# ADVANCING INDIVIDUALIZED, EVIDENCE-BASED REHABILITATION AFTER STROKE

by

Louis N. Awad

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biomechanics and Movement Science

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## ABSTRACT

The most commonly voiced rehabilitation goal for persons who have sustained a stroke is the restoration of walking ability[1]. However, despite an emphasis on walking retraining during rehabilitation, deficits[2–6] that limit walking function persist[7,8]. A recent critical review of poststroke walking therapies revealed comparable outcomes after treatment regardless of the mode or sophistication of the intervention studied, with all therapies failing to improve the majority of subjects' capacity for community walking[9]. Clearly, existing rehabilitation strategies do not sufficiently address the factors limiting poststroke walking performance. If the factors that are limiting walking performance after a stroke are adequately addressed during rehabilitation, better outcomes may be observed. However, rehabilitation efforts have been limited by a poor understanding of the clinical and biomechanical mechanisms underlying intervention-induced functional recovery, as well as a poor understanding of how the heterogeneous nature of poststroke motor impairment confounds treatment.

The first two aims of this research project were directed toward identifying clinical and biomechanical determinants of poststroke walking function. For aim one, the cross-sectional and longitudinal relationships between poststroke walking function – as measured by the 6-Minute Walk Test – versus five clinical variables previously identified as meaningful to either the short- or long-distance walking function of persons poststroke[10–17], were evaluated. Prior cross-sectional studies did not account for the influence of a key covariate, maximum walking speed[18], nor evaluate how changes in these determinants related to changes in walking function. As such, it was

unclear which should be targeted during poststroke walking intervention. Understanding how commonly targeted poststroke variables relate to *long-distance* walking function when controlling for *short-distance* maximum walking speed would elucidate the best targets for walking rehabilitation. We hypothesized that *short-distance* walking speed would be the primary determinant of *long-distance* walking function and that improvements in walking speed resulting from gait training would relate to improvements in long-distance walking function. Our findings confirmed these hypotheses, providing further support for the development and testing of poststroke interventions targeting an individual's maximum walking speed.

For aim two, the cross-sectional and longitudinal relationships between poststroke long-distance walking function, as measured via the 6MWT, versus six biomechanical variables grouped into three biomechanical constructs – stance phase mechanics, swing phase mechanics, and spatiotemporal symmetry – were evaluated. Previous investigators have shown meaningful relationships between variables from each of these constructs and poststroke walking function; however, the relative importance of each construct remained unclear. Moreover, the contribution of changes in each of these constructs to changes in poststroke walking function was unknown. The primary purpose of this study was to determine the relative importance of variables from each of these biomechanical constructs to the long-distance walking function of persons in the chronic phase of stroke recovery. A secondary aim was to identify the biomechanical changes underlying posttraining improvements in long-distance walking function. We hypothesized that stance phase mechanics would best predict long-distance walking function and that improvements in stance phase mechanics would account for improvements in long-distance walking function. Our findings confirmed these hypotheses, providing support for the development of interventions designed to improve poststroke walking by targeting the function of the paretic limb during late stance phase, especially in those more impaired at baseline.

The third aim of this research extended the findings of aims one and two by studying the effects of a novel, poststroke walking rehabilitation program designed to target the determinants identified in the first two aims. Specifically, this novel intervention combined maximal-speed treadmill training with the application of functional electrical stimulation to the paretic ankle musculature to target deficits in the paretic limb's ability to generate propulsion by simultaneously facilitating improvements in both the paretic trailing limb angle and activation of the plantarflexors during walking. Outcomes across the World Health Organization's ICF categories[19] were studied for subjects randomized to three treatment groups that trained at 1) self-selected speeds (SS), 2) maximum speeds (Fast), and 3) Fast combined with functional electrical stimulation to the paretic ankle musculature (FastFES). *A priori* mechanistic hypotheses were tested and moderation of outcomes by baseline walking speed and gait mechanics was evaluated. Our findings validated the hypothesized mechanisms underlying the FastFES intervention and demonstrated its efficacy, particularly in persons with slower baseline maximum walking speeds and larger baseline propulsion. Secondary analyses confirmed that the addition of functional electrical stimulation (FES) to maximum-speed treadmill training enhanced treatment effects, promoting greater neuromotor recovery than training without FES.

Aims 1 and 2 of this research project attempted to improve our understanding of the clinical and biomechanical factors that determine poststroke walking function. Aim 3 attempted to advance individualized, evidence-based rehabilitation. Ultimately, this work informs the development and implementation of effective poststroke walking therapies designed to build healthier lives for persons poststroke.

# Chapter 1

# INTRODUCTION

## Background

Over 5.5 million Americans are currently living with stroke – a leading cause of disability in the USA[20]. Poststroke walking dysfunction is common and has been linked to a delayed hospital discharge to home[21], a delayed return to work[22], and limited participation in the community[21]. Consequently, for the majority of stroke survivors the restoration of walking is the ultimate goal of rehabilitation[1]. As such, the development and testing of poststroke walking retraining programs has been a major focus of rehabilitation research. However, a recent critical review of current poststroke walking therapies revealed that, regardless of the mode or sophistication of training, current interventions fail to improve subjects' capacity for community ambulation[9]. Indeed, walking deficits that contribute to limitations in activity and participation persist for most patients after rehabilitation[7,8,21,23–25]. The impact on physical activity of such walking deficits is evidenced in a markedly reduced total number of steps walked per day by persons poststroke (<3500 steps) compared to sedentary healthy adults (>5000 steps)[26,27]. Considering that reduced physical activity is known to increase the risk of maladies such as heart disease and diabetes[20] and is associated with a reduced health-related quality of life[28], *a critical need exists for the development of rehabilitation programs capable of maximizing improvements in walking function after stroke.*

Current rehabilitation strategies for poststroke walking dysfunctions are not sufficiently improving the factors limiting walking performance after a stroke[9]. This impasse is likely a function of three problems facing current neurorehabilitation practice. First, it is generally unknown which poststroke impairments, when improved, will result in the recovery of walking function. Second, there is a dearth of hypothesis-driven, targeted, poststroke walking interventions. Third, the heterogeneous nature of poststroke impairments complicates intervention selection. This research is predicated on the proposition that if the factors limiting walking performance after a stroke are adequately targeted during rehabilitation, better outcomes will be observed. To address the first of these three problems, aims 1 and 2 were directed toward identifying the clinical and biomechanical determinants of poststroke walking function and quantifying the relationship between improvements in these determinants versus improvements in walking function. To address the second and third problems, Aim 3 evaluated the efficacy of a hypothesis-driven targeted walking intervention across patients with different baseline abilities. Through these research aims, this project aimed to provide a better understanding of the factors that determine walking function after stroke and provide evidence defining the efficacy of a promising targeted walking intervention.

## The Advancement of Poststroke Rehabilitation

A hallmark of poststroke walking following current rehabilitation efforts is the use of inefficient compensatory strategies, such as stiff-legged and circumduction gait, to advance the body through space[6,29]. Because a rapid achievement of walking independence – not necessarily the reduction of impairment – is the goal of current neurorehabilitation practice[30], the prevalence of such compensatory strategies following rehabilitation is not surprising as gains in walking function are achievable via improvements in compensatory strategies[31,32]. However, posttraining outcomes are *limited* as such strategies are known to increase the energy cost of walking, increase the risk of falls, reduce endurance, and reduce speed[6,21,29,33]. Consistent with current stroke clinical practice guidelines, conventional stroke rehabilitation programs are generally centered on exercise therapy and focused on muscle strengthening, cardiovascular fitness, task-related practice, aerobic endurance, balance, or joint range of motion[34]. Impairments in these areas may be important to address at some point during rehabilitation; however, a primary cause of poststroke walking dysfunctions is sensorimotor impairment of the paretic limb[35]. As such, rehabilitation programs that do not sufficiently address the function of the paretic limb during walking may facilitate the persistence of compensatory strategies during retraining, ultimately limiting treatment outcomes. Indeed, subjects may strengthen compensatory strategies instead of learning to utilize more physiologic gait patterns[31,32]. For persons in the chronic phase of stroke recovery, the development and testing of hypothesis-driven therapies capable of normalizing walking ability is warranted. *However, such an undertaking has been hindered by a lack of informative outcome measures*[36].

Until recently, the outcome measures used to evaluate improvements in walking performance following intervention did not have the capacity to differentiate between the recovery of impaired neuromotor processes versus the strengthening of existing compensatory strategies[36,37]. For example, improvements in self-selected walking speed – perhaps the most popular poststroke outcome measure[38] – do not necessarily indicate the recovery of neuromotor function. Indeed, patients walking at similar speeds present with different step length asymmetries[2,39] – a finding indicative of different compensatory mechanisms during walking[40,41]. *This dearth of informative outcome measures has limited our understanding of the changes that underlie the improvements in function observed following current therapies*, ultimately impeding the identification of deficits to target during rehabilitation and thus the development of hypothesis-driven therapies. Fortunately, advances in laboratory instrumentation have allowed a detailed quantification of treatment effects at the level of biomechanics[36], providing a sound theoretical foundation for the development and testing of novel walking therapies.

*This research project utilized such advanced instrumentation to advance poststroke walking rehabilitation efforts.* Specifically, aims 1 and 2 combined sophisticated motion analysis methods with clinical evaluations to identify the biomechanical and clinical determinants of walking function after stroke. Moreover, aim 3 – which tested the efficacy of a novel, hypothesis-driven walking intervention across the categories of the World Health Organization's International Classification of Function, Health, and Disability (ICF)[19] – utilized biomechanical evaluations conducted pretraining, posttraining, and at a 3-month follow-up to measure changes at the ICF level of *body structure and function* and to understand how such changes contributed to changes at the ICF level of *activity*.

## Motivating Aims 1 and 2

The design of targeted walking rehabilitation programs depends on the valid identification of poststroke deficits that limit walking function and are modifiable via intervention in a manner that improves walking function. Recent studies have recommended targeting specific deficits during poststroke rehabilitation based on correlative and regression analyses of cross-sectional data[10–16,42–45]. However, basing interventions on the findings of such analyses is problematic if key covariates are not controlled. For example, although lower extremity strength,[12–15,45] motor function,[16,45] and spasticity[45] have been shown to correlate with poststroke function, studies controlling for other variables have shown that they do not independently contribute to poststroke function[10–12,14,15]. That is, other variables mediate their relationship to functional performance. Similarly, despite previous biomechanical investigations identifying a myriad of single joint sagittal plane measures as variables meaningful to poststroke walking function, Cruz and colleagues demonstrated that multi-joint variables better estimated walking function[33]. While accounting for all possible covariates may be difficult to accomplish, *understanding the influence that key variables may have on the relationships of interest is critical to the valid identification of deficits to target during rehabilitation, and consequently the efficient development of targeted rehabilitation programs.*

Through cross-sectional investigation, aims 1.1 and 2.1 aimed to identify clinical and biomechanical variables related to poststroke walking function. *However, because cross-sectional studies only measure the degree that variables relate at a single moment in time, they are unable to identify whether a deficit is modifiable through intervention in a manner that relates to improvements in function*. That is, it does not necessarily follow from a strong cross-sectional relationship between a deficit and a measure of function that reducing the magnitude of the deficit in a lower functioning individual would improve their function. In contrast, longitudinal analyses that specifically examine the relationships between intervention-induced changes in particular deficits versus changes in function provide insight into the potential functional impact, for an individual, of improvements in a deficit[46–48]. Thus, aims 1.2 and 2.2 evaluated whether improvements in the identified clinical and biomechanical determinants related to improvements in walking function.

### Aim 1 Significance: Clinical Determinants of Walking Function

Preliminary work from our laboratory has suggested that the *short-distance* maximum walking speed of individuals poststroke, measured from the middle 6m of a

10m path as subjects walked as fast as they safely could, may be an important modifier of their *long-distance* ambulatory function.[18] Improved walking efficiency may be the mechanism by which better *long-distance* walking function, measured as the distance traveled during the 6-minute walk test,[49] may result from improvements in *short-distance* maximum walking speed. Indeed, previous work has shown that walking at a faster speed reduces the energy cost of walking after stroke.[25] However, previous studies have not accounted for the variability in maximum walking speed in their analyses of the relationships between walking deficits and long-distance walking function. Thus, whereas variables such as cardiovascular fitness,[13] lower extremity strength,[12–15] balance,[10,11,13,16,17] balance self-efficacy,[11] and lower extremity motor function[42] have been shown to correlate to the walking function of persons after stroke, *the extent that subjects' maximum walking speed mediates their relationships to long-distance walking function is unknown and warrants investigation.*

### Aim 2 Significance: Biomechanical Determinants of Walking Function

Elucidation of the relative importance of commonly targeted biomechanical variables to poststroke long-distance walking function would facilitate optimal intervention design. Previous investigators have identified spatiotemporal symmetry as meaningful to walking function after stroke[50–52]. Others have identified deficits in stance phase variables such as the propulsive force generating ability of the paretic limb and the posterior placement of the paretic limb during terminal stance as major contributors to walking dysfunction after stroke[2,3,53–59]. Others have also shown that deficits in swing phase ground clearance relate to poststroke walking dysfunction[12,15]. A better understanding of the independent contribution of deficits from each of these biomechanical constructs – spatiotemporal symmetry, stance phase, and swing phase –

to the walking function of persons poststroke would define the best targets for intervention. Moreover, considering that persons in the chronic phase of stroke recovery identify deficits in their ability to walk farther as limiting their engagement at home and in the community[60], *a better understanding of how these biomechanical constructs relate to long-distance walking function may facilitate clinical decision-making oriented towards a patient-identified need.*

### Motivating Aim 3: A Novel, Hypothesis-Driven, Locomotor Program

For individuals with hemiparesis following stroke, decreased propulsive force generation by the paretic limb during walking has been identified through simulation and cross-sectional studies as a major contributor to walking dysfunction[2,3,53–59]. Furthermore, recent studies show that propulsion symmetry during walking is able to differentiate individuals as limited community versus community ambulators[61], and that individuals who achieve clinically meaningful improvements in walking speed also improve propulsion symmetry[48]. Despite the strong evidence linking paretic propulsion to walking performance, large scale investigation of interventions specifically designed to improve paretic propulsion during walking are nonexistent[9,62]. Moreover, previous reports considering the effects of gait intervention on measures of paretic propulsion have failed to demonstrate significant changes in the paretic limb's capacity to generate propulsion[31,32,63], likely due – as posited by Hall and colleagues – to subjects utilizing a variety of compensatory strategies during training[32]. *Thus, it is currently unknown whether paretic propulsion is modifiable through intervention specifically targeting this impairment or whether such improvements would influence walking performance.* Preliminary work from our laboratory has demonstrated the feasibility and promise of a novel combination therapy hypothesized to improve performance across the ICF categories by directly targeting deficits in paretic propulsion[64], however, the efficacy of this intervention has yet to be evaluated.

## The FastFES Hypothesis

An immediate increase in the activation of the paretic plantarflexors during walking is achievable through functional electrical stimulation (FES). However, the translation of increased plantarflexor muscle activation during walking with FES into greater forward propulsion depends largely on the paretic limb's posterior position relative to the individual's center of mass during the double support phase of the paretic gait cycle[57]. Unfortunately, stroke survivors often do not achieve adequate paretic hip extension during walking[6]. However, walking at a faster speed is known to increase paretic hip extension[65,66], effectively increasing the posterior placement of the paretic limb relative to the individual's center of mass during walking. Based on this framework, our laboratory hypothesized that an intervention combining fast treadmill walking with FES to the paretic ankle musculature would maximize the translation of increased plantarflexor activity into forward propulsion, ultimately resulting in improved walking function. The FastFES intervention was thus conceived.

## Maximizing Effectiveness: Multidisciplinary Foundations

Poststroke walking therapies are predicated on the concept of activity-dependent neuroplasticity. That is, cortical reorganization of the central nervous system can be induced through therapies that maximize the principles of neuroplasticity during training – ie, repetitive, intense, skilled, and engaging therapies[67]. As such, the 12-week FastFES program integrates contemporary concepts from multiple domains to maximize its effectiveness. Specifically, based on motor learning theory, massed stepping practice and task specific (walking) training on a treadmill form the basis for the FastFES intervention. Indeed, one reason why treadmills have emerged as popular training tools for poststroke rehabilitation[68–74] is that they offer a simple mechanism by which repetitive and intense practice can be achieved in a safe and controlled environment. A period of overground walking is also included to facilitate transfer of gains made on the treadmill. Alternate bouts of walking with and without FES are also included to enhance learning[75]. From a physiological perspective, the FastFES program incorporates stimulation patterns that better mimic the nervous system's activation of muscle (ie, variable-frequency train patterns), facilitating a more rapid rate of rise in force production[76] and yielding greater changes in walking kinematics[77] as compared to traditionally-used FES patterns in persons poststroke.

### Individualized Care: For Whom Is This Intervention Appropriate?

Clinical research has evolved from answering questions such as "does the intervention work" to "for whom, how, and why does the intervention work". This paradigm shift refocuses clinical research to the level of the individual patient. To facilitate advancements in individualized poststroke walking rehabilitation, the final goal of Aim 3 was to determine which subgroups of patients benefited the most from FastFES intervention. As an intervention designed to improve the propulsive force generated by the paretic limb during walking through two main mechanisms – increasing paretic trailing limb position through fast treadmill walking and increasing plantarflexion function through functional electrical stimulation of the paretic plantarflexors – subjects' baseline walking speed and propulsive force-generating ability were likely factors that could impact the intervention's efficacy, and were thus considered as potential moderators.

## Summary of Significance of Proposed Research Project

A critical need exists for the development of rehabilitation programs capable of improving walking performance after stroke. Despite an emphasis on functional recovery during rehabilitation, walking deficits that limit physical activity and community participation often persist. This project attempted to advance our understanding of the clinical (aim 1) and biomechanical (aim 2) factors that determine poststroke walking function, and ultimately inform the development of more effective poststroke walking therapies. Moreover, aim 3 attempted to facilitate advances in evidence-based neurorehabilitation by testing the efficacy of a novel, hypothesis-driven targeted intervention. The significance of the proposed project is highlighted by the fact that the research aims parallel items from the American Physical Therapy Association's clinical research agenda[78]. Specifically, aims 1 and 2 parallel clinical research agenda item 1 as they seek to "determine the relationships among levels of functioning and disability," and aim 3 parallels clinical research agenda item 19 as it seeks to "develop and test the effectiveness" of a physical therapist intervention for walking dysfunction after stroke.

## Summary of Innovation of Proposed Research

This project studied post-intervention outcomes (aim 3) and relationships (aim 2) across the *body structure and function*, *activity*, and *participation* domains of the *International Classification of Function, Disability, and Health* (ICF) framework. By grouping variables across the domains of the ICF*,* this project presents its findings in a standardized disablement and recovery language that facilitates a better understanding of the path from disablement to ablement after stroke[19,79,80]. Ultimately, aims 1 and 2 of this project build a foundation for the development of targeted gait therapies. Indeed, this work is among the first to identify walking deficits across the clinical and biomechanical domains whose improvements relate to functional recovery. Moreover, by considering a measure of long-distance walking function – the 6-minute walk test – as a primary measure of walking function for each aim, this research facilitates clinical decision-making directed toward a patient-identified need. As previously mentioned, the majority of patients after stroke identify deficits in their ability to walk "farther" as limiting engagement at home and the community[60]. Although previous research has considered, to some extent, the biomechanical determinants of short-distance walking function (ie, walking faster), none have studied the biomechanical determinants of long-distance walking function; in this regard, aim 2 of the proposed project is novel and important. Additionally, by testing post-intervention outcomes across patients with varying baseline abilities, aim 3 of this project was innovative – particularly when considering that the criteria used for stratification was based on *a priori* hypotheses unique to the intervention studied. Finally, the multi-disciplinary theoretical framework that the FastFES intervention draws from may also serve as a foundation for the development of hypothesis-driven, targeted interventions for other patient populations (eg, spinal cord or peripheral nerve injury patients). Indeed, as an impairment-based intervention designed to simultaneously build capacity and provide a critical mass of task-specific training, the structure of the FastFES program is consistent with those rehabilitation programs posited to be the best producers of functional recovery by recent models of recovery[79].

## Specific Aims and Hypotheses

**Aim 1: To identify clinical determinant(s) of walking function.**

This aim evaluated cross-sectional and longitudinal relationships between poststroke walking function, as measured by the 6-Minute Walk Test, versus five clinical variables previously identified as determinants of short- or long-distance walking function after stroke[10–17]. Prior cross-sectional work did not account for the influence of a key covariate – maximum walking speed[18] – nor evaluate the relationships between changes in walking function versus changes in the determinants identified. The best targets for intervention are thus unclear.

*Hypothesis 1.1: Measures of walking speed, balance, self-efficacy, and lower extremity motor function will relate to walking function; however, these relationships will be primarily mediated by maximum walking speed.*

*Hypothesis 1.2: Improvements in short-distance maximum walking speed will highly relate to the recovery of long-distance walking function.*

**Aim 2: To identify biomechanical determinant(s) of walking function.**

This aim evaluated cross-sectional and longitudinal relationships between poststroke walking function versus six biomechanical variables grouped into three biomechanical constructs – stance phase mechanics, swing phase mechanics, and spatiotemporal symmetry – that quantified the function of the paretic limb during walking. The relative importance of stance phase mechanics (versus swing phase mechanics or spatiotemporal symmetry) to poststroke walking function is unknown, as is the relationship to the recovery of walking of improvements in each construct.

*Hypothesis 2.1: Stance phase mechanics will explain more of the variance in walking function than swing phase mechanics or spatiotemporal symmetry.*

*Hypothesis 2.2: Improvements in stance phase mechanics will highly relate to the recovery of walking function.*

**Aim 3: To determine the efficacy of a novel walking rehabilitation program designed to treat poststroke walking dysfunction through specific effects on late stance phase mechanics.**

Post-intervention outcomes across the World Health Organization's ICF categories[19] were studied for subjects randomized to one of three treatment groups: training at 1) self-selected speeds (SS), 2) maximum speeds (Fast), and 3) Fast combined with functional electrical stimulation (FastFES). Mechanistic hypotheses were tested via moderated regression and outcomes were evaluated across patients stratified according to pretraining walking speed and biomechanics.

*Hypothesis 3.1: Each intervention will produce improvements across the ICF categories, but FastFES will be more effective than SS training in slower walkers.*

*Hypothesis 3.2: Only FastFES training will improve walking ability by improving paretic propulsion.*

*Hypothesis 3.3: FastFES training will be most effective in slower walkers with larger propulsion deficits.*

## Chapter 2

## MAXIMUM WALKING SPEED IS A KEY DETERMINANT OF LONG DISTANCE WALKING FUNCTION AFTER STROKE


### Abstract

***Background.*** Walking dysfunctions persist following poststroke rehabilitation. A major limitation of current rehabilitation efforts is the inability to identify modifiable deficits that, when improved, will result in the recovery of walking function. Previous studies have relied on cross-sectional analyses to identify deficits to target during walking rehabilitation; however, these studies did not account for the influence of a key covariate – maximum walking speed. ***Objective.*** To determine the relationships between commonly studied poststroke variables and the long-distance walking function of individuals poststroke when controlling for maximum walking speed. ***Methods.*** Correlation analyses of cross-sectional data from 57 individuals more than 6 months poststroke measured the relationships between standing balance, walking balance, balance self-efficacy, lower extremity motor function, and maximum walking speed versus long-distance walking function. For a subgroup of subjects who completed training, the relationship between changes in maximum walking speed versus changes in long-distance walking function was assessed. ***Results.*** Each measurement of interest strongly correlated with long-distance walking function (*rs* from 0.448 to 0.900, all $P$s $\leq$ .001); however, when controlling for maximum walking speed, none of the other measurements remained related to long-distance walking function. In contrast, when controlling for each of the other measurements, maximum walking speed remained highly related. Moreover, changes in maximum walking speed resulting from training highly related to changes in long-distance walking function ($r$ = .737, $P \leq$ .001). ***Conclusions.*** For individuals in the chronic phase of stroke recovery, improving maximum walking speed may be necessary

to improve long-distance walking function. Final Published Version © 2014 Thomas Land Publishers. DOI: 10.1310/tsr2106-502 www.strokejournal.com

## Introduction

For the majority of individuals who have sustained a stroke, the restoration of walking ability is the ultimate goal of rehabilitation.[1] Impaired walking ability has been linked to a delayed hospital discharge to home,[21] a delayed return to work,[22] and limited participation in the community.[21] However, despite a focus on functional recovery during rehabilitation, residual walking deficits that increase the energy cost of walking and the likelihood of falls often persist.[21,23–25] A major limitation of current rehabilitation efforts is our inability to identify modifiable deficits that, when improved, will result in the recovery of walking function. A better understanding of this relationship would shape the development of targeted gait interventions[48,55] and enhance our ability to improve the walking function of individuals after stroke.

Recent studies have recommended targeting specific deficits during poststroke rehabilitation based on correlative and regression analyses of cross-sectional data.[10–16,42–45] However, basing interventions on the findings of such analyses may be problematic if key covariates are not controlled. For example, although lower extremity strength,[12–15,45] motor function,[16,45] and spasticity[45] have been shown to correlate with poststroke function, studies controlling for other variables have shown that they do not independently contribute to poststroke function.[10–12,14,15] That is, other variables mediate their relationship to functional performance. While it may be difficult to control for all potential mediating variables during cross-sectional analyses, understanding their influence on the relationships studied is critical to the valid identification of deficits to target during rehabilitation.

A recent study by Bowden and colleagues demonstrated that of 10 measurements considered, only improvements in *short-distance* maximum walking speed and the paretic limb's contribution to forward propulsion (paretic propulsion) – a commonly studied biomechanical variable directly linked to walking speed – correlated to improvements in *short-distance* comfortable walking speed.[48] Preliminary work from our laboratory has suggested that the *short-distance* maximum walking speed of individuals poststroke, measured from the middle 6m of a 10m path as subjects walked as fast as they safely could, may be an important modifier of their *long-distance* ambulatory function.[18] Improved walking efficiency may be the mechanism by which better *long-distance* walking function, measured as the distance traveled during the 6-minute walk test,[49] may result from improvements in *short-distance* maximum walking speed. Indeed, previous work has shown that walking at a faster speed reduces the energy cost of walking after stroke.[25] However, previous studies have not accounted for the variability in maximum walking speed in their analyses of the relationships between walking deficits and long-distance walking function. Thus, whereas variables such as cardiovascular fitness,[13] lower extremity strength,[12–15] balance,[10,11,13,16,17] balance self-efficacy,[11] and lower extremity motor function[42] have been shown to correlate to the walking function of persons after stroke, the extent that subjects' maximum walking speed mediates their relationships to long-distance walking function is unknown. Understanding how commonly targeted poststroke variables relate to *long-distance* walking function when controlling for *short-distance* maximum walking speed would elucidate the best targets for walking rehabilitation programs. We hypothesized that, for persons in the chronic phase of stroke recovery, *short-distance* maximum walking speed would be the primary determinant of *long-distance* walking function.

Additionally, as cross-sectional studies only measure the degree that variables relate at a single moment in time, they are unable to identify whether a variable is modifiable through intervention in a manner that relates to improvements in function. That is, it does not necessarily follow from a strong cross-sectional relationship between a variable and a measurement of function that reducing the magnitude of the deficit in that variable for a lower functioning individual would improve their function. In contrast, longitudinal analyses that specifically examine the relationships between changes in particular variables versus changes in function (change-score relationships) provide insight into the potential functional impact, for an individual, of improvements in a deficit.[46–48] Thus, a secondary aim of this study was to determine whether improvements in maximum walking speed resulting from gait training related to improvements in long-distance walking function.

## Methods

### Subjects

The baseline data presented in this report reflect the data collected for the first 57 individuals that were recruited to participate in a clinical study at the University of Delaware. The change-score data presented reflect the data collected for a subset of these subjects ($n$ = 31) who underwent 12 weeks of physical therapist–guided locomotor training. Subjects were recruited over a 2-year period from health care facilities and patient support groups in the Delaware, New Jersey, and Pennsylvania areas. This study was approved by the University of Delaware's institutional review board, and all subjects gave their informed consent prior to participating.

### Inclusion criteria

Subjects were included if they had a history of a single cortical or subcortical stroke, a duration poststroke of at least 6 months, were able to ambulate without the physical assistance of another person but with observable gait deficits, were able to follow instruction and communicate with the investigators, were able to walk for 6 minutes at a self-selected walking speed without orthotic support, and were able to passively dorsiflex the ankle to a neutral position with the knee extended and passively extend the hip at least 10°.

### Exclusion criteria

Individuals were excluded from participating if they had a history of cerebellar stroke, a history of lower extremity joint replacement, bone or joint problems that limited their ability to walk, a resting heart rate outside of the range of 40 to 100 beats per minute, a resting blood pressure outside of the range of 90/60 to 170/90 mm Hg, neglect and hemianopia, unexplained dizziness in the last 6 months, or chest pain or shortness of breath without exertion.

### Intervention

Subjects participated in a 12-week treadmill and overground walking retraining intervention. Training consisted of walking on a treadmill at each subject's maximum walking speed. Subjects walked either without (Fast) or with functional electrical stimulation delivered to the paretic ankle plantar flexors during terminal stance and dorsiflexors during swing phase (FastFES). The FES was applied in an alternating pattern of 1-minute on to 1-minute off. Further details on the FastFES intervention can be found in previous work from our laboratory.[64] Subjects trained 3 times per week, with each session comprised of up to five 6-minute walking bouts on a treadmill and one walking bout over ground for a total of up to 36 minutes of walking. Subjects were allowed rest breaks of up to 5 minutes between walking bouts. While walking on the treadmill, subjects were connected to an overhead harness system for safety; no body-weight was supported via the harness.

**Variables of interest and rationale**

Subjects underwent comprehensive clinical evaluations conducted by licensed physical therapists. The present investigation considered the 6-minute walk test (6MWT)[49] as its representative measure of walking function. This decision was based on the 6MWT being an excellent measure of poststroke walking capacity and community ambulation,[81,82] as indicative of community reintegration following stroke,[21,83] and as the most prominent area of difficulty poststroke.[21] Indeed, individuals with chronic stroke indicate a reduced ability to walk farther as a factor limiting engagement in the community.[60] Measures were considered as measurements of interest if they could be targeted through intervention to improve the distance traveled during the 6MWT. The Berg Balance Scale (BBS)[84] and the Functional Gait Assessment (FGA)[85] evaluate standing (BBS) and walking (FGA) balance and have good reliability and validity in individuals poststroke.[84,85] The Activities-specific Balance Confidence (ABC) scale[86] evaluates balance self-efficacy and has been shown to have good reliability and internal consistency in community-dwelling older adults[86] and internal and absolute reliability and construct validity in people during the first year poststroke.[87] The lower extremity motor function domain of the Fugl-Meyer Assessment Scale (LEFM) quantifies the impairments in lower extremity motor function[88] and has been shown to be highly reliable in persons poststroke.[89] Finally, maximum walking speed (MWS) (m/s) was determined via the 6-meter overground walk test.[90] Subjects were allowed the use of their regular assistive devices and orthotics during testing, if necessary.

**Cross-sectional analyses**

Statistical analyses were performed using the IBM SPSS 21 software package (IBM, Armonk, NY). Power analyses were conducted using G Power 3.1. The overall threshold for significance was set to *P* = .05. The Shapiro-Wilk test was used to determine data normality. To test our a priori hypothesis that maximum walking speed would be the primary determinant of long-distance walking function, correlation (zero-order) and partial correlation (first-order) analyses were performed. Specifically, Pearson *r* or Spearman rho correlation analyses – pending data normality – measured the zero-order relationships between 6MWT distance versus MWS, FGA, BBS, ABC, and LEFM performance. Subsequently, each measurement of interest was selected, in turn, as a control variable when determining first-order relationships. After a Bonferroni correction for the 25 comparisons performed, an alpha level of 0.002 was set as the threshold for significance for each zero- and first-order relationship considered.

**Longitudinal analyses**

To test our secondary hypothesis that improvements in maximum walking speed would relate to improvements in long-distance walking function, the changes following an intervention targeting maximum walking speed were studied. Baseline versus postintervention pair-wise comparisons were conducted to test whether changes in maximum walking speed and 6MWT distance followed the training. Group changes were also compared to known minimal clinically important difference (MCID) and minimal detectable change (MDC) scores. The relationship between changes in maximum walking speed and changes in 6MWT distance was determined using Pearson *r* correlation.

## Results

Complete baseline ($n = 57$) and change-score ($n = 31$) data sets were available for all variables studied (see Table 1 for subject demographics and characteristics). An a priori power analysis revealed that with 57 subjects, at an alpha of 0.002, this investigation would be powered at a level of 80% to detect a significant baseline $R^2$ of 0.24. With 31 subjects, at an alpha of 0.05, this investigation would be 80% powered to detect a significant change-score $R^2$ of 0.23.

### Cross-sectional zero- and first-order correlation analyses

Zero-order analyses demonstrated strong relationships (*r*s from 0.448 to 0.900) between each measurement of interest and performance on the 6MWT. However, when controlling for maximum walking speed, marked reductions in the strength of each of the other measurements' relationships to 6MWT performance were observed with none of these first-order relationships being significant. Likewise, controlling for walking balance resulted in a marked reduction in the strength of each of the other measurements' relationships to the 6MWT – except for maximum walking speed, which remained very strongly related to the 6MWT. In contrast, when controlling for standing balance, only balance self-efficacy no longer related to 6MWT performance. Controlling for either balance self-efficacy or lower extremity motor function did not result in substantial changes in any of the other measurements' relationships to the 6MWT (see Table 2).

Despite both maximum walking speed and walking balance markedly altering the strength of the other measurements' relationships to 6MWT performance, maximum walking speed clearly mediated a larger portion of each measurement's contribution to 6MWT performance. Moreover, only maximum walking speed remained very strongly related to 6MWT performance regardless of which of the other measurements was controlled (see Table 2).

**Longitudinal analyses**

Both maximum walking speed and the distance walked during the 6MWT improved following the 12-week intervention period (see Table 3). The average change in 6MWT distance of 77 m was larger than the established MDC of 54.1 m.[49] The average group change in maximum walking speed of 0.20 m/s was larger than the established walking speed MCID of 0.17 m/s.[91] Changes in maximum walking speed following the intervention strongly correlated to changes in 6MWT distance [$r(31) = .637$, $P \leq .001$].

**Outliers**

Graphical inspection of the Δ6MWT versus ΔMWS (Figure 1) relationship revealed that only one subject substantially improved 6MWT distance (184 m) but not maximum walking speed (0.01 m/s). This subject was beyond the 95% confidence interval for this correlation. When considering this subject as a statistical outlier and removing them from the analysis of this relationship, a markedly stronger correlation between changes in the 6MWT versus changes in maximum walking speed [Pearson $r(30) = .737$, $P \leq .001$] was observed (see Figure 1). Interestingly, this subject's baseline maximum walking speed (1.81 m/s) was the highest among all the subjects studied.

## Discussion

The present investigation identifies the short-distance maximum walking speed of individuals poststroke as an important determinant of their long-distance walking function and as a variable modifiable through intervention in a manner that highly relates to improvements in long-distance walking function. Taken together, the cross-sectional and longitudinal analyses presented support the development and study of poststroke interventions targeting an individual's maximum walking speed. Indeed, considering the established relationship between long-distance walking function and ambulation in the community,[81–83] the addition of interventions targeting short-distance maximum walking speed to poststroke walking rehabilitation programs is worthwhile.

It is not surprising that maximum walking speed accounted for a considerable amount of the variance in a timed walking test such as the 6MWT. However, the predominant perception in the clinical community is that the 6MWT is a measure of walking endurance. That is, performance on the 6MWT is thought to be reflective of a person's ability to maintain a moderate amount of exertion over a period of time similar to the activities of daily living. Previous work has shown that the walking performance of community ambulators living with stroke deteriorates during the final minutes of the 6MWT.[52] To the extent that the psychosocial (eg, self-efficacy) or physical (eg, balance or motor function) factors studied may have been considered as contributors to worse performance during the 6MWT, it is surprising and important to learn that when controlling for maximum walking speed, none of the measurements studied remained related to performance on the 6MWT. Indeed, when controlling for maximum walking speed, subjects with excellent or poor self-efficacy, standing balance, walking balance, and lower extremity motor function performed similarly on the 6MWT.

Recommendations to target specific deficits during rehabilitation to improve poststroke walking function are commonly put forth based on the observed relationships between various measurements and function.[10–16,42–45] For example, Patterson and colleagues posited that clinicians should primarily target balance impairments during poststroke rehabilitation, followed by cardiovascular fitness, based on their finding that standing balance – as measured by the BBS – explained the largest portion of long-distance walking function variance for slower walking individuals poststroke and that cardiovascular fitness explained the largest portion for faster walking individuals.[13] Similarly, Pohl and colleagues found that standing balance significantly predicted long-distance walking function and concluded that balance was a “powerful modifier” of the long-distance walking function of persons poststroke.[42] Consistent with these and similar cross-sectional studies, the present study demonstrates strong zero-order relationships between standing balance – as well as other measurements – and walking performance; however, the partial correlation analyses of these same relationships indicate that maximum walking speed plays a key mediatory role and should therefore be considered when designing rehabilitation programs.

In contrast, Schmid and colleagues recently published a comprehensive examination of the relationships between multiple poststroke mobility variables – including maximum walking speed – and measures of activity and participation, identifying only “balance self-efficacy, not physical aspects of gait,” as an independent contributor to activity and participation following stroke. Based on their findings, Schmid et al recommended addressing psychological factors related to balance self-efficacy “to obtain the best stroke recovery.”[43] In the present study, we observe a marked reduction in the strength of the balance self-efficacy versus walking function relationship when controlling for maximum walking speed (from a zero-order $r$ = 0.448,

$P < .001$, to a first-order $r = 0.096$, $P > .05$). Moreover, controlling for balance self-efficacy did not modify the relationship between maximum walking speed and walking function. The inconsistency between the Schmid et al findings and those of the present study is likely a product of differences in the dependent variable studied. Indeed, the present study considers an objective measure of ambulatory function – the 6MWT – whereas Schmid et al consider self-report measures of activity and participation. Another likely explanation for this inconsistency is that the cohort of subjects studied by Schmid et al walked, on average, 0.30 m/s faster than the cohort in the present study. Certain thresholds likely exist for each of the measurements studied where improvements beyond such thresholds would not contribute to improvements in walking function. For example, the subjects studied by Schmid et al may not benefit from improvements in maximum walking speed because they already walk at a very fast pace. Indeed, the single subject identified as an outlier in the present investigation was the fastest walker pretraining (see Results section and Figure 1). In contrast, the other subjects studied in the present investigation may benefit from the targeting of maximum walking speed until they achieve a certain speed threshold, at which point, modifying the target of rehabilitation efforts to balance self-efficacy may indeed facilitate the best stroke recovery.

The findings of the present investigation may not extend to the rehabilitation of individuals in the earlier phases poststroke. For example, Pohl and colleagues demonstrated that in individuals an average of 75 days poststroke, gains made in the 6MWT were only predictable by gains in balance for those unable to ambulate more than 213 m. In contrast, only gains in peak $VO_2$ and lower extremity motor function were predictive for individuals able to walk further than 213 m.[47] However, Pohl et al noted that only 16% of 6MWT variance was accounted for by gains in balance for the lower performing individuals, and only 28% of 6MWT variance was accounted for by gains in peak $VO_2$ and lower extremity motor function for the higher performing individuals. In contrast, the present study demonstrates that 54% of the variance in 6MWT change is explainable by improvements in maximum walking speed. Although maximum walking speed was not measured by Pohl et al, considering the relationship between walking speed and the measurement of peak $VO_2$ on a treadmill,[92] it stands to reason that significant gains in maximum walking speed may have accompanied the observed gains in peak $VO_2$. A similar study by Kollen and colleagues of individuals in the acute phase of stroke recovery identified changes in standing balance as the most "important determinant" of improved walking function.[46] However, similar to the Pohl study, they were only able to account for 18% of the variance in functional ability with $\beta$ regression coefficients < .09 for each determinant. An interesting future study would investigate whether the findings of the present study generalize to individuals in the earlier phases of stroke recovery.

**Limitations**

This study only considered the relationships between the 6MWT versus the maximum walking speed test, BBS, FGA, ABC scale, and the LEFM. The relationships between these measurements versus other measures of walking function, and the relationships between other measurements versus the 6MWT, are unknown.

**Conclusions**

This study supports the development of poststroke interventions targeting an individual's maximum walking speed. Previous studies recommending deficits to target during poststroke walking rehabilitation that did not account for the influence of maximum walking speed on the relationships studied should be considered cautiously.

**Table 1.** Subject demographics and characteristics.

| **Variable** | **Median (IQR) or frequency (%)** |
|---|---|
| *Baseline dataset (n = 57)* | |
| Age, years | 59.02 (54.23-64.91) |
| Time since stroke, years | 1.71 (0.88-3.51) |
| Sex, male | 58% |
| Side of paresis, right | 35% |
| Self-selected walking speed, m/s | 0.75 (0.55-0.97) |
| Lower extremity Fugl-Meyer score | 23 (20-27) |
| *Change score dataset (n = 31)* | |
| Age, years | 57.50 (54.59-63.83) |
| Time since stroke, years | 1.81 (0.94-6.24) |
| Sex, male | 65% |
| Side of paresis, right | 32% |
| Self-selected walking speed, m/s | 0.74 (0.60-0.94) |
| Lower extremity Fugl-Meyer score | 23 (18.50-27.50) |

**Table 2.** Zero-order and partial (first-order) correlation coefficients for the relationships between long-distance walking function (6MWT) versus each measurement.

| **Analysis** | **Deficits** | | | | |
|---|---|---|---|---|---|
| | **MWS** | **FGA** | **BBS** | **ABC** | **LEFM** |
| Zero-order 6MWT correlations | 0.900* $p$ = .000 | 0.785* $p$ = .000 | 0.729*[a] $p$ = .000 | 0.448*[a] $p$ = .000 | 0.557* $p$ = .000 |
| First-order MWS controlled | | 0.326 $p$ = .014 | 0.181 $p$ = .181 | 0.096 $p$ = .484 | -0.099 $p$ = .468 |
| First-order FGA controlled | 0.747* $p$ = .000 | | 0.249 $p$ = .064 | 0.302 $p$ = .024 | 0.336 $p$ = .011 |
| First-order BBS controlled | 0.807* $p$ = .000 | 0.563* $p$ = .000 | | 0.298 $p$ = .026 | 0.431* $p$ = .001 |
| First-order ABC controlled | 0.864* $p$ = .000 | 0.729* $p$ = .000 | 0.596* $p$ = .000 | | 0.476* $p$ = .000 |
| First-order LEFM controlled | 0.853* $p$ = .000 | 0.712* $p$ = .000 | 0.615* $p$ = .000 | 0.407* $p$ = .002 | |

6MWT = 6-minute walk test; MWS = maximum walking speed; FGA = Functional Gait Assessment; BBS = Berg Balance Scale; ABC = Activities-specific Balance Confidence Scale; LEFM = lower extremity motor portion of Fugl Meyer Scale.

[a]Spearman rho correlation coefficient.
* $p \leq .002$.

**Table 3.** Baseline and change score values.

| Variable | Mean (*SD*) and 95% CI | | ***T*** statistic | ***P*** value |
|---|---|---|---|---|
| | **Baseline** | **Change** | | |
| 6MWT (m) | 302 (134)<br>253-351 | 77 (63)<br>54-100 | 6.781 | <.001 |
| MWS (m/s) | 1.00 (0.46)<br>0.83-1.17 | 0.20 (0.22)<br>0.12-0.28 | 5.111 | <.001 |

6MWT = 6-minute walk test; MWS = maximum walking speed.

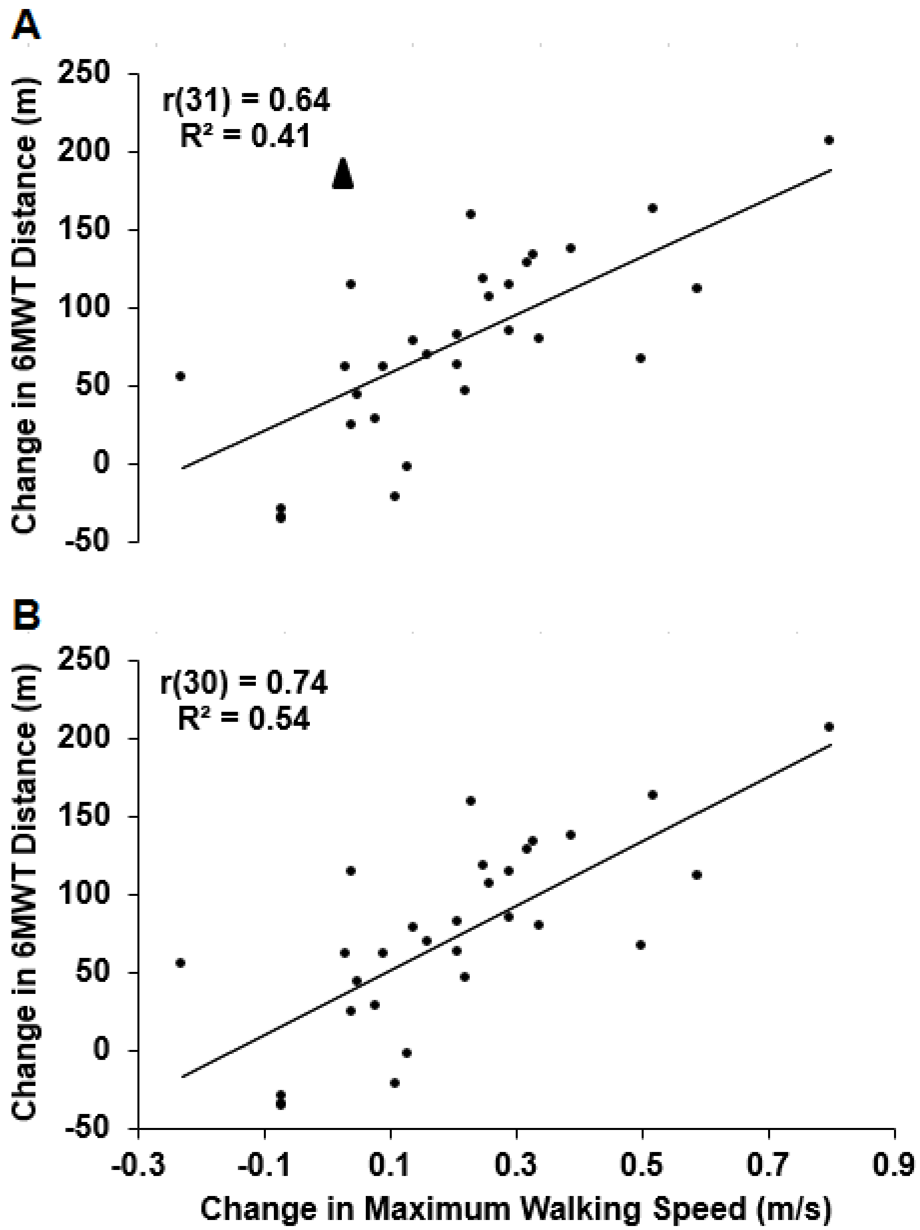


**Figure 1.** The relationship between changes in maximum walking speed (x-axis) and changes in long-distance walking function (6MWT) (y-axis) is presented with (A) and without (B) a statistically and clinically identified outlier – indicated by the triangle in panel A. Changes in maximum walking speed highly related to changes in 6MWT distance.

# Chapter 3

## PARETIC PROPULSION AND TRAILING LIMB ANGLE ARE KEY DETERMINANTS OF LONG-DISTANCE WALKING FUNCTION AFTER STROKE

### Abstract

***Background.*** Elucidation of the relative importance of commonly targeted biomechanical variables to poststroke long-distance walking function would facilitate optimal intervention design. ***Objectives.*** To determine the relative contribution of variables from 3 biomechanical constructs to poststroke long-distance walking function and identify the biomechanical changes underlying posttraining improvements in long-distance walking function. ***Methods.*** Forty-four individuals >6 months after stroke participated in this study. A subset of these subjects (n = 31) underwent 12 weeks of high-intensity locomotor training. Cross-sectional (pretraining) and longitudinal (posttraining change) regression quantified the relationships between poststroke long-distance walking function, as measured via the 6-Minute Walk Test (6MWT), and walking biomechanics. Biomechanical variables were organized into stance phase (paretic propulsion and trailing limb angle), swing phase (paretic ankle dorsiflexion and knee flexion), and symmetry (step length and swing time) constructs. ***Results.*** Pretraining, all variables correlated with 6MWT distance ($r$s = .39 to .75, $P$s < .05); however, only propulsion (Prop) and trailing limb angle (TLA) independently predicted 6MWT distance, $R^2 = .655$, $F(6, 36) = 11.38$, $P < .001$. Interestingly, only ΔProp predicted Δ6MWT; however, pretraining Prop, pretraining TLA, and ΔTLA moderated this relationship (moderation model $R^2$s = .383, .468, .289, respectively). ***Conclusions.*** The paretic limb's ability to generate propulsion during walking is a critical determinant of long-distance walking function after stroke. This finding supports the development of poststroke interventions that target deficits in

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## Introduction

More than 5.5 million Americans are currently living with stroke – the leading cause of disability in the USA[20]. For the majority of stroke survivors, the restoration of walking is the ultimate goal of rehabilitation[1]. As such, a major focus of rehabilitation research has been on the development and testing of poststroke gait rehabilitation programs. However, activity and participation are often limited even after rehabilitation[7,8,21,23–25]. Indeed, persons poststroke walk less than 3500 steps per day; in contrast, even the most sedentary healthy adults walk more than 5000 steps per day[26,27]. Given the relationship between physical inactivity and diseases such as heart disease and diabetes[20], a critical need exists for the development of interventions capable of increasing the physical activity of persons who have sustained a stroke.

The development of interventions directed toward improving poststroke walking function is confounded by the fact that improvements in walking function are achievable through a variety of recovery mechanisms – from improved neuromotor control to better compensation for lost neuromotor function[2,31,32,48]. Because compensatory strategies such as stiff-legged and circumduction gait are associated with a higher energy cost of walking, reduced endurance, and slower speeds[6,21,29,33], recovery strategies that rely on gait compensations may limit the gains in long-distance walking function that are achievable through intervention. This is important as persons poststroke indicate that a major contributor to their lack of engagement in the community is a deficit in their ability to walk farther distances[60]. Indeed, training someone to walk faster may not be sufficient to improve their ability to walk farther if the strategy they use to walk faster is not economical and sustainable. Given the relationships between long-distance walking function[93], community walking participation[94], and the energy cost of walking, a better understanding of the biomechanical determinants of poststroke long-distance walking function is needed.

Improvements in poststroke long-distance walking function may be achieved through any number of biomechanical mechanisms. Indeed, previous investigations have shown relationships between various biomechanical variables and walking function after stroke[3,12,15,52,54–59,95,96]. For example, Sibley et al demonstrated that changes in spatiotemporal asymmetry were associated with less distance walked during the final two minutes of the 6-Minute Walk Test (6MWT) in those with the worst long-distance walking function[52]. Others have identified stance phase variables related to the propulsive force generating ability of the paretic limb as major contributors to poststroke walking function[3,54–59,95]. Still, others have shown that deficits in variables related to swing phase ground clearance correlate with poststroke walking function[12,15,96]. The primary purpose of this study was to determine the relative importance of variables from each of these biomechanical constructs – spatiotemporal symmetry, stance phase, or swing phase – to the long-distance walking function of persons in the chronic phase of stroke recovery. A secondary aim of this study was to identify the biomechanical changes underlying posttraining improvements in long-distance walking function. We hypothesized that the stance phase construct would be the best predictor of long-distance walking function and that improvements in stance phase mechanics would account for improvements in long-distance walking function. Moreover, we hypothesized that baseline stance phase function would moderate the relationship between stance phase improvements and improvements in long-distance walking function; specifically, that improvements in stance phase mechanics would be more meaningful in those most impaired at baseline.

## Methods

### Subjects

Forty-five subjects with poststroke hemiparesis participated in this study. A subset of these subjects (n = 31) underwent 12 weeks of locomotor training as described below. Subjects were recruited over two years from Delaware, New Jersey, and Pennsylvania health care facilities, advertisements, and patient support groups. Subjects were at least 6 months post a single stroke, able to walk at a self-selected pace for six minutes without orthotic support but with observable gait deficits, were able to passively dorsiflex the ankle to a neutral position with the knee extended (tested in the prone position), and were able to passively extend the hip at least ten degrees (tested in a side lying position). Subjects were excluded if they had evidence of moderate to severe chronic white matter disease or cerebellar stroke on MRI, a history of lower extremity joint replacement due to arthritis, an inability to communicate with the investigators, neglect (tested via the star cancellation test[97]) or hemianopia, a score of >1 on question 1b and >0 on question 1c on the NIH Stroke Scale, or unexplained dizziness in the last 6 months. All subjects signed written informed consent forms approved by the Human Subjects Review Board of the University of Delaware, received written medical clearance from their physician, and completed a submaximal stress test to determine exercise safety prior to participation in the intervention protocol described below. Subjects completed clinical and biomechanical evaluations prior to (pretraining) and immediately following 12 weeks of training (posttraining).

## Clinical Testing

Clinical evaluations were conducted by licensed physical therapists and included the 6-meter walk test[90] and the 6-minute walk test (6MWT)[42]. Derived from the 6-meter walk test was each subject's self-selected and maximum walking speeds (m/s), which are reported in Table 4 as an indication of baseline walking disability[24]. The distance walked during the 6MWT served as our a priori measure of long-distance walking function. The 6MWT is thought to be reflective of a person's ability to maintain a moderate amount of exertion over a period of time similar to the activities of daily living, has been identified as an excellent measure of poststroke walking capacity and community ambulation[81,82], and as indicative of community reintegration following stroke[21,83]. Subjects were allowed the use of their regular assistive device (e.g. cane) during testing, if necessary. Subjects who used an assistive device at their pretraining evaluation also used one during their posttraining evaluation.

## Motion Analysis

Previous work has described in detail the methods used during this investigation[64,93,98]. Briefly, kinetic and kinematic data were collected using an 8-camera motion analysis system (Motion Analysis 3D Eagle, Santa Rosa, CA, USA) as subjects walked for thirty seconds at the maximum walking speed they could maintain for four minutes. For baseline motion analysis testing, this maximum walking speed was determined during an acclimatization session conducted prior to the start of training. The speed used for posttraining motion analysis was determined during the final week of training. During motion analysis testing, subjects walked on a dual-belt treadmill instrumented with two independent 6-degree of freedom force platforms. Ground reaction force (GRF) data were collected at 2000Hz (Bertec Corporation, Worthington, OH). Kinematic data were sampled at a rate of 100 Hz and based on the motion of retro-reflective markers placed over the pelvis, and bilaterally over the thigh, shank, and foot segments, and on the medial and lateral malleoli, at the medial and lateral femoral condyles, the greater trochanters, and the iliac crests. All kinematic and kinetic variables were computed for each stride and averaged across the first 15 strides recorded during motion analysis testing using a custom-written LabVIEW program (National Instruments, Austin, TX, USA).

Six biomechanical variables, divided into three biomechanical constructs – 1) stance phase, 2) swing phase, and 3) spatiotemporal symmetry – quantified biomechanical function during walking. These constructs were selected due to their prevalent study[2,3,12,15,40,50,52,54–59,95,96,99,100] and common consideration by clinicians during poststroke rehabilitation. Peak paretic propulsion and peak paretic trailing limb angle (measured during the paretic double support phase) comprised the stance phase construct, peak knee flexion and peak ankle dorsiflexion angles comprised the swing phase construct, and step length symmetry and swing time symmetry comprised the spatiotemporal symmetry construct. Peak propulsion was defined as the maximum anterior GRF recorded during the paretic double support phase, normalized to body weight. Peak trailing limb angle was defined as the maximum sagittal plane angle between the vertical axis of the lab and a vector joining the paretic limb's lateral malleolus and greater trochanter. Peak ankle dorsiflexion was defined as the maximum ankle dorsiflexion angle during the paretic swing phase. Peak knee flexion was defined as the maximum knee flexion angle during the paretic swing phase.

Step length, stride duration, and swing time were calculated bilaterally per stride to allow calculation of the symmetry measures of interest. Step length was defined as the distance between heel markers at the leading limb's initial contact. Stride duration was defined as the time from one initial contact to the subsequent ipsilateral initial contact. Swing time was defined as the time between toe off and initial contact. Swing time was normalized to stride duration. As per a previous study[101], to calculate step length symmetry, the following equation was used: [larger step length / (larger step length + smaller step length)]. To calculate swing time symmetry, the following equation was used: [longer swing time / (longer swing time + shorter swing time)]. A value of 0.50 reflects perfect symmetry. For step length asymmetry, a value of 1.00 reflects a step-to gait pattern and values greater than 1.00 reflect a walking pattern where one limb does not pass the other.

**Training Protocol**

A subgroup of subjects (n = 31) completed 12 weeks of high intensity locomotor training. Subjects walked at their maximum walking speeds with (n = 15) or without (n = 16) the application of functional electrical stimulation to the paretic ankle dorsiflexors during swing phase and plantarflexors during late stance phase. The training protocol used has been previously described[64,98]. Regardless of whether subjects trained with or without FES, the training provided task-specific practice of thousands of steps per treatment session. Training occurred at a frequency of 3 sessions per week for 12 weeks. Approximately 36 minutes of total walking were completed during each session. Because the present manuscript is only concerned with a mechanistic investigation of the biomechanical changes underlying changes in long-distance walking function, change-score data from these treatment groups have been combined. A subsequent manuscript will test treatment efficacy by investigating group-specific effects as they relate to a control group.

## Statistical Analyses

All statistical tests were performed in SPSS version 21. Sequential and moderated regression analyses[102,103] of cross-sectional (ie, pretraining) and longitudinal (ie, posttraining change) data were performed. Centered variables were used in the analysis. Standardized regression coefficients ($\beta$) are reported, allowing us to infer the strongest predictor of long-distance walking function based on magnitude. Residuals for each of the regression models were screened for the presence of outliers. Alpha level of 0.05 was set as the threshold for statistical significance. One-tail tests were used for effects with an *a priori* directional hypothesis.

Sequential linear regression was used to test our hypothesis that the stance phase construct would be the strongest predictor of long-distance walking function. The order by which the swing phase and spatiotemporal symmetry constructs were added to the model was based on the magnitudes of the bivariate correlations, with strongest added first. With 44 subjects, and alpha set at 0.05, this study had power = 0.80 to detect an $R^2$ increase between 0.20 (1-tail) and 0.24 (2-tail) when adding the swing phase and spatiotemporal symmetry constructs (ie, four variables) to the model containing the stance phase construct (ie, two variables).

Bivariate correlations of the longitudinal data were used to test our hypothesis that improvements in stance phase function would relate to improvements in long-distance walking function. Moderated regression was used to test our hypothesis that baseline stance phase function would moderate the relationship between changes in stance phase mechanics versus changes in long-distance walking function. Because only changes in paretic propulsion correlated to changes in long-distance walking function (see Results), only interactions with change in paretic propulsion were tested. The available sample size precluded us from examining all interactions in one model, so to avoid model over fit and to maintain adequate power, independent moderation models were generated to examine each interaction.

Specifically, the first model tested the interaction between pretraining propulsion and change in propulsion and the second tested the interaction between pretraining trailing limb angle and change in propulsion. Based on our finding of moderation by pretraining trailing limb angle (see Results), the third moderation model tested moderation by changes in trailing limb angle with an *a priori* hypothesis that changes in propulsion would have a stronger relationship to changes in long-distance walking function in those with concomitant changes in trailing limb angle. With 30 subjects, at an alpha level of 0.05, each moderated regression model was 80% powered to detect an $R^2$ increase (1-tail) of 0.22.

## Results

Clinical data were available for all subjects (see Table 4 for subject characteristics); however, due to technical issues during data collection, pretraining biomechanical data were not available for 1 of the 45 subjects studied. Moreover, a single subject was found to be a statistical outlier and was removed prior to the analyses presented. These 2 subjects were also among the cohort (n = 31) who underwent training. As such, the cross-sectional analyses presented reflect the data collected for 43 subjects and the longitudinal analyses reflect the data collected for 29 subjects. Table 5 presents means, standard deviations, minimums, and maximums for the pretraining and change-score variables included in the regression analyses conducted.

**Cross-Sectional Analyses**

Despite variables from all three constructs correlating with performance on the 6MWT (Figure 2), only paretic propulsion ($\beta$ = .339) and trailing limb angle ($\beta$ = .564) independently predicted 6MWT distance (Table 6; $R^2$ = .655, $F(6,36) = 11.38$, $p <$ 0.001).

**Longitudinal Analyses**

Bivariate correlations of the longitudinal data revealed that only changes in paretic propulsion ($r = 0.435$, $p = 0.009$) correlated with changes in the 6MWT. Interestingly, changes in trailing limb angle and in the swing phase and the symmetry variables studied did not (*r's* < 0.29 and *p's* > 0.05).

Moderated regression analyses revealed three independent moderators of the relationship between changes in paretic propulsion and changes in the 6MWT (see Table 7). The first was moderation by pretraining paretic propulsion (final model testing this interaction: $F(3,25) = 5.17$, $p = 0.006$, $R^2 = 0.383$, $\Delta R^2 = 0.193$). Specifically, changes in propulsion were strongly positively related to changes in the 6MWT for those with low pretraining propulsion – that is, those with baseline propulsion lower than one standard deviation *below* the mean (ie, < 3.67% BW). For those with average propulsion (ie, 8.67% BW), changes in propulsion weakly positively related to changes in the 6MWT. For those with pretraining propulsion greater than one standard deviation *above* the mean (ie, > 13.67% BW), a weak negative relationship was observed (Figure 3, panel A).

An even stronger effect was observed when testing moderation by pretraining trailing limb angle (Table 7; $F(3,25) = 7.34$, $p = 0.001$, $R^2 = 0.468$, $\Delta R^2 = 0.279$). Similar to the effect of pretraining propulsion, the strongest relationship between changes in paretic propulsion and changes in 6MWT distance was observed in those with a pretraining trailing limb angle lower than one standard deviation *below* the mean (ie, < 7.2 degrees). A weaker positive relationship was observed in those with the average pretraining trailing limb angle (ie, 15.35 degrees) and a weak negative relationship was observed in those with the largest pretraining trailing limb angle (ie, > 23.5 degrees) (Figure 3, panel B).

The weakest moderator of the relationship between changes in propulsion and changes in the 6MWT was changes in trailing limb angle (Table 7; $F(3,25) = 3.39$, $p = 0.034$, $R^2 = 0.289$, $\Delta R^2 = 0.094$). The relationship between changes in propulsion and changes in the 6MWT was strongest in those with the largest change in trailing limb angle (ie, > 7.41 degrees). Interestingly, for those with a change in trailing limb angle one standard deviation below the mean (ie, a decline of 1.89 degrees or greater), changes in propulsion were unrelated to changes in the 6MWT (Figure 3, panel C).

## Discussion

This report is the first to explore the relative importance of stance phase, swing phase, and spatiotemporal symmetry biomechanics to poststroke long-distance walking function. This investigation extends previous work that has studied the biomechanical determinants of *short-distance* walking function[32,56,58,63,104,105]. The present results reveal a relationship between the function of the paretic limb during stance phase – particularly the propulsive force generated during late stance – and *long-distance* walking function in persons in the chronic phase of stroke recovery. Moreover, the results of the moderated regression analyses indicate that this relationship is greatest in those persons presenting with large pretraining impairments in propulsion or trailing limb angle. Given that a majority of individuals in the chronic phase of stroke recovery identify deficits in their ability to walk farther as contributing to reduced engagement in the community[60], by identifying key biomechanical determinants of poststroke long-distance walking function, this investigation facilitates the development of targeted interventions with the potential to increase community participation after stroke.

Previous investigators have posited that an assessment of post-intervention outcomes is lacking if limited to only gross clinical measures such as walking speed[36]. The present investigation's elucidation of key biomechanical determinants of poststroke long-distance walking function therefore orients clinicians to important poststroke gait variables, ultimately informing clinical practice. Although task-specific practice forms a necessary basis for neurorehabilitation efforts[29,34,67,106], the present findings support structuring practice in a manner that targets the specific impairments that may be limiting performance. For example, although walking practice is commonly prescribed as a therapeutic intervention, the present results suggest that training walking at a fast speed will produce improvements in long-distance walking function associated with the recovery of paretic limb biomechanical function – especially in those most impaired. Further development and testing of hypothesis-driven targeted locomotor interventions for persons poststroke is warranted.

Interestingly, despite not relating to changes in long-distance walking function, changes in trailing limb angle moderated the relationship between changes in propulsion and changes in long-distance walking function. Specifically, only in those with a large improvement in the paretic trailing limb angle did gains in propulsion relate to gains in long-distance walking (see Figure 3, panel C). One explanation for these apparently contradictory findings is that improvements in trailing limb angle are not meaningful – in terms of improving long-distance walking function – if they do not result in improvements in propulsion. Indeed, although increasing the paretic trailing limb angle yields a more effective biomechanical position for the generation of propulsive forces by the ankle musculature[57], it is important to note that persons poststroke often use the hip flexors to advance the paretic limb during the stance to swing transition[5,54,107] – which is a strategy known to negatively correlate with the propulsive forces generated[6,57,108,109]. That is, merely providing better resources (ie, a larger paretic trailing limb angle) may be insufficient to alter the strategy used to walk faster. The specific training of use of the ankle musculature may be necessary.

Multiple factors may influence performance on the 6MWT – our measure of long-distance walking ability. We have previously shown that changes in maximum walking speed account for greater than 50% of the variance in changes in 6MWT performance[110]. Other factors certainly contribute. One possible factor is changes in the energy cost of walking. Although the present report does not directly investigate the role that changes in walking energetics may play in modifying long-distance walking function, recent work from our laboratory demonstrates a meaningful relationship between posttraining changes in walking kinematics, specifically step length asymmetry, and changes in the energy cost of walking[101]. Surprisingly, the present investigation revealed that changes in walking kinematics were unrelated to changes in 6MWT performance, suggesting that deficits in walking kinematics were not limiting long-distance walking function as measured via the 6MWT. In contrast, it has been shown that compensatory kinematic strategies are energetically costly[6,29,33,111] and previous work from our laboratory has shown that those with lower walking energy costs travel farther distances during the 6MWT[93]. Moreover, although not directly related to changes in the 6MWT in the present investigation, changes in the paretic trailing limb angle moderated the influence that changes in paretic propulsion had on changes in 6MWT performance. As such, further investigation of the interplay between walking kinematics, the energy cost of walking, and long-distance walking function is warranted.

Based on the findings of this investigation, a reasonable hypothesis would be that an intervention targeting deficits in paretic propulsion through specific effects on the paretic trailing limb angle could produce improvements in the functional status of persons in the chronic phase after stroke. Indeed, our laboratory recently published a preliminary study that supports this hypothesis by demonstrating improvements across the domains of the World Health Organization's International Classification of Functioning, Health, and Disability following training targeting deficits in paretic propulsion through specific effects on the function of the paretic limb during late stance[64]. The findings from this preliminary study validate the present study's emphasis on stance phase mechanics. However, future work is necessary to determine the efficacy of interventions targeting paretic propulsion across subgroups of patients stratified according to baseline biomechanical function.

An important point is that although this investigation considered the biomechanical constructs studied independently, for an individual, these variables are likely interrelated. That is, events during stance phase may have a direct impact on swing phase function, and changes in both stance phase and swing phase underlie changes in spatiotemporal symmetry. For example, increased propulsive force during late stance is one mechanism posited to increase knee flexion during swing[112–114]. Moreover, improvements in step length symmetry may result from a larger trailing limb angle – which would effectively increase the contralateral step length – or better propulsion – which may increase ipsilateral step length through its swing phase effects. Even so, by examining the relative importance of each of these constructs – particularly how changes in each relate to the changes in long-distance walking function observed after gait rehabilitation – this report reveals important information regarding the mechanisms that may be driving the recovery of poststroke walking function. Future work that examines how changes in other biomechanical measures, such as mechanical work or power, account for the variance in changes in long-distance walking function after poststroke locomotor intervention would further extend this work.

**Limitations**

A potential limitation of this study is that biomechanical testing occurred on a treadmill. Conceptually, relating changes in overground gait mechanics to changes in overground long-distance walking function would have been preferable; however, it should be noted that treadmill biomechanical assessment has several advantages over overground testing. These include the averaging of consecutive strides, the ability to control speed – a major determinant of gait mechanics, increased patient safety, and a marked reduction in efforts by both patient and researcher to generate data for a large number of strides. Previous work has also shown that treadmill biomechanical data provides relevant information for understanding overground walking[115,116].

A second potential limitation of this study is that some subjects utilized a handrail during testing. Specifically, subjects who typically used an assistive device or those who felt unsafe walking on the treadmill were allowed to use a handrail. The use of a handrail during testing may promote a forward trunk lean that could influence our measurement of trailing limb angle if the pelvis/trunk are not aligned with the vertical axis of the laboratory. However, it should be noted that subjects were only allowed to use a handrail located at the side of the treadmill. This mimicked walking with an assistive device and placed minimal constraint on the anterior/posterior displacement of the body during walking. It should also be noted that subjects were instructed to use the minimal amount of handrail support possible.

**Conclusions**

Because a rapid achievement of walking independence, not necessarily the reduction of impairment, is the goal of current neurorehabilitation practice[30], the high prevalence of inefficient walking strategies among persons in the chronic phase of stroke recovery is not surprising[6,29]. Maximizing posttraining outcomes for persons in the chronic phase of stroke recovery may therefore necessitate the learning of new walking strategies. The findings of this investigation support the development of poststroke locomotor interventions that include the targeting of paretic limb stance phase deficits during walking – specifically propulsion and trailing limb angle.

**Table 4.** Subject (n=44) Characteristics.

| Variable | Median (SIQR) or Frequency (%) |
| --- | --- |
| Age, years | 60.08 (2.49) |
| Time since stroke, year | 1.72 (0.73) |
| Sex, female | 39% |
| Side of paresis, left | 66% |
| Self-selected walking speed, m/s | 0.74 (0.12) |
| Maximum walking speed, m/s | 1.03 (0.15) |

SIQR, semi-interquartile range.

**Table 5.** Pretraining and Posttraining Change-Score Mean (SD) and Min/Max Values.

| **Variable** | **Mean (SD)** | **Min/Max** |
|---|---|---|
| Pretraining (n = 43) | | |
| Paretic propulsion, % body weight | 8.67 (5.00) | 0.00/20.12 |
| Paretic trailing limb angle, degrees | 15.35 (8.15) | –3.98/29.61 |
| Paretic knee flexion, degrees | 46.04 (14.79) | 14.43/71.39 |
| Paretic dorsiflexion, degrees | –1.65 (8.01) | –19.45/11.61 |
| Step length symmetry | 0.570 (0.147) | 0.501/1.250 |
| Swing time symmetry | 0.565 (0.057) | 0.504/0.738 |
| Six-Minute Walk Test distance, m | 285 (134) | 44/546 |
| Change-Scores (n = 29) | | |
| Δ Paretic propulsion, % body weight | 2.26 (3.78) | –4.26/14.74 |
| Δ Paretic trailing limb angle, degrees | 2.76 (4.65) | –4.62/16.00 |
| Δ Paretic knee flexion, degrees | 2.62 (6.82) | –11.40/20.72 |
| Δ Paretic dorsiflexion, degrees | 1.12 (6.29) | –10.94/18.23 |
| Δ Step length symmetry | 0.034 (0.141) | –0.055/0.746 |
| Δ Swing time symmetry | –0.011 (0.042) | –0.109/0.088 |
| Δ Six-Minute Walk Test distance, m | 72 (61.68) | –37/207 |

**Table 6.** Sequential Regression Models Predicting *Pretraining* 6MWT Distance (n=43).

| Model Statistics | | | | Predictor Statistics | | | | |
|---|---|---|---|---|---|---|---|---|
| Block | $R^2$ | $F$ | $P$ | Construct | Predictors | β | $t$ | $P$ |
| 1 | .615 | 31.92 | .000 | Stance | Paretic propulsion | .363 | 2.15 | .019 |
| | | | | | Trailing limb angle | .460 | 2.73 | .005 |
| 1 + 2 | .621 | 15.54 | .000 | Stance | Paretic propulsion | .331 | 1.86 | .035 |
| | | | | | Trailing limb angle | .415 | 2.19 | .018 |
| | | | | Swing | Ankle dorsiflexion | .098 | 0.73 | .472 |
| | | | | | Knee flexion | .017 | 0.14 | .887 |
| 1 + 2 + 3 | .655 | 11.38 | .000 | Stance | Paretic propulsion | .339 | 1.92 | .031 |
| | | | | | Trailing limb angle | .564 | 2.75 | .005 |
| | | | | Swing | Ankle dorsiflexion | .166 | 1.20 | .237 |
| | | | | | Knee flexion | .043 | 0.37 | .717 |
| | | | | Symmetry | Step length symmetry | .156 | 1.19 | .243 |
| | | | | | Swing time symmetry | .184 | 1.40 | .170 |

Abbreviations: 6MWT, 6-Minute Walk Test.

**Table 7.** Moderated Regression Analyses Predicting *Change* in the 6MWT (n=29).

| Model Statistics | | | | Predictor Statistics | | | |
|---|---|---|---|---|---|---|---|
| Model | $R^2$ | $F$ | $P$ | Predictors | β | $t$ | $P$ |
| Moderation by Pre-tx Prop | .383 | 5.17 | .006 | Δ Prop | .340 | 2.11 | .023 |
| | | | | Pre-tx Prop | .098 | 0.62 | .539 |
| | | | | Δ Prop × Pre-tx Prop | −.436 | −2.72 | .012 |
| Moderation by Pre-tx TLA | .468 | 7.34 | .001 | Δ Prop | .227 | 1.43 | .082 |
| | | | | Pre-tx TLA | .216 | 1.43 | .082 |
| | | | | Δ Prop × Pre-tx TLA | −.526 | −3.43 | .002 |
| Moderation by Δ TLA | .289 | 3.39 | .034 | Δ Prop | .213 | 1.02 | .160 |
| | | | | Δ TLA | −.049 | −0.25 | .403 |
| | | | | Δ Prop × Δ TLA | .408 | 1.82 | .041 |

Abbreviations: 6MWT, 6-Minute Walk Test; Prop, paretic propulsion; TLA, trailing limb angle; Pre-tx, pretraining.

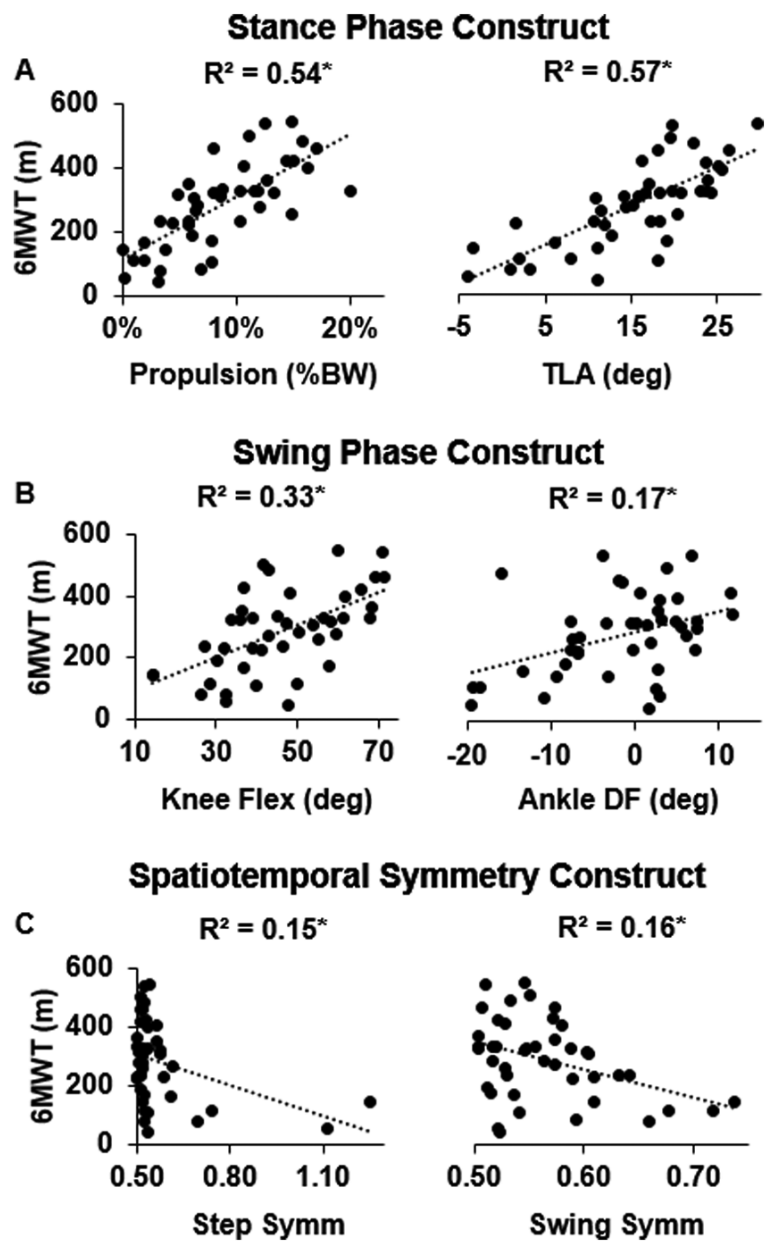


**Figure 2.** Scatter plots present the relationships between stance phase (panel A), swing phase (panel B), and spatiotemporal symmetry (panel C) biomechanics versus long-distance walking function. All variables considered were related to performance on the 6MWT; however, stance phase function (panel A) exhibited the highest degree of correlation. *Abbreviations:* 6MWT, 6-Minute Walk Test; %BW, percent body weight; TLA, trailing limb angle; deg, degree; Flex, flexion; DF, dorsiflexion; Step Symm, step length symmetry; Swing Symm, swing time symmetry. * $p < .05$.

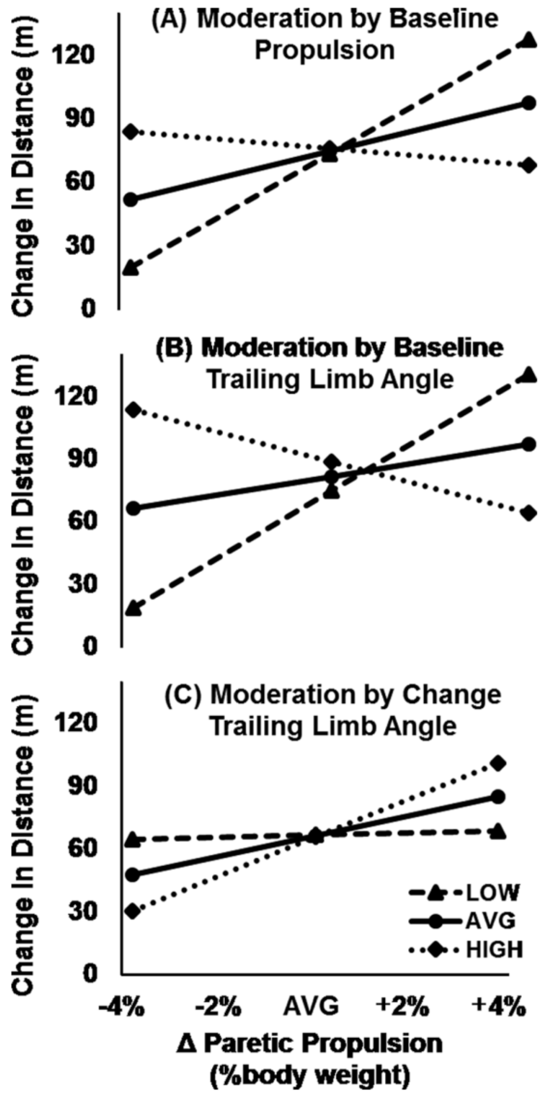


**Figure 3.** Moderated regression plots present a visual representation of the relationship between changes in paretic propulsion (*x*-axis) versus changes in long-distance walking function (*y*-axis) as moderated by pretraining propulsion (panel A), pretraining trailing limb angle (panel B), and changes in trailing limb angle (panel C). This relationship was strongest in those with LOW (ie, 1 standard deviation below the mean) pretraining levels of propulsion (<3.67% body weight, panel A) and trailing limb angle (<7.2°, panel B). Moreover, changes in paretic propulsion most strongly related to changes in long-distance walking function in those with the largest change in trailing limb angle (ie, 1 standard deviation above the mean: >7.41°) (panel C). Please note that panels A to C present simple slopes at each level of the moderator of interest (ie, LOW, -1 standard deviation; AVG, average; HIGH, +1 standard deviation), not a grouping of subjects.

# Chapter 4

## PARETIC LIMB NEUROMOTOR RECOVERY CONTRIBUTES TO WALKING RECOVERY FOLLOWING 12 WEEKS OF MAXIMUM-SPEED TREADMILL TRAINING COMBINED WITH FUNCTIONAL ELECTRICAL STIMULATION

### Abstract

***Background.*** Rehabilitation efforts have been unable to resolve the motor impairments limiting persons with chronic hemiparesis. Recent work has demonstrated proof-of-concept for a novel combination therapy designed to improve poststroke walking through paretic limb neuromotor recovery – specifically, by increasing paretic propulsion during walking. ***Objectives.*** To validate the hypothesized effects and mechanisms of a targeted poststroke locomotor program and identify effect modifiers. ***Methods.*** 29 subjects > 6 months poststroke participated in a 2-group, randomized mechanistic study, completing 12 weeks of maximum speed treadmill training combined with functional electrical stimulation to the paretic ankle musculature (FastFES) or training at self-selected speeds (SS). 6-minute walk test distance (6MWT) and comfortable walking speed (CWS) characterized walking function. Paretic propulsion (PROP) served as the biomechanical measure of interest. Moderated regression tested *a priori* mechanistic hypotheses and determined the influence of baseline level of impairment on treatment effects. ***Results.*** FastFES and SS produced within-group gains in the 6MWT (67±57, 36±58m), CWS (0.12±0.22, 0.12±0.16m/s), and PROP (1.25±2.34, 2.75±4.84%BW), respectively ($Ps \leq$ 0.03); however, only following FastFES did changes in PROP contribute to changes in the 6MWT and CWS, with participants' baseline maximum walking speeds further moderating effects ($R^2s$ ranged from 0.41 to 0.78). For subjects with baseline maximum speeds under 1.2m/s, FastFES was markedly more effective than SS in improving the 6MWT (76±56 versus 18±51m) and CWS (0.19±0.15 versus 0.06±0.14m/s) ($Ps \leq 0.03$).

***Conclusions.*** FastFES locomotor training improves the walking of persons poststroke through paretic limb neuromotor recovery and is particularly effective in persons with baseline maximum walking speeds under 1.2m/s.

## Introduction

Stroke is a leading cause of long-term disability[20]. Marked physical inactivity – with its increased risk of second stroke, heart disease and diabetes[20], and relation to hypertension, depression[117] and a reduced health-related quality of life[28,117] – is a concerning sequela of stroke[26,118]. For persons after stroke, rehabilitation is the cornerstone for recovery; however, current efforts are unable to resolve the motor impairments limiting walking function and community participation[7,8,21,23–25] and physical inactivity continues to worsen over the first year after stroke[119]. A critical need exists for novel interventions capable of restoring neuromotor function and ultimately improving poststroke walking ability.

Recently, our laboratory demonstrated the safety and feasibility of a novel, hypothesis-driven locomotor intervention that joins 2 independent therapies, maximum speed treadmill walking and functional electrical stimulation (FastFES), for the treatment of poststroke walking dysfunction[64]. In a preliminary study, we reported meaningful improvements across the *body structure and function, activity,* and *participation* domains of the World Health Organization's International Classification of Function, Disability and Health[19] following training. These exciting early findings prompted further study of this promising intervention.

A recent critical review of poststroke walking therapies demonstrated similar (and limited) outcomes following rehabilitation efforts of varying sophistication[9]; however, this assessment was based solely on the gains in walking speed observed following training. As a gross measure of walking ability, walking speed provides poor resolution for identifying the mechanisms underlying walking recovery[36], and thus offers only a limited understanding of an intervention's effects. Indeed, the strategy used to walk faster after intervention may be just as critical to improving community walking participation as the magnitude of improvement in walking speed. For example, recent work from our laboratory has demonstrated that the strategy used to walk faster after locomotor training influences the changes in the energy cost of walking observed following training[101]. As such, the present investigation aims to provide a detailed analysis of the effects and mechanisms of the impairment-targeting FastFES locomotor program. Specifically, this study aims to validate FastFES' hypothesized training effects and identify patient characteristics that modify treatment outcomes.

Validating the hypothesized effects of targeted locomotor training is important for the growth of a body of clinical interventions with sound mechanistic foundations. Moreover, considering the heterogeneous nature of poststroke motor impairments, answering the question, "for whom is this an appropriate intervention?" is also critical to the advancement of neurorehabilitation efforts. Drawing from a theoretical framework of poststroke locomotion that places substantial emphasis on the function of the paretic limb during late stance – a framework validated by recent work from our laboratory[64,120] – we designed the FastFES program to target the propulsive force generated by the paretic limb during walking (paretic propulsion)[64] and hypothesized that improvements in paretic propulsion would contribute to improvements in short- and long-distance walking ability. Moreover, based on prior work that has suggested that individuals poststroke may strengthen existing compensatory strategies during gait retraining instead of recover neuromotor function[31,32], we also hypothesized that improvements in walking ability produced by non-targeted locomotor training at self-selected, comfortable walking speeds (SS) would not relate to improvements in paretic propulsion.

Because the FastFES program is centered on treadmill training at maximum walking speed, we hypothesized that subjects' baseline maximum walking speed would moderate treatment outcomes. Specifically, we hypothesized that FastFES would be more effective than SS in participants with maximum walking speeds under 1.2 m/s. This hypothesis draws from our belief that in subjects with baseline maximum speeds faster than 1.2m/s, the effects of SS training may be enhanced whereas the effects of FastFES may be attenuated. Two points support this speculation. First, previous work has shown that treadmill walking at faster speeds directly improves the biomechanical positioning of the paretic trailing limb[66], which is an important determinant of propulsion[57]. As such, SS treadmill training in faster participants is inherently different, and presumably more effective, than SS treadmill training in slower participants. Second, a training speed cutoff value of 1.2m/s may be meaningful as previous work has demonstrated that faster walking in persons with baseline maximum walking speeds already faster than 1.2m/s – a critical threshold for safe and normal community walking[121–123] – does not produce a reduction in the energy cost of walking, but does for individuals that walk at speeds <1.2m/s[25].

## Methods

### Participants

Twenty-nine individuals in the chronic phase of stroke recovery (see Table 8) participated in this study. The data included in the present report are a subset of the data collected for a larger multidisciplinary study of treadmill-based locomotor training. Participant recruitment occurred over 24 months from local health facilities and patient support groups in Delaware, New Jersey, and Pennsylvania. Participant inclusion criteria included: a single cortical or subcortical stroke, observable gait deficits but the ability to walk unsupported and without orthotic support for six minutes, passive ankle dorsiflexion to neutral with the knee extended, 10 degrees of passive hip extension, and the ability to communicate with investigators and follow instruction. Participant exclusion criteria included: cerebellar stroke, conditions other than stroke that limit walking ability, neglect or hemianopia, or unexplained dizziness during the prior 6 months. Written informed consent and physician medical clearance was obtained for each participant prior to their participation in the study. Participants also underwent a submaximal stress test and secured cardiac clearance prior to the start of training. All study procedures were approved by the Institutional Review Board of the University of Delaware.

**Clinical Testing**

Licensed physical therapists blinded to treatment group conducted all evaluations. Participant performance on the 6-meter walk test[90] and the 6-Minute Walk Test (6MWT)[42] characterized short- and long-distance walking ability, respectively. Specifically, self-selected, comfortable walking speed (CWS) (m/s) was used to assess short-distance walking function and was calculated for each subject based on the time taken to walk the middle 6 meters of a 10 meter walk path. The distance (m) traveled during the 6MWT served to measure long-distance walking function. Assistive devices were allowed during testing, if necessary. Subjects who used an assistive device at their pretraining evaluation also used one during subsequent evaluations.

**Motion Analysis**

As the primary target of the FastFES intervention, peak paretic limb propulsive force during late stance phase (paretic propulsion) served as this study's biomechanical measure of interest. Paretic propulsion was calculated as the maximum anterior ground reaction force recorded during the paretic double support phase, normalized to body weight (%body weight). Prior work has described in detail our methods for biomechanical assessment[64,93,98,120]. Briefly, ground reaction force data were collected at 2000Hz as participants walked at their comfortable walking speeds on a dual-belt treadmill instrumented with two independent 6-degrees-of-freedom force platforms (Bertec Corporation, Worthington, OH). Data for the first 15 strides of recorded walking were averaged using a custom-written computer program (National Instruments, Austin, TX, USA).

**Training**

Subjects were randomly assigned to either 12 weeks of non-targeted or targeted locomotor training. In the non-targeted walking program (SS), subjects practiced walking at their self-selected, comfortable speeds. In the targeted walking program (FastFES), participants trained at the maximum walking speed they could maintain for four minutes on a treadmill. In this group, participants also received functional electrical stimulation to the paretic ankle plantarflexors during late stance phase and dorsiflexors during swing phase in an alternating pattern of 1 minute on to 1 minute off. Stimulation was triggered by two compression-closing foot switches attached to the sole of the paretic limb's shoe. Greater detail regarding the FastFES system and training has been provided[64,77,93,98,124–126]. Subjects were trained at a frequency of 3 times per week, for a total of 36 sessions. Each session was comprised of 5 bouts of 6 minutes of treadmill walking followed by 1 bout of overground walking for 6 minutes, for a total of 36 minutes of walking per session. Rest breaks were provided between bouts. While walking on the treadmill, an overhead harness was attached for safety. No body weight was supported by the harness.

**Statistical Analyses**

Independent t-tests tested for between-group differences in baseline 6MWT, CWS, and paretic propulsion. Paired t-tests (1-tail) tested for within-group baseline versus posttraining and baseline versus 3-month follow-up improvements. Means±SDs, 90% confidence intervals (CI), and *p* values are reported for each group (see Table 10). Moreover, the number of subjects who achieved posttraining changes larger than known minimal clinically important difference (MCID) or minimal detectable change (MDC) scores are reported to provide details regarding intervention efficacy at the level of individual subjects (see Table 9). These analyses were repeated in participants with baseline maximum walking speeds under 1.2 m/s. Moreover, independent t-tests tested difference scores between groups in the measurements of interest with an *a priori* directional hypothesis that FastFES would outperform SS in the cohort of participants with baseline maximum walking speeds under 1.2 m/s.

Moderated regression[127,128] tested *a priori* hypotheses that (1) FastFES would produce improvements in paretic propulsion that contribute to improvements in walking function, whereas SS would not and (2) baseline maximum walking speed would influence outcomes such that a greater FastFES treatment effect would be observed in participants with maximum speeds under 1.2 m/s. The main effects tested in the models were treatment group (TxGroup), baseline maximum walking speed group (MWSgroup), and change in propulsion (ΔProp). Specifically, the interaction terms

[TxGroup*ΔProp] and [TxGroup*MWSgroup] were tested in regression models predicting pre- to posttraining and pretraining to 3-month follow-up changes in both the 6MWT and CWS. The 3-way interaction [TxGroup*ΔProp*MWSgroup] was also tested. Centered variables were used and residuals were screened for the presence of outliers. All analyses were performed in SPSS version 22 with alpha set to 0.05. Sample sizes of n = 9, 5, and 11 were required for this study to be 80% powered to detect within-group pretraining to 3-month follow-up changes in the 6MWT, CWS, and paretic propulsion of similar magnitude to those reported in a preliminary study[64]. Moreover, a sample of n = 26 was required to detect significant 2-way interactions with a change in $R^2$ of .30 using moderated regression.

## Results

Complete data sets were available for all subjects (n = 29, FastFES n = 15, SS n = 14). There was no difference between treatment groups at baseline (all *ps* > 0.05). The average pretraining 6MWT distance was 277±136m, CWS was 0.70±0.32m/s, and magnitude of paretic propulsion (PROP) was 7.24±5.45% body weight. Assumptions for the moderated regression analyses were met after removing two outliers in the 6MWT models and 3 outliers in the CWS models.

### Posttraining Changes: All Participants

Both FastFES and SS produced within-group gains in the 6MWT, CWS, and PROP following 12 weeks of training (see Table 10). Only for the 6MWT did a difference between groups approach significance ($p_{(1\text{-}tail)} = 0.08$, see Figure 4). Moreover, only the FastFES intervention produced a mean change larger than the 54.1 MDC previously established for the 6MWT[49]. Likewise, at the level of individual subjects, FastFES produced meaningful gains in the 6MWT for a markedly larger percentage of participants (73% versus 36%, see Table 9). Interestingly, the magnitude of improvements in CWS and PROP were similar between treatment groups and the improvements within each group were less than the 0.17m/s CWS MCID[91] and 2.85 %bodyweight PROP MDC[129] (see Table 10, Figure 4).

Similarly, at the 3-month follow-up, each treatment group produced within-group gains in the measurements of interest (see Table 10); however, only the FastFES treatment produced a mean change in the 6MWT that approached the MDC (see Table 10, Figure 4). Moreover, at the level of individual subjects the percentages of participants in the FastFES group that surpassed the established 6MWT MDC (40%) and CWS MCID (33%) were greater than those observed in the SS group (21% and 14%, respectively). Moreover, 4 of the 6 FastFES participants who surpassed the 6MWT MDC achieved gains of over 100m; none of the SS participants exceeded 100m (see Table 9). The changes in CWS and PROP were similar between groups (see Table 10, Figure 4).

**Mechanistic Changes**

Despite FastFES and SS each producing improvements in the 6MWT and CWS, moderated regression revealed that the changes in PROP were unrelated to changes in either the 6MWT or CWS following SS, but were strongly positively related to the changes observed following FastFES (see Table 11 and Figure 5). That is, FastFES and SS produced functional changes through different mechanisms. Moreover, moderation of treatment effects by baseline maximum walking speed group was observed (see Table 11). Evaluation of this interaction revealed that in participants with baseline maximum speeds slower than 1.2m/s, FastFES was markedly more effective than SS (see Figure 4). The 3-way interaction, [TxGroup*ΔProp*MWSgroup] was not significant for any model, and was thus not included. The final models were able to explain between 41 to 78% of the variance in posttraining outcomes (see Table 11).

**Posttraining Changes: Participants Walking < 1.2 m/s**

As hypothesized, the removal of participants with baseline maximum walking speeds faster than 1.2 m/s (SS group n = 4 and FastFES group n = 3 participants removed) yielded a marked reduction in the efficacy of SS (see Table 9 for individual subject data and Table 10 for group results). Indeed, the majority of SS participants who achieved posttraining changes that were larger than known MDC/MCID scores in the 6MWT (3 of 5), CWS (4 of 7), and PROP (4 of 6) were among this cohort of fast walkers that was removed. In contrast, only 1 of the 11, 0 of the 6, and 1 of the 5 FastFES participants with changes larger than the MDC/MCID scores in the 6MWT, CWS, and PROP, were removed (see Table 9). Moreover, consistent with our hypothesis that the effects of FastFES would be attenuated in faster walkers, removal of this cohort of fast participants resulted in mean gains that were substantially larger than observed in all participants. Specifically, the mean gain in the 6MWT for the FastFES participants with maximum speeds less than 1.2m/s was 76±56m (up from 67±57m) and the mean gain in CWS was 0.19±0.15m/s (up from 0.12±0.16). In contrast, SS training in these slower walkers produced gains of only 18±51m in the 6MWT (down from 36±58m) and 0.06±0.14m/s in CWS (down from 0.12±0.16m/s). Consequently, in this cohort of "slow" participants, FastFES was markedly more effective than SS with a mean between-group difference in the 6MWT of 58±23m (90%CI: 19 – 98m, $p_{(1\text{-}tail)}$ = 0.01, see Figure 4) and in CWS of 0.13±0.06m/s (90%CI: 0.02 – 0.024m/s, $p_{(1\text{-}tail)}$ =

0.02, see Figure 4). Moreover, it should be noted that in this cohort of slower walkers, only the FastFES group met the 6MWT MDC and CWS MCID thresholds.

In the cohort of participants with maximum walking speeds *slower* than 1.2m/s, 3-month follow-up changes were similar to those observed at the posttraining evaluations. Specifically, the removal of participants with baseline speeds *faster* than 1.2m/s resulted in reduced improvements for the SS group and increased improvements for the FastFES group (see Figure 4 and Table 10). Interestingly, the between-group difference in the pretraining to 3-month follow-up changes in the 6MWT only approached significance ($p_{1\text{-}tail} = 0.14$), despite the fact that only the FastFES group produced a mean gain larger than the MDC (see Figure 4). Moreover, evaluation of the pretraining to 3-month follow-up changes in CWS revealed a substantially larger mean change in CWS for FastFES versus SS (0.12±0.13m/s versus 0.03±0.04m/s, 90%CI: 0.002 – 0.19m/s, $p_{(1\text{-}tail)} = 0.047$, see Figure 4).

## Discussion

This study aimed to determine if a hypothesis-driven, targeted locomotor therapy (FastFES) would improve poststroke walking by restoring the paretic limb's ability to generate propulsion during late stance. Specifically, we aimed to answer the clinically relevant research questions, "does the intervention work via its hypothesized mechanisms?" and "for whom is this an appropriate intervention?" Ultimately, this study validated the hypothesized mechanisms of the FastFES intervention and demonstrated its efficacy in persons with baseline maximum walking speeds slower than 1.2m/s. Of more general importance, we have demonstrated for the first time that in persons with chronic stroke, targeting locomotor impairments during rehabilitation produces changes in walking function that are fundamentally different than the changes that are produced by non-targeted rehabilitation. Specifically, FastFES training produced changes in both short- and long-distance walking function that tracked the recovery of paretic propulsion; in contrast, the functional improvements following non-targeted gait training (SS) were unrelated to changes in propulsion (see Figure 5). These findings suggest that not all walking practice is the same and provide a striking example of the importance of the specific structure and parameters of training.

Beyond providing an opportunity for massed stepping practice that capitalizes on the specificity and repetition principles of experience-dependent neuroplasticity[67] – features shared by the SS intervention and previously studied walking interventions that produced limited gains[130–133] – the FastFES intervention was designed to provide direct training of increased paretic propulsion during walking[64]. Ultimately, the sensorimotor cues provided by the faster walking and functional electrical stimulation produced changes in walking function of a fundamentally different character than walking practice that did not provide such stimuli. These findings warrant consideration of how other task-specific training programs are structured. Indeed, whether practicing sitting to standing, walking, or stair climbing, the mechanics underlying such practice will likely define the nature of the outcomes observed.

Despite these mechanistic findings supporting our *a priori* hypotheses, the fact that both training programs produced similar gains in paretic propulsion (see Table 10) is surprising. This finding would appear to suggest that improvements in propulsion do not automatically translate into improvements in walking and that the manner by which propulsion is improved appears to be important. Indeed, FastFES training was designed to promote a larger trailing limb angle and increased activation of the plantarflexors[64] – both physiologically-consistent mechanisms to improving propulsion. In contrast, no such structure was given during SS training, as subjects merely practiced walking. A likely consequence of this non-directed training was that – as previously suggested[31,32,48] – participants reinforced and strengthened existing compensatory strategies. The reliance on existing compensatory strategies by the SS participants may explain why only FastFES-induced improvements in propulsion resulted in better walking.

An interesting finding was that removal of those subjects with baseline maximum walking speeds faster than 1.2m/s from the FastFES group resulted in an increase in the mean 6MWT and CWS improvements for the remaining subjects. In contrast, for the SS group, removal of these participants resulted in a decrease in the mean improvements (see Figure 4). This finding indicates that the effects of FastFES are attenuated, whereas the effects of SS are enhanced, in faster walkers. We believe that the attenuation of FastFES' effects in subjects with baseline speeds faster than 1.2m/s is the result of there being little advantage for fast walkers to train at speeds faster than their self-selected speeds. This conjecture is supported by single-session work by Reisman et al that demonstrated a more efficient gait when poststroke subjects with baseline speeds less than 1.2m/s were made to walk faster, but no change in walking efficiency in subjects with baseline speeds faster than 1.2m/s[25]. Furthermore, it is likely that the enhancement of SS training in subjects with baseline speeds faster than 1.2m/s was due to the fact that these participants actually trained at a relatively fast speed, which promoted neuromotor recovery rather than compensatory strategies[120].

An interesting point to consider is that most previous intervention studies in the chronic stroke population targeted only individuals with baseline preferred walked speeds less than 0.80m/s. This strict inclusion criteria has prevented the study of interventions in an important subgroup of patients after stroke – that is, persons with near normal walking speeds but low levels of community participation. Our finding that non-targeted training was effective in producing further improvements in walking speed in these already fast walkers, but FastFES was not, warrants further study of interventions for this group. It is conceivable that walking patterns in fast walkers are already so optimized that FastFES was unable to train a more physiologic walking pattern, whereas SS was able to strengthen existing patterns.

The rehabilitation superiority of targeted versus non-targeted training in individuals with baseline maximum speeds *slower* than 1.2m/s is particularly evident when comparing FastFES to SS and previously studied interventions in persons with chronic stroke. Specifically, FastFES training produced an average increase of 76±56m in the distance traveled during the 6MWT, which was substantially larger than the gain produced by SS training (18±51m). Furthermore, a recent randomized controlled trial studying the effects of 3 months of fast overground training reported a gain in the 6MWT of only 34.5m[131]. Similarly, recent systematic reviews of treadmill and body weight support training[134] and mixed cardiorespiratory and strength training[135] reported pooled mean differences of only 30.6m and 41.6m, respectively. Likewise, a meta-analysis examining the effects of strength training after stroke reported a 28m gain in the 6MWT[136]. Even the top performing group in the STEPS randomized controlled trial, which received body-weight supported locomotor training combined with a lower extremity strength program, achieved an average gain of only 45.3±33.5m following training[132]. Furthermore, when examining the data at the level of individual subjects, it is found that 10 of the 12 FastFES participants, versus only 2 of the 10 SS participants, exceeded the 6MWT MDC. These results are consistent with the results of a preliminary study on the FastFES intervention in a different cohort of participants that reported an average 89±64m gain in the 6MWT following training[64]. These results highlight the rehabilitation promise of the FastFES intervention.

Because the FastFES program is a combination therapy (fast treadmill training + FES), the exact training mechanism underlying its effects is unknown. A future report from our laboratory will explore this question; however, it should be noted that single-session work has demonstrated that the combination of fast treadmill walking with FES outperformed fast treadmill walking alone or comfortable speed treadmill walking with or without FES[125]. Moreover, the merits of FES as an adjuvant to task-specific walking retraining have been shown previously[137]. Specifically, in a recent study of FES-assisted, body-weight supported treadmill and overground training that focused on restoring coordinated movement during poststroke walking through 8 implanted FES electrodes, a 6MWT gain of 57m was observed. Although this gain was not significantly larger than the 45m gain observed in participants who trained without FES, more participants who received FES demonstrated improvements in gait coordination. The findings of the present study extend this interesting work by demonstrating a link between walking recovery and improvements in the function of the paretic limb during walking following 2-channel, surface FES-enhanced treadmill training.

**Conclusions**

FastFES locomotor training improves the short and long distance walking ability of persons poststroke via paretic limb neuromotor recovery. Moreover, for those with baseline maximum speed under 1.2m/s, FastFES is substantially more effective than non-targeted training. Future studies should stratify subjects based on baseline characteristics when evaluating the effects of intervention. Future work should elucidate the specific contributions of the fast walking and the FES to the outcomes observed, replicate this work, and explore how baseline characteristics other than speed modify the effects of the FastFES intervention.

**Table 8.** Participant characteristics.

| Subject | Group | Sex | Age (y) | Time Since Stroke (y) | Side of Paresis |
|---|---|---|---|---|---|
| 1 | FastFES | F | 65.39 | 22.90 | L |
| 2 | FastFES | M | 60.01 | 2.68 | L |
| 3 | FastFES | M | 55.68 | 0.73 | L |
| 4 | FastFES | M | 42.71 | 0.57 | L |
| 5 | FastFES | M | 67.91 | 0.77 | L |
| 6 | FastFES | M | 69.47 | 8.29 | R |
| 7 | FastFES | M | 54.94 | 1.66 | L |
| 8 | FastFES | F | 64.91 | 24.66 | L |
| 9 | FastFES | F | 63.25 | 3.02 | R |
| 10 | FastFES | M | 57.50 | 0.59 | L |
| 11 | FastFES | M | 68.69 | 2.86 | L |
| 12 | FastFES | M | 70.74 | 1.71 | L |
| *13 | FastFES | M | 63.49 | 7.99 | R |
| *14 | FastFES | F | 56.00 | 3.51 | L |
| *15 | FastFES | M | 25.31 | 1.70 | L |
| 16 | SS | M | 63.35 | 0.57 | L |
| 17 | SS | M | 79.78 | 1.33 | R |
| 18 | SS | M | 59.09 | 1.04 | L |
| 19 | SS | F | 47.26 | 3.11 | L |
| 20 | SS | M | 27.71 | 0.62 | L |
| 21 | SS | F | 77.59 | 1.04 | R |
| 22 | SS | F | 69.59 | 6.49 | L |
| 23 | SS | F | 70.01 | 3.95 | R |
| 24 | SS | M | 35.26 | 2.44 | R |
| 25 | SS | F | 57.78 | 0.73 | L |
| *26 | SS | M | 60.69 | 0.47 | L |
| *27 | SS | F | 61.41 | 2.49 | R |
| *28 | SS | M | 78.03 | 8.51 | L |
| *29 | SS | M | 61.47 | 1.72 | L |
| | **Cohort** | **%M** | **Medians (SIQR)** | | **%R** |
| | ***All:*** | *66* | *61.5(6.4)* | *1.7(1.4)* | *28* |
| | ***All FastFES:*** | *73* | *63.3(5.4)* | *2.7(2.3)* | *20* |
| | ***All SS:*** | *57* | *61.4(5.9)* | *1.5(1.1)* | *36* |
| | ***<1.2m/s FastFES:*** | *75* | *64.1(5.5)* | *2.2(1.8)* | *17* |
| | ***<1.2m/s SS:*** | *50* | *61.2(10)* | *1.9(1.1)* | *40* |

*Participant with a baseline maximum walking speed faster than 1.2m/s. All – all subjects, <1.2m/s – cohort of subjects with baseline maximum walking speeds slower than 1.2m/s.

**Table 9.** Participant indicators of meaningful posttraining changes.

| | Pre to Post Change > MDC[a]/MCID[b] | | | Pre to Follow-up Change > MDC[a]/MCID[b] | | |
|---|---|---|---|---|---|---|
| **Subject** | **6MWT[a]** | **CWS[b]** | **PROP[a]** | **6MWT[a]** | **CWS[b]** | **PROP[a]** |
| 1 | | | | | | X |
| 2 | X | X | X | X | X | X |
| 3 | X | X | | X | X | X |
| 4 | XX | X | X | XX | X | X |
| 5 | XX | X | X | XX | | |
| 6 | X | | | | | |
| 7 | X | | | XX | X | |
| 8 | X | | | -X | | |
| 9 | X | | | | | |
| 10 | | X | | | | |
| 11 | XX | | | | X | |
| 12 | XX | X | X | XX | | |
| *13 | X | | | | | |
| *14 | | | X | | | |
| *15 | | -X | -X | | -XX | -X |
| 16 | | | | | | |
| 17 | | | | | | |
| 18 | X | X | XX | X | | X |
| 19 | | | X | | | X |
| 20 | | | X | | | X |
| 21 | | X | | | | |
| 22 | | X | | | | X |
| 23 | X | | | X | | |
| 24 | | | XX | | | |
| 25 | -X | -X | -X | -X | -X | -X |
| *26 | XX | X | X | | X | X |
| *27 | XX | X | | X | | |
| *28 | X | XX | X | | X | X |
| *29 | | X | | | | |
| **Cohort** | **Percent (%) of subjects with changes > MDC/MCIDs** | | | | | |
| ***All:*** | *55* | *45* | *38* | *31* | *24* | *34* |
| ***All FastFES:*** | *73* | *40* | *33* | *40* | *33* | *27* |
| ***All SS:*** | *36* | *50* | *43* | *21* | *14* | *43* |
| ***<1.2m/s FastFES:*** | *83* | *50* | *33* | *50* | *42* | *33* |
| ***<1.2m/s SS:*** | *20* | *30* | *40* | *20* | *0* | *40* |

MCID – minimal clinically important difference, MDC – minimal detectable change, "X" – change > MCID/MDC. "XX" – change > 2x MCID/MDC. "-X" – negative change > MCID/MDC.

**Table 10.** Baseline, Posttraining, and 3-month Follow-up Values.

| Var | Sub | Tx | PRE | Change PRE to POST | | | Change PRE to 3-Mo FU | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Mean± SD | Mean± SD | 90% CI | *p* *(1-tail)* | Mean± SD | 90% CI | *p* *(1-tail)* |
| 6MWT (m) | A | C | 250± 126 | 36± 58 | 9–63 | .018 | 34± 39 | 15–52 | .003 |
| | | D | 302± 145 | 67± 57 | 41–92 | .001 | 50± 100 | 5–95 | .037 |
| | B | C | 208± 120 | 18± 51 | -12–47 | .150 | 28± 41 | 4–52 | .030 |
| | | D | 251± 109 | 76± 56 | 47–105 | .001 | 65± 106 | 10–120 | .030 |
| CWS (m/s) | A | C | 0.63± 0.29 | 0.12± 0.16 | .05–.20 | .008 | 0.08± 0.13 | .01–.14 | .024 |
| | | D | 0.76± 0.34 | 0.12± 0.22 | .02–.22 | .024 | 0.07± 0.17 | -.01–.15 | .063 |
| | B | C | 0.54± 0.27 | 0.06± 0.14 | -.02–.14 | .118 | 0.03± 0.04 | -.04–.10 | .258 |
| | | D | 0.66± 0.26 | 0.19± 0.15 | .11–.27 | .001 | 0.12± 0.13 | .05–.19 | .004 |
| PROP (%BW) | A | C | 7.42± 5.49 | 2.75± 4.84 | .46–5.03 | .027 | 1.55± 2.52 | .09–3.00 | .020 |
| | | D | 7.10± 5.61 | 1.25± 2.34 | .18–2.31 | .029 | 1.28± 2.24 | .26–2.30 | .022 |
| | B | C | 6.03± 5.47 | 2.64± 5.75 | -.69–5.97 | .090 | 1.11± 2.88 | -.55–2.79 | .126 |
| | | D | 5.80± 5.30 | 1.52± 2.11 | .43–2.62 | .015 | 1.85± 1.95 | .84–2.87 | .004 |

Var – Variable; 6MWT – 6-Minute Walk Test distance; CWS – Comfortable, Self-Selected Walking Speed; PROP – Paretic Propulsion; %BW – percent body weight; Sub – subject cohort (A – All, B - <1.2m/s); ALL – all subjects (FastFES n = 15, SS n = 14); <1.2m/s – subjects with baseline maximum walking speeds under 1.2 m/s (FastFES n = 12, SS n = 10); Tx – treatment group (C – SS, D – FastFES); SS – Self-Selected Speed Training; FastFES – Fast treadmill training combined with functional electrical stimulation; PRE – pretraining; POST – posttraining; 3-Month FU – 3 month follow-up; CI – Confidence Interval

**Table 11.** Moderated regression models predicting 6MWT (n=27) and CWS (n=26) change.

| Model Statistics | | Predictor Statistics | | | | | |
|---|---|---|---|---|---|---|---|
| **Dependent Variable** | **Statistics** | **Predictors** | $\Delta R^2$ | $\Delta R^2$ $p$ | $b$ | **B** | $p$ |
| **Pre to Post Δ6MWT** | $R^2$ .488 <br> $F$ 4.00 <br> $p$ .005 | TxGroup | .084 | .071 | -25.13 | -.251 | .225 |
| | | MWSgroup | .001 | .447 | -52.93 | -.463 | .021 |
| | | ΔPropPP | .043 | .150 | -37.73 | -.028 | .441 |
| | | TxGroup × MWSgroup | .211 | .007 | 90.89 | .892 | .011 |
| | | TxGroup × ΔPropPP | .150 | .011 | 1341.7 | .469 | .011 |
| **Pre to Post ΔCWS** | $R^2$ .784 <br> $F$ 14.52 <br> $p$ .000 | TxGroup | .045 | .148 | -.315 | -.958 | .000 |
| | | MWSgroup | .015 | .275 | -.169 | -.458 | .002 |
| | | ΔPropPP | .021 | .245 | -.845 | -.192 | .069 |
| | | TxGroup × MWSgroup | .389 | .000 | .391 | 1.179 | .000 |
| | | TxGroup × ΔPropPP | .314 | .000 | 6.266 | .680 | .000 |
| **Pre to 3-Mo FU Δ6MWT** | $R^2$ .413 <br> $F$ 2.95 <br> $p$ .018 | TxGroup | .013 | .289 | -10.89 | -.075 | .416 |
| | | MWSgroup | .037 | .170 | -13.12 | -.079 | .366 |
| | | ΔPropPF | .090 | .067 | 102.43 | .052 | .397 |
| | | TxGroup × MWSgroup | .075 | .080 | 66.34 | .451 | .127 |
| | | TxGroup × ΔPropPF | .197 | .007 | 2222.7 | .537 | .007 |
| **Pre to 3-Mo FU ΔCWS** | $R^2$ .615 <br> $F$ 6.40 <br> $p$ .000 | TxGroup | .025 | .219 | -.186 | -.653 | .023 |
| | | MWSgroup | .014 | .285 | -.138 | -.432 | .019 |
| | | ΔPropPF | .332 | .001 | .067 | .010 | .484 |
| | | TxGroup × MWSgroup | .146 | .010 | .226 | .787 | .017 |
| | | TxGroup × ΔPropPF | .097 | .018 | 4.981 | .579 | .018 |

6MWT – 6 minute walk test distance (m); CWS – Self-selected, comfortable walking speed (m/s); TxGroup – FastFES or SS training; ΔPropPP – Pre to Post change in Paretic Propulsion (% body weight); ΔPropPF – Pre to Follow-up change in Paretic Propulsion (% body weight); MWSgroup – Baseline maximum walking speed group (>1.2m/s or <1.2m/s).

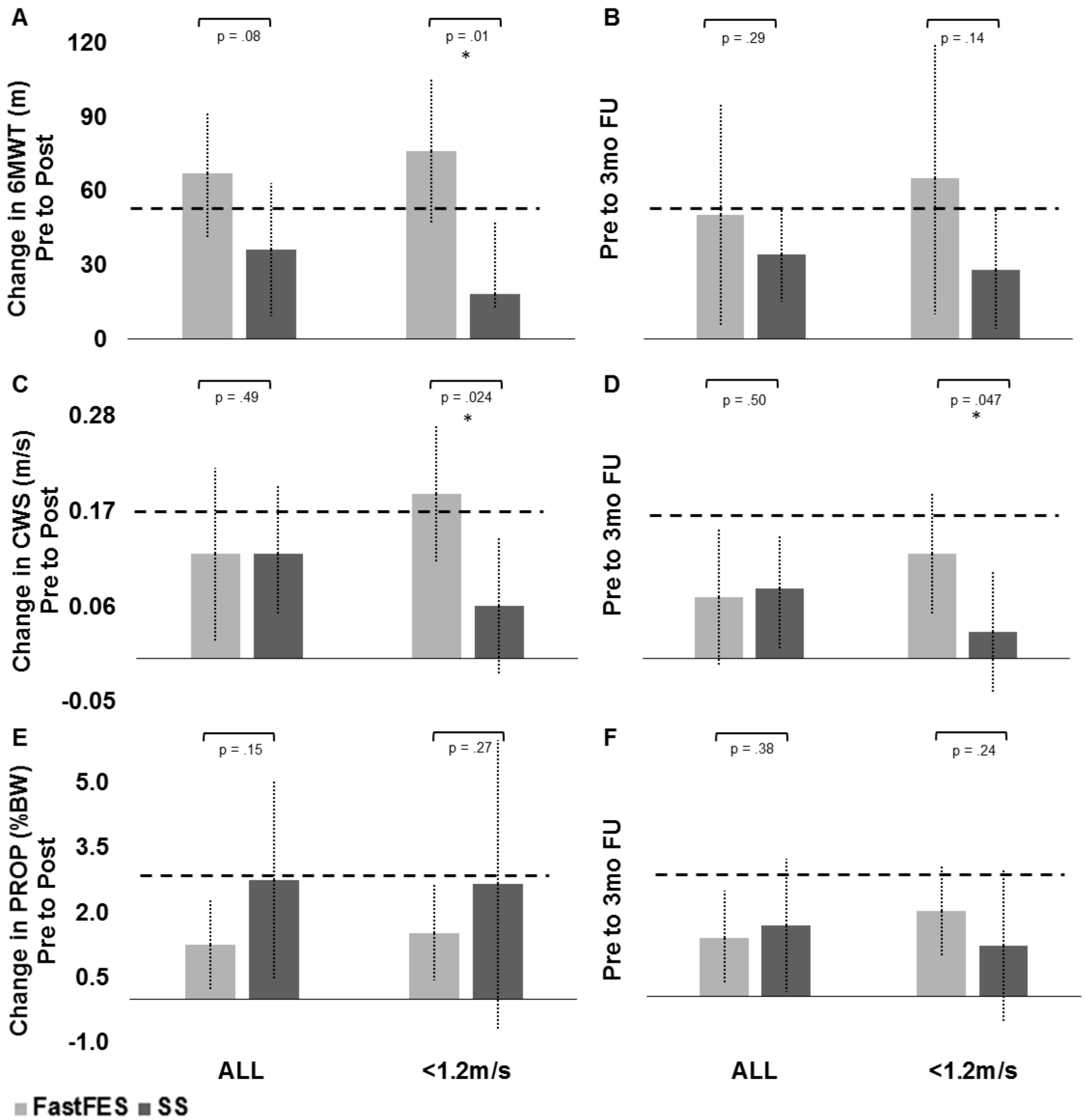


**Figure 4.** Between-group comparisons of pretraining (Pre) to posttraining (Post) (panels A, C, and D) and 3-month follow-up (3mo FU) (panels B, D, and F) changes in the distance traveled during the 6-minute walk test (6MWT, panels A and B), comfortable walking speed (CWS, panels C and D), and paretic propulsion (PROP, panels E and F). Comparisons are made between treatment groups for all participants studied (n = 29) and for only those participants with baseline maximum walking speeds slower than 1.2m/s (n = 22). Means and 90% confidence intervals are presented for each group. In the 6MWT and PROP graphs, the horizontal dashed lines represent minimal detectable change scores. In the CWS graph, this line represents the minimal clinically important difference score.

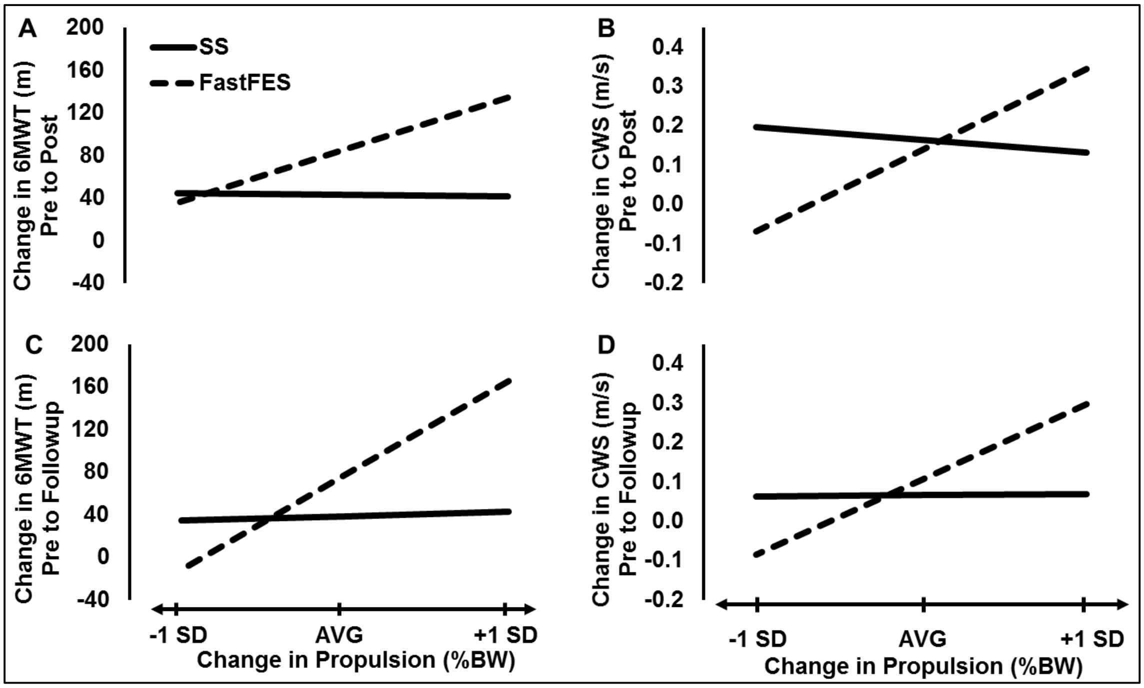


**Figure 5.** Visual presentation of the contribution of changes in propulsion to changes in long-distance walking ability (6MWT, panels A and C) or short-distance walking ability (CWS, panels B and D) as moderated by treatment group. Pretraining to posttraining (panels A and B) and pretraining to 3-month follow-up (panels C and D) data are presented. Changes in propulsion positively related to changes in walking following FastFES training, but not SS training.

# Chapter 5

## FUNCTIONAL ELECTRICAL STIMULATION ENHANCES THE EFFECTS OF A 12-WEEK MAXIMUM-SPEED TREADMILL TRAINING PROGRAM AFTER STROKE


### Abstract

***Background.*** Our previous work has shown that the novel combination of maximal speed treadmill training with functional electrical stimulation (FES) to the paretic ankle musculature (FastFES) improves the short- and long-distance walking of persons poststroke by increasing the paretic limb's contribution to forward propulsion. The specific contribution of FES to these results remains unknown. ***Objectives.*** To compare the effects and underlying biomechanical mechanisms of FastFES versus maximal speed treadmill training alone (Fast). ***Methods.*** 23 subjects >6 months poststroke were randomized to 12 weeks of either FastFES or Fast. Participants' comfortable walking speed (CWS) and the distance walked during the 6-Minute Walk Test (6MWT) measured short- and long-distance walking function, respectively. Paretic limb propulsion and trailing limb angle (TLA) were the biomechanical measures of interest. Variables were measured pretraining, posttraining, and after a 3-month follow-up. Moderated regression tested group-specific mechanistic hypotheses. ***Results.*** Despite both groups producing comparable gains in CWS and the 6MWT, the mechanisms underlying gains in CWS differed substantially between groups. Generally, larger gains in paretic propulsion contributed to faster posttraining walking speeds following FastFES, but not Fast, and this relationship was moderated by changes in TLA ($R^2$=0.91). Interestingly, despite posttraining changes in propulsion being largely dependent on changes in TLA following Fast, they were not for FastFES ($R^2$=0.71). This between-group difference did not remain significant at the 3-month follow-up. ***Conclusions.*** The addition of FES altered the

mechanisms underlying functional recovery, promoting changes more strongly linked to gains in paretic propulsion but not dependent on parallel changes in trailing limb angle.

## Introduction

Functional electrical stimulation (FES) is a common neurorehabilitation adjunct used to treat walking dysfunctions after stroke[64,72,137–147]. Primarily, FES has been used for its orthotic effects with recent evidence demonstrating its equivalence[138–140], and in some cases superiority[141], to ankle-foot orthoses. FES has also recently gained popularity as a therapeutic aide[64,72,137,142–144]; however, it remains unclear if FES provides therapeutic effects superior to those produced by non-FES interventions[137,139,142,145–147]. The study of FES applications in persons in the chronic phase of stroke recovery has also been restricted in scope, with most investigators focusing only on paretic dorsiflexor FES to reduce foot drop. Although foot-drop is perceived as a disabling swing phase deficit, recent work has cast doubt on its commonly professed role in impairing limb advancement and limiting the walking function of persons poststroke[120,148]. Indeed, findings from our laboratory have shown that late stance phase mechanics, particularly the propulsive-force generated by the paretic limb during walking, better explain across-subject variance in long-distance walking function after stroke[120]. As such, the development and evaluation of therapeutic FES applications that target the propulsive-force generating ability of the paretic limb warrants investigation.

Early work from our laboratory showed that the orthotic application of FES to both the paretic ankle dorsiflexors during swing phase (ie, targeting foot drop) and plantarflexors during stance phase (ie, targeting propulsion) outperformed the conventional FES approach of stimulating only the dorsiflexors[124]. Subsequently, we demonstrated that combining this novel FES approach with fast treadmill walking yielded larger within-session improvements in gait mechanics than when FES was combined with self-selected speed treadmill walking[125]. These early findings set the foundation for the development and testing of a hypothesis-driven locomotor therapy centered on the novel combination of maximal-speed treadmill walking with plantarflexor and dorsiflexor FES (FastFES). Through the integration of these two independent walking therapies, the FastFES intervention was designed to improve poststroke walking ability through its effects on the propulsive-force generating ability of the paretic limb during walking[64].

A preliminary study of the FastFES intervention demonstrated the safety and feasibility of this innovative training program and its efficacy at the level of individual subjects[64] across the *body structure and function*, *activity*, and *participation* domains of the World Health Organization's international classification of functioning, disability, and health[19]. Additionally, in a more recent study, the hypothesized mechanisms underlying the FastFES intervention were validated (unpublished observations, paper in review[149]). Specifically, we demonstrated that the improvements in short- and long-distance walking ability produced by 12 weeks of FastFES training were directly linked to therapeutic changes in the paretic limb's contribution to forward propulsion – a finding not observed in a control group receiving an equivalent dose of treadmill walking training at their self-selected, comfortable walking speeds. However, because FastFES combines two independent interventions – maximal speed treadmill training and paretic ankle FES – the particular contribution of the FES to the outcomes observed is not clear. Indeed, previous work has demonstrated that training at fast speeds outperforms training at slow speeds[65,71]. Consequently, it is possible that FastFES' superiority to locomotor training at comfortable speeds may have been merely the result of participants training at faster speeds and not due to any particular contribution of the FES. Thus, the purpose of this investigation was to determine the contribution of FES to the outcomes observed following FastFES training.

The theoretical framework underlying the FastFES intervention's merging of maximal speed treadmill training with FES to the paretic ankle musculature has been detailed previously[64]. In summary, we hypothesized that walking at fast speeds on a treadmill would increase the posterior placement of the paretic trailing limb relative to the center of mass during late stance, maximizing the translation of increased plantarflexor activity (produced via the FES) into forward propulsion. As such, FastFES training was designed to exploit two mechanisms for increasing forward propulsion: improved trailing limb angle and improved plantarflexor force generation. In contrast, only improved trailing limb angle would theoretically underlie improved paretic propulsion following Fast treadmill training. Thus, for the present study, we hypothesized that changes in paretic propulsion would more strongly contribute to functional recovery following FastFES versus Fast and that changes in trailing limb angle would explain more of the variance in changes in propulsion following Fast versus FastFES.

## Methods

### Participants

Twenty-three individuals with poststroke hemiparesis participated in this study (see Table 11). Participants were recruited over 2 years from local medical facilities and support groups. Participants were in the chronic phase of stroke recovery (>6 months poststroke), had a single cortical or subcortical stroke, demonstrated observable gait deficits but were able to walk for six minutes without the assistance of another individual and without orthotic support, demonstrated passive ankle dorsiflexion range of motion to neutral when the knee was extended, at least 10 degrees of hip extension passive range of motion, and were able to communicate with investigators and follow instructions. Participants could not have had a cerebellar stroke, any condition other than stroke that limited their ability to walk, neglect or hemianopia, or unexplained dizziness during the prior 6 months. Participants were consented as per a protocol approved by the University of Delaware's institutional review board. Medical clearance by a physician was required before participants entered the study and a submaximal stress test was administered prior to the start of training. The data presented are a subset of the data collected for a larger study of treadmill walking interventions. Only participants with baseline maximum walking speeds slower than 1.2m/s were included in this study of the FastFES intervention due to a previous report from our laboratory demonstrating an attenuation of FastFES' effects in subjects with walking speeds faster than 1.2m/s at baseline[149].

**Testing and Variables of Interest**

The testing procedures have been previously described[64,93,98,120,149]. Briefly, participants underwent clinical and motion analysis evaluations pretraining, posttraining, and at a 3-month follow-up under the supervision of licensed physical therapists blinded to treatment group. The 6-meter walk test[90] and the 6-Minute Walk Test (6MWT)[42] characterized short- and long-distance walking ability, respectively. Peak paretic limb propulsive force during late stance phase (paretic propulsion) and peak paretic trailing limb angle (TLA) served as this study's biomechanical measures of interest. Paretic propulsion was measured during the double support phase of the paretic gait cycle as the maximum anterior ground reaction force, and was subsequently normalized to body weight. Peak paretic TLA was measured as the maximum sagittal plane angle during double support between the motion lab's vertical axis and a vector joining the lateral malleolus and greater trochanter. Biomechanical data were collected as participants walked on a dual-belt treadmill instrumented with two independent 6-degrees-of-freedom force platforms (Bertec Corporation, Worthington, OH) at each their comfortable walking speeds and maximal walking speeds. Biomechanical data from the first 15 strides of recorded walking were averaged using a custom-written program (National Instruments, Austin, TX, USA) and used in the analyses performed. Specifically, comfortable speed biomechanics were used in our analyses of changes in comfortable walking speed, and, because participants were directed to walk as fast as they safely could during the 6MWT, maximal speed biomechanics were used in our analyses of changes in 6MWT distance.

**Training**

Participants (n = 23) completed 12 weeks of maximal speed treadmill training. All participants trained at the maximal speed they could maintain on a treadmill for four minutes. Training occurred at a frequency of 3 sessions per week, for a total of 36 sessions. Within each session, participants completed 5 treadmill walking bouts of 6 minutes each followed by 1 bout of overground walking, for a total of 36 minutes of walking per session. During the 5 treadmill walking bouts, a subgroup (n = 12) received functional electrical stimulation (FES) to the paretic dorsiflexors during swing phase and plantarflexors during late stance phase in an alternating pattern of 1 minute on to 1 minute off (FastFES). This subgroup thus received an equivalent dose of walking practice as those undergoing just maximal-speed treadmill training (Fast), with 15 of the total 36 minutes of walking practice per session assisted by FES. Stimulation was triggered by compression-closing foot switches attached to the heel and toe of the paretic limb's shoe. See previous work from our laboratory for greater detail regarding the customized FES system used and FastFES training[64,77,93,98,124–126]. Subjects were allowed rest breaks between bouts as necessary.

**Statistical Analyses**

Independent t-tests were used to determine if differences between groups were present at baseline in the measures of interest and to test for between-group differences at posttraining and the 3-month follow-up. Paired t-tests (1-tail) tested for within-group improvements at the pretraining, posttraining, and the 3-month follow-up timepoints. Moderated regression[127,128] was used to test our hypothesis that the mechanisms underlying functional recovery would be different between groups. Specifically, to test whether the contribution of changes in propulsion to functional recovery differed between groups, the interaction term *TxGroup*Change in Propulsion* was tested in regression models predicting pre-to-posttraining and pre-to-3-month follow-up changes in each comfortable walking speed (CWS) and the distance walked during the 6MWT. Based on our prediction that for the Fast group the changes in trailing limb angle would be the primary driver of changes in propulsion and thus changes in walking function, we further tested the 3-way interaction *TxGroup*Changes in Propulsion*Changes in Trailing Limb Angle* in each of the models of interest. This 3-way moderated regression analysis was designed to reveal how changes in trailing limb angle moderated the contribution of changes in propulsion to changes in walking function in each group.

As previously stated, we hypothesized that relative to FastFES, Fast-induced changes in paretic propulsion would be largely dependent on changes in trailing limb angle. Thus, moderated regression was used to directly test whether paretic propulsion was changed via the same mechanisms in each group. Specifically, the interaction terms *TxGroup*Changes in Comfortable-Speed Trailing Limb Angle* and *TxGroup*Changes in Maximal-Speed Trailing Limb Angle* were respectively tested in models predicting changes in comfortable-speed paretic propulsion and maximal-speed paretic propulsion. Baseline paretic propulsion and trailing limb angle were controlled for in these models. All analyses were performed using SPSS version 22. Centered variables were used to reduce multicollinearity. Residuals were screened for the presence of outliers, who were subsequently removed. Alpha was set to 0.05.

## Results

Complete data sets were available for all subjects included in this study. The analyses presented reflect the data collected for 11 Fast participants and 12 FastFES participants. No differences were present between groups at baseline (all *Ps* > 0.05) with the average (n = 23) pretraining 6MWT distance being 252±112m, CWS being 0.63±0.28m/s, paretic propulsion (PROP) at self-selected speeds being 6.32±4.78%BW, TLA at self-selected speeds being 10.93±12.18º, PROP at maximum speeds being 8.20±5.75%BW, and TLA at maximum speeds being 13.60±7.79º. Assumptions for the moderated regression analyses were met following the removal of outliers. Specifically, 2 outliers were removed from the pretraining to posttraining CWS regression analysis (both FastFES participants), 1 outlier was removed from the pretraining to 3-month follow-up CWS regression analysis (a Fast participant), and 2 outliers were removed from the pretraining to 3-month follow-up PROP at maximum walking speed regression analysis (both FastFES participants).

## Treatment Effects: Magnitude of Changes

Both the FastFES and Fast treatment groups produced substantial gains in the 6MWT and CWS that were retained at the 3-month follow-up; however, no between-group differences were observed (see Figure 6). Interestingly, after 12 weeks of training, the Fast group did not achieve significant gains in either comfortable-speed paretic propulsion or trailing limb angle, whereas the FastFES group did (see Figure 7A and 7C). However, by the 3-month follow-up, changes in these measures reached significance in both groups. Surprisingly, neither group's posttraining changes in maximum-speed paretic propulsion achieved significance; however, by the 3-month follow-up, the Fast group had achieved significance (see Figure 7B). In contrast, both groups achieved significant posttraining and 3-month follow-up gains in maximum-speed paretic trailing limb angle (see Figure 7D).

## Treatment Effects: Mechanisms Underlying Functional Recovery

Despite observing no differences between groups in the collected measures of walking function or biomechanics, the mechanisms underlying the recovery of walking speed differed between groups as an interaction between changes in TLA, changes in propulsion, and treatment group was observed in the CWS regression analyses (see Table 12, models 1 and 2). The posttraining CWS model accounted for a remarkable 91% of the variance in changes in CWS after the 12 weeks of training, whereas the 3-month follow-up CWS model accounted for 66% of the variance in changes in CWS after this no-intervention 3-month period. A similar 3-way interaction was not observed for the 6MWT.

Specifically, changes in the paretic TLA moderated the contribution of changes in propulsion to changes in walking speed differently between groups (see Figure 8). In the Fast group, regardless of the magnitude of the change in the paretic TLA, posttraining changes in propulsion remained weakly positively related to changes in walking speed. At the 3-month follow-up, in Fast subjects with small changes in TLA, changes in propulsion even became weakly negatively related to changes in walking speed. In contrast, in the FastFES group, the smaller the posttraining change in TLA, the stronger was the relationship between changes in propulsion and changes in walking speed. This effect was enhanced at the 3-month follow-up as the largest gains in comfortable walking speed were observed in FastFES participants with large (ie, one SD above the mean) changes in propulsion and small (ie, one SD below the mean) changes in TLA (see Figure 8D).

**Treatment Effects: Mechanisms Underlying The Recovery Of Propulsion**

After 12 weeks of training, the mechanisms underlying improvements in paretic propulsion also differed between groups. Specifically, immediately posttraining the changes in the paretic TLA impacted changes in paretic propulsion more strongly following Fast than FastFES training (see Table 12, model 3 and Figure 9). Interestingly, despite a similar pattern, the between-group difference did not remain significant at the 3-month follow-up (see Table 12, model 4 and Figure 9).

## Discussion

The major finding of this study is that despite the addition of FES to maximum-speed treadmill training not producing larger improvements in walking function following training, it did alter the biomechanical mechanisms underlying the recovery of walking function. Specifically, improvements in comfortable walking speed following FastFES training were highly related to gains in paretic propulsion, with the largest gains in comfortable walking speed occurring in those subjects with the smallest gains in the paretic trailing limb angle. In contrast, improvements in comfortable walking speed following Fast training were only very weakly related to gains in paretic propulsion with changes in trailing limb angle having little effect on this relationship. Taken together with our previous work demonstrating similar mechanistic differences when comparing FastFES training with comfortable-speed treadmill training (unpublished observations, paper in review[149]), the unique contribution of training with paretic ankle FES is the recovery of walking ability via the restoration of the paretic limb's ability to generate forward propulsion.

Our observation of no differences between groups in the magnitude of recovery is consistent with the findings of a recent systematic review studying whether the therapeutic effects of training with FES were specific to FES intervention or merely a product of the general training provided (ie, overground walking, treadmill training, gait trainer, etc.)[145]. Specifically, when evaluating the therapeutic effects of FES training relative to control training without FES, the authors concluded that "no definite conclusions can be drawn regarding the unique superiority of FES". However, the present study extends previous work by demonstrating differences in the mechanisms underlying the recovery of walking following FES-assisted locomotor training versus training without FES, with FES-assisted training producing functional changes due to the restoration of more physiologic walking patterns. This finding is consistent with recent work by Daly et al that demonstrated comparable gains in walking function following body-weight supported treadmill training (BWSTT) and FES-assisted BWSTT, but also demonstrated that more of the participants who trained with FES achieved improvements in gait coordination, the specific target of their application of FES[137]. A likely explanation for why differences in *how* walking was recovered, but not differences in the *magnitude* of walking recovery, were observed in the present study is that our measures of walking recovery – speed and distance – while common, do not offer the resolution necessary to detect differences in the mechanisms underlying walking recovery[36]. Measures of gait efficiency, community walking activity, or even health-related quality of life, had they been included in this investigation, may have better reflected the impact on the lives of stroke survivors of improving comfortable walking speed via more physiologic mechanisms.

The importance of *how* poststroke walking function is changed is a critical discussion presently active in the field of poststroke locomotor rehabilitation[150]. Previous work from our laboratory supports the perception that *how* walking is changed matters. Specifically, we demonstrated that after gait intervention, faster and more symmetrical walking led to a larger reduction in the energy cost of poststroke walking than simply faster walking[101]. Considering that walking energetics are thought to play an important role in determining community walking participation, training with FES does appear to be a worthwhile adjunct to locomotor training after stroke[94]. Further study of how FES-assisted training influences the energy cost of walking and community-based measures of walking activity is warranted.

Interestingly, we did not observe a between-group difference in the mechanisms underlying the recovery of long-distance walking function as measured by the 6MWT. However, it is important to note that we have previously shown that across treatment groups, improvements in paretic propulsion contribute to farther distances walked with this relationship increasing in strength in those more impaired at baseline[120]. Our failure to demonstrate differences between groups in the present study may thus be explained by our small sample size. Similarly, another likely reason for our inability to demonstrate a group-specific effect in the mechanisms underlying gains in the 6MWT, as compared to a measure of short-distance walking function such as the 6-meter walk test, is that domains beyond walking mechanics play a larger role in determining 6MWT performance, making any effect that may be due to differences in how walking mechanics were changed within each group inherently harder to detect. Indeed, as a test designed to reflect an individual's ability to maintain a moderate level of exertion over a period of time similar to the activities of daily living, factors such as motivation and self-efficacy play a larger role in 6MWT performance than they would in a test of short-distance walking. Another possible explanation is that individuals in the chronic phase of stroke recovery may adopt a less physiologic walking pattern when asked to cover as much distance as possible during a timed walk test than when asked to walk at a comfortable pace over a short distance. That is, having the capacity to increase walking speed with better forward propulsion may not directly translate into using this strategy to increase walking speed in the context of the 6MWT. A better understanding of how persons poststroke manipulate their walking patterns and speeds in response to different environmental contexts would be an interesting area for future study.

Another interesting finding is that both treatment groups produced comparable gains in paretic propulsion. However, consistent with our theoretical framework, the addition of paretic ankle FES to maximal-speed treadmill training appears to shift the mechanisms underlying improved paretic propulsion, and ultimately improved walking speed, from a kinematic-based strategy to a kinetic-based strategy. Indeed, in the Fast group, changes in paretic propulsion were primarily driven by changes in the paretic trailing limb angle, whereas FastFES-induced changes in paretic propulsion were largely unrelated to changes in the paretic trailing limb angle (see Figure 9). Although we did not directly measure changes in the function of the plantarflexors for this study, previous work from our laboratory supports the notion that FastFES training produces meaningful changes in plantarflexor function that are associated with improved walking mechanics, such as improved forward acceleration of the center of mass and increased knee flexion acceleration during swing phase[113]. Thus, changes in paretic propulsion following FastFES training were likely primarily due to changes in the force-generating ability of the plantarflexors, which were directly targeted by the FES[64,113]. Because changes in propulsion following Fast training were only weakly related to changes in walking speed, whereas changes in propulsion following FastFES training were strongly related to changes in walking speed (see Figure 8), a kinetic-based strategy to improving propulsion appears to be preferable to a kinematic-based strategy.

Future study of the particular mechanisms that make FES an effective adjunct to locomotor intervention is warranted, and if exploited, could improve the therapeutic effects of FES. Indeed, FastFES subjects received only ~15 minutes of FES per training session. While the dosage threshold necessary to induce neuromotor changes in participants' walking strategy may have been met, perhaps this effect was not leveraged enough to induce a larger magnitude of recovery. Indeed, it is possible that subjects would have benefited from an FES system for home-use in addition to training with FES in the clinic. The orthotic effects of a home unit may have further reinforced the new walking strategy learned during training, potentially enhancing the therapeutic effects of the clinic-based training with FES. Moreover, it is unknown if the benefits of FES are derived from its production of *motor* responses of correct timing and amplitude during walking, or if *sensory*-level stimulation to cue correct timing is sufficient. Additionally, varying the method of FES integration into walking programs may modify its effects. Indeed, although FES was applied in an alternating pattern of 1 minute on to 1 minute off in this study, perhaps longer periods of "on" time would have promoted greater adaptation and thus improved performance during training periods without FES.

In contrast, perhaps longer “off” durations would have promoted increased learning and encouraged better volitional activation carryover. Such future work is necessary to elucidate the optimal method for FES application during poststroke gait rehabilitation.

**Conclusions**

The present study extends previous work by our laboratory that demonstrated the efficacy of FastFES locomotor training in individuals with maximum walking speeds slower than 1.2 m/s (unpublished observations, paper in review[149]) by showing a unique contribution of functional electrical stimulation to the outcomes observed. Specifically, despite not increasing the magnitude of walking recovery observed following maximal-speed training, the addition of paretic ankle functional electrical stimulation altered the mechanisms underlying the recovery of walking speed. Indeed, treadmill training with paretic ankle functional electrical stimulation yielded a recovery of walking speed that was substantially more related to changes in paretic propulsion than following locomotor training without functional electrical stimulation. Moreover, the recovery of paretic propulsion was largely independent of changes in the paretic trailing limb angle, and presumably more related to changes in the function of the paretic ankle plantarflexors, following training with versus without paretic ankle functional electrical stimulation. Finally, improving paretic propulsion via increased trailing limb angle appears to be less preferable to improving paretic propulsion via improved paretic ankle plantarflexor function, however this hypothesis should be directly tested in future studies.

**Table 12.** Participant baseline characteristics.

| Subject | Treatment Group | Sex | Age (y) | Time Since Stroke (y) | Side of Paresis |
|---|---|---|---|---|---|
| | | | | | |
| 1 | FastFES | Female | 65.39 | 22.90 | Left |
| 2 | FastFES | Male | 60.01 | 2.68 | Left |
| 3 | FastFES | Male | 55.68 | 0.73 | Left |
| 4 | FastFES | Male | 42.71 | 0.57 | Left |
| 5 | FastFES | Male | 67.91 | 0.77 | Left |
| 6 | FastFES | Male | 69.47 | 8.29 | Right |
| 7 | FastFES | Male | 54.94 | 1.66 | Left |
| 8 | FastFES | Female | 64.91 | 24.66 | Left |
| 9 | FastFES | Female | 63.25 | 3.02 | Right |
| 10 | FastFES | Male | 57.50 | 0.59 | Left |
| 11 | FastFES | Male | 68.69 | 2.86 | Left |
| 12 | FastFES | Male | 70.74 | 1.71 | Left |
| 13 | Fast | Female | 55.46 | 1.87 | Left |
| 14 | Fast | Male | 57.83 | 0.54 | Right |
| 15 | Fast | Female | 55.13 | 0.90 | Right |
| 16 | Fast | Female | 63.03 | 1.19 | Right |
| 17 | Fast | Male | 45.09 | 3.35 | Left |
| 18 | Fast | Female | 56.71 | 0.94 | Left |
| 19 | Fast | Female | 48.71 | 7.08 | Right |
| 20 | Fast | Male | 61.51 | 6.94 | Right |
| 21 | Fast | Female | 47.58 | 3.77 | Left |
| 22 | Fast | Male | 55.10 | 5.54 | Left |
| 23 | Fast | Female | 64.17 | 1.56 | Left |
| | | **%M** | **Medians (SIQR)** | | **%Right** |
| | | *57* | *57.8(4.7)* | *1.9(1.9)* | *30* |

SIQR – semi-interquartile range

**Table 13.** Moderated regression models predicting pretraining-to-posttraining and pretraining-to-3-month follow-up changes in walking speed and paretic propulsion.

| Models | | | Predictor Statistics | | | | | |
|---|---|---|---|---|---|---|---|---|
| **#** | **DV** | **Stats** | **Predictors** | ***ΔR²*** | ***ΔR² p*** | ***b*** | **B** | ***p*** |
| **1** | **PP ΔCWS** | ***R²***<br>.906<br>***F(df)***<br>17.93<br>(7, 13)<br>***P***<br>.000 | ΔPropPP* | .802 | .000 | 1.832 | .494 | .003 |
| | | | ΔTLAPP* | | | .009 | .375 | .059 |
| | | | Group$^{\%}$ | .006 | .240 | .015 | .054 | .325 |
| | | | Group × ΔPropPP$^{\wedge}$ | .071 | .042 | 3.444 | .394 | .002 |
| | | | Group × ΔTLAPP$^{\wedge}$ | | | -.014 | -.448 | .033 |
| | | | ΔPropPP × ΔTLAPP$^{\wedge}$ | | | .080 | .158 | .119 |
| | | | Group × ΔPropPP × ΔTLAPP$^{\#}$ | .027 | .037 | -.436 | -.282 | .037 |
| **2** | **PF ΔCWS** | ***R²***<br>.659<br>***F(df)***<br>3.861<br>(7, 14)<br>***P***<br>.008 | ΔPropPF* | .375 | .006 | 1.395 | .255 | .164 |
| | | | ΔTLAPF* | | | -.001 | -.037 | .455 |
| | | | Group$^{\%}$ | .021 | .219 | .067 | .237 | .133 |
| | | | Group × ΔPropPF$^{\wedge}$ | .056 | .339 | 4.579 | .456 | .054 |
| | | | Group × ΔTLAPF$^{\wedge}$ | | | -.002 | -.039 | .454 |
| | | | ΔPropPP × ΔTLAPF$^{\wedge}$ | | | .556 | .469 | .020 |
| | | | Group × ΔPropPF × ΔTLAPF$^{\#}$ | .206 | .006 | -1.992 | -.624 | .006 |
| **3** | **PP ΔPROP** | ***R²***<br>.713<br>***F(df)***<br>8.45<br>(5,17)<br>***P***<br>.000 | Group* | .119 | .241 | -.021 | -.340 | .012 |
| | | | PropPre* | | | -.149 | -.199 | .163 |
| | | | TLAPre* | | | .003 | .647 | .003 |
| | | | ΔTLAPP$^{\%}$ | .469 | .000 | .008 | 1.173 | .000 |
| | | | Group × ΔTLAPP$^{\wedge}$ | .125 | .008 | -.005 | -.568 | .008 |
| **4** | **PF ΔPROP** | ***R²***<br>.535<br>***F(df)***<br>3.92<br>(5,17)<br>***P***<br>.008 | Group* | .081 | .325 | -.010 | -.189 | .139 |
| | | | PropPre* | | | -.196 | -.358 | .087 |
| | | | TLAPre* | | | .002 | .476 | .039 |
| | | | ΔTLAPF$^{\%}$ | .425 | .000 | .006 | .891 | .001 |
| | | | Group × ΔTLAPF$^{\wedge}$ | .030 | .157 | -.003 | -.262 | .157 |

DV – dependent variable; Stats – statistics; df – degrees of freedom; PP – pre to post; PF – pre to followup; CWS – comfortable walking speed (m/s); Group – FastFES or Fast training; ΔProp – change in Paretic Propulsion (% body weight); ΔTLA – change in Trailing Limb Angle (deg). For each model, predictors were tested sequentially as part of blocks. Block designations are as follows: *block 1, $^{\%}$block 2, ^block 3, $^{\#}$block 4.

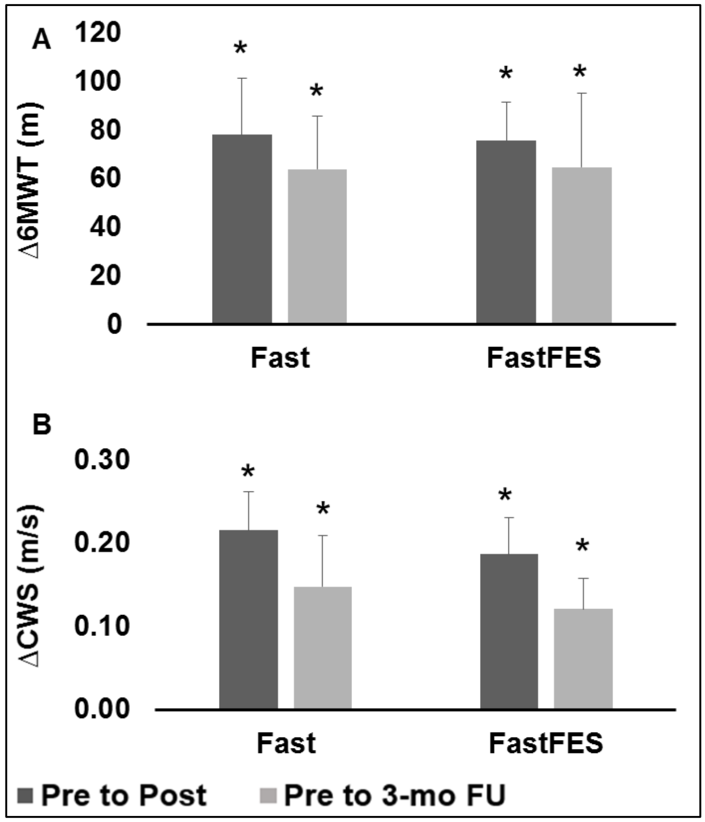


**Figure 6.** Pretraining to posttraining and pretraining to 3-month follow-up changes in the 6-Minute Walk Test (Δ6MWT, panel A) and comfortable walking speed (ΔCWS, panel B). Both groups achieved meaningful gains in these measures of walking function following training that were retained at the 3-month follow-up, however no between-group differences were observed.

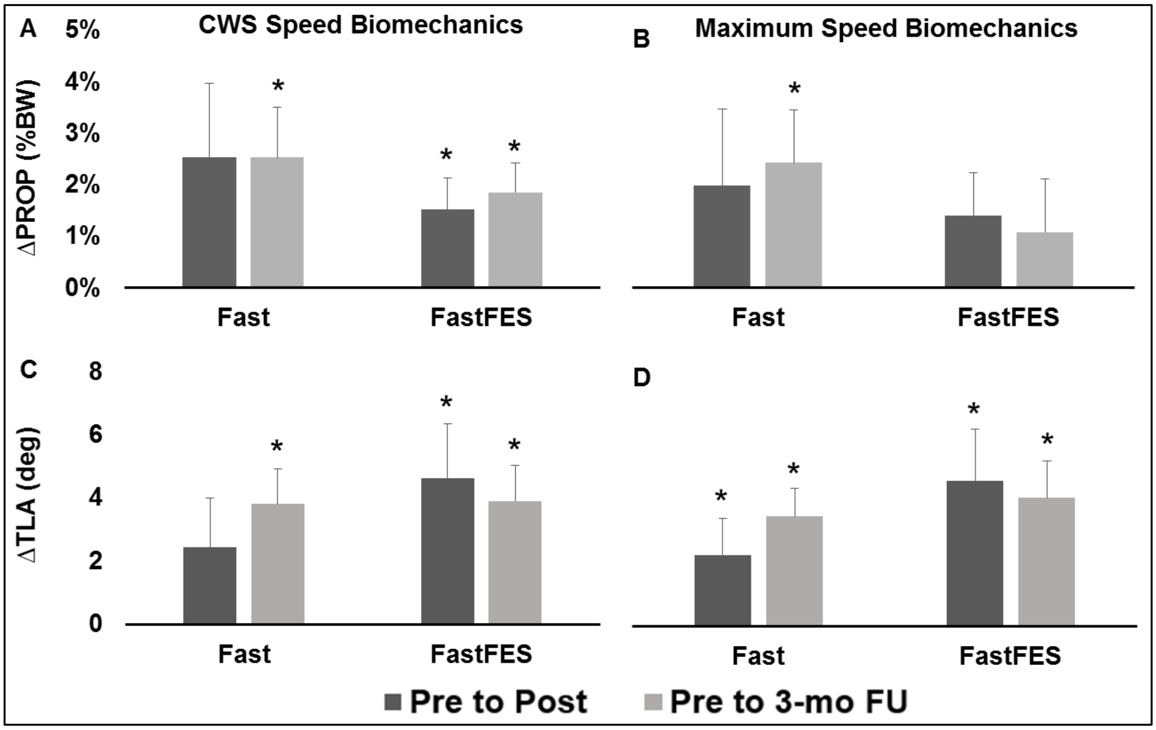


**Figure 7.** Pretraining to posttraining and pretraining to 3-month follow-up changes in comfortable-speed (panels A and C) and maximal-speed (panels B and D) paretic propulsion (ΔPROP) and trailing limb angle (ΔTLA) are presented for each training group. No between-group differences were observed and by the 3-month follow-up both treatment groups had produced comparable changes in each measure. The one exception was that the FastFES group did not achieve a significant improvement in maximum-speed propulsion (panel B), despite there being no difference between groups.

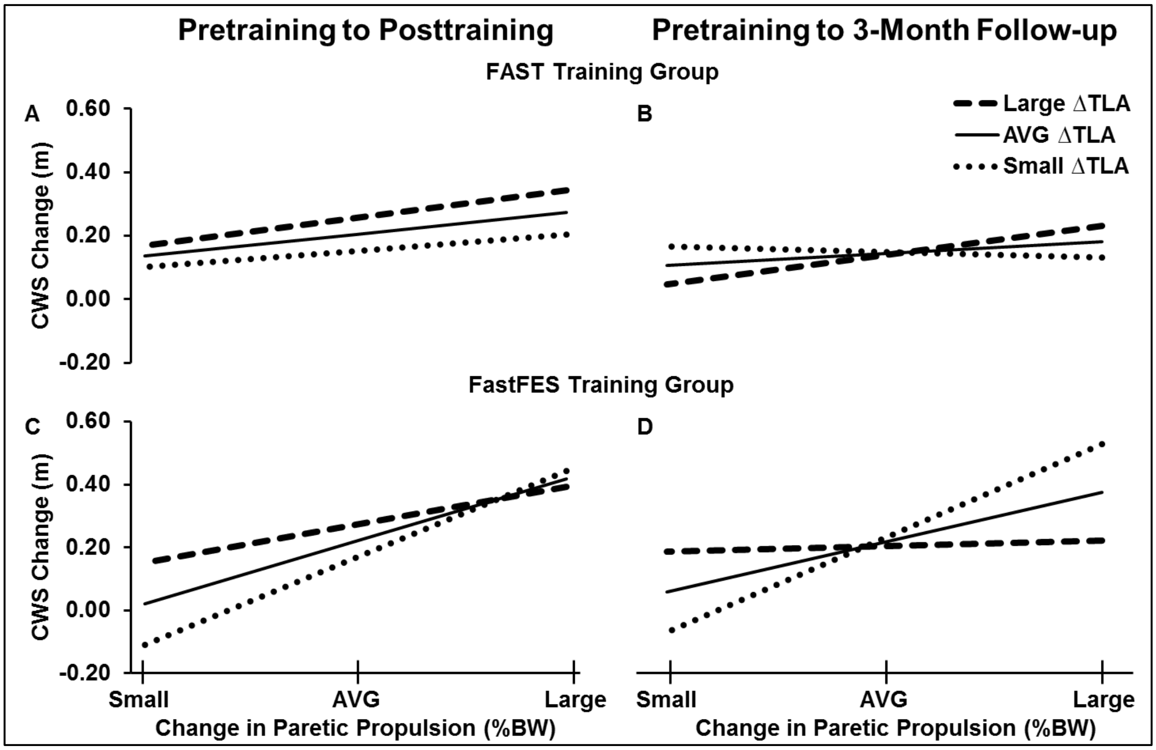


**Figure 8.** Visual presentation of the relationship between changes in paretic propulsion versus changes in comfortable walking speed for each treatment group (see panels A and B for Fast group and panels C and D for FastFES group) as moderated by changes in the paretic trailing limb angle. Changes from pretraining to posttraining (panels A and C) and pretraining to 3-month follow-up (panels B and D) are presented. The relationship between changes in propulsion and changes in comfortable walking speed remained relatively weak for the Fast group regardless of the change in trailing limb angle. In contrast, in the FastFES group, the impact of changes in propulsion on changes in walking speed was markedly stronger in participants with a small (ie, one SD below the mean) change in trailing limb angle and markedly weaker in participants with a large (ie one SD above the mean) change in trailing limb angle.

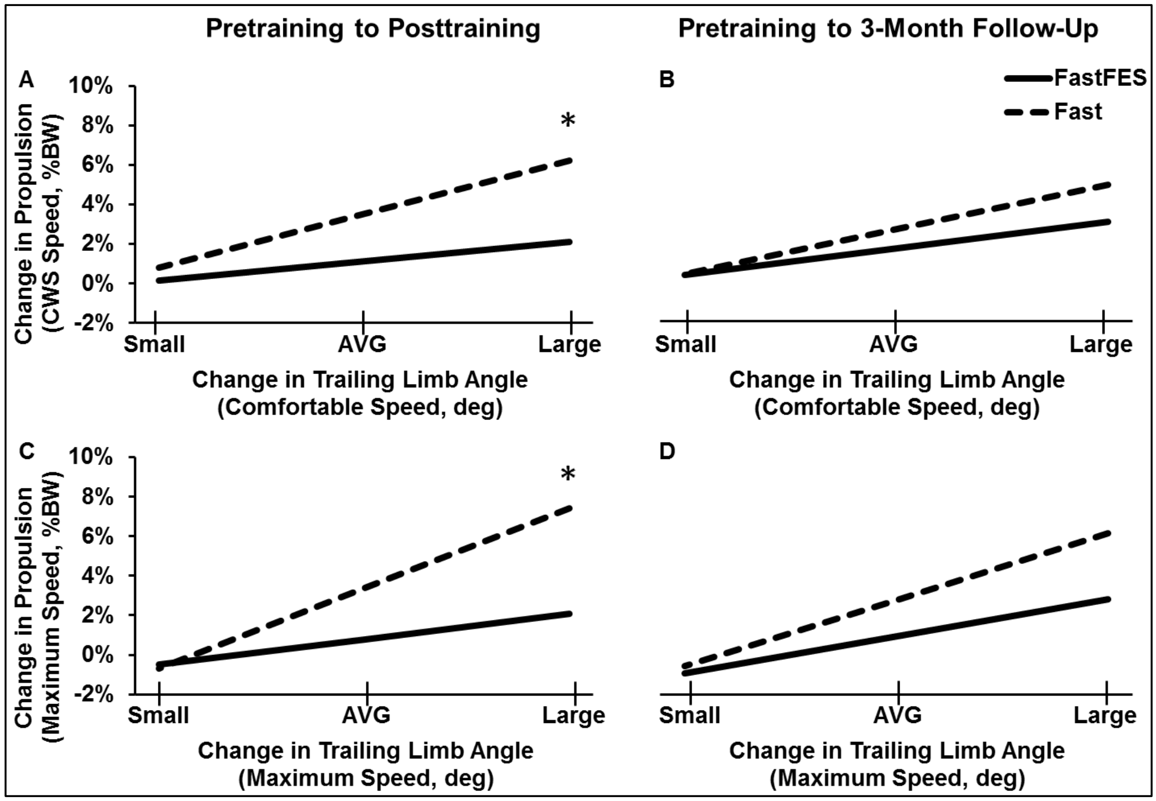


**Figure 9.** Visual presentation of the relationship between changes in trailing limb angle versus changes in paretic propulsion as moderated by treatment group assignment. Both comfortable-speed biomechanics (panels A and B) and maximal-speed biomechanics are presented (panels C and D). Also, both pretraining to posttraining (panels A and C) and pretraining to 3-month follow-up (panels B and D) relationships are presented. The contribution of changes in trailing limb angle to changes in paretic propulsion was markedly stronger in participants undergoing maximal-speed training (Fast) than in participants undergoing maximal-speed training combined with paretic ankle functional electrical stimulation (FastFES). *CWS moderated regression findings:* pretraining-to-posttraining $R^2 = 0.713$, $F(5,17) = 8.45$, $p = 0.000$ and pretraining-to-3-month follow-up $R^2 = 0.535$, $F(5,17) = 3.92$, $p = 0.008$. *MWS moderated regression findings:* pretraining-to-posttraining $R^2 = 0.695$, $F(5,17) = 7.75$, $p = 0.001$ and pretraining-to-3-month follow-up $R^2 = 0.632$, $F(5,15) = 5.16$, $p = 0.006$. *indicates significant treatment Group*change in trailing limb angle interaction. See Table 12 for individual predictor statistics for the CWS models.

## Chapter 6

## PARTICIPANTS' BASELINE WALKING SPEED AND GAIT MECHANICS INTERACT TO INFLUENCE THE EFFECTS OF LOCOMOTOR TRAINING AFTER STROKE


### Abstract

***Background.*** The heterogeneous nature of poststroke motor impairments limits optimal intervention as the effectiveness of treatments may vary as a function of participants' particular abilities. The objective of this study was to determine how participants' baseline walking speed and gait mechanics influence the efficacy of a targeted locomotor training program. ***Methods.*** 27 subjects >6 months poststroke underwent a 12-week treadmill training program combining maximum-speed walking with paretic ankle functional electrical stimulation (FastFES). Improvements in comfortable walking speed (CWS) measured functional recovery. Baseline walking speed, paretic propulsion (propulsion), and trailing limb angle (TLA) were selected as potential moderators of functional recovery due to their importance in the FastFES framework. Moderation of posttraining and 3-month follow-up outcomes were investigated. ***Results.*** FastFES produced CWS gains that were retained at the 3-month follow-up. Only participants' baseline walking speed correlated with both posttraining and 3-month follow-up CWS gains ($R^2$s=0.12 and 0.22, respectively). However, a baseline speed × propulsion interaction was observed posttraining (moderation $R^2$=0.68) and at the 3-month follow-up (moderation $R^2$=0.56) such that for those with below average baseline walking speed, larger baseline propulsion predicted larger CWS gains. In contrast, for those with above average baseline walking speeds, baseline propulsion was unrelated to CWS gains posttraining and negatively related to CWS gains at the 3-month follow-up. ***Conclusions.*** The present findings demonstrate the value of investigating the interactions among

participants' baseline characteristics when predicting the efficacy of locomotor training after stroke.

## Introduction

Stroke is a leading cause of long-term disability[20], with the restoration of walking ability being the most commonly voiced goal of rehabilitation by stroke survivors[1]. Many factors contribute to the limitations of current interventions[9]. One major factor is the heterogeneity of poststroke motor impairments. Indeed, the effectiveness of particular interventions may vary across individuals as a function of their baseline abilities. As such, intervention studies that report outcomes across individuals with a wide range of abilities and impairments may not accurately estimate the effects of an intervention for a particular individual. A better understanding of how participants' baseline abilities influence the effects of poststroke locomotor interventions would both facilitate optimal intervention design and advance individualized, evidence-based rehabilitation efforts in this complex population.

Previous investigators have attempted to address this problem by reporting results across subgroups of participants, with walking speed serving as a common stratification criteria[149,151–154]. Indeed, walking speed has been named the 6$^{th}$ vital sign[38] for its robust measurement and prediction of walking performance[61], community walking capacity[24], rehabilitation potential[155], and quality of life[156]. However, across individuals poststroke, different motor impairments may underlie the same walking speed[2,39] and changes in walking speed may occur via a variety of biomechanical mechanisms, including the restoration of symmetrical gait mechanics or improved compensatory strategies[2,31,32,48]. As such, it is not clear if baseline walking speed alone is a sufficient predictor of posttraining outcomes as baseline walking speed may interact with baseline gait mechanics to differentially influence the effects of locomotor training.

Many biomechanical variables could serve as moderators of posttraining outcomes and ultimately interact with walking speed to further influence the effects of locomotor training; however, the most likely moderators of an intervention's effects may depend on the particular intervention studied. For example, baseline self-efficacy may be a key moderator of posttraining outcomes for an intervention designed to improve walking ability by improving participants' balance self-efficacy. The present investigation studies, as a model, a biomechanics-targeting intervention shown to improve poststroke walking ability through specific effects on the paretic limb's ability to generate propulsion[64,149]. The intervention studied combines maximal-speed treadmill walking with functional electrical stimulation to the paretic ankle musculature (FastFES) to target deficits in paretic propulsion by synergistically facilitating better posterior positioning of the paretic trailing limb relative to the body's center of mass and better function of the paretic plantarflexors during late stance phase[64]. Based on this framework, it is conceivable that both baseline paretic trailing limb angle and propulsion could moderate the effects of FastFES intervention. Indeed, prior work from our laboratory has shown that these particular biomechanical variables positively relate to the changes in comfortable walking speed observed following FastFES training[64]. Moreover, recent work has shown that the effects of FastFES training are attenuated in individuals with baseline maximum walking speeds faster than 1.2m/s (unpublished observations, paper in review[149]). Based on this prior work, we hypothesized an interaction between participants' baseline walking speed and gait mechanics such that the largest posttraining gains in walking speed would be observed in slower walkers with above average biomechanical function.

## Methods

The data analyzed for this study come from a larger clinical investigation conducted at the University of Delaware studying treadmill-based locomotor training in persons poststroke. The twenty-seven individuals included in the present study were all those that underwent targeted locomotor training (ie, FastFES). Participants were at least 6 months post a single cortical or subcortical stroke, had observable gait deficits but were able to walk for six minutes without the assistance of another individual or orthotic support, had sufficient passive ankle dorsiflexion range of motion to dorsiflex the ankle to neutral with the knee extended, had at least 10 degrees of passive hip extension range of motion, and were able to communicate with investigators and follow instructions. Cerebellar stroke, any condition other than stroke that limited walking ability, neglect or hemianopia, or unexplained dizziness during the prior 6 months each served as exclusion criteria. The University of Delaware's institutional review board approved the protocol executed for this study. Medical clearance and a submaximal stress test were required prior to the start of training.

### Testing

The study's clinical and biomechanical testing procedures and variables of interest have been previously described[64,93,98,120,149]. Briefly, data were collected from clinical and motion analysis evaluations pretraining, posttraining, and at a 3-month follow-up. The 6-meter walk test[90] was used to characterize participants' short-distance walking function. From the 6-meter walk test, participants' self-selected, comfortable walking speeds (CWS) and maximum walking speeds (MWS) were determined. Participants' peak paretic limb propulsive force (propulsion) and trailing limb angle (TLA) – both generated after the paretic limb's midstance – served to measure the paretic limb's biomechanical function during walking. Biomechanical data were collected as participants walked on a dual-belt treadmill instrumented with two independent 6-degrees-of-freedom force platforms (Bertec Corporation, Worthington, OH) at their comfortable walking speeds. For each subject and at each timepoint, fifteen strides of recorded walking were averaged for each biomechanical variable using a custom-written computer program (National Instruments, Austin, TX, USA).

**Training**

Participants completed 12 weeks of FastFES training. Functional electrical stimulation was delivered to the paretic plantarflexors during late stance phase and dorsiflexors during swing phase in an alternating pattern of 1 minute on to 1 minute off (FastFES). See previous work from our laboratory for greater detail regarding the customized FES system used and FastFES training[64,77,93,98,124–126]. Each participant's training speed was set to the fastest speed they could maintain for four minutes while walking on a treadmill. Training took place over 12 weeks for a total of 36 sessions, with each session comprised of 5 treadmill walking bouts of 6 minutes each followed by 1 bout of overground walking. Subjects were allowed rest breaks between bouts as necessary.

**Analyses**

All analyses were performed using SPSS version 22. Paired t-tests were used to test for improvements in comfortable walking speed from pretraining to posttraining and pretraining to the 3-month follow-up. The bivariate relationships between baseline walking speed, propulsion, TLA, and changes in CWS were assessed. Moderated regression[101,120,127,128] subsequently tested interactions among the baseline variables. Moderation of both the posttraining and 3-month follow-up changes in CWS was tested.

Included in these two regression models were the main effects of baseline maximum walking speed (MWS), propulsion, TLA, and all two-way interactions among these variables. The 3-way interaction between these three baseline variables was also tested but was not significant, and was therefore not included in the final models. Due to issues with multicollinearity in the model, only the baseline propulsion × baseline TLA and baseline propulsion × baseline MWS interactions were included in the final models. It should be noted that both baseline CWS and MWS were initially considered, but due to the high correlation between these two variables, including both in the model caused multicollinearity. As such, only MWS was included due to our prior work demonstrating the importance of MWS in determining both short and long-distance walking function after stroke[149,157]. Centered variables were used to reduce multicollinearity. Residuals were screened for the presence of outliers, who were subsequently removed. Alpha was set to 0.05.

## Results

Complete data sets were available for only 24 of the 27 participants (see Table 13); biomechanical data for 3 subjects were not available due to technical issues during data collection. The average baseline CWS was 0.65±0.31m/s, MWS was 0.84±0.39m/s, propulsion was 5.40±4.90%BW, and trailing limb angle was 11.39±7.14º. One outlier was removed from the posttraining moderated regression model and another outlier was removed from the 3-month follow-up model based on the screening of residuals.

**Moderation Of Posttraining Changes**

Significant gains in CWS followed FastFES training and were retained at the 3-month follow-up (see Figure 10). Changes in CWS were weakly correlated with participants' baseline MWS immediately after the 12 weeks of training ($R^2$=0.13) and the 3-month follow-up ($R^2$=0.22) (see Figure 11A and 11B). Additionally, 3-month follow-up changes in CWS were also weakly correlated with participants' baseline TLA ($R^2$=0.14) and propulsion ($R^2$=0.17) (see Figure 11D and 11F). A baseline propulsion × baseline MWS interaction was observed when predicting both posttraining and 3-month follow-up changes in CWS (see Table 14). The baseline propulsion × baseline TLA interaction was not significant in either model (see Table 14). These regression models explained substantially more of the variance in posttraining and 3-month follow-up changes in CWS ($R^2s$=0.68 and 0.56, respectively) than any of the baseline measures alone (see Figure 12).

It is important to note that both baseline propulsion and MWS were included in the moderated regression models as continuous variables. The average ± 1SD values reported here and in the figures were calculated for probing moderation effects as suggested by Aiken and West[103]. In those with a baseline MWS at least one standard deviation *below* the mean (ie, ≤ 0.45m/s), baseline propulsion was strongly *positively* related to the changes in CWS observed immediately after training. In those with an average baseline MWS (ie, 0.84m/s), baseline propulsion was moderately *positively* related to changes in CWS. Finally, in those with a baseline MWS at least one standard deviation *above* the mean (ie, ≥ 1.23m/s), baseline propulsion was unrelated to changes in CWS. The magnitude of the moderation present at the 3-month follow-up was reduced. Specifically, in those with a baseline MWS at least one standard deviation *below* the mean, baseline propulsion was moderately *positively* related to changes in

CWS. In those with an average baseline MWS, baseline propulsion was unrelated to changes in CWS. Finally, in those with a baseline MWS at least one standard deviation *above* the mean, baseline propulsion moderately *negatively* related to changes in CWS.

## Discussion

This investigation aimed to determine how participants' baseline abilities influenced the efficacy of a targeted locomotor program. Specifically, this study aimed to elucidate the influence of participants' baseline walking speed and gait mechanics, and the interactions among these variables, on the magnitude of functional recovery produced by a locomotor intervention that specifically targeted gait mechanics. To this end, the major contribution of this work is our demonstration of substantial increases in predictive power due to a better understanding of how these particular variables interacted to influence the recovery of walking speed after intervention. Moreover, to our knowledge, this is the first study to report an interaction between walking speed and gait mechanics when predicting the effects of poststroke locomotor training. These findings build on recent work calling for a quantification of the biomechanical deficits underlying walking function to guide clinical intervention[36,158]. Ultimately, this study suggests that future work studying how participants' baseline characteristics interact to influence the effects of locomotor intervention may be critical to the advancement of individualized, evidence-based rehabilitation efforts in this heterogeneous population.

Our finding of an interaction between baseline walking speed and gait mechanics when predicting the effects of FastFES intervention extends preliminary work from our laboratory that has investigated the best candidates for the FastFES program[64,149]. Indeed, prior work has shown that independently, baseline walking speed[19] and paretic propulsion[7] each influence the efficacy of FastFES training. In the present study, we demonstrate that the additional knowledge of the interaction between baseline maximum walking speed and baseline propulsion increases our power to predict the recovery of walking speed following intervention from ≤ 22% when considering either variable alone, to nearly 70%. Indeed, we demonstrate that FastFES' ability to improve walking speed is increased in those with slower baseline maximum walking speeds *and* larger baseline propulsion. Although this particular interaction may be specific to the effects of the FastFES intervention, a more general implication of this finding is that poststroke walking speed – despite being a common stratification variable[149,151,154,159,160] – may not provide sufficient information regarding an individual's suitability for a particular intervention. Indeed, the importance of knowing *both* a participant's baseline walking speed and propulsion is that knowing the baseline walking speed of a person in the chronic phase of stroke recovery does not reveal their baseline propulsion. Indeed, in this heterogeneous population it may not be appropriate to define two persons walking at the same baseline speed as having the same level of baseline ability if person A walks with low levels of propulsion while person B walks with moderate levels of propulsion. The additional knowledge of a person's baseline propulsion thus better defines their baseline level of function, and ultimately improves our ability to predict the efficacy of locomotor intervention. Future study of how other baseline characteristics interact to influence the efficacy of poststroke walking interventions would be a worthwhile direction for future research.

It is interesting to note that FastFES training was most effective in those with *larger* baseline propulsion. However, as an intervention specifically designed to target propulsion, it would have been conceivable to hypothesize that FastFES would be most effective in those with the *smaller* baseline propulsion. Nonetheless, it is important to note that, in this study, even those with the largest baseline propulsion were still markedly impaired in their ability to generate propulsion via the paretic limb as only one of the participants studied presented with baseline propulsion comparable to the average observed in neurologically-intact elderly subjects (20 %BW)[161]. One explanation for why FastFES training was not as effective in those with low levels of baseline propulsion is that FastFES training may not be sufficient to overcome certain pre-existing compensatory strategies that may be indicated by low levels of paretic propulsion at baseline. That is, for participants largely dependent on compensatory strategies known to impair the propulsive-force generating ability of the paretic limb[6,57,108,109], FastFES training may not provide a sufficient stimulus to alter this walking strategy, and ultimately improve walking function. Indeed, gains in walking function following FastFES training have been shown to be so strongly linked to gains in paretic propulsion that in those who don't change propulsion, no gains in walking function are observed (unpublished observations, paper in review[149]). Ultimately, our finding that FastFES training was more effective in participants with larger baseline propulsion may suggest that FastFES training is able to enhance an already present, but impaired, propulsion-based walking strategy, but may not be as appropriate for participants with low baseline propulsion due to their reliance on propulsion-impairing compensatory strategies. An alternative explanation is that participants with low baseline levels of paretic propulsion may simply not have the capacity to walk via propulsion due to insufficient neural substrate. For these individuals, any training centered on improving paretic propulsion (eg, FastFES) may not be appropriate. Preliminary (unpublished) work from our laboratory supports this hypothesis. Specifically, we have observed that across persons poststroke, the contribution of plantarflexor force to paretic propulsion during walking is moderated by participants' baseline corticomotor excitability. Indeed, in persons with less impaired corticomotor excitability, propulsion during walking was more likely to be related to plantarflexor force generation, and not due to compensatory mechanisms. Investigation of the interaction between neural correlates of poststroke walking recovery and gait mechanics would be an exciting direction for future research.

**Conclusions**

This report demonstrates the value of investigating how the baseline characteristics of individuals poststroke interact to influence the effects of particular interventions. Indeed, for a population as heterogeneous as those in the chronic phase of stroke recovery, a better understanding of such interactions may be critical for the advancement of individualized, evidenced-based rehabilitation. Moreover, this study suggests that the criteria used to predict the effects of an intervention may be suitably defined by the targets of the intervention. Indeed, for a biomechanics-targeting locomotor intervention such as the FastFES program, knowledge of how baseline walking biomechanics interacted with baseline walking speed substantially improved our ability to predict the recovery of walking speed.

**Table 14.** Participant baseline characteristics.

| Subject | Sex | Age (y) | Time Since Stroke (y) | Side of Paresis |
|---|---|---|---|---|
| | | | | |
| 1 | F | 65 | 22.90 | Left |
| 2 | M | 60 | 2.68 | Left |
| 3 | M | 56 | 0.73 | Left |
| 4 | M | 43 | 0.57 | Left |
| 5 | M | 68 | 0.77 | Left |
| 6 | M | 70 | 8.29 | Right |
| 7 | M | 55 | 1.66 | Left |
| 8 | F | 65 | 24.66 | Left |
| 9 | F | 63 | 3.02 | Right |
| 10 | M | 58 | 0.59 | Left |
| 11 | M | 69 | 2.86 | Left |
| 12 | M | 71 | 1.71 | Left |
| 13 | M | 64 | 7.99 | Right |
| 14 | F | 56 | 3.51 | Left |
| 15 | M | 25 | 1.70 | Left |
| 16 | M | 67 | 1.83 | Left |
| 17 | M | 51 | 9.25 | Left |
| 18 | M | 58 | 9.17 | Right |
| 19 | M | 71 | 5.83 | Right |
| 20 | M | 66 | 1.58 | Right |
| 21 | M | 70 | 1.75 | Left |
| 22 | F | 65 | 1.25 | Right |
| 23 | F | 65 | 1.5 | Right |
| 24 | F | 54 | 4.58 | Right |
| 25 | F | 58 | 1.00 | Right |
| 26 | M | 46 | 0.67 | Right |
| 27 | F | 70 | 0.75 | Left |
| | **%M** | **Medians (SIQR)** | | **%Right** |
| | *67* | *63.5(5.8)* | *1.8(2.0)* | *41* |

**Table 15.** Moderated regression models predicting posttraining and 3-month follow-up changes in comfortable walking speed.

| Models | | | Predictor Statistics | | | | | |
|---|---|---|---|---|---|---|---|---|
| **#** | **DV** | **Statistics** | **Predictors** | $\Delta R^2$ | $\Delta R^2$ *p* | *b* | **B** | *p* |
| | | $R^2$ | | | | | | |
| | | 0.68 | PropPre[#] | .262 | .050 | 2.775 | .868 | .006 |
| | **POST** | ***F(df)*** | MWSPre[#] | | | -.251 | -.644 | .011 |
| **1** | **ΔCWS** | 7.53 | TLAPre[#] | | | -.005 | -.228 | .215 |
| | **(m/s)** | (5, 18) | PropPre × TLAPre[%] | .414 | .000 | .001 | .002 | .498 |
| | | ***P*** | MWSPre × PropPre[%] | | | -5.807 | -.800 | .010 |
| | | 0.001 | | | | | | |
| | | $R^2$ | | | | | | |
| | | 0.56 | PropPre[#] | .257 | .054 | .936 | .348 | .171 |
| | **3-mo FU** | ***F(df)*** | MWSPre[#] | | | -.095 | -.290 | .174 |
| **2** | **ΔCWS** | 4.63 | TLAPre[#] | | | -.005 | -.254 | .219 |
| | **(m/s)** | (5, 18) | PropPre × TLAPre[%] | .305 | .004 | .021 | .073 | .428 |
| | | ***P*** | MWSPre × PropPre[%] | | | -4.548 | -.744 | .027 |
| | | 0.007 | | | | | | |

DV – dependent variable; CWS – comfortable walking speed (m/s); POST – posttraining; 3-mo FU – 3-month follow-up; PropPre – baseline paretic propulsion (% body weight); MWSPre – baseline maximum walking speed (m/s); TLAPre – baseline paretic trailing limb angle (deg). For each model, predictors were tested sequentially as part of blocks. Block designations are as follows: [#]block 1 and [%]block 2.

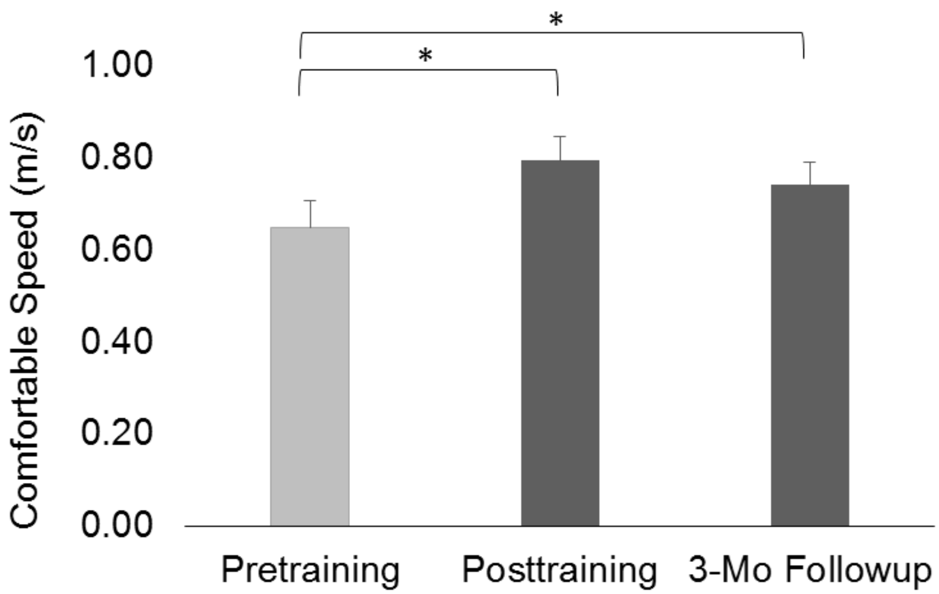


**Figure 10.** Changes in comfortable walking speed observed following 12 weeks of targeted locomotor training (Posttraining) and after a 3-month no-intervention period (3-Mo Follow-up). Both pretraining to posttraining and pretraining to 3-Mo Follow-up gains were observed. * $p < 0.05$.

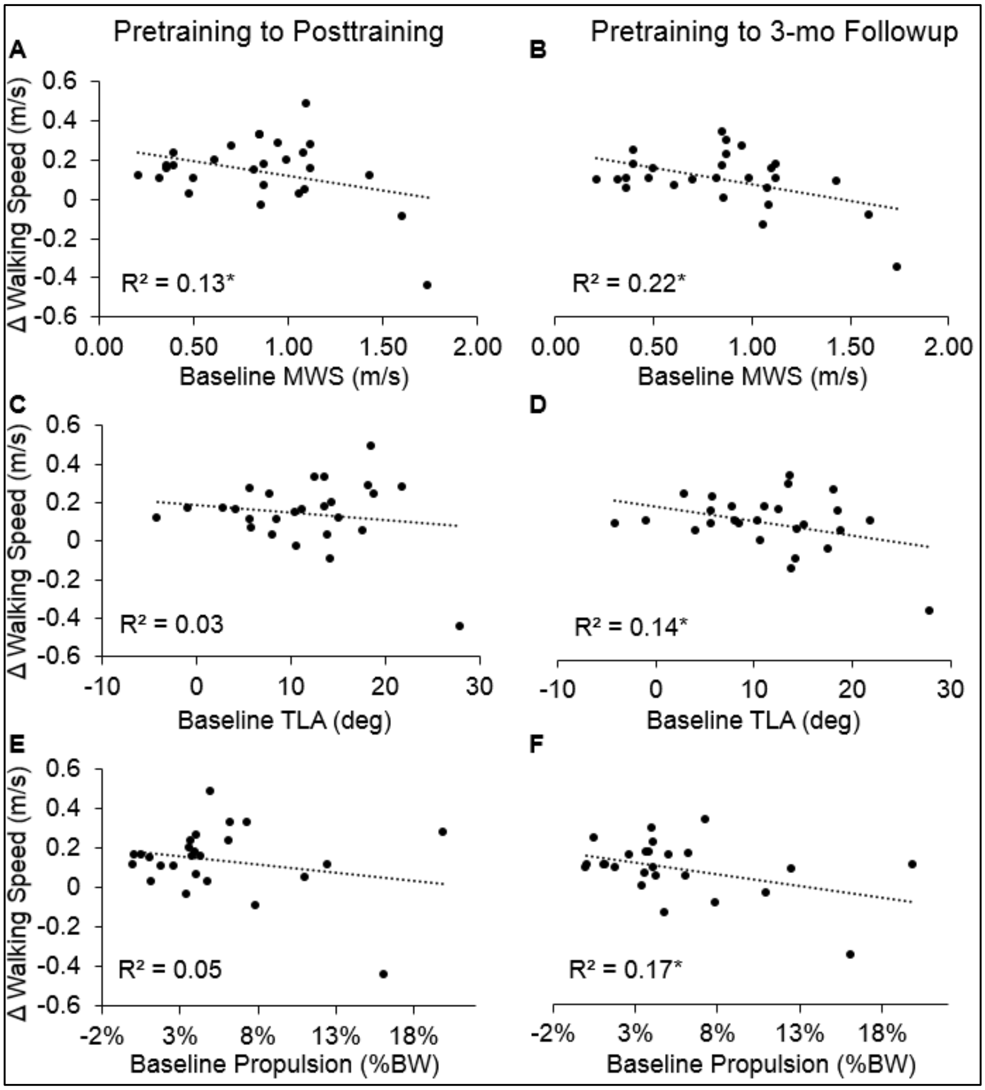


**Figure 11.** Bivariate correlations between baseline maximum walking speed (MWS), trailing limb angle (TLA), and paretic propulsion versus changes (Δ) in comfortable walking speed (y-axis). Pretraining to posttraining (panels A, C, and E) and pretraining to 3-month follow-up (panels B, D, and F) changes are presented. Only baseline MWS correlated to both posttraining and 3-month follow-up changes in comfortable walking speed. Baseline TLA and propulsion also correlated with 3-month follow-up changes in comfortable walking speed. However, all of these relationships were weak. * $p < 0.05$.

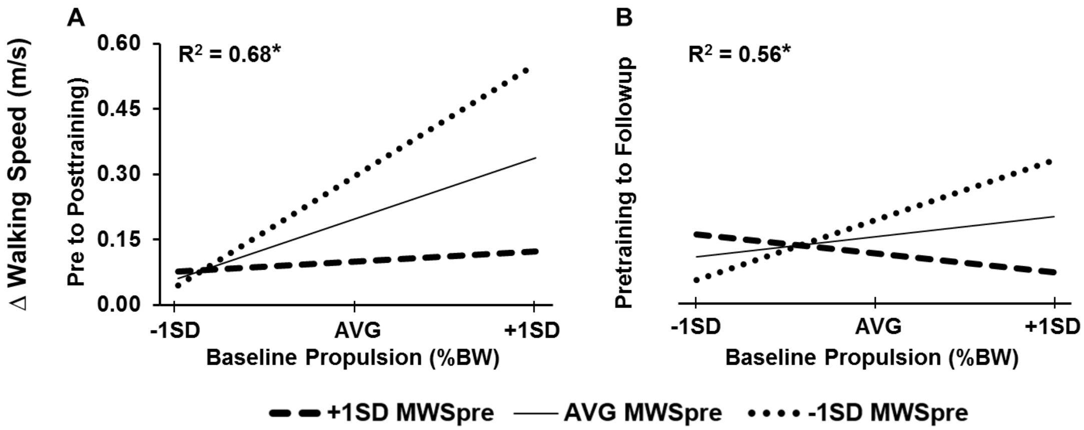


**Figure 12.** Visual presentation of how the interaction between baseline maximum walking speed (MWS) and paretic propulsion influenced the magnitude of functional recovery observed following targeted locomotor training. Both pretraining to posttraining (panel A) and pretraining to 3-month follow-up (panel B) changes in walking speed are presented. For the slowest participants, baseline propulsion was strongly positively predictive of posttraining changes in walking speed. For the fastest participants, baseline propulsion was not predictive of posttraining changes in walking speed and was negatively related to 3-month follow-up changes in walking speed. The simple slopes presented were calculated using the unstandardized regression coefficients (b) found in table 14 and the averages ± 1SD for each of the two baseline variables. * $p < 0.05$.

## Chapter 7

## CONCLUSION

Among the major contributions of this work are the identification of clinical and biomechanical determinants of poststroke walking performance that, when improved through intervention, contribute to improvements in the walking ability of persons in the chronic phase of stroke recovery. Specifically, in aim one of this dissertation, the *short-distance* maximum walking speed of persons poststroke was identified as a key mediator of the cross-sectional relationships existing between standing balance, walking balance, balance self-efficacy, and lower extremity motor function versus long-distance walking function as measured by the 6-Minute Walk Test (6MWT). Moreover, changes in *short-distance* maximum walking speed were shown to highly correlate with changes in *long-distance walking function.* The findings of aim one thus supported the investigation conducted in aim two, which delved into the level of gait biomechanics and demonstrated that the function of the paretic limb during late stance explained a substantial amount of the variance in long-distance walking function that was observed across persons poststroke. Indeed, if balance, and not speed, had been shown to be a critical mediator of walking ability in this population, it would have made little sense to investigate gait mechanics largely associated with walking speed in aim two, as the investigation of variables related to fall-risk (e.g. margins of stability, etc.) may have been preferable.

A critical finding from aim two was our demonstration that changes in paretic propulsion contributed to changes in long-distance walking function, with this relationship gaining strength in those participants presenting with larger deficits in forward propulsion and trailing limb angle at baseline. These findings thus extend the findings from aim 1, revealing that not only is improving maximum walking speed important, but the mechanics underlying those improvements matter. Indeed, relevant work that we recently conducted, but was not part of this dissertation, revealed a meaningful relationship between the biomechanical strategy used to walk faster after intervention and the energy burden of poststroke walking[101], supporting the notion that the mechanics underlying poststroke walking recovery are important to consider.

This dissertation culminated with a three-part clinical study testing the efficacy and mechanisms underlying the effects of a hypothesis-driven, targeted locomotor intervention designed to treat poststroke walking dysfunction through specific effects on the propulsive force-generating ability of the paretic limb during walking (FastFES). The major contribution of this work was providing evidence supporting the use of the FastFES intervention in persons in the chronic phase of stroke recovery. Specifically, it was demonstrated that the FastFES intervention improves the short- and long-distance walking function of persons poststroke through improvements in paretic propulsion – an effect not observed following control training at self-selected (SS) or maximal (Fast) walking speeds. The importance of this finding is that when the goal of rehabilitation is to improve walking ability via the restoration of a more physiologic walking pattern, the FastFES intervention is a clear winner. This remains true even given the interesting finding that the magnitude of recovery following FastFES training was similar to the magnitudes of recovery following Fast and SS training. Even so, a noteworthy finding was the demonstration that FastFES was markedly superior to conventional locomotor training at SS speeds when limiting the cohort studied to only those subjects with maximum walking speeds slower than 1.2 m/s – a subgrouping supported by *a priori* hypotheses related to the mechanisms underlying the effects of FastFES. Moreover, we observed an interaction between baseline maximum walking speed and paretic propulsion when predicting functional recovery following FastFES such that training was more effective in participants with larger baseline propulsion and slower baseline maximum walking speeds. These findings highlight the importance of considering the particular baseline abilities of participants when evaluating the effects of gait intervention in a population as heterogeneous as those poststroke.

This work supports the development and testing of interventions targeting poststroke walking speed and the function of the paretic limb during late stance, and ultimately demonstrated that FastFES training is a worthwhile intervention for persons poststroke. However, it is unknown how the FastFES intervention would fare against other interventions that target these key variables via other mechanisms. For example, if subjects were provided feedback of propulsion during maximum-speed training instead of functional electrical stimulation, perhaps a larger magnitude of recovery would have been observed as greater volitional activation of the plantarflexors may have resulted. Of course, with a new intervention strategy comes the question, *for whom is this particular intervention appropriate*? Such a direction for future clinical research would be worthwhile. This dissertation also supports future engineering and design research as developing the technology necessary to translate the FastFES intervention from the treadmill to overground is a critical prerequisite to providing FastFES gait retraining in more salient and challenging environments. Finally, this work also directs future neurophysiologic research. Indeed, considering the neuromotor recovery observed at the level of biomechanics following FastFES training, many interesting questions abound regarding how combining locomotor training with functional electrical stimulation influences the damaged brain and enhances the experience-dependent neuroplasticity critical to neurorehabilitation efforts after stroke. Moreover, a better understanding of the relationship between participants' corticomotor excitability and the biomechanical strategy used to walk after stroke would inform future rehabilitation efforts.

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## Appendix A
## USE OF PREVIOUSLY PUBLISHED WORKS

Chapters 2 and 3 of this dissertation have each been published by scientific journals. Specifically, chapter 2, entitled "Maximum Walking Speed Is A Key Determinant Of Long-Distance Walking Function After Stroke," appeared in the Nov-Dec 2014 issue of the interdisciplinary journal *Topics in Stroke Rehabilitation*, which is published by Thomas Land Publishers (TLP). Chapter 3, entitled "Paretic Propulsion And Trailing Limb Angle Are Key Determinants Of Long-Distance Walking Function After Stroke," was electronically published through an exclusive license agreement by Sage Publications (SAGE) ahead of print on November 10, 2014 in the journal *Neurorehabilitation and Neural Repair*.

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# Appendix B
## PROTECTION OF HUMAN SUBJECTS

This work necessitated human subjects testing. All testing procedures were approved by the University of Delaware's Institutional Review Board. All participants provided informed consent. The approved research protocol, entitled "[151783-1] Fast Treadmill Training/Functional Electrical Stimulation to Improve Walking Study #2-Randomized Controlled Trial," was approved on February 7, 2010 following full board review and was renewed on an annual basis until project completion in the Fall of 2014. A copy of the original approval letter is included on the next page.

RESEARCH OFFICE

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| | |
|---|---|
| DATE: | February 7, 2010 |
| TO: | Stuart Binder-Macleod, PT, PhD |
| FROM: | University of Delaware IRB |
| STUDY TITLE: | [151783-1] Fast Treadmill Training/Functional Electrical Stimulation to Improve Walking Study #2- Randomized Controlled Trial |
| IRB REFERENCE #: | |
| SUBMISSION TYPE: | New Project |
| ACTION: | APPROVED |
| APPROVAL DATE: | February 7, 2010 |
| EXPIRATION DATE: | January 19, 2011 |
| REVIEW TYPE: | Full Committee Review |

Thank you for your submission of New Project materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Full Committee Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.