present with decreased cadence, asymmetries in step length and temporal variables with respect to the paretic and non-paretic limbs, and decreased single limb support percentage. Our participants demonstrated improved spatiotemporal gait characteristics across all variables. However, Group$_{MCID}$ had significantly greater increase in gait cadence, approaching normative values for healthy adults reported at 111.6 ± 8.3.[128] It is plausible that a transfer of training contributed to increased gait cadence and thus, increased gait velocity, as those who cycled at a higher cadence exhibited the greatest improvements.

Step length for the paretic limb increased more for the Group$_{MCID}$ compared to Group$_b$. Notably, all participants demonstrated increased paretic and non-paretic limb

step length toward the normative value of 68 cm, (Supplemental Figures 2.1c and 2.1d).[128] Increases in step length were accompanied by improvements in step symmetry approaching 0.5 at EOT. This convergence of step symmetry is evident in Supplemental Figure 2.1b and indicate that participants were more confident in single limb stance to allow for a longer contralateral step. Supporting this theory are data demonstrating a significant increase in single limb support percentage. Overall, as shown in Supplemental Figures 2.1e and 2.1f, an increase in percentage of time spent in single limb stance was observed for both limbs, indicative of improved balance and single limb stance stability.

The Effects of FE on Kinematic Gait Parameters

Overall, participants demonstrated modest improvements in sagittal plane kinematics of the hip, knee and ankle following the 8-week FE intervention. Numerous mechanisms are responsible for diminished ROM post-stroke, including the inability to rapidly activate and relax the limb extensors in a rhythmic manner.[129] This impaired motor control interferes with smooth and timely transitions between stance and swing phases of gait and is characterized by abnormal muscle co-contractions.[130] High cadence cycling may train muscles to work synergistically, ensuring smooth intra- and interlimb reciprocal activation, similar to activation patterns used to coordinate joint angle accelerations and decelerations during gait.[111-113]

Changes in Kinetic Variables following FE

The ability to generate power in the hemiparetic limb is also diminished post-stroke.[24,129,130] While increased total power generation was evident at the hip, knee, and ankle for all participants, the Group$_{MCID}$ demonstrated the greatest increases in power.

Hip extension and ankle plantarflexion power provide the main propulsive forces in human gait.[28] Although increased values of total power were also evident with ankle plantarflexion, gait testing was conducted with participants wearing AFOs as prescribed, limiting the ability to generate propulsive power during plantarflexion through terminal stance. Increases in hip extension and ankle plantarflexion moments were also observed, complementary to the changes seen in hip and ankle power generation, but may have been blunted by AFOs.

Improvements in GRF were also measured, with significant differences among Group$_{MCID}$ compared to Group$_b$. Increased magnitude of breaking forces and propulsion forces were observed with loading response and terminal stance, respectively.[29] Increased breaking forces with loading response indicate normalization of deceleration which results in posterior shear forces that occur as the limb initiates weight acceptance.[29] At terminal stance, anterior shear occurs with forward propulsion as the individual's center of mass progresses anterior to the foot.[29] Increased lateral GRF values were also observed, indicating greater weight shift onto the paretic limb.[29] These data align with changes observed in the spatiotemporal variables, as improvements in single limb support percentage and increased step symmetry are noted with normalization of lateral paretic limb weight shifting.

Modest improvements in peak vGRF data were also observed for the paretic limb approaching non-paretic limb values, indicating increased load symmetry. An additional observation was a change in the shape of the vGRF curve. Neurologically healthy adults present an M-shaped curve as shown in Figure 2.3a, with the first peak occurring with weight acceptance and the second peak during terminal stance. At mid-stance, knee

extension displaces the center of mass upwardly, reducing the vGRF typically to less than

the individual's body weight. Following stroke, impairments in power generation, range

of motion, balance, the use of orthoses, and UE support collectively impact vGRF in both

the paretic and non-paretic limbs, often resulting in a flattened or parabolic-shaped curve,

as shown in Figure 2.3b. Takahashi and colleagues quantified this by computing ratios

between the mid-stance vGRF value and each peak value, providing a ratio of $\leq$ .85 as

normal.[1] Both ratios improved in both limbs at EOT. A sample participant's data is

shown in Figures 2.3c-2.3d. Collectively, changes GRF data are indicative of
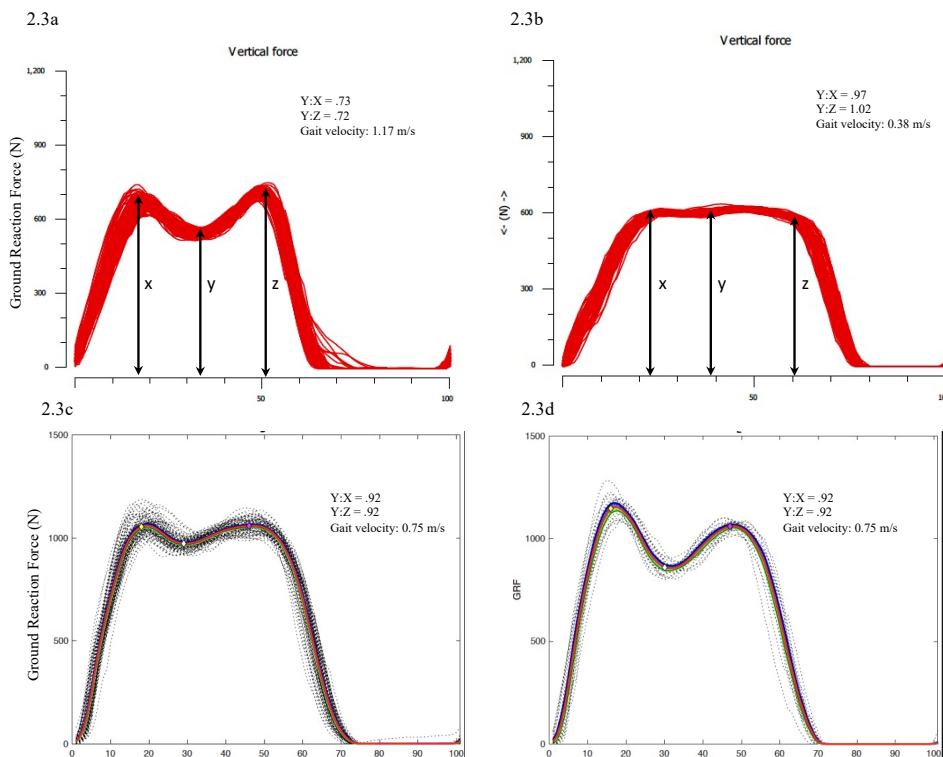
Figure 2.3   Vertical ground reaction force data from a neurologically healthy individual (2.3a).
Quantifying the normal M-shaped vGRF curve is done by computing the Y:X and Y:Z ratios, with
normal values reported at ≤.85. Several vGRF curves for the participants in our stroke study deviated
from the normal M-shaped curve, and presented as flat or parabolic shapes, as shown in Figure 2.3b.
These data indicate that the momentum-driven activity and propulsive characteristics of gait were
reduced. Figures 2.3c and 2.3d depict a single participant's data at baseline and end of treatment,
demonstrating increased gait velocity accompanied by normalization of the M-shaped vGRF curve from
baseline (2.3c) to EOT (2.3d).

normalization of the kinetic forces that are responsible for the momentum-driven action in human gait.

Using FE to Overcome Limitations of High-Intensity and High-Repetition Training

Stationary cycling, and in particular FE cycling, has numerous advantages for individuals post-stroke including safety, the ability to complete thousands of repetitions in a single session, replicating high cadence associated with normal gait, and the global benefits to aerobic exercise. Cycling on a semi-recumbent stationary ergometer requires less postural control than walking, providing a safe modality to train in an intense manner without considerable focus on balance. Cycling at an average cadence of 75.3 RPM, our participants completed an average of 2635 revolutions per session during the main 35-minute exercise set, which, if calculated to strides, would equate to walking 896 meters. From a training perspective, cycling and walking do not directly equate; however, it is apparent that the FE approach provided a highly repetitious, intensive, and consistent exercise rate, which cannot be easily replicated during overground or treadmill-based gait training.

Study Limitations and Conclusions

There are several limitations to this study. We report the effects of FE cycling on a cohort of individuals without control group data for comparison. Our data included 14 participants limiting the precision of the estimates of effect. Biomechanical gait data were obtained during treadmill walking, which may not be characteristic of overground ambulation[131] despite acclimatization trials as a mitigation strategy. The primary inclusion criteria for this trial were related to UE function which may have enhanced heterogeneity of baseline ambulatory status. Participants were tested using AFOs they

wore during community ambulation and used one or both handrails, potentially impacting

biomechanical gait data. However, these conditions were kept consistent for each

participant during baseline and post-intervention trials. Therefore, these results may still

be used as a basis of comparison between the pre- and post-intervention time points and

support the use of moderate- to high-intensity cycling to improve gait velocity,

biomechanics, and walking capacity in individuals with chronic stroke.

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3   Manuscript 2: Forced aerobic cycling improves locomotor function in individuals with chronic stroke

3.1   Introduction

Gait dysfunction contributes significantly to disability and diminished quality of life in individuals post-stroke. Rehabilitation interventions that facilitate the recovery of walking focus primarily on task-specific gait training, as motor learning theory emphasizes task-specificity to drive neuroplastic change. However, in pilot studies, we observed improvements in walking capacity in individuals participating in an 8-week aerobic cycling intervention while no change was observed in a non-cycling control group. The primary clinical outcome demonstrating these improvements was the six-minute walk test, which while clinically relevant in quantifying the distance walked over 6-minutes, did not provide insight regarding gait quality. To further explore these observations, we have included biomechanical gait assessment as an exploratory outcome in our ongoing clinical trial. Chapter 3 addresses our question regarding the effects of aerobic cycling on change in locomotor control in individuals with chronic stroke as we present an interim analysis comparing biomechanical gait data from participants randomized to aerobic cycling versus a non-aerobic control group.

Forced aerobic cycling improves locomotor function in individuals with chronic stroke

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Introduction

Stroke is a leading cause of severe, long-term disability among older adults in the United States.[105] The recovery of walking has been reported as particularly critical by individuals with stroke, as walking-related disability negatively impacts participation in daily activities, community reintegration, and quality of life.[106] A recently published clinical guideline reported that various motor learning-based approaches focused primarily on task-specific gait training were found effective in restoring walking ability post-stroke with and without the use of technology.[18] The most effective interventions reported were moderate to high aerobic intensity walking programs and virtual reality-based walking programs. Interestingly, despite numerous well-designed clinical trials investigating the use of body weight-supported treadmill training and robotic-assisted gait training, neither were recommended.[107,108] Additionally, the guideline cited weak and insufficient evidence for cycling interventions to improve walking capacity, although high-intensity cycling interventions were more promising to improve locomotor function than low intensity cycling.[108]

In contrast to the findings of the clinical guideline, we have reported improvements in gait velocity and walking capacity following both forced- and voluntary-rate aerobic cycling interventions.[100] Additionally, we have recently demonstrated that improvements in gait velocity were accompanied by improved biomechanics in a cohort of individuals participating in an 8-week forced-rate aerobic cycling intervention. Thus, individuals did not exaggerate existing compensatory strategies to walk faster as increases in gait velocity were accompanied by improved

locomotor control, evidenced by the normalization of spatiotemporal, kinematic, and kinetic parameters of gait.

Following stroke, individuals present with diminished muscle power and abnormal timing and coordination of muscle agonists and antagonists which disrupt the modulation of phasic muscle activity, resulting in abnormal co-contractions and inefficient movement patterns during gait.[109,132] Cycling and walking both involve cyclical movements of alternating flexion and extension at an approximate frequency of 1 Hz, with most of the propulsive power generated through extension.[16] Following stroke, asymmetrical power generation between the paretic and non-paretic limbs and excessive negative work during flexion phases are distinct characteristics found in both walking and cycling.[133] While cycling does not involve task-specificity for gait training, we theorized that high intensity cycling may train muscle groups to work synergistically to ensure smooth intra- and interlimb reciprocal activation, similar to activation patterns used to coordinate joint angle accelerations and decelerations during phases of the gait cycle.[111-113]

The specific mode of aerobic cycling we investigated was forced exercise (FE). Forced exercise is a mode of training in which the voluntary efforts of individuals are supplemented, allowing them to achieve and sustain a greater exercise rate and intensity.[94,96,97,100,117] With FE, a semi-recumbent cycle ergometer is custom engineered with a motor that assists individuals to pedal at a greater rate than what they can achieve without assistance. It is important to note that the voluntary efforts of participants are supplemented, but not replaced, as participants' heart rate (HR) and pedaling torques are monitored continuously to ensure that they are contributing to the exercise to elicit an

aerobic response. The primary aim of the study was to determine changes in spatiotemporal, kinematic, and kinetic components of gait in individuals with chronic stroke completing an 8-week forced-rate aerobic exercise (FE) intervention compared to a control group participating in upper extremity task practice only. Our secondary aim was to examine exercise-related variables that were predictive of increased gait velocity among FE participants. We hypothesized that those participating in FE would demonstrate increases in gait velocity accompanied by normalization of spatiotemporal, kinematic, and kinetic parameters of gait, while no improvements in gait were expected for the control group.

<u>Methods</u>

This study was part of a larger randomized clinical trial aimed at determining effects of an 8-week FE intervention combined with upper extremity repetitive task practice (UE RTP) on UE motor recovery compared to time-matched UE RTP only (K01HD092556, clinicaltrials.gov registration number NCT03819764). Given observations from our pilot studies that individuals participating in the FE intervention demonstrated improvements in walking capacity and locomotor control, biomechanical gait data were collected in a subset of FE and control participants using three-dimensional (3D) motion capture. The study was approved by the Cleveland Clinic Institutional Review Board and all participants completed the informed consent process.

Participants

Individuals $\geq$ 6 months following a single, unilateral ischemic or hemorrhagic stroke confirmed with neuroimaging with residual UE hemiparesis were recruited for participation, as the primary aim of the study was to determine the effects of FE on the

recovery of UE function. Additional inclusion criteria were as follows: 1) Fugl-Meyer motor score 19-55 in the involved UE, 2) Ambulatory $\geq$ 20 meters with no more than contact guard assistance, and 3) 18-85 years of age. Exclusion criteria included: 1) hospitalization for myocardial infarction, heart failure or heart surgery within 3 months, 2) cardiac arrhythmia, 3) hypertrophic cardiomyopathy, 4) severe aortic stenosis, 5) pulmonary embolus, 6) significant contractures, 7), anti-spasticity injection within 3 months of enrollment and 8) other contraindication to exercise. All participants meeting criteria for participation underwent a metabolic exercise stress test using a ramp protocol on an electronically controlled cycle ergometer to ensure safe cardiopulmonary response to maximal exertion and to determine target heart rate (HR) and cadence parameters for those randomized to undergo FE.

Forced Exercise and Upper Extremity Repetitive Task Practice (FE+RTP)

The FE protocol was based on methodology from our previous studies[94,96,97,100,117] and involved supervised and monitored exercise on a custom-engineered stationary semi-recumbent cycle. The custom-engineered cycle was equipped with a motor that augmented pedaling rate by 30% greater than the participant's voluntary rate achieved during their baseline exercise stress test. The target heart rate zone for each participant was determined using the Karvonen formula[118] at the 60-80% range, based on resting and peak HR values obtained during the baseline cardiopulmonary stress test. The FE sessions consisted of a 5-min warm-up, 35-min main exercise set, and 5-min cool down. Participants were instructed to exercise within their target heart rate zone during the 35-minute main exercise set. Heart rate was measured continuously using a Wahoo chest strap (Wahoo, Atlanta, GA) and synchronized via Bluetooth to an Apple iPad (Apple,

Inc, Cupertino, CA) allowing for both the participant and therapist to monitor aerobic intensity and encourage exercise within the prescribed HR zone. Cycling shoes with cleats were used to ensure a secure interaction between the individual's feet and pedals, and training sessions were conducted without ankle foot orthoses. All sessions were administered under the supervision of a physical therapist or physical therapist assistant certified in Basic Cardiac Life Support. Following FE, participants completed a 45-minute session of UE RTP.

Upper Extremity Repetitive Task Practice (UE RTP)

Repetitive task practice is considered the current standard of care for UE stroke rehabilitation, with Class IA evidence supporting its use[134,135]. Tasks performed with the more impaired UE were identical to the approach used in our preliminary studies[136]. Tasks were practiced repeatedly and graded to challenge each individual's abilities. Functional tasks that require a combination of reaching, grasping, manipulating and/or moving, and releasing an object were included. Tasks were graded to increase difficulty by requiring movement out of synergy, increasing range of motion requirements for task accomplishment, incorporating increasingly difficult grasp types, increasing force requirements, varying the size/shapes of the objects, and varying the use of adaptive equipment. Repetitions and time dedicated to RTP were recorded. All RTP was administered by a neurologic physical therapist or physical therapist assistant experienced in stroke rehabilitation and trained in RTP. To ensure a time-matched intervention for both groups, the FE+RTP group completed a 45-min session of FE followed by 45-min of UE RTP, while the control group completed a 90-min session of UE RTP.

Gait Analysis

The Computer Assisted Rehabilitation ENvironment (CAREN) (Motekforce Link, Amsterdam, Netherlands) system was used to collect biomechanical gait data at baseline and following the 8-week FE intervention. The CAREN system engineer, blinded to group allocation, was responsible for all aspects of gait data collection. Briefly, the CAREN system consists of a 10-camera 3D motion capture system (Vicon Inc., Oxford, UK), D-Flow control software (Motekforce Link), 180° curved projection screen, and a six degree of freedom motion platform (Moog Inc., Elma, New York) with an instrumented treadmill (Bertec Corp., Columbus, Ohio). Twenty-six retroreflective markers were placed on anatomic landmarks on the lower extremities and trunk of each participant as defined by the Human Body Model 2 (HBM2) to characterize gait function.[103,119] The retroreflective marker position data were filtered using a 2nd order low-pass Butterworth filter with a 6 Hz cut-off frequency.

Gait Outcomes

The primary outcome was change in comfortable gait velocity from baseline to end of treatment (EOT). All walking trials were completed at a comfortable fixed speed on the treadmill. To determine comfortable gait velocity, treadmill speed on the CAREN system was gradually increased during a practice trial until the participant stated that he/she was at a comfortable pace, then slightly increased to verify that the comfortable pace was not underestimated; at which point the treadmill speed was fixed for the duration of data collection. Once a comfortable speed was established, two 2-minute trials were completed. A 2- to 3-minute seated rest break was provided between trials. The initial walk to determine comfortable velocity and the first 2-minute gait trial were

used to acclimatize participants to the CAREN system and to the gait analysis set-up. Gait data from the second trial were used for the analysis.

Secondary outcomes included spatiotemporal, kinematic and kinetic gait parameters, which were computed using the Gait Offline Analysis Tool (GOAT; version 4.1, Motekforce Link, Amsterdam, Netherlands) and custom MATLAB code (MathWorks, Natick, MA). The following spatiotemporal variables were computed: gait cadence, paretic and non-paretic limb step length, paretic and non-paretic limb single limb support percentage, and paretic and non-paretic stance and swing time. Two symmetry indices were also computed. Step symmetry was calculated as the ratio between the step length of the paretic limb versus the sum of paretic and non-paretic step lengths.[120] A step symmetry value of exactly 0.50 implies perfect symmetry. Temporal symmetry was determined by calculating the ratio of swing time to stance time for each limb and dividing the paretic limb ratio by the non-paretic limb ratio. A value of 1.0 represents perfect temporal symmetry between the paretic and non-paretic limbs.[19] Given that asymmetries were present in both directions, deviation from perfect symmetry for both indices regardless of the direction was reported in the results, while figures represented actual symmetry index values.

Kinematic variables were computed with the GOAT software native to the CAREN system. Sagittal plane kinematics were of greatest interest; therefore, hip flexion/extension, knee flexion/extension, and ankle plantar-/dorsiflexion were computed for the paretic and non-paretic limbs.

Kinetic data were computed using the GOAT software, and customized MATLAB code was used to identify relevant components of the gait cycle and to extract

variables of interest. Vertical ground reaction force (GRF) data were used to identify

stance and swing phases of gait in addition to initial contact, loading response, mid-

stance, and terminal stance. Additional GRF outcomes included peak vertical GRF

(vGRF), peak anterior-posterior breaking forces (peak $AP_{breaking}$), peak anterior-posterior

propulsion forces (peak AP_{prop}), and peak lateral GRF. To quantify the shape of the vGRF

curve, ratios between mid-stance and peak values at loading response and terminal stance

were computed according to methods described by Takahashi and colleagues.[1] Hip

extension, knee extension, and ankle plantarflexion total positive power (ie: power

generation) were computed by calculating the positive area under the curve. Peak hip

extension moment, knee extension moment and ankle plantarflexion moment during

stance were obtained.

Six-minute Walk Test

The six-minute walk test (6MWT) was used to assess walking capacity during

overground ambulation.[116] Participants were asked to self-select a brisk but safe walking

speed to cover their greatest distance along a 200-foot (61 meter) oval path in 6 minutes

with a trained assessor guarding against loss of balance while ensuring to not influence

self-selected walking pace. Total distance traveled was obtained using a measuring

wheel.

Statistical Analysis

Descriptive statistics were computed to describe demographic characteristics for

both groups and exercise variables for the FE+RTP group. Groups were compared on

demographic characteristics using ANOVA for normally distributed variables, the Mann-

Whitney *U* test for non-normally distributed continuous variables, or the Chi-square test

for categorical variables. Normality of data was determined using visual inspection of histograms and normal Q-Q plots, along with the Shapiro-Wilk test. The primary outcome, change in comfortable gait velocity from baseline to EOT, was analyzed using an analysis of covariance (ANCOVA), with baseline gait velocity as the covariate and an alpha of 0.05 to determine significance. The 6MWT was also analyzed using an ANCOVA. The remaining spatiotemporal, kinematic, and kinetic (GRF, power, and moment) variables were compared using 2-way multivariate analysis of variance (MANOVA) linear models. If the MANOVA was significant, post-hoc comparisons were conducted using separate univariate linear models. Finally, a multivariate linear regression was constructed for the FE group only to determine predictors of greatest improvement in gait velocity with change in gait velocity as the dependent variable as exercise variables as independent variables.

RESULTS

Twenty-four participants ranging from 7 to 241 months post-stroke were randomized to undergo FE+RTP (FE, N=14) or UE RTP only (Control, N=10). Participant demographics, baseline characteristics, and exercise variables are summarized in Table 3.1. Of note, kinetic gait data were not available for one participant in the control group as all gait cycles occurred on the same half of the split-belt treadmill, eliminating valid GRF data. Thus, kinetic analysis includes only 9 participants in the control only group.

FE improves spatiotemporal parameters of gait

Table 3.1 Participant Demographics and Exercise Variables

	FE+RTP Participants n=14	Control Participants n=10	P-value
Age (years)	63.6 ± 13.4	57.0 ± 11.1	0.22
Male sex (versus female), n	11 (78%)	5 (50%)	0.41
Dominant Side Affected, n	6 (43%)	4 (40%)	0.41
Months Since Stroke	39 [14, 80]	18 [13, 78]	0.67
Cadence (RPM)	75.3 ± 7.1	N/A	N/A
Percentage of HRR	59 ± 10%	N/A	N/A
Power (watts)	70.3 [9.5, 113.9]	N/A	N/A
Summary statistics presented as mean ± standard deviation, median [Q1, Q3], or n (%) for categorical data; RPM-revolutions per minute; HRR-heart rate reserve			

Changes in spatiotemporal parameters of gait from baseline to EOT for both groups are shown in Table 3.2. The primary outcome was change in comfortable gait velocity from baseline to EOT. Change in gait velocity for all participants is shown in Figure 3.1a. Those in the FE group improved from 0.61 m/s at baseline to 0.70 m/s at EOT while the control group declined from 0.90 m/s at baseline to 0.83 m/s at EOT. However, the ANCOVA did not reveal a significant effect of group ($F(1, 21) = 3.73$, P = 0.067). Those in the FE group demonstrated improvements in gait cadence, paretic and non-paretic limb step length, and decreased single limb support percentage bilaterally as shown in Figure 3.2a-3.2e. Using Pillai's trace, the group by time interaction effect was not significant, $V = 0.33$, $F(5, 18) = 1.78$, P = 0.166. Step symmetry ratios demonstrated convergence of values from baseline to EOT toward 0.50 as shown in Figure 3.2f and modest improvements in temporal symmetry are depicted in Figure 3.2g.

Table 3.2 Spatiotemporal, Kinematic, and Kinetic Gait Variables

	Limb	FE+RTP (N=14)		Control (N=10)		P-Value
		Baseline	EOT	Baseline	EOT	
Spatiotemporal Variables						0.166[b]
Gait Velocity (m/sec)	N/A	0.61 ± 0.34	0.70 ± 0.32	0.90 ± 0.28	0.83 ± 0.26	0.067[a]
Cadence (steps/min)	N/A	84.8 ± 19.5	89.8 ± 19.1	95.3 ± 14.8	93.6 ± 14.2	
Step Symmetry Ratio	N/A	0.49 ± 0.06	0.49 ± 0.04	0.50 ± 0.02	0.51 ± 0.02	
Temporal Symmetry Ratio	N/A	1.21 ± 0.24	1.18 ± 0.22	1.07 ± 0.06	1.05 ± 0.06	
Step Length (cm)	Paretic	40.8 ± 16.7	45.6 ± 14.5	55.2 ± 10.4	52.7 ± 9.7	
	Non-paretic	42.2 ± 17.6	46.6 ± 14.7	56.1 ± 11.3	51.7 ± 11.7	
Stance Time (sec)	Paretic	1.09 ± 0.51	0.98 ± 0.34	0.88 ± 0.16	0.90 ± 0.15	
	Non-paretic	1.14 ± 0.49	1.03 ± 0.34	0.90 ± 0.17	0.91 ± 0.16	
Swing Time (sec)	Paretic	0.44 ± 0.06	0.43 ± 0.08	0.40 ± 0.04	0.40 ± 0.04	
	Non-paretic	0.39 ± 0.05	0.38 ± 0.06	0.38 ± 0.03	0.39 ± 0.03	
Single Support Time (%)	Paretic	26.7 ± 4.8	28.2 ± 3.5	30.1 ± 2.5	30.1 ± 2.6	
	Non-paretic	29.7 ± 5.8	30.6 ± 4.9	31.5 ± 2.2	30.9 ± 2.3	
Kinematic Variables						0.079[b]
Hip flex/ext, degrees	Paretic	32.5 ± 10.6	34.8 ± 10.8	44.3 ± 8.5	42.4 ± 6.4	
	Non-paretic	37.8 ± 10.0	41.7 ± 10.9	45.5 ± 5.2	45.1 ± 5.3	
Knee flex/ext, degrees	Paretic	39.7 ± 15.4	42.5 ± 15.8	59.7 ± 14.1	58.0 ± 10.8	
	Non-paretic	51.2 ± 14.3	52.2 ± 13.1	64.5 ± 9.2	63.2 ± 7.2	
Ankle dorsi-plantarflexion, degrees	Paretic	17.7 ± 5.6	19.4 ± 5.3	22.8 ± 5.5	22.8 ± 5.5	
	Non-paretic	21.6 ± 7.7	23.8 ± 7.9	27.5 ± 6.2	25.5 ± 7.6	
Clinical Walking Test						
Six Minute Walk Test (m)	N/A	**272.1 ± 128.4**	**325.1 ± 147.6**	**414.7 ± 141.5**	**427.8 ± 138.8**	**0.006[a]**
Kinetic Variables for Paretic Limb						
	Variable	Baseline	EOT	Baseline	EOT	

Ground Reaction Force (N)						0.438[b]
	Peak vGRF	790 ± 177	798 ± 195	837 ± 290	825 ± 332	
	Peak AP Breaking	70.4 ± 44.7	75.0 ± 44.9	95.5 ± 56.5	90.1 ± 62.7	
	Peak AP Propulsion	-57.2 ± 37.5	-67.1 ± 38.8	-98.7 ± 65.7	-98.6 ± 66.0	
	Peak Lateral GRF	-28.3 ± 23.6	-30.8 ± 24.7	-29.9 ± 20.9	-20.4 ± 11.7	
Vertical GRF Ratios	*vGRF$_{MS}$: vGRF$_{LR}$*	.93 ± .21	.87 ± .13	.84 ± .11	.85 ± .09	
	vGRF$_{MS}$: vGRF$_{TS}$	.94 ± .11	.91 ± .11	.87 ± .12	.88 ± .09	
Joint Moment (Nm/kg)						**0.050[b]**
	Hip ext	0.22 ± 0.17	0.29 ± 0.21	0.34 ± 0.18	0.26 ± 0.09	**0.013[c]**
	Knee ext	0.54 ± 0.24	0.50 ± 0.29	0.61 ± 0.28	0.52 ± 0.24	0.673[c]
	Ankle plantarflexion	0.94 ± 0.40	1.06 ± 0.34	1.30 ± 0.38	1.24 ± 0.24	0.132[c]
Total Power Generation (W)						**0.031[b]**
	Hip	**8.8 ± 6.4**	**11.3 ± 7.7**	**19.8 ± 11.5**	**14.4 ± 6.2**	**0.014[c]**
	Knee	9.8 ± 7.5	10.4 ± 9.1	16.5 ± 9.5	12.3 ± 7.2	0.090[c]
	Ankle	9.4 ± 9.4	11.6 ± 9.8	22.2 ± 12.2	21.6 ± 11.4	0.145[c]
ROM: range of motion; flex/ext: flexion/extension; GRF: ground reaction force; MS: mid-stance; LR: loading response; TS: terminal stance.						

P ≤ 0.05 results denoted in bold

a: Results of ANCOVA

b: Results of MANOVA

c: Univariate post-hoc analysis

3.1a
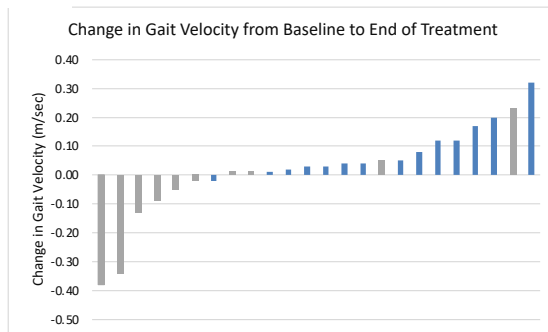
3.1b
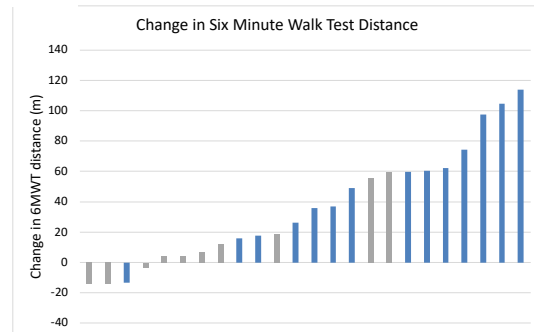
Figure 3.1 Change in gait velocity (3.1a) and Six Minute Walk Test performance (3.1b) for all FE participants depicted in blue and control participants in gray. The greatest improvements in both gait metrics were observed among those participating in the FE intervention.
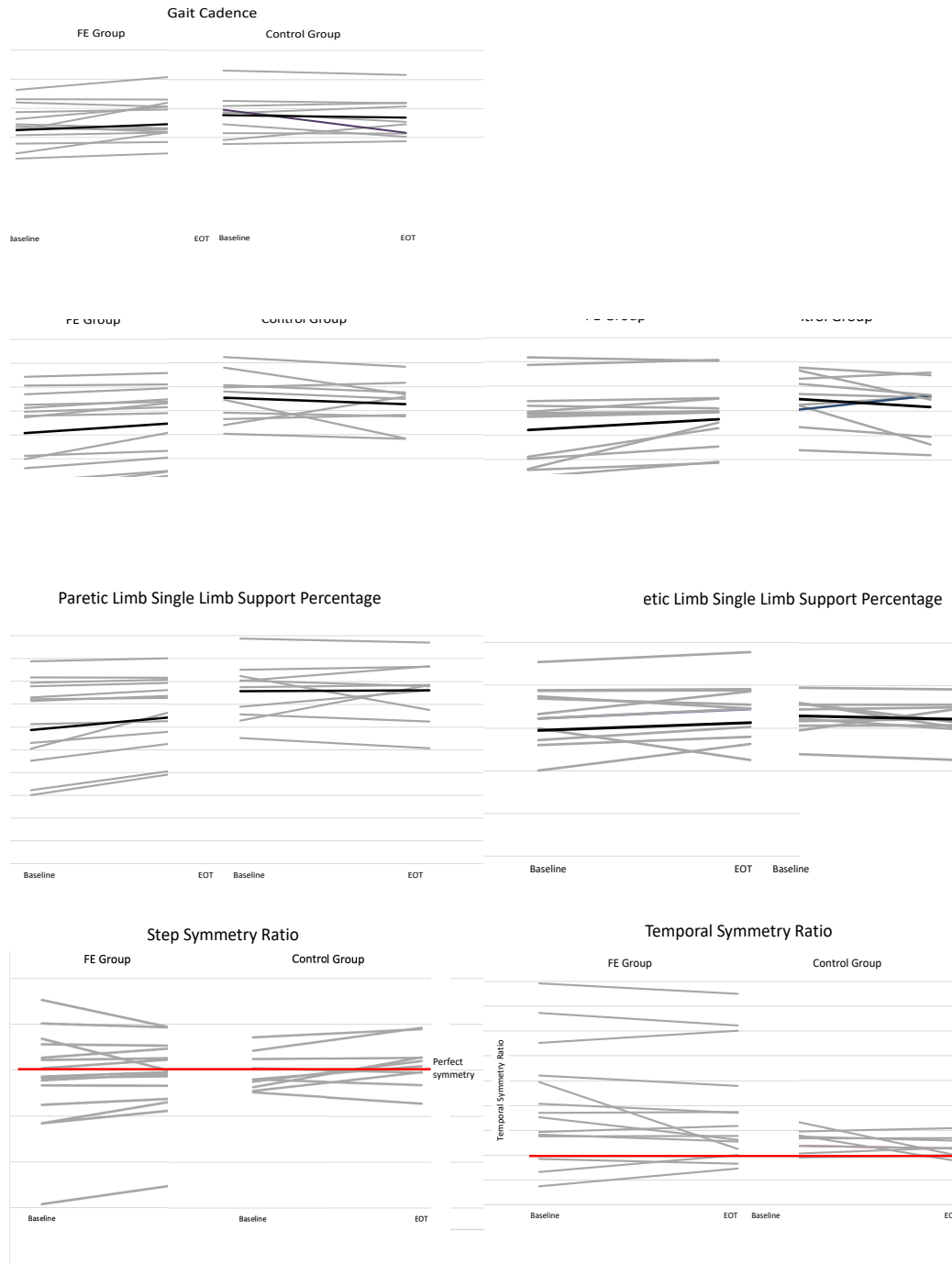
: Spaghetti plots of select spatiotemporal variables depicting results for individuals in the FE and control groups at baseline and EOT. Values for each participant (gray lines) and the cohort (black bold-faced line) are shown at baseline and EOT for the following variables: gait cadence (3.2a); paretic (3.2b) and non-paretic (3.2c) limb step length; and paretic (3.2d) and non-paretic (3.2e) single limb support percentage. Step symmetry ratio values for both groups are shown in Figure 3.2f, with values in for the FE group converging toward perfect symmetry or 0.5, with greater variability in control group symmetry ratio values at EOT. Temporal symmetry is shown in Figure 3.2g with 1.0 representing perfect symmetry. Considerable variability was evident in the FE group at baseline, with trends toward improving symmetry at EOT, while the control group demonstrated more symmetry at baseline with little to no change at EOT.

motion in all joints was observed post-intervention for the FE group, while the control group demonstrated no change or slight decrease in joint kinematics. Using Pillai's trace, the MANOVA did not reveal a significant group by time effect, $V = 0.45$, $F(6, 17) = 2.33$, $P = 0.079$.

Effects of FE on Kinetic Gait Characteristics

Baseline and EOT data for ground reaction forces (GRF), joint power, and joint moments for both groups are shown in Table 3.2. Overall, the FE group demonstrated normalization of gait kinetics. Using Pillai's trace, the MANOVA did not reveal a significant group by time effect for GRF from baseline to EOT ($V = 0.180$, $F(4, 18) = 0.99$, $P = 0.44$).

Increased total hip, knee, and ankle power were observed from baseline to EOT for the FE group as shown in Table 3.2. Using Pillai's trace, the MANOVA revealed a significant group by time effect for change in joint power from baseline to EOT ($V = 0.367$, $F(3, 19) = 3.67$, $P = 0.031$). Post-hoc univariate models revealed that total hip power generation ($F(1, 21) = 7.12$, $P = 0.014$) had a significant group by time interaction effect while total knee power generation ($F(1, 21) = 3.12$, $P = 0.090$) and total ankle power generation ($F(1, 21) = 2.30$, $P = 0.145$) were not statistically significant.

Changes in hip, knee, and ankle joint moments from baseline to EOT for both groups are in Table 3.2. Using Pillai's trace, the MANOVA revealed a significant group by time effect for change in joint moment from baseline to EOT ($V = 0.330$, $F(3, 19) = 3.12$, $P = 0.050$). Post-hoc univariate linear models revealed that peak hip extension moment ($F(1, 21) = 7.40$, $P = 0.013$) had a significant group by time interaction effect

while peak knee extension moment $(F(1, 21) = 0.18, P = 0.673)$ and peak ankle

plantarflexion moment $(F(1, 21) = 2.45, P = 0.132)$ were not statistically significant.

FE improves walking capacity

Overground walking capacity was assessed using the 6MWT. The ANCOVA

revealed a significant effect of group, $F(1,22) = 9.32, P = 0.006$. Participants in the FE

group improved an average of 53 ± 36 meters, surpassing the MCID value of 34.4

meters,[122] while the control group improved by an average of 13 ± 26 meters. A bar plot

depicting change in 6MWT performance for all participants in both groups is shown in

Figure 3.1b.

Exercise-related predictors of greatest improvement in gait velocity

Cycling cadence, aerobic intensity, and exercise power were evaluated to

determine whether these variables measuring exercise intensity were predictive of

greatest improvements in gait velocity. The multivariate linear regression model was not

significant, $F_{3,10}=1.83, P = 0.205$.

DISCUSSION

Our results indicate that the FE cycling intervention resulted in increased

comfortable gait velocity in individuals with chronic stroke by an average of 0.09 m/s.

While a statistically significant effect of group was not identified, the results may be

clinically relevant as all but two of the fourteen FE participants demonstrated

improvements in gait velocity with five exceeding the minimal clinically important

difference (MCID) value of 0.1 m/s.[137] These improvements occurred in the absence of

task-specific gait training and were accompanied by improvements in spatiotemporal,

kinematic and kinetic characteristics of gait, indicating normalization of gait

biomechanics and improvements in locomotor control. Additionally, while biomechanical

metrics were obtained during self-selected comfortable velocity on a treadmill,

significant improvements in overground ambulation and walking capacity were observed

in those participating in FE. Collectively, these findings are encouraging, as they provide

rationale to incorporate aerobic cycling interventions as an option to improve locomotor

function in persons with chronic stroke. Furthermore, our findings were in contrast to a

recently published clinical practice guideline that found weak evidence for cycling to

improve locomotor function in individuals with chronic stroke.[108]

Improvements in Spatiotemporal Characteristics of Gait Following FE

Improvements in spatiotemporal gait characteristics were evident among

individuals in the FE group, with increases in gait cadence, increased paretic and non-

paretic stride length toward normal values, and increased time spent in single limb

support bilaterally. Increases in single limb support percentage for the FE group were

primarily driven by decreased time spent in stance, as swing times bilaterally were not

appreciably different from baseline to EOT. While it is not uncommon for spatiotemporal

variables to increase in proportion to faster gait velocities,[22] improvements were seen in

the paretic and non-paretic limbs with improvements in both step and temporal symmetry

metrics. Improvements in symmetry indices indicate that individuals participating in FE

demonstrated functional recovery and normalization of gait characteristics instead of

exaggerating compensatory strategies to walk faster.[22] Our findings are in contrast to a

trial in which individuals with chronic stroke demonstrated improvements in walking

speed following four weeks of high-intensity speed-based treadmill training; however,

changes in walking speed were not associated with change in spatial or temporal symmetry.[138]

Kinematic Gait Changes Following FE

Modest improvements were also observed in gait kinematics for those in the FE group, with increases in hip, knee, and ankle sagittal plane range of motion (ROM) for both the paretic and non-paretic limbs. However, no change or a slight decrease in sagittal plane kinematics was observed in the control group. Investigating the kinematics associated with increased gait velocity is important to understand mechanisms undertaken by participants to walk faster. For example, in a study investigating kinetic and kinematic characteristics of gait and their relationship to walking speed in persons with stroke, Eng and Kim found that individuals who had the fastest self-selected walking speed did not exhibit profiles resembling neurologically healthy adults.[26] In fact, compensatory strategies at the hip (ie: reduced sagittal plane kinematics and the use of abduction rather than flexion to advance the limb) were more common amongst those who walked the fastest.[26] Yet the aim of stroke rehabilitation is to normalize gait mechanics, in part to prevent secondary impairments or injuries that may derive from poor gait mechanics. Swing phase compensatory strategies such as hip abduction, circumduction, or hip hiking may cause back or hip pain due to overuse of the trunk and lower limb muscles, soft tissue strain, and biomechanical malalignment. Similarly, abnormal stance phase mechanics such as genu recurvatum and decreased knee flexion with loading response can place excessive strain on the spine, hip, knee, ankle, or connective tissue, which over time can cause pain and musculoskeletal pathology. Therefore, our findings that those

participating in FE demonstrated normalization of kinematics bilaterally is suggestive of functional recovery.[25]

Changes in Gait Kinetics Following FE

The analysis of gait kinetics provides a window into the causes of abnormal movement patterns and underlying muscle and joint malfunction.[28] Improvements in GRF values were evident for those participating in FE, while no improvements were evident for the control group. Notably, GRF data for the control group were closer to normal ranges at baseline than for the FE group. Nonetheless, improvements for the FE group were indicative of increased lateral weight shift onto the hemiparetic limb, increased peak loading with weight acceptance and normalization of anterior-posterior breaking forces with loading response and propulsion at terminal stance.[29] As it relates to vGRF profiles, Takahashi and colleagues noted the relationship between functional performance and the shape of vGRF curves, with normal M-shaped curves indicative of better function.[1] To quantify the vGRF curve profile, they measured the ratio from the dip that occurs at mid-stance relative to 1) the peak that occurs with loading response, and 2) the peak that occurs at terminal stance, indicating normal values of .85 for both calculations. The calculation of these ratios and a typical M-shaped vGRF curve from a neurologically healthy individual are shown in Figure 3.4. Improvements in both ratios were evident in the FE group, with values approaching .85 at EOT, while the control group demonstrated near-normal values at baseline with no appreciable change at EOT. Collectively the improvements in GRF profiles in those participating in FE indicate normalization of the momentum-driven activity of human gait.

Hip extension and ankle plantarflexion during stance are the main sources of propulsion during gait.[129,130] Power and joint moment improved significantly for the FE group compared to the control group, with greatest improvements observed with total hip extension power and peak hip extension moment during stance. Collectively, improvements in hip extension power, hip extension moment, and ground reaction forces following FE are indicative of improved alignment, improved limb loading, and improved force generation, all of which likely contributed to increased gait velocity.[25,28]

Task-Specificity versus Transfer of Training

As motor learning approaches were incorporated into practice by experts in stroke rehabilitation toward the end of the 20th century, the concept of task specificity was emphasized to optimize carryover to function.[30,31,37,43] However, a transfer of training has been shown to occur between distinct motor tasks, particularly when the kinematic and kinetic requirements of the tasks are similar.[42] Therefore, while cycling and walking are different motor tasks, both require the rapid reciprocal activation and relaxation of lower extremity muscles in a synergistic manner.[111,112,123-127] The propulsive energy in both cycling and walking are generated by extension.[111] Raasch and Zajac described the synergistic action of muscle groups during cycling, finding that the hip extensors, knee extensors, and ankle plantarflexors work synergistically during downstroke, similar to patterns of activation measured during walking.[112,133] While the timing and coordination of muscle groups is not identical in cycling and walking, it is plausible that the improvements in power generation observed during gait at EOT were facilitated through a training effect from the FE cycling intervention.

In addition to the similarities in cycling and walking with force generation, prolonged excitation of the quadriceps has been found during the up-stroke phase of cycling, resulting in excessive negative work.[123,124] This alteration in normal activation patterns during cycling is not dissimilar to prolonged activation and abnormal coactivation of the extensors that is observed during terminal stance through initial swing, that often results in stiff-legged gait and compensatory strategies for limb advancement.[27,129] Therapies such as functional electrical stimulation and biofeedback have been used in conjunction with cycling training to improve the reciprocal activation of muscles to coordinate smooth pedaling. Instead of electrical stimulation or biofeedback, our FE approach involved a controlled pedaling rate and consistent pattern of exercise to train the rapid reciprocal activation and relaxation of lower extremity muscles in a synergistic manner that is required for cycling and walking.

Numerous advantages exist to FE training for individuals post-stroke including safety, the ability to complete thousands of repetitions in a single session, replicating high cadence associated with normal human gait, and the potential global benefits to aerobic exercise training.[67,92,139] Seated cycling, particularly on a semi-recumbent stationary ergometer, requires less postural control than walking, providing a safe modality to train without individuals having to focus on balance. The FE approached provided a highly repetitious and consistent exercise rate, which cannot be easily replicated during traditional overground or treadmill-based gait training. Thus, our findings that improvements in gait velocity following FE were accompanied by improvements in gait biomechanics are clinically relevant as these data provide a viable and safe aerobic intervention for individuals with chronic stroke to improve locomotor control

Study Limitations and Conclusions

There are several limitations to this study; namely, our data were limited to 14 FE and 10 control participants, limiting statistical power to measure change between groups from baseline to EOT. Using MCID values may provide clinical relevance considering this statistical limitation. Given the primary aim of the clinical trial was to improve UE function, criteria for participation were related to UE impairment and did not consider the degree to which gait was impaired. Our primary outcome, change in comfortable gait velocity, was obtained during treadmill walking, which may not be indicative of participants' gait pattern overground, though similarities between the two approaches have been reported.[131] To account for this, an acclimatization period was used our participants, and data only after the period of acclimatization were used for this data analysis. Additionally, participants were permitted to use ankle foot orthoses as prescribed for community ambulation during gait testing in addition to upper extremity support of one or both handrails. To mitigate this study limitation, the use of orthoses and/or handrails was kept consistent within participants at both testing time points. Therefore, these results may still be used as a basis of comparison between the pre- and post-intervention time points and support the use of FE to improve locomotor function in individuals with hemiparesis due to chronic stroke.

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4 Manuscript 3: Increased comfortable gait speed is associated with improved gait biomechanics in persons with Parkinson's disease completing an 8-week aerobic cycling intervention

4.1 Introduction

Gait dysfunction is a common clinical symptom in individuals with Parkinson's disease (PD), typically characterized by shuffling, decreased velocity, diminished arm swing, and truncal rigidity. The current model for rehabilitation of gait is to address active PD-related impairments that negatively impact walking and to prevent or delay anticipated impairments common with disease progression. Aerobic cycling interventions have been shown efficacious in improving gait velocity in individuals with PD, although the impact on gait quality is not well understood. To determine the changes in gait quality following an aerobic cycling intervention, a subset of participants participating in a large randomized clinical trial investigating the effects of aerobic cycling on motor function underwent biomechanical gait assessment. The effects of aerobic cycling on spatiotemporal characteristics of gait and on gait kinematics and kinetics are reported from this secondary analysis.

Increased comfortable gait speed is associated with improved gait biomechanics in persons with Parkinson's disease completing an 8-week aerobic cycling intervention

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ABSTRACT

Objectives: To determine the effects of an 8-week aerobic cycling intervention on gait velocity and locomotor control in individuals with idiopathic Parkinson's disease (PD).

Design: Cohort study

Setting: Research laboratory

Participants: Individuals with mild to moderate idiopathic PD (N=14).

Interventions: Participants completed 24 sessions of cycling, exercising at a targeted aerobic intensity of 60-80% of their heart rate reserve.

Main Outcome Measures: Change in comfortable walking speed, the Motor Section of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS III), in addition to spatiotemporal, kinematic, and kinetic gait variables using motion capture were obtained. To determine the biomechanical mechanisms associated with increased walking speed, change in spatiotemporal, kinematic, and kinetic variables

were analyzed separately for those who met the minimal clinically important difference (MCID) for change in gait velocity compared with those who did not.

Results: Significant increases were observed in gait velocity from 0.86 to 1.00 m/s (P=0.016), accompanied by a significant reduction in PD motor symptoms measured by the UPDRS (P=0.033). Overall, increased gait velocity was accompanied by normalization of gait biomechanics. Those who met the MCID value for change in gait velocity demonstrated significantly greater improvements in spatiotemporal parameters (P=0.004) and ground reaction forces (P=0.037) compared to those who did not meet the MCID.

Conclusions: Individuals with PD demonstrated significant improvements in gait velocity and a reduction of PD motor symptoms following 8-weeks of moderate- to high-intensity cycling. Increased gait velocity was accompanied by normalization of gait biomechanics, suggestive of improvements in locomotor control.

MeSH Key Words: gait, Parkinson's disease, exercise**,** biomechanics

INTRODUCTION

Gait dysfunction is a disabling symptom associated with Parkinson's disease (PD), caused by the loss of dopaminergic-producing cells within the substantia nigra.[49,51] The subsequent loss of basal ganglia function disrupts the production of coordinated and purposeful movement resulting in bradykinesia, rigidity, postural instability, freezing of gait, and festination.[51] Pharmacological management of PD involves the use of dopaminergic medications which, in the early stages of the disease, are effective in mitigating certain aspects of gait dysfunction including velocity and step length, but fail to improve gait kinematics, kinetics, freezing of gait or postural instability.[49] Therefore, the rehabilitation management of gait dysfunction is paramount in PD, as deficits in walking are a significant source of disability and negatively affect participation and quality of life.[52]

Deficits in spatiotemporal, kinematic, and kinetic components of gait are observed in persons with PD, with symptoms initially presenting unilaterally and eventually progressing to bilateral involvement.[49] The symptoms of PD which include diminished power and rigidity contribute to reduced forward propulsion, which from a spatiotemporal perspective, result in decreased gait velocity, reduced step length, impaired cadence, and increased double limb support percentage.[49] The kinematic deficits are characterized by decreased sagittal plane range of motion at the hip, knee, and ankle, in addition to truncal rigidity and diminished arm swing.[47] Altered gait kinetics in persons with PD are primarily associated with changes in ground reaction forces (GRF), and are often more pronounced than gait kinematics.[51] When evaluating gait kinetics in persons with PD compared to healthy, age-matched controls, Oh and colleagues reported reduced

vertical GRF (vGRF), abnormal shape of the vGRF curve, and diminished AP propulsive forces.[51] These kinetic findings support the clinical observations that PD symptoms such as bradykinesia and rigidity negatively impact the momentum-driven and propulsive activity inherent to human gait.

The current model for rehabilitation of gait for persons with PD is to address active PD-related impairments and to prevent or delay anticipated impairments common with disease progression.[48] Increasing gait velocity is a common rehabilitation goal for persons with PD, as increased gait velocity is associated with reduced risk of falls, increased independence with activities of daily living and instrumental activities of daily living, and decreased mortality.[48,140] A recently published clinical practice guideline found that improvements in gait velocity were achieved through various rehabilitation approaches including moderate- to high-intensity aerobic exercise, progressive resistance training, multimodal balance training, external sensory cueing, and gait training.[48] Most of the studies cited used clinical outcomes such as the six-minute walk test, timed up and go, or the timed 10-meter walk. While relevant, clinical outcomes fail to evaluate the biomechanical mechanisms associated with increased gait velocity. Evaluating changes in gait biomechanics as a result of rehabilitation interventions would provide insight into how training impacts locomotor control and whether the normalization of gait biomechanics is induced.

Biomechanical gait assessment is used in the management of individuals with PD to develop an understanding of disease progression, identify links between clinical impairments and their manifestation during gait, and to evaluate the precise and quantitative impact of rehabilitation interventions. While numerous cycling studies have

shown improvements in gait velocity[104,141-143] or walking capacity,[104,141,142,144] the

biomechanical mechanisms associated with change in walking speed have not been

systematically measured. The aim of this study was to determine the effects of an 8-week

moderate- to high-intensity cycling intervention on changes in biomechanical

characteristics of gait and motor symptoms in persons with PD. We hypothesized that the

intensive aerobic cycling intervention would induce improvements in gait velocity from

baseline to end of treatment, accompanied by improvements in locomotor control and

diminished motor symptoms.

METHODS

A cohort study was conducted as part of a larger randomized clinical trial[95] to

determine the effects of a supervised 8-week aerobic cycling intervention on locomotor

control quantified using biomechanical gait data in individuals with PD (R01NS673717,

clinicaltrials.gov registration number NCT01636297). The full study protocol has been

previously published.[95]   The study was approved by the Cleveland Clinic Institutional

Review Board and all participants completed the informed consent process.

Participants

Individuals with mild to moderate idiopathic PD (Hoehn and Yahr II-III) who met

the following criteria were eligible for participation in the Cyclical Lower Extremity for

Exercise (CYCLE) Trial: 1) between 30 and 75 years of age, 2) no history of dementia or

stroke, 3) no contraindications to participate in aerobic exercise, and 4) not engaged in

physical therapy.[95] One hundred participants were enrolled in the full clinical trial and

randomized 2:2:1 to forced rate aerobic cycling (N=40), voluntary rate aerobic cycling

(N=40) or a non-exercise control group (N=20). A subset of participants who

randomized to one of the exercise groups (N=14) opted to complete biomechanical gait assessment at baseline and end of treatment (EOT) as part of this exploratory aim, not an original aim within the trial registry.

Aerobic Cycling Intervention

Upon enrollment, all participants underwent a maximal exertion metabolic stress test on a cycle ergometer.[145] Participants in the aerobic cycling groups completed 50-minute sessions of aerobic cycling 3 times per week for 8 weeks. Each session consisted of a 5-minute warm-up, 40-minute main set, and 5-minute cool-down. During the main set, participants were encouraged to exercise at 60-80% of their heart rate reserve (HRR) computed using the Karvonen formula and based on resting and peak heart rate (HR) values obtained during the baseline stress test. Heart rate was measured continuously using a Garmin chest strap (Garmin, Ltd, Olathe, Kansas) and displayed to facilitate adherence with prescribed aerobic intensity. Clip-in cycling shoes were used to ensure secure contact between participants' feet and pedals. Aerobic intensity (%HRR), power, and cadence were recorded for each session. All sessions were administered by an exercise physiologist or physical therapist trained in Basic Cardiac Life Support.

Gait Analysis

Biomechanical gait data were collected at baseline and EOT with participants "off" anti-Parkinsonian medication with the Computer Assisted Rehabilitation ENvironment (CAREN) (Motekforce Link, Amsterdam, Netherlands). The CAREN system engineer was responsible for all aspects of data collection. The CAREN system consists of a 10-camera 3D motion capture system (Vicon Inc., Oxford, UK), D-Flow control software (Motekforce Link), 180° curved projection screen, and a six degree of

freedom motion platform (Moog Inc., Elma, New York) with an instrumented dual-belt treadmill (Bertec Corp., Columbus, Ohio). The full body marker set was used for this study, consisting of 47 retroreflective markers as defined by the Human Body Model to characterize gait function.[103,119] The retroreflective marker position data were filtered using a 2nd order low-pass Butterworth filter with a 6 Hz cut-off frequency.

Gait Outcomes

The primary outcome was change in comfortable gait velocity from baseline to EOT. To determine comfortable gait velocity, treadmill speed on the CAREN system was gradually increased during a practice trial until the participant reported that he/she was at a comfortable pace, then slightly increased to verify that the comfortable pace was not underestimated; at which point the treadmill speed was fixed for the duration of data collection. Following acclimatization to the CAREN system and gait analysis set-up, a 2-minute trial was completed at the individual's comfortable speed.

Secondary outcomes included spatiotemporal, kinematic and kinetic gait parameters, computed using the Gait Offline Analysis Tool (GOAT; version 4.1, Motekforce Link, Amsterdam, Netherlands) and custom MATLAB code (MathWorks, Natick, MA). In addition to gait velocity, spatiotemporal variables computed included gait cadence, left and right step length, and stance percentage. Kinematic variables were computed with the GOAT software native to the CAREN system. Sagittal plane kinematics (hip flexion/extension, knee flexion/extension, and ankle plantar-/dorsiflexion) were computed for the left and right limbs. Spatiotemporal and kinematic variables were analyzed based on right versus left in addition to more versus less affected

limbs and were found to be not statistically different; thus, values were averaged across limbs.

Kinetic data were computed using the GOAT software, and customized MATLAB code was used to identify relevant components of the gait cycle and to extract variables of interest. Vertical ground reaction force (GRF) data were used to identify stance and swing phases of gait in addition to initial contact, loading response, mid-stance, and terminal stance. Primary outcomes of interest included peak vGRF, peak anterior-posterior braking forces (peak $AP_{braking}$), peak anterior-posterior propulsion forces (peak AP_{prop}), and peak lateral GRF. Exploratory vGRF outcomes to investigate change in the shape of the vGRF curve included vGRF at loading response ($vGRF_{LR}$), vGRF at mid-stance ($vGRF_{MS}$), and vGRF at terminal stance ($vGRF_{TS}$),

Clinical Outcomes

The Motor Section of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III) was administered by a trained board-certified neurologic physical therapist at baseline and end of treatment (EOT) with participants off anti-Parkinsonian medication. Postural Instability and Gait Difficulty (PIGD) subscores were extracted from the MDS-UPDRS-III to describe participant demographics.

Statistical Analysis

Descriptive statistics were computed to describe demographic characteristics, exercise variables, and gait outcomes at baseline and EOT for the cohort. Normality of data was determined using visual inspection of histograms and normal Q-Q plots, along with the Shapiro-Wilk test. The primary biomechanical and clinical outcome, change in comfortable gait velocity and change in MDS-UPDRS III scores from baseline to EOT

were analyzed using paired *t*-tests. The cohort was then dichotomized to those who met

Table 4.1 Participant Demographics and Exercise Characteristics

	Overall (n=14)	≥ MCID (n=9)	< MCID (n=5)	P-value
Age (years)	64.9 ± 5.5	65.1 ± 6.5	64.4 ± 3.8	0.827
Male sex (versus female), n	8 (57%)	5 (56%)	3 (60%)	0.593
Baseline MDS-UPDRS III	35.0 ± 10.4	**29.7 ± 5.5**	**40.8 ± 8.3**	**0.010**
Baseline PIGD	2.3 ± 1.5	**1.3 ± 1.1**	**3.0 ± 1.5**	**0.039**
Exercise characteristics				
Cadence (RPM)	76.4 ± 13.6	79.2 ± 9.4	71.5 ± 19.3	0.331
Percentage of HRR	68.5 ±9 .8	69.5 ± 9.7	66.7 ± 10.9	0.628
Power (watts)	37.1 [20.7, 65.6]	34.8 [22.4, 63.0]	56.5 [18.4, 97.2]	0.595

Summary statistics presented as mean ± standard deviation, median [Q1, Q3], or n (%) for categorical data; MCID – minimal clinically important difference for change in gait velocity; RPM- revolutions per minute; HRR- heart rate reserve

the MCID for change in gait velocity, defined as 0.1 m/sec[146] (group$_{≥MCID}$) and those who

did not meet the MCID for change in gait velocity (group$_{<MCID}$). The dichotomized

groups were compared on demographic characteristics using ANOVA for normally

distributed variables or the Chi-square test for categorical variables. The remaining

spatiotemporal, kinematic, and kinetic variables were compared using 2-way multivariate

analysis of variance (MANOVA) linear models. If the MANOVA was significant, post-

hoc comparisons were conducted using separate univariate linear models. An alpha of

0.05 determined significance.

RESULTS

Fourteen individuals with mild-moderate idiopathic PD presenting with a mean

MDS-UPDRS III score of 35.0 ± 10.4 participated in this cohort study. Participant

demographics, baseline characteristics, and exercise variables are summarized in Table

4.1.

Improved spatiotemporal characteristics of gait following moderate- to high-intensity cycling

Changes in spatiotemporal parameters of gait from baseline to EOT are shown in Table 4.2. Participants demonstrated a significant improvement in the primary outcome, change in comfortable gait velocity from baseline to EOT ($P = 0.016$), Figure 4.1a. In general, participants demonstrated normalization of spatiotemporal gait characteristics. With respect to the MANOVA analyzing group$_{\geq MCID}$ compared with group$_{<MCID}$, there was a significant group*time interaction effect for change in spatiotemporal gait variables, $V = 0.72$, $F(3, 10) = 8.47$, $P = 0.004$. Separate univariate linear models revealed a significant interaction effect for stance percentage, $F(1, 12) = 13.55$, $P < 0.003$; while gait cadence $F(1, 12) = 1.24$, $P = 0.287$ and step length, $F(1, 12) = 3.55$, $P = 0.084$ did not achieve significance.

Table 4.2 Clinical and Biomechanical Gait Outcomes

	Baseline	EOT	Difference	P-Value
Primary Outcome				
Gait Velocity (m/sec)	**0.86 ± 0.24**	**1.00 ± 0.23**	**0.14 ± 0.20**	**0.016[a]**
Clinical Outcome				
MDS-UPDRS III	**35.0 ± 10.4**	**32.4 ± 11.7**	**-3.6 ± 6.0**	**0.033[a]**
Spatiotemporal Variables				**0.004[b]**
Cadence (steps/min)	102 ± 19	106 ± 16	4 ± 14	0.287[c]
Normalized Step Length (cm)	62.2 ± 21.3	70.1 ± 16.9	7.9 ± 15.1	0.084[c]
Stance %	**67.7 ± 1.4**	**66.5 ± 2.0**	**-1.2 ± 2.0**	**0.003[c]**
Kinematic Variables				0.125[b]
Hip flex/ext, degrees	36.3 ± 9.0	39.3 ± 8.9	3.0 ± 4.1	
Knee flex/ext, degrees	53.8 ± 9.5	55.5 ± 9.4	1.7 ± 5.1	

Ankle dorsi-plantarflexion, degrees	25.9 ± 7.1	27.8 ± 6.7	1.9 ± 3.0	
Trunk rotation (degrees)	11.7 ± 4.5	13.4 ± 4.8	1.7 ± 2.5	
Kinetic Variables in MANOVA				**0.037[b]**
Peak vGRF (N)	770 ± 215	791 ± 224	21 ± 48	0.059[c]
Peak AP Braking (N)	**81 ± 48**	**91 ± 56**	**9.7 ± 28.7**	**0.013[c]**
Peak AP Propulsion (N)	**89 ± 56**	**101 ± 47**	**12.2 ± 26.1**	**0.001[c]**
Peak Lateral GRF (N)	6.4 ± 4.7	8.0 ± 6.8	1.6 ± 8.6	0.191[c]
Additional vGRF Outcomes (N)				
$vGRF_{LR}$	750 ± 222	788 ± 226	38 ± 78	N/A
$vGRF_{MS}$	663 ± 154	631 ± 156	-31 ± 59	N/A
$vGRF_{TS}$	728 ± 198	721 ± 193	-7 ± 38	N/A
$vGR_{MS} : vGRF_{LR}$	.91	.82	N/A	
$vGR_{MS} : vGRF_{TS}$	.92	.88	N/A	

MDS-UPDRS III: Motor section of the Movement Disorder Society Unified Parkinson's Disease Rating Scale; flex/ext: flexion/extension; vGRF: vertical ground reaction force; AP: anterior-posterior; $vGRF_{LR}$:vGRF at loading response; $vGRF_{MS}$: vGRF at mid-stance; $vGRF_{TS}$: vGRF at terminal stance

$P \leq 0.05$ denoted in bold
a: Results of paired t-test (whole cohort)
b: Results of MANOVA (analyzing group$_{\geq MCID}$ versus group$_{<MCID}$)
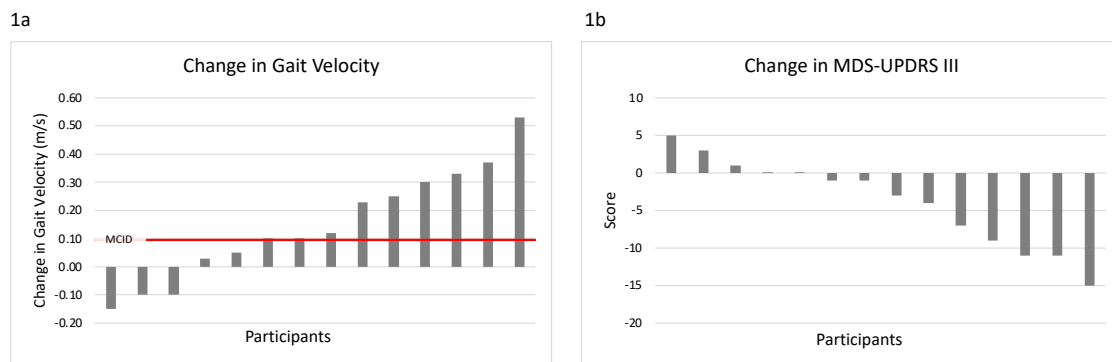c: Univariate post-hoc analysis

Figure 4.1 Change in gait velocity (Fig 1a) and MDS-UPDRS motor scores (1b) are shown. Nine of the fourteen participants met or exceeded the MCID value for change in gait velocity of 0.1 m/s. Similarly, nine participants demonstrated improvements in motor symptoms as measured by the MDS-UPDRS III. All outcomes were obtained with patients off anti-Parkinsonian medications.

Moderate- to high-intensity cycling improves kinematic parameters of gait

Changes in kinematic variables from baseline to EOT are shown in Table 4.2. Modest improvements in sagittal plane ROM were observed overall within the cohort. When analyzing change in gait kinematics in the group$_{\geq MCID}$ versus group$_{<MCID}$, the MANOVA did not reveal a significant group*time interaction effect V = 0.52, F(4, 9) = 2.41, P = 0.125.

Moderate- to high-intensity cycling improves kinetic parameters of gait

Improvements in GRF variables were observed from baseline to EOT as shown in Table 4.2. When analyzing differences between the group$_{\geq MCID}$ versus the group$_{<MCID}$, the MANOVA showed a significant group*time interaction effect V = 0.65, F(4, 9) = 4.10, P = 0.037. Separate univariate linear models revealed a significant interaction effect for peak AP braking forces F(1, 12) = 8.37, P = 0.013 and peak AP propulsion forces, F(1, 12) = 17.16, P = 0.013; while peak vGRF, F(1, 12) = 4.34, P = 0.059, and lateral GRF, F(1, 12) = 2.64, P = 0.130 were not significant.

Moderate- to high-intensity cycling improves clinical symptoms of PD

Clinical symptoms of PD measured by the MDS-UPDRS III improved significantly (P = 0.033) as shown in Table 4.2 and Figure 4.1b.

DISCUSSION

Our results suggest that an 8-week moderate- to high-intensity aerobic cycling intervention elicited increased gait velocity accompanied by improvements in locomotor control, evidenced by normalization of gait biomechanics. Gait velocity improved in the cohort as a whole by 0.14 m/sec, with nine of the 14 participants exceeding the MCID value.[146] When examining characteristics of the group$_{\geq MCID}$ versus the group$_{<MCID}$, age

and sex were not statistically significant; however, the group$_{<MCID}$ presented with significantly worse motor symptoms at baseline as measured by the MDS-UPDRS III and worse PIGD subscores. Exercise parameters were not significantly different across the dichotomized groups, indicating that baseline motor symptoms, and in particular baseline PIGD, may be a more important factor to consider when predicting the efficacy of aerobic cycling interventions as it relates to improving gait velocity. While not statistically significant, a potentially clinically relevant exercise variable that may have contributed to improvements in gait velocity was cycling cadence, as the group$_{\geq MCID}$ cycled more than 10% faster than the group$_{<MCID}$. Cycling cadence has been a relevant exercise variable in our previous studies which found higher cadence to be a predictor of greatest improvement in cardiovascular outcomes,[145] motor symptoms,[94] and manual dexterity.[94,147] Motor symptoms as measured by the MDS-UPDRS III also improved in the cohort following the 8-week aerobic cycling intervention, corroborating our previous findings and those of others that aerobic exercise is effective mitigating PD symptoms.[94,148]

Normalizing Spatiotemporal Gait Parameters through Intensive Aerobic Cycling

The symptoms of PD which include stooped posture, rigidity, bradykinesia, and difficulty coordinating smooth movements directly impact spatiotemporal gait variables, resulting in abnormal cadence, decreased step length, and increased double limb support percentage. When individuals volitionally increase walking speed, either spatial (step length) or temporal (cadence) parameters are increased.[149] However, individuals with PD often resort to a disproportionate increase in cadence rather than step length when asked to walk at a faster speed, perpetuating the shuffling characteristic of gait inherent to

PD.[50,149] Our results indicate that participants not only increased self-selected walking speed, but also exhibited proportionate increases in both cadence and step length, comparable to what is seen in neurologically healthy adults.[149,150] These findings suggest improvements in locomotor control following high intensity cycling, which, while not task-specific to gait, may train muscle groups to work synergistically to ensure smooth intra- and interlimb reciprocal activation, similar to activation patterns used to coordinate joint angle accelerations and decelerations during phases of the gait cycle.[111-113]

Improving Gait Kinematics Following Intensive Aerobic Cycling

Similar to what is observed with spatiotemporal parameters of gait, increased ranges of joint kinematics are typically correlated with increased gait velocity. Our cohort demonstrated increased sagittal plane ROM at the hip, knee, and ankle, in addition to trunk rotation, with values proportionate to what is observed in healthy individuals.[151] Rigidity, which contributes to decreased limb and axial kinematics in persons with PD, may have been altered with the high cadence cycling intervention to improve range of motion at EOT. Importantly, a modest improvement in trunk rotation was also observed, despite trunk rigidity being a particularly characteristic gait quality in persons with mild-to moderate PD. Interestingly, similar improvements in joint kinematics were observed across all participants, regardless of change in gait velocity at EOT.

Normalizing Gait Kinetics Following Intensive Aerobic Cycling

Abnormalities in gait kinetics have been observed in persons with PD, characterized by a reduction in peak vGRF, changes in the shape of the vGRF curve (ie: plateaued valley and/or reduced vGRF with loading response and terminal stance), and

reduced AP propulsion.[51] It has been hypothesized that reduced vGRF values are caused by the inability to maintain postural stability, as peak vGRF has been linked with balance maintenance during gait.[51,152] Similarly, reductions in AP braking and propulsion forces have been reported in persons with PD, indicative of difficulty with controlled deceleration and propulsion.[51] These deficits are particularly evident clinically during shuffling gait. Participants in our study demonstrated increased peak vGRF, AP braking forces, AP propulsion forces, and peak lateral GRF. Increased peak vGRF may represent improved postural stability, or confidence in single limb stance, which is supported by increased lateral GRF values. Complementing these increases in vGRF and lateral GRF values was evidence of increased peak AP braking and AP propulsion forces. Collectively, these findings suggest normalization of the momentum-driven activity inherent to human gait. Changes in GRF were significant in the group$_{\geq MCID}$ compared with group$_{<MCID}$. These results help us explain the kinetic mechanism associated with increased gait velocity, as those who made greater improvements may have walked faster by increasing AP GRF resulting in greater efficiency in braking forces with loading response and propulsion at toe off.

As it relates to vGRF, neurologically healthy individuals present with a traditional M-shaped curve, with the first peak occurring with loading response and the second peak during terminal stance.[51] At mid-stance, the center of mass is displaced in an upwardly direction, reducing the vGRF typically to less than the individual's body weight. Flattening of the vGRF has been observed in persons with PD, characteristic of increased reliance on mid-foot loading, with difficulty absorbing load and pushing off. Considerable heterogeneity was observed among our participants, ranging from typical-

appearing M-shaped curves, curves with asymmetrical peaks, and parabolic-shaped curves. Similar irregularities have been observed in conditions including osteoarthritis, stroke, and cerebral palsy.[1] Takahashi and colleagues quantified the shape of the vertical GRF curve by computing ratios between mid-stance and peak values at loading response and terminal stance, reporting .85 as the value observed in healthy adults.[1] As shown in the detailed vGRF data in Table 4.2, participants as a whole increased vGRF with loading response and decreased vGRF values at mid-stance, both indicative of improved kinematics. A modest decline was observed at terminal stance. However, both ratios demonstrated normalization of the M-shaped curve from baseline to EOT, with the $vGRF_{MS}:vGRF_{LR}$ ratio improving to from .91 to .82 and the $vGRF_{MS}:vGRF_{TS}$ ratio improving from .92 to .88. While these novel outcomes are exploratory in nature, they align with the kinematic, spatiotemporal, and primary GRF data presented in demonstrating normalization of gait biomechanics following the 8-week aerobic cycling intervention.

Intensive Aerobic Cycling in the Management of PD

Over the past two decades, considerable evidence has mounted demonstrating the benefits of aerobic cycling to reduce motor symptoms, and improve balance, strength, flexibility, turning, movement initiation, and gait in persons with PD.[148] We have also shown increased cortical and subcortical patterns of activation in the primary motor cortex, supplementary motor area, thalamus, globus pallidus, and putamen, similar to activation patterns seen after levodopa, suggesting that medication and high rate cycling likely use the same pathways to produce symptomatic relief.[91] Aerobic cycling, while not necessarily goal-oriented, provides an optimal and safe method of maintaining high levels

of physical activity, which has been shown to have neuroprotective and neuroplastic effects in persons with PD.[73] Individuals with PD can often continue to cycle after losing the ability to walk for fitness, thereby obtaining a greater dosage of intensive physical activity that is likely needed to mitigate PD symptoms.[148] Our novel findings that aerobic cycling not only increases gait velocity but facilitates normalization of gait biomechanics provides additional evidence regarding the benefits of cycling in persons with PD.

Study Limitations and Conclusions

Our findings are based on a subset of individuals who participated in the larger CYCLE clinical trial and contain numerous outcomes spanning spatiotemporal, kinematic, and kinetic variables, increasing the likelihood of Type I errors. Gait data were collected on an instrumented treadmill which may not represent overground ambulation. To mitigate this risk, an acclimatization period was provided. Our cohort involved individuals with mild- to moderate PD; therefore, our results may not translate persons at different stages of disease progression. Nonetheless, we are careful to not over-interpret our results which across all outcomes demonstrated promising improvements in gait biomechanics following 8-weeks of moderate- to high-intensity aerobic cycling.

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5   Manuscript 4: An 8-week aerobic cycling intervention elicits improved gait velocity and biomechanics in persons with Parkinson's disease

5.1   Introduction

Gait pathology is a hallmark symptom associated with Parkinson's disease (PD), manifested in part by the cardinal motor signs of the disease which include bradykinesia, postural instability, rigidity, and resting tremor. Although the course of PD is progressive, rehabilitation has been found effective in improving impairments which contribute to gait dysfunction. Rehabilitation goals often focus on increasing gait velocity, as increased gait velocity is correlated with reduced fall risk, decreased disability associated with activities of daily living, and reduced mortality. In a recently completed randomized clinical trial, a subset of participants underwent biomechanical gait analysis following observations of improved gait velocity following the 8-week aerobic cycling intervention. We hypothesized that the intensive aerobic cycling intervention induced improvements in gait velocity accompanied by improvements in locomotor control evidenced by normalization of gait biomechanics. This secondary analysis compares biomechanical gait outcomes for those undergoing an 8-week aerobic cycling intervention compared to a no-intervention control group.

An 8-week aerobic cycling intervention elicits improved gait velocity and biomechanics in persons with Parkinson's disease

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ABSTRACT

Background: To compare the effects of an 8-week aerobic cycling intervention on gait velocity and locomotor control in individuals with idiopathic Parkinson's disease (PD).

Research Question: Can an 8-week aerobic cycling intervention elicit improvements in locomotor control in individuals with mild to moderate PD?

Methods: A secondary analysis of data from a randomized clinical trial was conducted in individuals with mild to moderate idiopathic PD (N=28). Participants were randomized to an aerobic cycling intervention ($PD_{ex,}$ N=14) consisting of 24 sessions at a targeted aerobic intensity of 60-80% of heart rate reserve or to a no intervention control group (N=14). Change in comfortable walking speed in addition to gait kinematics, kinetics, and spatiotemporal variables using motion capture were obtained at baseline and end of treatment (EOT).

Results: The PD_{ex} group made significantly greater improvements in the primary outcome, change in comfortable gait velocity, from 0.86 ± 0.24 m/s at baseline to 1.00 ± 0.23 m/s at EOT compared to the control group who declined from 0.91 ± 0.23 m/s at baseline to 0.80 ± 0.29 at EOT ($P = 0.002$). Improvements in gait velocity for the PD_{ex} group were accompanied by improvements in gait kinematics, kinetics, and spatiotemporal parameters, while the control group demonstrated slight worsening in all gait parameters over the 8-week period.

Significance: The 8-week moderate- to high-intensity cycling intervention elicited significantly greater improvements in gait velocity compared to the control group.

Increased gait velocity was accompanied by normalization of gait biomechanics, suggestive of improvements in locomotor control. Aerobic cycling may be a viable treatment approach to improve gait velocity and gait biomechanics in individuals with mild to moderate PD and may mitigate declines in mobility.

MeSH Key Words: gait, Parkinson's disease, exercise, biomechanics

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and nonmotor symptoms affecting just over one million individuals in the United States.[47] Parkinson's disease results in the loss of dopaminergic-producing cells within the substantia nigra which disrupts basal ganglia function, resulting in diminished motor control.[47] Gait pathology is a hallmark symptom associated with PD, manifested in part by the cardinal motor signs of the disease which include bradykinesia, postural instability, rigidity, and resting tremor.[49] The gold standard treatment for PD is pharmacological management which targets dopaminergic neurons to produce more dopamine and are introduced when symptoms begin to impact the individual's quality of life. While dopaminergic medications have been shown effective in early stages of the disease to increase gait velocity and step length, they do not mitigate altered gait kinematics, kinetics, freezing of gait, or postural instability, and are less effective with disease progression.[49]

Changes in spatiotemporal gait parameters commonly seen in persons with PD include decreased velocity and step length, impaired cadence, and reduced single limb support percentage, thought to be caused in part by truncal and limb rigidity and diminished power.[49] Classic kinematic deficits include diminished sagittal plane range of motion (ROM) at the hip, knee, and ankle, decreased trunk rotation, and reduced arm swing. Abnormalities in gait kinetics are characterized by reduced vertical ground reaction forces (vGRF), abnormal shape of the vGRF curve, and diminished anterior-posterior (AP) propulsive forces.[51] Collectively, the gait deviations associated with PD

shed light on the loss of the momentum-driven and propulsive activity inherent to human gait.

Although the course of PD is progressive, rehabilitation has been found effective in improving impairments which contribute to gait dysfunction. Rehabilitation goals often focus on increasing gait velocity, as increased gait velocity is correlated with reduced fall risk, decreased disability associated with activities of daily living, and reduced mortality.[140,147] The American Physical Therapy Association recently published a clinical guideline, recommending moderate- to high-intensity aerobic exercise, progressive resistance training, multimodal balance training, external sensory cueing, and gait training as effective approaches to increase gait velocity.[48] The clinical outcomes used in the studies cited provide relevant information about the impact on gait velocity but do not assess change in biomechanics associated with increased gait velocity. Biomechanical gait assessment provides a window into locomotor control through high resolution data that quantify the mechanisms associated with change in gait velocity.

While not task-specific, cycling interventions have been shown effective in improving gait velocity[104,141-143] and walking capacity,[104,141,142,144] in individuals with PD. In fact, a recent systematic review and meta-analysis evaluating pooled data from ten studies examining gait velocity found a positive effect overall, with longer duration interventions leading to more favorable results.[148] However, a gap exists in the literature to understand the biomechanical mechanisms associated with increased gait velocity following cycling interventions. Therefore, the aim of this study was to determine the effects of an 8-week moderate- to high-intensity cycling intervention on changes in biomechanical characteristics of gait in persons with PD. We hypothesized that the

intensive aerobic cycling intervention would induce improvements in gait velocity accompanied by improvements in locomotor control evidenced by normalization of gait biomechanics.

METHODS

A secondary analysis was conducted as part of a larger randomized clinical trial[95] to determine the effects of an 8-week aerobic cycling intervention on locomotor control compared to a no intervention control group in individuals with PD (R01NS673717, clinicaltrials.gov registration number NCT01636297). The full study protocol has been previously published.[95] The study was approved by the Cleveland Clinic Institutional Review Board and all participants completed the informed consent process.

Participants

Individuals with mild to moderate idiopathic PD (Hoehn and Yahr II-III) were recruited for participation in the Cyclical Lower Extremity for Exercise (CYCLE) Trial: 1) between 30 and 75 years of age, 2) no history of dementia or stroke, 3) no contraindications to participate in aerobic exercise, and 4) not engaged in physical therapy.[95] One hundred participants were enrolled in the full clinical trial and randomized 2:2:1 to forced rate aerobic cycling (N=40), voluntary rate aerobic cycling (N=40) or a non-exercise control group (N=20). A subset of participants who randomized to one of the exercise groups (PD$_{ex}$, N=14) or to the control group (N=14) opted to complete biomechanical gait assessment at baseline and end of treatment (EOT) as part of this exploratory aim, not an original aim within the trial registry.

Aerobic Cycling Intervention

All participants, regardless of group allocation, underwent a maximal exertion metabolic stress test on a cycle ergometer.[145] The PD$_{ex}$ group completed 50-minute sessions of aerobic cycling 3 times per week for 8 weeks. Each session included a 5-minute warm-up, 40-minute aerobic exercise set, and 5-minute cool-down. During the aerobic exercise set, participants were encouraged to exercise at 60-80% of their heart rate reserve (HRR) computed using the Karvonen formula using resting and peak heart rate values obtained during the metabolic stress test. Heart rate was monitored continuously with a Garmin chest strap (Garmin, Ltd, Olathe, Kansas) and displayed using a Garmin bike computer to facilitate adherence with aerobic intensity prescribed in the protocol. Clip-in cycling shoes were used to ensure secure contact between participants' feet and pedals. Aerobic intensity measured as percent of HRR, power, and cycling cadence were recorded for each session. All sessions were administered by an exercise physiologist or physical therapist trained in Basic Cardiac Life Support.

Control Group

The control group received no intervention but completed all testing at baseline and following an 8-week period, aligning with the testing schedule for the PD$_{ex}$ group. Participants were asked to not participate in formal therapy and to not initiate a new exercise program during study enrollment. Continued participation in existing fitness programs was permitted.

Gait Analysis

Biomechanical gait data were collected at baseline and EOT with participants "off" anti-Parkinsonian medication using the Computer Assisted Rehabilitation ENvironment (CAREN) (Motekforce Link, Amsterdam, Netherlands). The CAREN

system engineer blinded to group allocation was responsible for all aspects of data collection. The CAREN system consists of a 10-camera 3D motion capture system (Vicon Inc., Oxford, UK), D-Flow control software (Motekforce Link), 180° curved projection screen, and a six degree of freedom motion platform (Moog Inc., Elma, New York) with an instrumented dual-belt treadmill (Bertec Corp., Columbus, Ohio). The full body marker set consisting of 47 retroreflective markers as defined by the Human Body Model was used to characterize gait function.[103,119] Marker position data were filtered using a 2nd order low-pass Butterworth filter with a 6 Hz cut-off frequency.

Gait Outcomes

The primary outcome was change in comfortable gait velocity from baseline to EOT, which was determined on the CAREN system during a practice trial before data collection commenced. Treadmill speed was gradually increased until the participant reported that he/she was at a comfortable pace, then slightly increased to verify that the comfortable pace was not underestimated; at which point the treadmill speed was fixed for the duration of data collection. Following acclimatization to the CAREN system, a 60-second trial was completed at the individual's comfortable speed.

Spatiotemporal, kinematic and kinetic gait variables were included as secondary outcomes, computed using the Gait Offline Analysis Tool (GOAT; version 4.1, Motekforce Link, Amsterdam, Netherlands) and custom MATLAB code (MathWorks, Natick, MA). In addition to gait velocity, spatiotemporal variables of interest included gait cadence, left and right step length, and stance percentage. Kinematic variables of interest computed with the GOAT included hip flexion/extension, knee flexion/extension, and ankle plantar-/dorsiflexion for the left and right limbs and trunk rotation.

Spatiotemporal and kinematic variables were analyzed based on right versus left in addition to more versus less affected limbs and were found to be not statistically different; thus, values were averaged across limbs.

Ground reaction force (GRF) data were computed using the GOAT software, with customized MATLAB code written to identify relevant components of the gait cycle and to extract variables of interest. Vertical GRF data (vGRF) were used to identify stance and swing phases of gait in addition to initial contact, loading response, mid-stance, and terminal stance. Primary outcomes of interest included peak vGRF, peak anterior-posterior braking forces ($AP_{braking}$), peak anterior-posterior propulsion forces (AP_{prop}), and peak lateral GRF. Exploratory vGRF outcomes to investigate the shape of the vGRF curve included vGRF at loading response ($vGRF_{LR}$), mid-stance ($vGRF_{MS}$), and terminal stance ($vGRF_{TS}$).

Statistical Analysis

Descriptive statistics were computed to describe demographic characteristics, exercise variables for the PD_{ex} group, and outcomes at baseline and EOT for both groups. Normality of data was determined using visual inspection of histograms and normal Q-Q plots, along with the Shapiro-Wilk test. The groups were compared on demographic characteristics using ANOVA for normally distributed variables or the Chi-square test for categorical variables. The primary biomechanical outcome, change in comfortable gait velocity, was analyzed using analysis of covariance (ANCOVA), with baseline values serving as the covariate. The remaining spatiotemporal, kinematic, and kinetic variables were compared using 2-way multivariate analysis of variance (MANOVA) linear models.

If the MANOVA was significant, post-hoc comparisons were conducted using separate

univariate linear models. An alpha of 0.05 determined significance. Finally, to determine

predictors of greatest improvement in gait velocity, a multivariate linear regression was

constructed for the PD_{ex} group with change in gait velocity as the dependent variable and

exercise variables and baseline MDS-UPDRS motor scores as independent variables.

RESULTS

Twenty-eight individuals with mild to moderate idiopathic PD were included in

this secondary analysis. Group demographics, baseline characteristics, and exercise

variables are summarized in Table 5.1.

Table 5.1 Participant Demographics and Exercise Characteristics

	PD_{ex} Group (n=14)	Control Group (n=14)	P-value
Age (years)	64.9 ± 5.5	62.3 ± 8.4	0.345
Male sex (versus female), n	8 (57%)	9 (64%)	0.257
Baseline MDS-UPDRS III	35.0 ± 10.4	36.9 ± 13.0	0.463
Baseline PIGD	2.3 ± 1.5	2.9 ± 1.5	0.165
Cadence (RPM)	76.4 ± 13.6	N/A	N/A
Percentage of HRR	68.5 ± 9 .8	N/A	N/A
Power (watts)	37.1 [20.7, 65.6]	N/A	N/A
Summary statistics presented as mean ± standard deviation, median [Q1, Q3], or n (%) for categorical data; MDS-UPDRS III – Motor Section of the Movement Disorder Society Unified Parkinson's Disease Rating Scale; PIGD – Postural Instability and Gait Difficulty subscale of the MDS-UPDRS; RPM- revolutions per minute; HRR- heart rate reserve; N/A – not applicable			

Improved spatiotemporal characteristics of gait following intensive cycling

Changes in spatiotemporal parameters of gait from baseline to EOT for both

groups are shown in Table 5.2. The PD_{ex} group made significantly greater improvements

in the primary outcome, change in comfortable gait velocity from baseline to EOT

compared to the control group ($P = 0.002$). The MANOVA also revealed a significant

group*time interaction effect for the remaining spatiotemporal variables, V = 0.29, F(3, 24) = 3.21, *P* = 0.041. Separate univariate linear models revealed a significant interaction effect for stance percentage, F(1, 26) = 8.44, P = 0.007; gait cadence, F(1, 26) = 4.17, P = 0.050; and normalized step length, F(1, 26) = 5.77, P = 0.024.
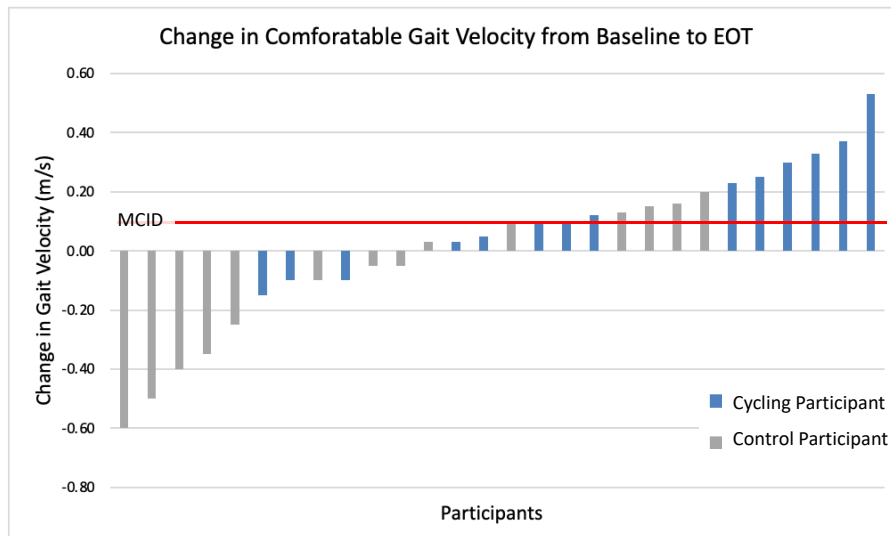

Figure 5.1 Change in gait velocity for all participants, depicting PD$_{ex}$ participants in blue and PD control group participants in gray. Nine of the fourteen participants who met or exceeded the minimal clinically important difference (MCID) value for change in gait velocity were from the PD$_{ex}$ group. Note that gait assessments were obtained with participants "off" anti-Parkinsonian medications.

Intensive cycling elicits modest improvements in gait kinematics

Changes in kinematic variables from baseline to EOT are shown in Table 5.2. Modest improvements in sagittal plane ROM were observed in the group$_{ex}$ while slight worsening of gait kinematics was observed amongst control participants. When comparing the two groups, the MANOVA did not reveal a significant group*time interaction effect V = 0.26, F(3, 24) = 2.86, *P* = 0.058.

Table 5.2 Clinical and Biomechanical Gait Outcomes

	Cycling Group (N=14)		Control Group (N=14)		
	Baseline	**EOT**	**Baseline**	**EOT**	**P-Value**
Primary Outcome					

Gait Velocity (m/s)	**0.86 ± 0.24**	**1.00 ± 0.23**	**0.91 ± 0.23**	**0.80 ± 0.29**	**0.002[a]**
Spatiotemporal Variables in MANOVA					**0.041[b]**
Cadence (steps/min)	102 ± 19	106 ± 16	105 ± 10	98 ± 17	**0.050[c]**
Normalized Step Length (cm)	62.2 ± 21.3	70.1 ± 16.9	61.2 ± 12.8	56.0 ± 13.6	**0.024[c]**
Stance %	67.7 ± 1.4	66.5 ± 2.0	66.5 ± 2.2	67.7 ±3.0	**0.007[c]**
Kinematic Variables in MANOVA					0.058[b]
Hip flex/ext, degrees	36.3 ± 9.0	39.3 ± 8.9	35.2 ± 4.8	34.2 ± 5.2	
Knee flex/ext, degrees	53.8 ± 9.5	55.5 ± 9.4	55.1 ± 13.6	53.5 ± 8.6	
Ankle dorsi-plantarflexion, degrees	25.9 ± 7.1	27.8 ± 6.7	27.1 ± 6.5	25.6 ± 5.2	
Trunk rotation (degrees)	11.7 ± 4.5	13.4 ± 4.8	12.5 ± 4.8	11.6 ± 4.6	
Kinetic Variables in MANOVA					
Peak vGRF (N)	770 ± 215	791 ± 224	926 ± 205	887 ± 205	0.170[b]
Peak AP Braking (N)	81 ± 48	91 ± 56	95 ± 40	77 ± 38	
Peak AP Propulsion (N)	89 ± 56	101 ± 47	102 ± 39	90 ± 36	
Peak Lateral GRF (N)	6.4 ± 4.7	8.0 ± 6.8	7.5 ± 6.4	5.6 ± 5.2	
Additional vGRF Outcomes (N)					
$vGRF_{LR}$	750 ± 222	788 ± 226	926 ± 205	881 ± 213	N/A
$vGRF_{MS}$	663 ± 154	631 ± 156	763 ± 173	766 ± 187	N/A
$vGRF_{TS}$	728 ± 198	721 ± 193	830 ± 196	811 ± 215	N/A
$vGR_{MS} : vGRF_{LR}$	.91	.82	.83	.88	N/A
$vGR_{MS} : vGRF_{TS}$	.92	.88	.92	.95	N/A
flex/ext: flexion/extension range of motion; vGRF: vertical ground reaction force; AP: anterior-posterior; $vGRF_{LR}$:vGRF at loading response; $vGRF_{MS}$: vGRF at mid-stance; $vGRF_{TS}$: vGRF at terminal stance					

$P \leq 0.05$ denoted in bold

a: Results of paired t-test (whole cohort)

b: Results of MANOVA (analyzing $group_{ex}$ versus control)

c: Univariate post-hoc analysis

Intensive cycling improves kinetic parameters of gait

Overall, improvements in GRF variables were observed from baseline to EOT in

the $group_{ex}$ as shown in Table 5.2. When analyzing differences between the two groups,

the MANOVA did not reveal a significant group*time interaction effect V = 0.24, F(4, 23) = 1.77, P = 0.170.

Exercise parameters and baseline PD symptoms are not predictive of change in gait velocity

The multivariate linear regression model was not significant ($F_{4,9}$ = .632; P = .652; adjusted R^2 = -.128), and exercise parameters as a whole did not correlate with change in gait velocity among exercise participants.

DISCUSSION

Our results suggest that an intensive aerobic cycling intervention elicited increased gait velocity as those in the PD$_{ex}$ group demonstrated significantly greater improvements of 0.14 m/s, while the control group declined by 0.09 m/s over the 8-week trial. Importantly, increased gait velocity was accompanied by normalization of gait biomechanics and was not accomplished by worsening mechanics. These changes suggest improvements in locomotor control and increased automaticity of gait. While there is rationale in exercise physiology literature to hypothesize that increased exercise intensity leads to more favorable outcomes, we did not find a relationship between exercise variables (cycling cadence, power, or aerobic intensity) and improvements in gait velocity. We have previously found that cycling cadence was a significant predictor of change in cardiovascular outcomes among a larger cohort of exercise participants;[145] however, cadence did not appear to influence changes in gait velocity. These findings align with a recent systematic review and meta-analysis that did not find a difference in effect size based on interventions that employed high versus low cadence cycling.[148]

Normalizing Spatiotemporal Gait Parameters through Intensive Aerobic Cycling

The characteristic clinical presentation of PD includes stooped posture, rigidity, bradykinesia, and difficulty coordinating smooth movements. These symptoms directly impact spatiotemporal gait variables, resulting in abnormal cadence, decreased step length, and increased double limb support percentage. Variability is observed in persons with PD as it relates to gait cadence, in that shuffling or festinating gait often results in increased cadence and markedly decreased step length.[49] Conversely, both step length and gait cadence are decreased in individuals who present with bradykinesia as a predominant clinical symptom.[50] It has been shown that when neurologically healthy individuals volitionally increase walking speed, either spatial (step length) or temporal (cadence) parameters are increased.[149] However, individuals with PD often resort to a shuffling gait pattern, characterized by a disproportionate increase in cadence rather than step length.[50,149] Increased gait velocity among participants in our PD$_{ex}$ group were accompanied by proportionate increases in both cadence and step length, similar to what is observed in healthy adults.[149,150] Arcolin and colleagues reported similar improvements in gait velocity and spatiotemporal variables following a 3-week intervention, which interestingly, was not different from a group that underwent treadmill training.[141] These findings suggest that high intensity cycling, while not task-specific to walking, may improve locomotor control by training muscle groups to work synergistically to facilitate smooth intra- and interlimb reciprocal activation, similar to activation patterns used to coordinate joint angle accelerations and decelerations during phases of the gait cycle.[111-113]

Improving Gait Kinematics Following Intensive Aerobic Cycling

While changes in gait kinematics were not statistically significant between groups, summary data revealed modest increases in sagittal plane ROM at the hip, knee, and ankle, in addition to trunk rotation for the PD$_{ex}$ group and modest declines in the control group, with values proportionate to what is observed in healthy individuals with changes in gait velocity.[151] While previous cycling interventions in PD have not reported change in gait kinematics,[104,141-144,153,154] increased limb and axial ROM may be reflective of reduced rigidity/stiffness, which is thought to contribute to alterations in gait mechanics and may be mitigated through repetitive, high cadence cycling.[49,150]

Normalizing Gait Kinetics Following Intensive Aerobic Cycling

Gait kinetics provide insight into locomotor control and how the body responds to the forces acting upon it.[29] Characteristic changes to gait kinetics in PD include reduced peak vGRF, changes in the shape of the vGRF curve, and reduced AP propulsion.[51] These deficits are particularly evident clinically during shuffling gait.[150] Rehabilitation strategies that focus on taking "big" steps to consciously increase amplitude of movements and reduce shuffling are unlikely to result in the normalization of GRF data, as step length is emphasized rather than gait fluidity.[155] Participants in our PD$_{ex}$ group demonstrated increased peak vGRF, AP braking forces, AP propulsion forces, and peak lateral GRF at EOT while slight declines in all values were observed in the control group. Increased peak vGRF may represent improved postural stability and confidence in single limb stance, which is supported by increased lateral GRF values and reduced stance percentage.[51,152] Increased peak AP braking and AP propulsion forces are indicative of improved deceleration with loading response and propulsion at terminal stance, both of which are reduced in persons with PD.[51] Collectively, these findings suggest

normalization of the momentum-driven characteristics of human gait. A normalization of

the traditional M-shaped vGRF curve was also observed in the PD$_{ex}$ group. The shape of
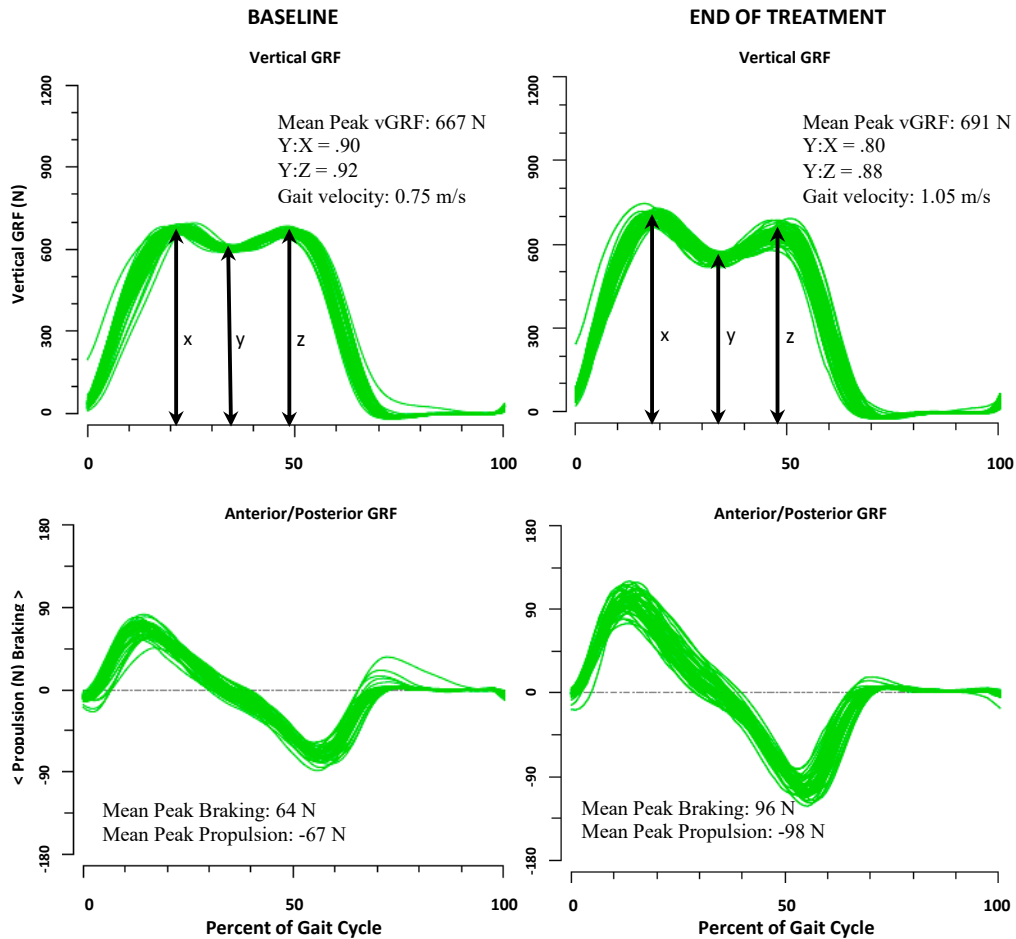

Figure 5.2 Vertical (top graphs) and AP (bottom graphs) GRF data for the same participant at baseline (left panel) and end of treatment (right panel). This individual's self-selected gait velocity increased from 0.75 m/s at baseline to 1.05 m/s at EOT. Vertical GRF data depict a plateau of the typical M-shaped curve at baseline, indicative of mid-foot loading and characteristic of individuals with diminished postural stability. Normalization of the vGRF curve is evident at EOT, quantified by ratios comparing mid-stance values to each peak value, as described by Takahashi and colleagues,[1] who reported normal ratios of .85 in healthy adults. Anterior-posterior braking and propulsion forces both increase from baseline to EOT, indicative of greater efficiency with deceleration with loading response and propulsion at terminal stance.

the vGRF curve was quantified by computing ratios between mid-stance and peak values

at loading response and terminal stance as described by Takahashi and colleagues, with

data from a sample exercise participant shown in Figure 5.2.[1] Ratios improved in the PD$_{ex}$ group toward the .85 value reported in healthy adults as shown in Table 5.2, which may be indicative of decreased reliance on mid-foot loading and increased efficiency absorbing load and pushing off.[1,51]

Intensive Aerobic Cycling in the Management of PD

Evidence of the benefits of aerobic cycling as a tool to mitigate PD symptoms and improve functional mobility has mounted in recent years.[148] It is difficult to decipher whether the aerobic intensity of the intervention or the cyclical nature of the exercise is responsible for the improvements we and others have observed, as aerobic exercise has been shown to have neuroplastic and neuroprotective effects.[67,68,73,83,85,88] We have also shown increased cortical and subcortical patterns of activation during neuroimaging following a single bout of high-rate aerobic cycling, similar to activation patterns seen after levodopa, suggesting that medication and high rate cycling may use the same pathways to treat symptoms.[90,91] However, as it relates to the changes observed with gait, aerobic cycling, while not necessarily task-specific, may induce a transfer of training to gait, as both tasks have similar kinematic and spatiotemporal requirements.[42,112,156] Importantly, aerobic cycling is a safe method of maintaining high levels of physical activity, and can complement pharmacological therapies to mitigate PD symptoms.[148] Our novel findings that aerobic cycling induces increased gait velocity accompanied by normalization of gait biomechanics provide additional evidence supporting the benefits of cycling in persons with PD.

Study Limitations and Conclusions

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Our results are from a subset of participants from the CYCLE trial, which included persons with mild to moderate PD; therefore, our results may not translate to other stages of disease progression. Biomechanical gait analysis involves numerous outcomes spanning spatiotemporal, kinematic, and kinetic variables, increasing the likelihood of Type I errors. Therefore, we are careful to not over-interpret our results which demonstrated promising improvements in gait biomechanics for those completing an 8-week aerobic cycling intervention compared to a no intervention control group. Additional studies designed to delineate the effects of aerobic exercise versus cycling would be valuable to guide precise exercise prescription for individuals to manage PD-related symptoms.

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6   Conclusion

Gait dysfunction is a common clinical symptom of both acquired and degenerative neurological conditions such as stroke and Parkinson's disease (PD). Walking-related deficits contribute significantly to disability and have a negative impact on quality of life and participation in activities. For these reasons, a common goal of rehabilitation is to improve locomotor control. Rehabilitation interventions aimed at improving locomotion often employ principles of motor learning including task-specific training. However, we have observed increases in walking capacity in individuals with stroke and increased gait velocity in persons with PD following an 8-week aerobic cycling intervention, in the absence of task-specific gait training. These findings were encouraging but did not provide insight into the biomechanical mechanisms associated with increased velocity to determine whether improvements in locomotor control were achieved or if individuals exaggerated compensatory strategies to walk faster.

The data presented in this dissertation demonstrate that an 8-week aerobic cycling intervention results in improved gait velocity accompanied by improvements in gait biomechanics, indicative of improved locomotor control. These findings were common across persons with stroke and PD, despite very different neuropathology. While cycling and walking are different tasks, both require the rapid reciprocal activation and relaxation of lower extremity muscles synergistically. It is plausible that high cadence cycling may train muscles to work synergistically, ensuring smooth intra- and interlimb reciprocal activation, similar to activation patterns used to coordinate joint angle accelerations and decelerations during gait.

While our results are encouraging, there are several limitations to our studies. The aims of the projects presented in this dissertation were secondary; therefore, inclusion and exclusion criteria for the clinical trials were based on primary outcomes measuring upper limb function. Individuals in both clinical trials presented with considerable heterogeneity as it relates to baseline walking ability making generalizability challenging. The relatively small sample sizes in each study also limited the investigation of which exercise variables contributed most to desirable gait outcomes. Additionally, biomechanical gait analysis generates a vast amount of data, complicating data processing and interpretation. To simplify its interpretation, the biomechanical data were categorized into three constructs: spatiotemporal, kinematic, and kinetic. The kinetic data were further categorized into ground reaction forces, joint moment, and power. The analysis of each of these constructs using a relatively small data set increased the likelihood of Type I errors.

Future Directions

Future well-designed clinical trials investigating gait outcomes as a primary aim and adequately powered to adjust to multiple comparisons are needed to make definitive conclusions about the impact of cycling on gait biomechanics. Given the novelty of our findings that aerobic cycling may improve locomotor function, investigating cycling biomechanics alongside gait biomechanics may provide insight into whether cycling induces a transfer of training effect to walking. Including electromyography to identify patterns of muscle activation during various phases of the gait cycle in our participants with neurological impairment and comparing those data to EMG obtained during recumbent cycling would further delineate the link between cycling and gait as it relates

to motor control. Lastly, neuroimaging to elucidate the acute and long-term effects of aerobic cycling on brain function in persons with stroke and PD may provide insight into the role of aerobic exercise on neuroplasticity and the recovery of locomotor function.

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Cleveland Clinic Institutional Review Board (IRB)
Federalwide Assurance (FWA 00005367)

Cleveland Clinic

January 19, 2022

Susan Linder, DPT

RE: IRB# 22-045: The effects of cycling on gait biomechanics in individuals with Parkinson's disease

Dear Dr. Linder:

Your new study application received on 10/18/2022 was **approved** on 1/19/2022 as **Exempt Human Subject Research**.

This is minimal risk research using/involving secondary research for which consent is not required and the research involves only information collection and analysis involving the investigator's use of PHI when that use is regulated by HIPAA for the purposes of health care operations, research, or public health activities and purposes.

The documents reviewed include: New Study Application 10/18/2022, Data Collection Sheet, Complete Protocol.

The stamped approved documents are available online under the Approved Documents tab. Any additional variables you propose to collect must be submitted to the IRB for review and approval prior to collection.

Waiver
A waiver of Informed Consent and waiver of HIPAA authorization is approved to allow access to PHI by the research team however, sharing or releasing identifiable data to anyone other than the study team is not permitted without additional IRB approval.

Changes or amendments that would impact the exempt status of this project require IRB review and approval prior to implementation. Unanticipated problems including adverse events and deviations are to be reported in accordance with IRB Policy 60: Adverse Events and IRB Policy 70: Unanticipated Problems.

Continuing review is not required for this research, but there will be alternative reporting requirements which the IRB will relay via correspondence.

Please note that human subjects research at Cleveland Clinic has been impacted by COVID-19. The study team is responsible for compliance with the enterprise-wide restrictions related to research. This information is available on the Intranet, including the Center for Clinical Research homepage.

The PI is responsible to ensure research team members are knowledgeable of the study protocol and appropriately trained.

If you have any questions regarding study changes or modifications, please call the IRB office at 216-444-2924.

Sincerely,

Bridget Howard

Bridget Howard, Esq., CIP
Executive Director, IRB and Human Research Protections

BH/rf

This letter is available online under the Correspondence tab

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