2019

Effects of differential fore aft resistance on propulsive force generation during walking in nonimpaired and poststroke individuals

Avantika Naidu
University of Alabama at Birmingham

EFFECTS OF DIFFERENTIAL FORE-AFT RESISTANCE ON PROPULSIVE FORCE GENERATION DURING WALKING IN NONIMPAIRED AND POSTSTROKE INDIVIDUALS

by

AVANTIKA NAIDU

DAVID A. BROWN, COMMITTEE CHAIR
CHRISTOPHER P. HURT
VICTOR W. MARK
TAPAN S. MEHTA
DARCY REISMAN

A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

BIRMINGHAM, ALABAMA

2019

EFFECTS OF DIFFERENTIAL FORE-AFT RESISTANCE ON PROPULSIVE FORCE GENERATION DURING WALKING IN NONIMPAIRED AND POSTSTROKE INDIVIDUALS

AVANTIKA NAIDU

PHD IN REHABILITATION SCIENCES

ABSTRACT

Background: Impaired loading dynamics and muscle function due to hemiparesis are partially responsible for permanent locomotor deficits poststroke. During walking, inability of the paretic limb to generate sufficient propulsive-forces causes reliance on compensatory strategies, wherein the nonparetic limb generates the majority of propulsive-forces needed for forward progression and speed modulation. Purpose: Investigation of combined fore-aft (FA) and differential FA resistance on interlimb propulsion during walking in nonimpaired and individuals poststroke. I present four studies of which the first pertains to protocol outlining a 6-week training study to improve walking function poststroke, while the other studies concern a mechanistic exploration of propulsive-force generation ability during walking against combined and differential FA resistance demands in nonimpaired and poststroke participants. Methods: Study 1 describes a 6-week challenge-based training approach using two body-weight-support (BWS) paradigms in chronic stroke survivors (N=29) designed to improve comfortable walking speed (CWS). Study 2 utilized the novel walking environment of a robotic-treadmill interface to assess limb propulsion in nonimpaired individuals (n=17) walking at a self-controlled target speed of 1m/s against combined FA resistance, applied in percentages of vertical body weight (N=17) at the center of mass (COM). Study 3, utilized the same walking environment to assess differences in relative interlimb propulsion in poststroke (N=27, walking at a target CWS inside device) and nonimpaired (N=15, walking at 0.5 m/s) against combined FA resistance. Study 4, also utilized the same walking environment, however with a modification that allowed one treadmill-belt to be controlled/drive by the participant (i.e. self-drive/SD), while the other was automatically controlled (i.e. machine-driven/MD). Using this device modification, we assessed interlimb-propulsion asymmetry during split-belt walking (2:1 speed ratio) against FA resistance applied to the SD belt i.e. differential resistance in nonimpaired (N=15, 0.5 &1 m/s speed) and individuals poststroke (N=15, CWS and ½ CWS). Results: Study 2 results highlight that limb propulsion proportionally increased to the amount of applied FA resistance during target-speed walking without affecting vertical forces, possibly through greater fore-aft limb loading. Study 3 results showed that individuals poststroke asymmetrically increased interlimb propulsion while nonimpaired individuals symmetrically increased interlimb propulsion against increasing levels of FA resistance. These results indicate that although stroke participants increased P limb propulsion, the relative propulsion between the P and NP limbs remained constant perhaps due to fixed propulsion-calibration between both limbs. Study 4, showed that nonimpaired participants selectively increase slower-limb propulsive force compared to the faster-limb due to greater fore-aft loading. Paretic propulsion significantly increased without affecting nonparetic propulsion when the paretic limb moved slower speed. Conclusions: Maintaining target speed against greater FA resistance symmetrically increases interlimb propulsion and asymmetrically increases in nonimpaired and poststroke individuals, respectively. Walking against differential FA resistance increased propulsion-asymmetry in nonimpaired while individuals poststroke decreased interlimb propulsion asymmetry during, when the paretic limb moved slowed than the non-paretic limb.

Keywords: Poststroke, nonimpaired, walking, asymmetric-limb propulsion, differential fore-aft resistance, split-belt robotic-treadmill interface

DEDICATION

This dissertation is dedicated to my loving family. My parents Shalini and Vikram Naidu and my brother Prithvi for always believing in me, and helping me pursue and achieve my dreams and especially my grandparents Rama and Waman Naidu for their tremendous love and support. Thank you all for letting me be “me”, and always backing my decisions throughout my life, and always being there for me.

My mentor Dr. David A. Brown, for been an inspiration and my scientific father. Thank you for being a great role model, guiding me every step of my PhD journey, and providing me with exceptional training. I am forever grateful for your unwavering support, patience, compassion, and belief in my abilities.

ACKNOWLEDGMENTS

I would like to thank all my committee members, especially Dr. Christopher P. Hurt for patiently helping me navigate through the world of gait biomechanics, always being willing to discuss science and data, and always lending a helping hand in times of crises. Dr. Victor W. Mark for his meticulous approach to research and teaching me to look at research questions from both clinical and scientific lens. Thank you, for always being willing to help me and encouraging my research endeavors. Dr. Tapan S. Mehta for his rigorous approach to experimental analysis that has helped me focus my research methods. Dr. Darcy Reisman, for being my inspiration for poststroke split-belt treadmill research and taking time out of her busy schedule to be an integral part of my committee and provide valuable insight.

My LocoLAB sisters Sarah Graham and Deanna Rumble my "LAB MENTORS" and best friends and, Rebecca Hennessey, and Jennifer Uzochukwu. Thank you all, for spending hours both in and outside the lab, discussing science and life. I will always cherish our times together. Lastly, to all my friends back in India and here, especially Byron and Katrina Lai for good times, laughs and making memories that last a lifetime.

Sources of funding: This work was supported by a UAB Center on Disability Health and Rehabilitation Science Internal Small Project Grant.

TABLE OF CONTENTS

LIST OF TABLES

Table *Page*

A CHALLENGE-BASED APPROACH TO BODY WEIGHT SUPPORT TREADMILL TRAINING POSTSTROKE: PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

FORE-AFT RESISTANCE APPLIED AT THE CENTER OF MASS USING A NOVEL ROBOTIC INTERFACE PROPORTIONALTELY INCRESES PROPUSLIVE FORCE GENERATION IN NONIMPAIREDINDIVIDIUALS WALKING AT A CONSTANT SPEED

COMPARISON OF INTERLIMB CONTRIBUTIONS TO PROPULSION BETWEEN POSTSTROKE AND NONIMPAIRED INDIVIDUALS WALKING AGAINST FORE-AFT RESISTANCE

EXPLORING EFFECTS OF DIFFERENTIAL FORE-AFT RESISTANCE ON PROPULSIVE FORCE GENERATION DURING SPLIT-BELT TREADMILLWALKING IN NONIMPAIRED AND INDIVIDUALS POSTSTROKE

LIST OF FIGURES

Figure *Page*

INTRODUCTION

A CHALLENGE-BASED APPROACH TO BODY WEIGHT SUPPORT TREADMILL TRAINING POSTSTROKE: PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

FORE-AFT RESISTANCE APPLIED AT THE CENTER OF MASS USING A NOVEL ROBOTIC INTERFACE PROPORTIONALTELY INCRESES PROPUSLIVE FORCE GENERATION IN NONIMPAIRED INDIVIDIUALS WALKING AT A CONSTANT SPEED

COMPARISON OF INTERLIMB CONTRIBUTIONS TO PROPULSION BETWEEN POSTSTROKE AND NONIMPAIRED INDIVIDUALS WALKING AGAINST FORE-AFT RESISTANCE

EXPLORING EFFECTS OF DIFFERENTIAL FORE-AFT RESISTANCE ON PROPULSIVE FORCE GENERATION DURING SPLIT-BELT TREADMILLWALKING IN NONIMPAIRED AND INDIVIDUALS POSTSTROKE

LIST OF ABBREVIATIONS

ABC	Activities Specific Balance Confidence
BBS	Berg Balance Scale
BWSTT	Body Weight Support Treadmill Training
COM	Center of Mass
CWS	Comfortable walk speed
FWS	Fast walk speed
DGI	Dynamic Gait Index
GRF	Ground Reaction Force
HF	Hands free
HF+C	Hands free + Challenge
SIS	Stroke Impact Scale
GAS	Gastronemius
SOL	Soleus
TA	Tibialis Anterior

QUOTES

"In science, as in the playing card experiment, novelty emerges only with difficulty, manifested by resistance, against a background provided by expectation."

— Thomas S. Kuhn, *The Structure of Scientific Revolutions*

INTRODUCTION

In this section, I will introduce how leg muscle forces, specifically "push-off" propulsive forces are vital for maintaining walking speed and locomotor function. I will describe how hemiparesis, i.e. paralytic weakness in one-half of the body following a stroke, affects walking function in chronic stroke survivors. I will go over the biomechanical and clinical characteristics of hemiparetic gait due to impaired muscle-force generation ability of the affected paretic lower limb, and describe the individual and societal impact of hemiparesis in chronic stroke survivors. I will summarize the current understanding of neuromechanical control of walking, importance of propulsive-force generation for maintaining walking speed, and will specifically focus on how impaired propulsive-force generation ability of the paretic limb negatively impacts walking function in stroke survivors. I will discuss the theoretical framework I used to explore the overarching hypothesis that limb-loading feedback during walking influences propulsive-force generation function in both nonimpaired individuals and individuals poststroke. I will describe the novel experimental gait environment to apply combined and differential limb-loading resistance during walking I used to test my overarching hypothesis and explore differences in propulsive-force generation mechanisms in both nonimpaired individuals and individuals poststroke. In the following chapters, I will discuss the undertaking and findings of my dissertation research.

Chronic stroke survivors have slow walking speeds that reduce functional capacity and negatively impacts quality of life

Stroke is the leading cause of chronic neurological disability in the U.S, annually affecting 795,000 individuals [24]. Currently, the American Heart Association (AHA) reports that there are an estimated 7 million stroke survivors residing in the U.S, with an additional 4 million expected to be added to this number by the year 2020 [1]. Loss of productivity and socio-economic costs associated with stroke-related impairments amount to $35-56 billion annually, while the total costs associated with chronic poststroke impairments is projected to reach $240 billion by the year 2030 [9, 11]. Although, the old age is often synonymous with the incidence of stroke, the AHA reports that a third of all stroke survivors are below the age of 60 years. Only 5-20% of all stroke survivors are expected to completely recover, while the majority are left with significant sensorimotor impairments, severely affecting functional independence [25]. Among these impairments, hemiparesis i.e., paralytic weakness in one half of the body following cortical damage poststroke, affects greater than 80% of all survivors, and is partially responsible for causing locomotor deficits that severely limit walking function [2, 10]. Compared to age-matched populations, hemiparesis significantly decreases functional ambulatory capacity in chronic stroke survivors [26] with reports indicating that less than 50% on can independently ambulate within their communities. On average 50-80% of most chronic stroke survivors have an average comfortable walking speed (CWS) between [35] 0.4-0.8 m/s [36]. In contrast, the average nonimpaired individuals walks between 1.2-1.5m/s. While a minimum CWS of 0.8 m/s is required for successful community ambulation [34], most chronic stroke survivors are unable to achieve such

CWS. Apart from limiting community participation, such slow CWS place ambulatory stroke survivors at a fourfold risk of fall. On the other hand, stroke survivors classified as household ambulatory have CWS between 0.1-0.4 m/s, and unable to ambulate in their communities and have severely restricted ability to participate in their activities of daily living.

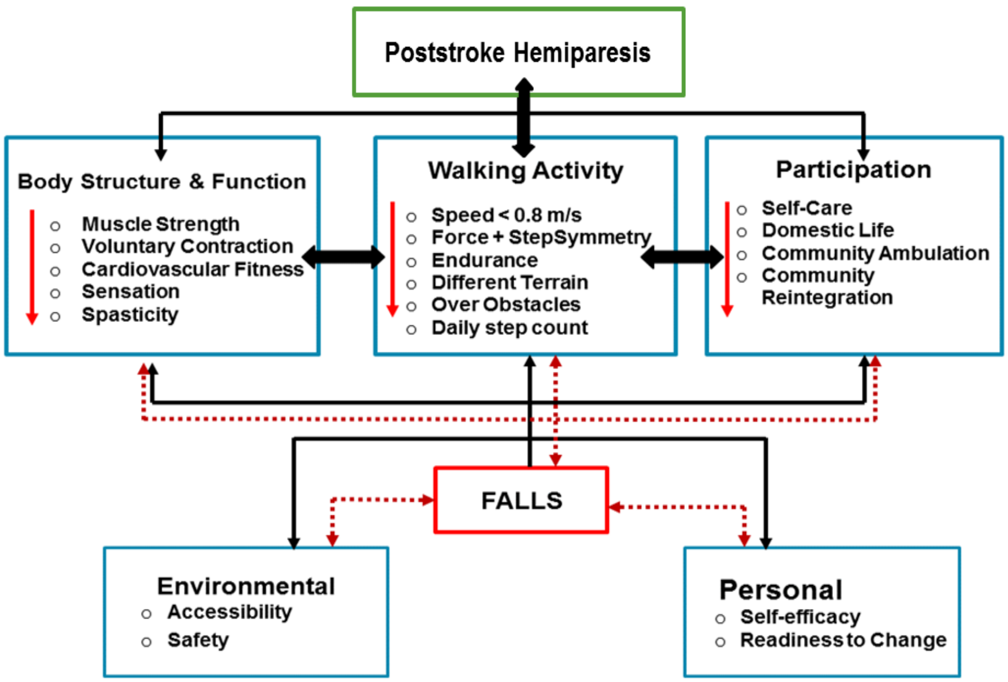


Fig.1: International classification of function disability and health (ICF) framework of poststroke impairments and predisposition to falls © ICF stroke classification.

Factors influencing muscle-force generation to maintain walking speed in nonimpaired individuals

To better understand poststroke walking function, it is first essential to recognize that functional walking patterns requires symmetric generation of ground reaction forces (GRF), by each limb, to advance the center of mass (COM) forward. GRF's are produced by each lower-limb on a step-by-step basis during the stance phase (i.e., supported phase of walking **(Fig.2)**). However, the fore-aft (anterior to posterior) component of the GRFs is mainly involved in the forward progression of the COM, while maintaining walking speed and balance. The fore-aft GRF's are forces are a measure of lower-limb force production and control, critical for modulating CWS. Simplistically, these fore-aft forces are referred to braking and propulsive forces, as from initial contact to mid-stance the stance limb produces decelerating i.e. negatively directed "braking" forces to stabilize the COM, while from mid to terminal stance the COM is accelerated forward through the generation of positively directed push-off, propulsive forces [5]. To maintain comfortable walking speed, nonimpaired individuals, produce equal magnitude and oppositely directed braking and propulsive impulses (i.e., time integral of each fore-aft component **(Fig.2)**).

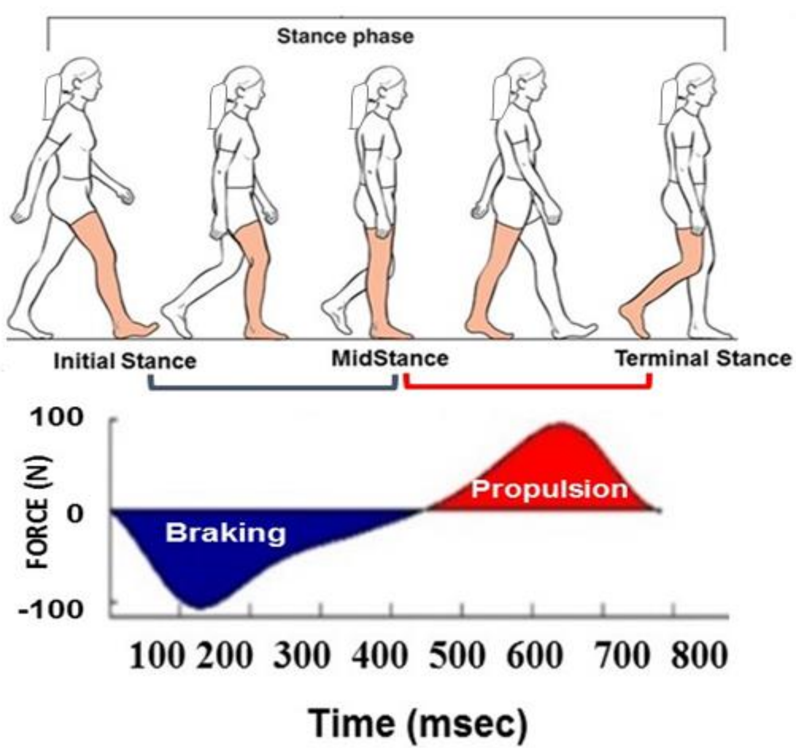


Fig.2: Force by time plot for generation of fore-aft (braking and propulsion) ground reaction forces during the stance phase of walking

Similar production of braking and propulsive impulses by each limb maintain interlimb symmetry vital for efficient walking energetics and maintenance of functional walking movement patterns. Studies in both nonimpaired individual have investigated individual lower-limb muscle contribution during stance phase, using computational modeling techniques such as forward dynamics, inverse dynamic, electromyography based modular organization, etc [43-46], in. These studies have revealed that the primary muscles involved during braking are unilateral hip extensors and knee extensor muscle (i.e. Gluteus and Quadriceps (vasti) group), with contraction beginning at early stance and ceasing at mid stance, respectively. While, the primary muscles involved during propulsion are the planterflexors (i.e., medial and lateral gastrocnemius, and soleus) from mid to terminal stance i.e., second half of gait cycle. Planterflexors activity are involved in COM movement with stabilization of the trunk over the lower limbs stabilization vital for maintenance of posture and lower-limb forward translation walking [46, 47]. During initial stance, both gastrocnemius and soleus undergo eccentric activity to provide trunk support. Through this action, these muscles decelerate the stance limb from forward progression while accelerating the trunk in the vertical direction. During mid-swing the switch from eccentric to isometric contraction takes place [43]. Energetic transfer between the trunk and limb takes place, with gastrocnemius contributing to leg muscle energetics while soleus contributing to trunk energetics, and has an opposite effect on the gastrocnemius. Typically, planterflexor concentric activity begins at late stance (~40% of late stance) and ends at toe-off (~60% of gait cycle), to accelerate the trunk forward while deaccelerating the limb. Various studies highlight the importance of planterflexors in providing vertical support from initial to mid-stance, isometric stabilization at midstance (with opposition actions at hip and knee), and forward progression from mid-to terminal stance. The soleus is mainly involved in regulating mechanical energy pertaining to COM loading conditions, while the gastrocnemius is the primarily associated with generation of (pre-swing) propulsion forces and is directly correlated with walking speed. Thus, planterflexors along with hip-flexors help regulate stance phase loading demands. Mechanical work demands analyzed through inverse pendulum single-limb models state that planterflexors enable positive work through greater propulsive-force production production during double limb support to propel the COM forward within the body's base of support at a faster rate. Thus, symmetric increase in interlimb propulsion is essential for energetic regulation of walking speed increase.

Interlimb paretic-limb propulsion asymmetry causes slow, asymmetric and energetically expensive poststroke gait patterns

Although the level poststoke hemiparetic impairment differs across survivors, depending on lesion location, type, and severity of the cardiovascular insult, across stroke survivors, impaired neuromechanical control due to paretic-limb distal muscle weakness has been mainly associated with reduced poststroke walking function[29-31]. Reduction in neural drive following stroke affects paretic limb neuromuscular responses, muscle coordination patterns, and the rate of muscle force development (isometric and isokinetic) in static and dynamic motor tasks. During walking, these changes impact P limb loading dynamics and produce inappropriately timed and exaggerated braking forces while P

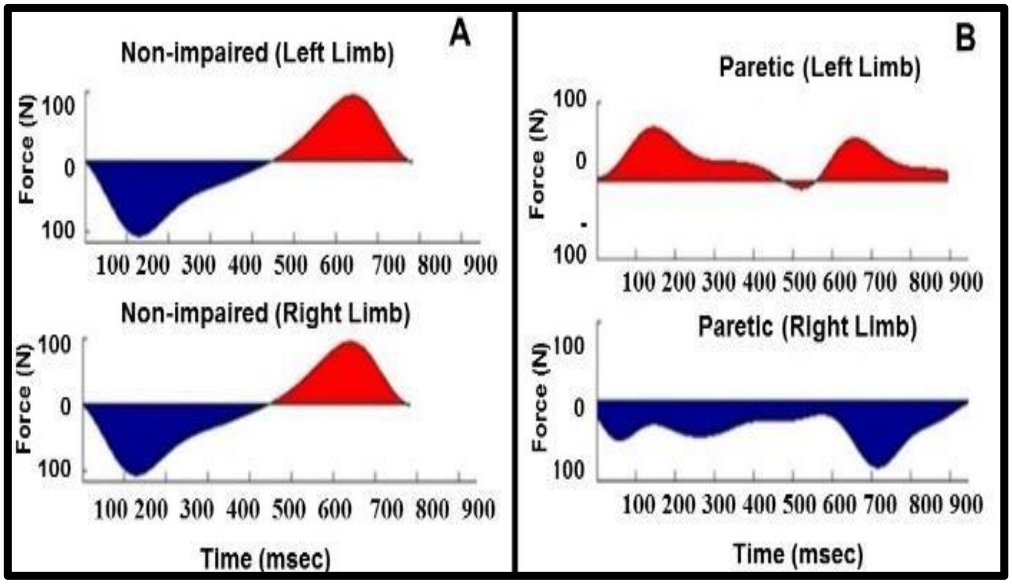


Fig.3 (A). Fore-aft ground reaction force for a single step of a non-impaired individual (A) walking at a constant speed with symmetric braking (Blue) and propulsion (Red) forces. An individual poststroke (B), walks with increased paretic braking force (Blue) and greater non-paretic limb propulsion for a single step at comfortable walking speed (Red).

To move the COM forward and modulate walking speed, stroke survivors rely limb propulsive forces are significantly reduced **(Fig.3.B)** [53] due to planterflexor weakness. on compensatory strategies by using the nonparetic (NP) limb as the primary driver for production of propulsive forces [6]. The resulting asymmetric interlimb propulsion is directly correlate with hemiparetic severity impairment, step-length asymmetry producing slow and energetically gait patters (i.e., circumduction gait, step-to-gait). Regarding paretic limb muscle activity, compensatory strategies increase braking forces through greater P limb knee extensor (vasti group) activation at initial contact and/or prolonged contraction of hip-flexor groups (rectus femoris) from mid-stance to mid-swing [53, 56]. While an atypical earlier phase shift of planterflexor activation also increases braking force generation and limits timely generation of propulsive during pre-swing. Studies by Kautz et al. found that reduction in propulsion and planterflexor activity corresponded with prolonged tibialis anterior activity and reduced hip extensor (gluteus medius) activity during pre-swing corresponded [6, 32, 49, 53]. Such impaired P muscle activity decreases mechanical output. Olney at al. reported that during walking the overall mechanical force output of the paretic limb is ~40% less than the nonparetic limb [54, 55]. At an individual joint level, regardless of hemiparetic severity, the P ankle joint moments (i.e. rotatory torque of muscle about the joint) and ankle power output are reduced, especially during terminal stance and pre-swing phases of gait i.e. period of propulsion [49].

While impaired P limb propulsion negatively correlates with step-length, the direction of step length asymmetry depends the type of compensatory strategies adopted i.e., the P limb can have either a longer step-length (i.e. circumduction gait) or a shorter step length (i.e. step-to gait) compared to the NP limb. Typically, longer P step-length strategies are due to the NP limb acting like a pivot. In an effort to reduce P limb loading during walking, greater NP limb weight bearing and propulsion generation occurs, resulting in larger NP ankle, knee and hip joint moments to swing the COM forward. Alternatively, strategies with a shorter P limb step-length (step-to-gait) are due to decreased P hip flexor moment and reduced ankle power to propel the limb forward producing a biomechanical disadvantage. However, some stroke survivors utilize compensatory strategies that do not result in step-lengths asymmetries, due to bilateral-limb hip moment compensation interlimb propulsion weakness resulting in overall slower comfortable walking speeds, and reduced endurance. Taken together these studies highlight how reduced P limb propulsive-force generation causes affects interlimb propulsion and functional walking capacity in chronic stroke survivors.

Impact of compensatory strategies on poststroke gait rehabilitation and need for improved neuromechanistic research to determine factors that decrease reliance on compensatory gait strategies

Although stroke survivors consistently rank improvement in walking function as their main rehabilitation goal, dependence on compensatory strategies persists despite gait-rehabilitation efforts and remains a major obstacle in regaining functional walking patterns. Long-term use of compensatory gait strategies offer little to no benefit in improving walking quality, endurance or independence in day in to day activities, and can actually cause overuse musculoskeletal injury/damage [8] of the nonpareitc limb, with disuse atrophy of the affected paretic limb [39]. In is not surprising that such inefficient gait mechanics, limit desire of stroke survivors in partaking in functional activities and promote adoption of sedentary lifestyles[40]. Such lifestyles in turn, predispose stroke survivors to a sequel of secondary health conditions such as fatigue, musculoskeletal pain, sarcopenia, decreased bone mineral density and cardiovascular function, etc.[41]. *Thus, to optimize current rehabilitation measures, there is an urgent need to better understand the neuromuscular basis for persistence of compensatory strategies, and identify specific factors that can increase paretic-limb propulsive force generation and participation during walking*[12, 42]. Such, knowledge can aid in the design of targeted and task-specific strength-training interventions, and rehabilitation environments that help promote functionally efficient gait patterns, increase in CWS and thus, overall walking function poststroke. Evidence suggests that individuals poststroke are capable of walking at faster speeds and can scale their dynamic force production to a perceived sense of effort relative to a maximum force output capacity.

In particular, studies by Nadeau et al. [50, 57] found that a significant trade-off between paretic limb PF and hip-flexor activation during stance causes adaptation of compensatory strategies, which can be modified with increase in ankle PF strength following strength training to improve kinetic and kinematic gait patterns. Hence, slower poststroke comfortable walking speeds (CWS) may not be due to weakness alone, but instead may result from purposeful limitations in maximum force production, particularly of the ankle plantarflexor and hip flexor muscle groups [51, 52, 58]. From a biomechanics perspective, paretic limb position also plays an important role in influencing leg muscle forces. Several studies have found that the P limb trailing limb angle (i.e. angle between LAB vertical axis and vector connecting greater trochanter to toe) can be used a good measure of propulsion force generation. Evidence supports larger trailing limb angles at terminal correspond to a most posterior-limb extension position, and a mechanical advantage to increase propulsive force generation and reduces reliance on hip-flexor moment for forward progression [59, 60]. Therefore, task-specific rehabilitation strategies that strengthen and encourage planterflexore force output may be one way to facilitate increase in P limb propulsion and participation during walking.

Locomotor adaptability poststroke revealed through split-belt experiments

Various studies exploring motor control during walking through split-belt treadmill paradigms over the decades have demonstrated that nonimpaired and individuals poststroke can acclimatize to novel gait perturbations, and adapt their walking patterns by adjusting spatiotemporal interlimb and intralimb parameters [61-65]. Particularly, Reisman et al. [63, 66-70] observed that individuals poststroke were able to adapt their gait patterns during split-belt walking and following a period of adaptation to the split-condition, demonstrated post-adaptation (aftereffects) with improvements in poststroke interlimb step symmetry. This work along with several other studies have demonstrates that split-belt treadmill paradigms that provide specific challenging walking conditions, cause individuals poststroke to utilize novel movement strategies that help them adapt to the gait environment. Using the principle of "error-augmentation" that capitalizes on feedforward mechanisms as possible motor control mechanism, Bastian et al, Finley, Torres-Alvedo, Ryan, Reisman et al. exacerbated possstroke step-length asymmetry during split-belt walking. an adaptation period (ten-fifteen minutes) following which, the belts moved at the same speed (i.e. postadapatation period-two to five minutes). In all cases, analysis of locomotor aftereffects revealed a significant improvement in interlimb step symmetry [62, 65, 71] with transferable gains to overground walking function [72]. These studies demonstrate that individuals poststroke can indeed improve their walking function through measures of step length symmetry, peak paretic propulsive force and trailing limb angle, all of which correspond with improved propulsion force production [60, 66, 73].

Need for split-belt paradigms exploring application of resistance to increase paretic limb propulsion during walking

While split-belt studies have explored spatiotemporal locomotor adaptations on 2:1 speed rations in different conditions, limited work has been undertaken in examining the effects of limb-loading resistance during split-belt walking. Although studies have used pulley-systems [19] and rubber-tubing [74] to provide unilateral resistance perturbation during split-belt, surprisingly few studies have explore effects of stance phase resistance applications on propulsive-force generation. In our view, it is more difficult to create a split-belt resistance paradigm that specifically influences stance-phase biomechanics while individuals control their walking speed, in controlled experiments to quantify walking function. However, prior published work for our laboratory utilized a robotic-interface to apply fore-aft (backward directed) resistance forces at their COM while poststroke stroke participants walked at their self-selected overground walking and treadmill walking found that instead of slowing down, stroke participants maintained their walking speed against greater resistance, indicating a reserve paretic propulsion capacity. More recently, studies have explored application of stance phase FA resistance, while maintaining a target speed, in older adults and individuals poststoke and found improvements in peak propulsive force generation. However, to our knowledge, biomechanical understanding of effect of FA resistance during self-selected and split-treadmill walking is yet to be determined.

Theoretical premise underlying the investigations in this dissertation

The ideas for our current proposal are influenced from prior published work in our laboratory and from a conceptual model of locomotor control and rhythm modulation proposed by Duysens et al.[13] In their original model of locomotion, Duysens et.al state that while supraspinal input is important for locomotor control a group of specialized interneurons in the central nervous system, are the key regulators of locomotor rhythm ad identified the role of central pattern generators (CPGs). The CPG's are thought to be located in the spinal cord and consists of a group of externsor and flexor interneurons that reciprocally inhibit each other. Each interneuron send motor output to extensor and flexor motorneurons for activation of reciprocal extensor and flexor muscle synergies, during the stance and swing phases of human locomotion, respectively **(Fig.4a,b)**.

Fig.4. A

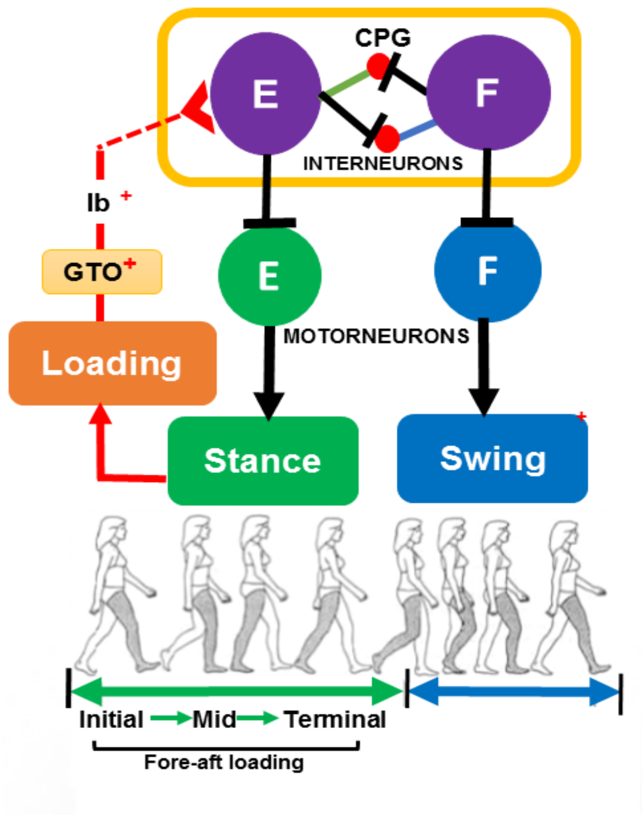


Fig.4.A Duysens et al. Model of locomotor control (E=extensor motor neuron, F=flexor motor neuron) Proprioceptive limb-loading feedback via golgi tendon organs (GTOs) and cutaneous receptors from early to midstance, trigger Ib excitatory mechanisms

Fig.4. B

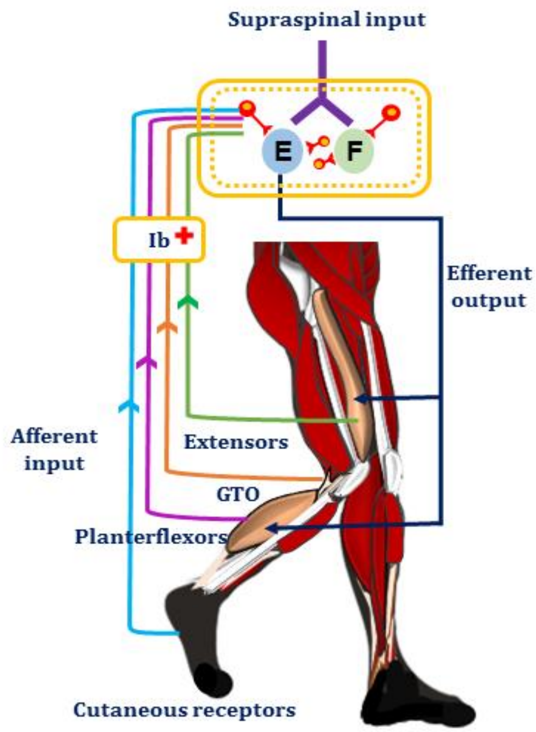


Fig.4.B Duysens et al. Model of locomotor control (E=extensor motor neuron, F=flexor motor neuron) Ib excitatory mechanisms prevent limb collapse at midstance, and facilitate generation of propulsive-forces from mid to terminal stance to propel the limb forward

Although the CPG's automatically regulate walking, both descending supraspinal input and sensory input from the environment influence their function. In particular, this model states that during walking, from early to mid-stance, limb-loading proprioceptive feedback is gathered and relayed the CPG's via the Golgi tendon organs (GTOs) (located at musculo-tendinious junctions of lower-limb extensor muscles), muscle spindles (Ia), and cutaneous sole receptors. This afferent input triggers autogenic excitation of the Ib extensor mechanism, which outside context of walking, is inhibitory in nature. Excitation of the Ib mechanism excites the extensor interneurons that triggers an extensor limb synergy, and activate all the extensor muscles at the hip, knee, and ankle, respectively. While at the same time, this mechanism, reciprocally inhibiting the flexor interneurons and flexor muscle activity in the limb, thereby delaying the onset of flexion.

The Ib extensor mechanism thus allows enable weight acceptance and prevention of limb collapse from early to midstance via generation of appropriate braking forces, while from mid to terminal stance, this mechanism facilitates limb forward progression via planterflexor propulsive-force generation. Moreover, reduction in limb-loading feedback, sensed at terminal stance (i.e. toe off), triggers reciprocal activation of CPG flexor interneurons to promote flexor synergy with flexor muscle activation of the limb during swing. Thus, limb-loading proprioceptive feedback during stance enables reciprocal excitation and inhibition of CPG interneurons to help regulate breaking and propulsive forces.

In principle, load-related feedback can reinforce stance activity either directly through spinal reflex pathways or indirectly through an excitatory effect on the part of the generator network involved in the production of extensor activity. Through their animal studies, Duysens and Dietz et al.[77] observed that absence of sensory feedback during stance in cats [76], induced an earlier onset of swing and increased stance duration of contralateral limb. This notion is in conjunction with seminal work on locomotion by Grillner et al. [78] Dietz et al. [79] and Zehr et al. [80] who also observed that sensory manipulation contralateral limb affected bilateral stance phase and interlimb symmetry.

This notion that sensory feedback can influence muscle activity and phasing responses in nonimpaired individuals was first assessed using pedaling paradigms where position and torque of the pedaling limb influenced intralimb and interlimb muscle phasing parameters. More recently, split-belt paradigms have elaborated on this work and highlights how sensory feedback influences temporal modulation of interlimb motor output [62, 81]. Taken together these studies underscore the importance of sensory feedback influencing both intralimb and limb motor responses, kinetic and kinematic gait parameters.

Thus, we subscribe to the idea that absence of appropriate sensory limb-loading feedback during stance impairs locomotor modulation poststroke, and leads to abnormal muscle timing, reduced amplitude of contractions, and decreased muscle force generation by the paretic limb. Evidence suggests that individuals poststroke scale their dynamic force production to a perceived sense of effort or maximum force output [17, 18, 82]. While, typical poststroke rehabilitation interventions frequently incorporate the principle of greater limb-loading demands via resistance to increase muscle force production. It is frequently observed that even with gains in isometric/isokinetic muscle force generation, such interventions have little carry over effect to walking, as they are carried out in seated positions, and may be a cause for individuals poststroke to revert or continue using compensatory mechanisms. Therefore, providing environments that encourage P limb muscles to increase their propulsive force output during walking, may be one way to facilitate greater P limb participation and improve walking efficiency poststroke.

Combining my interests in poststroke gait rehabilitation, split-belt treadmill research, and prior LAB research on resistance application during walking, for my dissertation research, I worked with a unique split-belt treadmill interface that allowed application of limb-loading resistance during walking at self-selected speeds. Using this interface, in investigated the effects of combined and differential fore-aft resistance during self-selected walking in both nonimpaired and poststroke individuals.

Overview of the following dissertation chapters

In chapter 2, I present the study protocol for a 6-week randomized control clinical trial examining a challenge based approach to body-weight support treadmill training in chronic stroke survivors. I was involved with this training study during the initial two years of my dissertation research. This study utilized the novel environment of the KineAssist-treadmill interface for treadmill training to assess the efficacy of incorporating real-world walking challenges, encountered during community ambulation, with body weight support treadmill training (BWSTT) on balance and walking function outcomes in chronic stroke survivors. We designed and compared two unique BWSTT paradigms of similar aerobic-training intensities, the first protocol emphasized walking without any handrail support on a self-driven treadmill (i.e., hands-free walking), while the second protocol involved practicing nine essential walking tasks that mimic common environmental barriers along with hands-free walking, respectively. The primarily outcome measure was change in comfortable walking speed between groups, post-training. The study results revealed that while both groups improved CWS, there were no significant between group differences. These results are similar to other poststroke BWSTT and collectively suggest that although modulation of limb-loading demands using BWS provides some benefit via enabling greater paretic limb excursion and control during walking, perhaps it does not provide enough of a "functional" stimulus to improve paretic limb-loading mechanics and propulsive force production. Considering that propulsive forces are produced in the fore-aft direction, manipulation of fore-aft limb-loading demands by increasing fore-aft (FA) resistance without changing vertical limb-loading during walking at a self-controlled target speed, can perhaps increase proprioceptive sensory feedback and encourage greater paretic limb weight-bearing via extensor mechanisms and thus increase propulsion generation.

Thus, in *chapter 3* to test this hypothesis I utilized the unique environment of the KineAssist robotic interface and its fore-velocity relationship to apply FA resistance, applied in percentages of vertical body weight (10%,15%,20%,25% B.W), while nonimpaired participants walked at a self-controlled target speed of 1 m/s. I explored the hypothesis that walking against graded greater FA resistance will proportionally increase limb propulsion without affecting vertical loading.

In *Chapter 4*, my primary aim was to assess the relative P and NP limb propulsion contribution in individuals poststroke stroke compared to age-similar NI participants, while maintained a self-controlled target speed against increasing levels of FA resistance (applied at the COM). I utilized the force-velocity relationship of our treadmill interface to design our experiment, and ensure that both groups experienced similar sense of effort demands , regardless of their body weight and target speed, when walking against six fore-aft resistance levels (6%, 9%, 12%, 15%, 18%, 21% B.W). I explored the hypothesis that individuals poststroke walking at a self-selected against greater fore-aft resistance will demonstrate a reserve paretic-propulsion capacity and asymmetrically increase interlimb propulsion (NP>P). In comparison, nonimpaired individuals will symmetrically increase interlimb propulsion during walking at a constant speed of 0.5 m/s against increasing FA resistance.

In *Chapter 5*, I explore how a software modification to the KA-split belt treadmill interface created a unique split-belt walking environment. This modification allowed the user to drive or control the velocity of one treadmill via the interface's force-velocity relationship i.e. self-drive (SD) belt while the other belt was externally programmed by the examiner at a set speed i.e. machine-drive (MD) belt. By selecting a target velocity for the SD belt and setting the MD speed at twice the speed (2:1) speed ratio, we can apply fore-aft resistance to the SD belt such that both limbs will experience fore-aft resistance in a differential manner. I assessed this novel environment's ability to electively influencing the relative propulsion output of one limb over the other in nonimpaired amd poststroke participants. Participants in both groups walked in different split-speed combinations of the SD and MD belts against six-increasing levels of FA resistance (6%,9%,12%,15%,18%,21% B.w.). For nonimpaired participants, I explored the hypothesis walking while targeting a slower speed on the SD belt while the MD belt is set at twice the speed against increasing FA resistance, the slower SD limb will increase propulsive force generation due greater time proprioceptive limb loading and force-generation requirements of the SD limb that engage limb-extensor mechanisms for propulsion generation. For poststroke participants, I explored the hypothesis that when the P limb is targeting a slower speed on the SD belt and the NP limb moves on the MD belt at twice, the P limb will increase its relative propulsion force output over the NP limb. This will be due to increase in limb-loading time and force-generation requirements of the SD P limb to maintain target speed that will engage limb-extensor mechanisms and increase propulsion output.

In Chapter 6, I summarize the main findings from each manuscript presented in this dissertation document, discuss implications of these findings for stroke rehabilitation practices, and recommend future research directions.

A CHALLENGE-BASED APPROACH TO BODY WEIGHT SUPPORT TREADMILL TRAINING POSTSTROKE: PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

AVANTIKA NAIDU, DAVID A BROWN, ELLIOT J. ROTH

Journal of Medical Internet Research 2018

Format adapted for dissertation

ABSTRACT

Background

Body weight support (BWS) treadmill training protocols in conjunction with other modalities are commonly used to improve poststroke balance and walking function. However, typical BWS paradigms tend to use consistently stable balance conditions, often with handrail support and or manual assistance.

Objective

In this paper, we describe our study protocol, which involved 2 unique BWS treadmill training paradigms of similar training intensity that integrated dynamic balance challenges to help improve ambulatory function post stroke. The first paradigm emphasized walking without any handrails or manual assistance, that is, hands-free (HF) walking, and was the control group, whereas the second paradigm incorporated practicing 9 essential challenging (C) mobility skills, akin to environmental barriers encountered during community ambulation, along with HF walking (ie, HF+C).

Methods

We hypothesized greater walking improvements in the HF+C group following training because of increasing practice opportunity of essential challenging mobility skills along with HF walking. We recruited participants with chronic poststroke hemiparesis and randomized them to either group. Participants trained for 6 weeks on a self-driven, robotic treadmill interface that provided BWS and a safe gait-training environment. We assessed participants at pre-, mid- and postintervention and at 6-month follow-up.

Results

We assessed 77 individuals with chronic hemiparesis and enrolled and randomized a total of 39 individuals post stroke for our study (HF group=19 and HF+C group=20), from June 2012 to January 2015. Data collection along with 6-month follow-up continued until January 2016. Our primary outcome measure is change in comfortable walking speed (CWS) from pre- to postintervention. We will also assess feasibility, adherence, postintervention efficacy, and changes in various exploratory secondary outcome measures. In addition, we will also assess responses to a survey, conducted at the end of each training week, to gauge participants' responses to their training.

Conclusions

These treadmill training protocols represent advances in standardized approaches to selecting BWS levels without the necessity for using handrails or manual assistance, while progressively providing dynamic challenges for improving poststroke ambulatory function during rehabilitation.

Trial Registration

Clinicaltrials.gov NCT02787759 retrospectively registered June 1st, 2016

INTRODUCTION

Stroke continues to remain the leading cause of long-term neurological disability in the United States [1]. Although there is heterogeneity in the severity and level of disability post stroke, greater than 80% of all stroke survivors are likely to experience walking deficits due to hemiparesis [2]. Altered hemiparetic motor control causes balance and gait impairments, which result in asymmetric, slow (ie, 0.1 to 0.8 m/s), and inefficient walking patterns [3-5]. Such walking patterns place stroke survivors at a greater fall risk, with ambulatory stroke survivors being twice as likely to experience falls compared with elderly individuals [6,7]. Fear of falling, along with generalized deconditioning, comorbidity burden, and lack of social support and self-confidence, confines stroke survivors to sedentary lifestyles [8]. Such lifestyles limit participation in daily activities and predispose stroke survivors to secondary health conditions that negatively impact their overall quality of life [9].

Treadmill based locomotor intervention for poststroke rehabilitation

Not surprisingly, improving walking function is the most common rehabilitation goal stated by the majority of stroke survivors [10]. Unfortunately, most gait rehabilitation paradigms are limited in their ability to generate transferable training gains, to help improve poststroke community ambulatory function [11]. To promote motor learning and activity-dependent neuroplasticity changes during rehabilitation, increased practice of locomotor skills in different situational contexts is required [12]. However, various factors have been shown to limit context-based task practice and transferable training gains during rehabilitation, such as decreased active participation, low cardiovascular training intensities, lack of dynamic balance challenges, over-reliance on clinician manual assistance, and lack of opportunities for prolonged practice of skills applicable to real-world community ambulation [13,14]. To collectively address these factors and to promote greater opportunity for motor learning during gait rehabilitation, several studies recommend treadmill-based gait training paradigms [15], including the recent American Heart Association (AHA) scientific report for exercise training in stroke survivors [16]. However, most treadmill paradigms, especially those that integrate limb unweighting via body weight support (BWS), have had varying degrees of success over the past few decades, with some studies reporting no significant outcome differences compared with over-ground training approaches [17,18].

Need for challenge-based body weight support treadmill training poststroke

Most BWS treadmill paradigms also tend to use external supports (ie, safety harnesses, handrails) and/or therapist- or robot-guided movements that may limit stroke survivors from independently training at desired exercise intensities and/or the ability to challenge their dynamic balance [13,19]. In addition, the lack of context in providing training challenges to help balance confidence and walking independence for navigating through common real-world obstacles further limits training gains [20,21]. Given the variability of results with BWS treadmill training, a recent Cochrane review calls for further investigation of BWS training outcomes using task-specific paradigms of greater training intensities, without handrail support in ambulatory stroke survivors [22]. Unfortunately, safety concerns and limitations in technology restrict most BWS paradigms in their ability to provide challenging yet safe dynamic balance tasks, while training at higher intensities to help stroke survivors overcome their fear of falling and improve their walking function [16, 24].

Thus, the purpose of our study was to examine 2 unique intent-driven, BWS treadmill training paradigms, of similar cardiovascular intensity that emphasizes different dynamic walking challenges encountered during community ambulation. The first paradigm involved walking without any handrail support or manual assistance (ie, hands-free [HF] walking [control group]), whereas the second paradigm incorporated practicing 9 essential challenging (C) mobility skills along with HF walking (ie, HF+C walking), relevant for navigation through common environmental obstacles/hazards. We designed both paradigms based on current neurorehabilitation [14] and AHA exercise recommendations for stroke survivors [16]. We used a novel, robotic, intent-driven, treadmill walking system [25] to provide BWS and a safe gait training environment for both groups. We were primarily interested in assessing the feasibility and impact of both treadmill-training paradigms on poststroke walking performance and community ambulation capacity, respectively. We hypothesized that the HF+C group would demonstrate greater balance and functional gait improvements compared with the HF group due to increased practice opportunity of essential challenging mobility skills [26] along with HF walking.

METHODS

Study design

We conducted a 6-week, single-blinded, randomized, and parallel-arm study to examine the effects of 2 intent-driven, BWS treadmill training intervention groups (ie, HF training, and challenge (C) with HF (HF+C) training), on improving balance and functional walking outcomes in community-dwelling chronic stroke survivors, with mild-to-moderate hemiparetic gait impairments.

Sample size estimation and group allocation

We used a single-factor repeated measures analysis of covariance (ANCOVA; ie, initial walking speed as a covariate) at 80% power, 2-tail level of significance of .05 (ie, $P<.05$), and an effect size of 0.4 for a gait velocity difference of 0.16 m/s (ie, minimally clinically important difference [25]), to determine our sample size for each group. Our estimated sample size was 16 individuals per group; however, we aimed to recruit 20 participants in each group to account for attrition. Thus, our goal was to recruit a total of 40 individuals with poststroke hemiparesis, over a period of 3 years.

Study center

We conducted all study meetings, participant assessments, and training sessions at the University of Alabama at Birmingham (UAB) Locomotor Control and Rehabilitation Robotics Laboratory.

Ethics and Recruitment

We obtained study approval from the UAB Institutional Review Board (IRB protocol no: F120425008). The LocoLab program coordinator recruited study participants from the greater Birmingham area, using the UAB Stroke Registry list and an initial phone-screening form (Multimedia Appendix 1). Screened participants and their caregiver (if necessary) met with the program coordinator, who explained the study protocol in detail. We scheduled participants who provided informed consent for their baseline assessments.

Initial screening

An experienced physical therapist, blinded to the training interventions, evaluated all consented participants using our study inclusion or exclusion criteria to approve participants for study enrollment (Textboxes 1 and 2)

Textbox 1. Study inclusion criteria.

Inclusion criteria:

1. Age 19 years and above, community-dwelling, unilateral stroke survivors
2. History of cerebrovascular accident (ie, ischemic or hemorrhagic) confirmed by computed tomography, magnetic resonance imaging, or clinical criteria
3. At least 5 months after stroke incident
4. Able to ambulate at least 14 m with/without an assistive device or the assistance of one person, with a self-selected comfortable walking speed of ≤1.0 m/s
5. Able to demonstrate receptive and expressive communication ability.
6. Primary care physician approval for exercise (obtained via the Health Insurance Portability and Accountability Act, that is, HIPPA-approved guidelines)
7. Willing to provide voluntary informed consent

Textbox 2. Study exclusion criteria.

Exclusion criteria:

1. Presence of serious or uncontrolled cardiovascular conditions
    - Resting systolic blood pressure >180 mm Hg
    - Resting diastolic blood pressure >110 mm Hg
    - Resting heart rate >100 bpm
    - History of uncontrolled arrhythmias/angina/syncope

2. Presence of amputations and/or any severe musculoskeletal problems that restrict walking, for example:
    - Recent fractures of the lower limb
    - Open wounds/abscess

3. Use of spasticity management drug therapies for affected lower limb before participation, for example:
    - Botulinum toxin injection (<4 months earlier)
    - Phenol block injection (<12 months earlier)
    - Intrathecal baclofen or oral baclofen (within the past 30 days)

4. Any cognition involvement impairing ability to follow instructions and/or Mini-Mental State Exam Score <24

5. Past participation in any study examining the effects of long-term body weight support treadmill training in (>4 weeks of training); limb-loaded pedaling or lower extremity strengthening; or enrolled in any ongoing study that evaluates lower extremity function

6. Participant was unable to arrange for transportation to the study site for all evaluations and intervention sessions
7. Participant planned to move out of the area within 18 from the time of study enrollment

Randomization and stratification

We randomized participants to each of the 2 training groups (HF or HF+C) and aimed for a 1:1 allocation ratio to minimize bias and group confounding. We also stratified participants within each group, based on their self-selected over-ground comfortable walking speed (CWS) as having mild (initial CWS<0.5 m/s) or severe (initial CWS≥0.5 m/s) locomotor impairment, using the walking speed classification by Perry et al [27] (Figure 1). We used a random number generator website [28] to generate 2 lists, of 0 and 1 sequences. We assigned participants in group 0 to the HF group and participants in group 1 to the HF+C group, using an open-ended block randomization scheme. The principal investigator (PI) assigned participants to either training group. The program coordinator gave participants their group assignment in opaque envelopes and sequentially enrolled and scheduled all training sessions and assessments, for each participant, for the duration of the study. We also blinded participants to their intervention outcomes.

Robotic treadmill interface for hands-free gait training in both groups

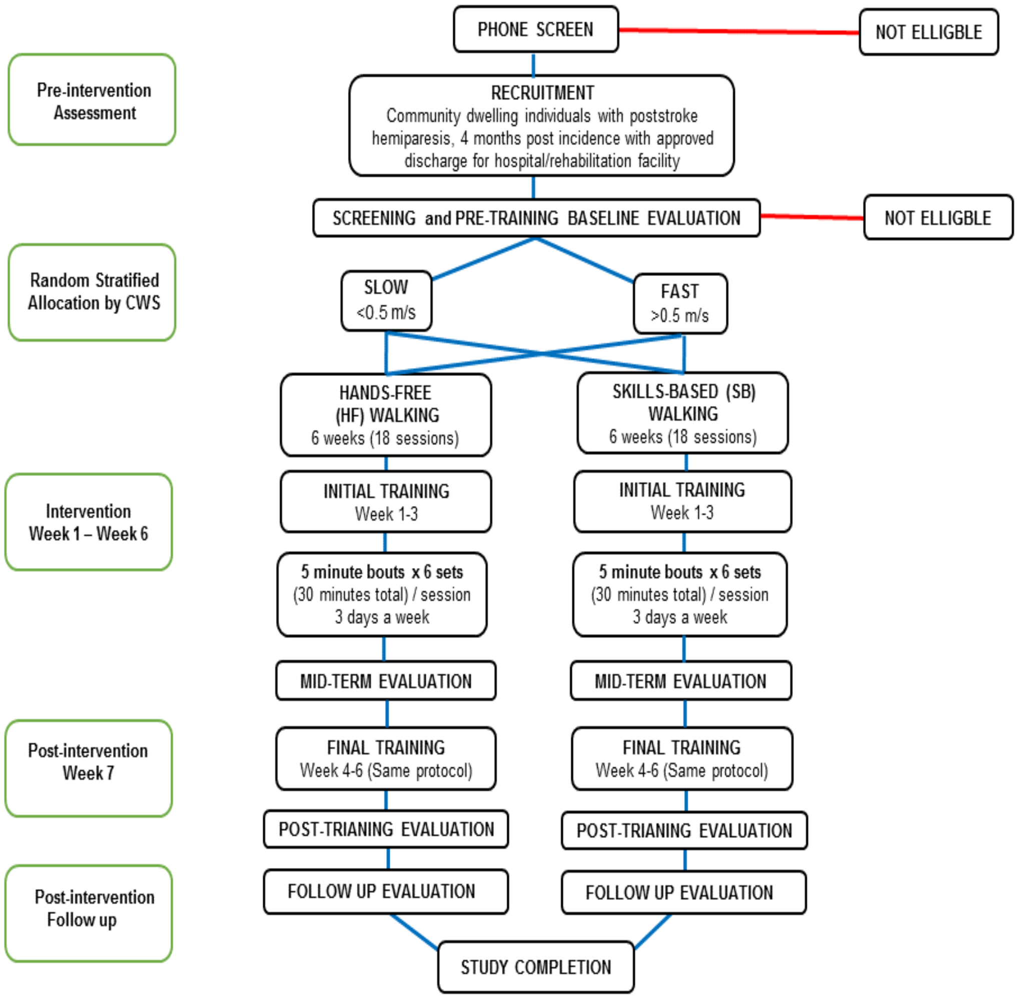


Figure 1: Study-flow for both paradigms from initial screening, randomization, and stratification to training (6 weeks) with follow-up at 6-months. *CWS: comfortable walking speed.

Both groups trained on a novel robotic treadmill interface, which consists of a robotic-assistive device, called the KineAssist (KA; HDT Robotics, Salon Ohio, US) [29,30], synced to a Bertec treadmill [31]. The KA has been used in various studies to investigate both poststroke and nonimpaired walking biomechanics under different conditions [29,31-34]. The KA interacts with an individual walking inside it through a pelvic harness that secures their hips and waist through flexible cloth straps (Figure 2). The pelvic harness is attached to the KA's pelvic mechanism that rests at the height of the individual's center of mass (COM) and can provide vertical BWS (for a maximum body weight of 350 pounds and maximum height of 6 feet 5 inches). Two bidirectional force transducers at each hip enable the mechanism to sense drops in height and essentially *catch* the individual in the event of a misstep or loss of balance. This feature provides a safe environment and prevents falls during training. In addition, the force transducers and treadmill belt are paired through software to form a "force-velocity relationship"; the transducers sense the net force applied to the pelvic mechanism and send a signal to move the treadmill belt, making it an intent-driven treadmill. Thus, an individual walking inside the interface can control the speed of the treadmill and walk at their self-selected CWS (ie, intent-driven), with or without varying levels of BWS.

Unlike nonrobotic environments that use motorized treadmills combined with overhead BWS harness systems, with or without handrails/external support [17, 35, 36], the KA interface eliminates reliance on any external support and offers the user control over their own gait speed through the intent-driven treadmill. When the *safety-catch* feature is triggered, force rings on either arm of the pelvic mechanism (see Figure 2) allow the researcher/therapist to interactively assist the individual back to a standing position by amplifying applied forces to each ring in the vertical direction. Thus, participants learn to address their falls and stumbles inside the interface as "errors" that they can then learn to formulate strategies to prevent, as opposed to developing fears and avoiding walking behaviors that might trigger them. The pelvic mechanism also allows movement of the COM in all 3 planes through 6 degrees of freedom (DOF). Unlocking the DOFs enables the individual to explore their limits of stability, whereas locking the

DOF provides external stability for those with poor balance. This feature is unique in comparison with other robotic devices, which offer limited mobility or mobility in only one plane [37]. A trunk harness also secures the individual's trunk when they walk inside the device and prevents excessive forward lean. The KA requires a short participant setup time (5-10 min) with assistance of only 2 individuals, due to a simple computerized user interface and an easily customizable pelvic mechanism. In comparison, more sophisticated robotic treadmill gait trainer systems or nontreadmill-based robotic exoskeleton systems tend to have a long setup time and require more than 2 individuals to help set up a participant [38-40]. We have previously published details on walking biomechanics in the KA interface and its different modes in another paper [25]. However, for this study, we used 3 distinct modes of the KA treadmill interface with and without varying levels of BWS:

1. Intent-driven mode: Uses the KA's force-velocity software relationship, which allows participants to drive the belt at their self-selected CWS.
2. Joystick mode: Enables the researcher/therapist to control (externally) the speed of the treadmill belt using a joystick controller. This mode is similar to a typical motor-driven treadmill; however, the operator is able to impose smooth or abrupt speed transitions via the KA software. We used this mode during HF+C training for speeding up and slowing down tasks.
3. KA software modifications: In either of the aforementioned modes, we used the KA software to create some of the 9 essential challenging mobility for the HF+C group. For example, using the joystick mode, we could additionally program variable speed

changes, which abruptly changed the speed of the motorized treadmill belt at random intervals. In another instance, we programmed perturbations that disrupted an individual's forward progression, while walking in the intent-driven mode.

Training Paradigms

Hands-free body weight support gait training

This group served as our "control," in that participants did not perform any additional essential challenging mobility skills during their 6-week training period. We felt that the inclusion of an active training control group was necessary to determine if adding essential challenging mobility skills practice to a gait-training program would improve walking outcomes above and beyond improvements gained from walking practice alone. However, it is important to note that because of the safety features of our robotic device, we were able to eliminate provision of handrail support and/or manual assistance from the clinician. Although walking upright with handrail support can provide sufficient training challenge and fall safety, because of poor hemiparetic trunk-control poststroke, survivors are likely to adopt stooped postures by leaning forward and holding onto handrails for trunk support [41]. Such postures not only decrease training intensity and metabolic output but also minimize functional improvements [42, 43]. Thus, treadmill training without handrail support can offer a more practical dynamic balance challenge that pertains to real-world independent ambulation. In addition, we did not offer participants any walking instructions (eg, how to step or correct their movements) and did not offer any passive assistance during training. Our governing principle regarding walking rehabilitation post stroke was to provide the individual with a safe environment to practice walking, solve the problem, and learn from mistakes during training. We followed AHA guidelines for exercise training [16]. Participants in this group walked for a total duration of 30 min per session, at 60% to 80% of their heart rate (HR) reserve (ie, moderate to high intensity) based on the Karvonen formula [44] with or without their prescribed BWS level (ie, between 0 and 30% support; assigned as described below). By taking advantage of the KA interface's safety mechanism and DOF, participants in this group were able to explore their limits of stability while controlling the treadmill belt speed, and thus, train independently without assistance or external support.

Challenge with hands-free body weight support gait training

This group served as our "experimental" group, in that participants additionally performed 9 different essential challenging (C) mobility skills, along with HF walking during their 6-week training period (Table 1). The purpose of practicing these 9 essential training challenges along with HF walking was to offer participants opportunities to navigate through common environmental hazards that they may encounter during community ambulation. This protocol was innovative, as it involved exposing stroke survivors to challenging tasks that required strong skills in anticipatory and reactive balance and functional mobility. The KA's safety features allowed us to provide participants with this experience and to treat losses of balance or stumbles as "learning experiences," from which participants could learn to formulate new strategies without any negative consequences. At the start of each training week, the program coordinator would randomly select and assign 3 challenges for each session using a random number generator [28]. Participants practiced training for each of the 3 skills for 30 min (10 min per skill), without handrail support at 60% to 80% of their HR reserve intensity per session. We did not have a prescribed challenge progression for each skill; however, we encouraged participants to perform each skill at a level that was challenging for them (see task difficulty, Table 1).

Table 1. Description of the 9 essential locomotor challenges used in training the challenge and hands-free (challenge with hands-free walking) group.

Challenge task	KA interface mode	Rationale	Training practice	Task difficulty
Long stepping	KA[a] self-drive mode	To step over common environmental hazards, for example, puddles	Using infrared laser beams, we defined a visual line on the treadmill surface in front of the participant's feet participants instructed to take long steps, such that the heels of both feet crossed the line	If the participant was able to consistently step over the line, the distance was increased by 1-inch increments
Speeding up and slowing down	KA joystick mode	To improve the ability to speed and slow down during ambulation	The training staff the controlled the belt speed for 20 s at individual's CWS[b], 20 s at double their CWS, and 20 s at CWS per each minute of training	If the participant was able to successfully keep up with the fast speed, the top speed increased by 0.2 m/s
Head turns	KA self-drive mode	To simulate the need to look in different directions while walking in the community	Participants walked at their CWS. Every 10 s, staff provided instructions to turn the head either right, left, up, or down, and maintain it for 10 s	If the participant maintained walking speed with head turns, they were instructed to shake their head side-to-side or up/down for 10 s each

Variable walking speeds	KA joystick mode	To improve reactionary balance and gait speed control	KA software controlled the treadmill belt speed within a range of the participants' CWS±0.2 m/s. Participants adapted to abrupt changes in speed	If the participant was able to successfully maintain balance and walk comfortably, speed ranges were increased by 0.2 m/s
Hurdles	KA self-drive mode	To improve ability to step over objects in the environment (eg, curb)	Participants were instructed to walk at their CWS while stepping over a hurdle positioned at height to challenge foot clearance; 5 min practice per foot	If participants consistently cleared the current hurdle height, height increased by 1-inch increments
Perturations	KA self-drive mode	To improve reactionary balance control	Participants were instructed to walk at their CWS, while experiencing abrupt disturbances (ie, brief backward accelerations) to forward progression delivered by the KA software	If participants walked through forward perturbations without experiencing disturbances (ie, missteps or backward steps), the intensity of the perturbation would be increased
Backward walking	KA self-drive mode	To improve balance control, simulate instances where stepping backward to maneuver over obstacles	Participants walked backward	If the participant successfully walked backward, they were encouraged to step faster
Walking with foam shoes	KA self-drive mode	To improve ability proprioception, to walk on uneven	Participants walked with foam shoes strapped to their typical footwear. Shoes ranged from 2	If the participant successfully maintained their CWS, the height of the foam shoes

		surfaces, and stepping height	to 6 inches in thickness	increased from 4 to 6 inches in thickness
Narrow stepping	KA self-drive mode	To decrease reliance on external support and improve dynamic balance	Participants walked on a straight infrared while taking narrow steps at their self-selected CWS without hand support or manual assistance	If the participant successfully maintained their CWS, they were verbally encouraged to walk faster

Note: [a]KA: KineAssist. [b]CWS: comfortable walking speed (m/s).

Intervention Protocol for Each Training Session

This training protocol comprised 6 weeks of 18 total training sessions for both groups (summary in Table 2). Each group trained 3 times per week with alternate rest days to prevent undue fatigue.

Table 2. Summary of the hands-free and challenge with hands-free walking intervention training parameters.

Intervention	**Hands-free walking**	**Challenge+hands-free walking**
Duration	6 weeks	6 weeks
Total sessions	18 sessions	18 sessions
Weekly training	3 days a week	3 days a week
Session duration	1 hour	1 hour
Intervention duration	30 min	30 min
Training speed	Comfortable walk speed at chosen BWS[a] level	Comfortable walk speed at chosen BWS level
Intervention goal	Perform 30 min of walking at fastest 10MWT[b] with/without BWS as prescribed	Perform 30 min of walking at fastest 10MWT with/without BWS while performing additional walking skills

Session design	5-min bouts × sets, or as long as continuously tolerated	5-min bouts × 6 sets, or 10-min bouts × 3 sets to allow for skill changes
Session goal	Target 60% to 80% of heart rate reserve during all trials	Target 60% to 80% of heart rate reserve during all trials
Locomotor challenge	Hands-free and without manual assistance	3 new randomized locomotor total challenges per day × 3 sessions=9 per week
Instruction	Maintain heart rate in the target zone while walking	Maintain heart rate in the target zone while performing different walking skills
Physiological measures monitored	Heart rate—using heart rate, monitor each minute; rate of perceived exertion—using Borg scale every 2 min; blood pressure—pre/post	Heart rate—using heart rate monitor each minute; rate of perceived exertion—using Borg scale every 2 min; blood pressure—pre/post
Additional session measurements	Total number of steps (using step watch) and distance covered (using distance wheel)	Total number of steps (using step watch) and distance covered (using distance wheel)
Rest breaks	Every 5 min if necessary; standing breaks if heart rate exceeded zone; voluntary breaks if requested by participant (rare)	Every 5 min if necessary; standing breaks if heart rate exceeded zone; voluntary breaks if requested by participant (rare)
Training personnel	Physical therapist × 1; research assistant × 1	Physical therapist × 1; research assistant × 1
Training setting	Clinical laboratory	Clinical laboratory

Note: [a]BWS: body weight support. [b]10MWT: 10-meter walk test.

Participant body weight support level determination for each training session

We used a unique approach to determine BWS levels for all participants for each training session. Instead of automatically applying a specific level of BWS for all participants, we instead allowed BWS to vary per training day, depending on the participant's fastest CWS inside the device. At the start of each session, participants walked in the self-drive mode for 5 m at 4 different levels of BWS (0%, 10%, 20%, and

30%). Some of the taller individuals were unable to use 30% because of height constraints of the KA (n=5). We calculated 10-m walk speed at each level of BWS and selected the participant's fastest CWS using a speed difference of ≥0.08 m/s faster than 0%. The participant used this level of BWS to train for the session. This method ensured each participant's BWS levels were individualized, unbiased, and varied according to their optimal walking speed performance. We were interested in whether participants would gradually decrease BWS over the duration of the training protocol.

Participant training intensity heart rate zone determination for each training session

Before commencement of each training session, we documented the participant's baseline blood pressure and HR for individuals in both training groups. We calculated the maximum HR for each participant using their age (ie, HR_{max}=220 − age) and calculated the desired 60% to 80% training intensity using the Karvonen formula (ie, training intensity=(max HR − resting HR) × (desired %) + resting HR) based on AHA training recommendations [16]. If the participant was taking a beta-blocker, we revised this formula to use a max HR calculated as HR_{max}=164 − age [45]. Thus, we individually customized the participant's training intensity for each session. We encouraged participants to walk fast enough during training to achieve these zones; however, we also measured rating of perceived exertion (RPE; see below) to obtain a proxy measure of training intensity in the event that HRs did not reach the desired intensity. We used a GARMIN HR monitor that was strapped to each participant's chest to record actual HR measurements for each session. We recorded HR values each minute; thus, we recorded a total of 30 HR values per training session (6 × 5-min bouts=30 min).

Recording training intensity rating of perceived exertion for each training sesion

We used the Borg Scale (ie, 6 to 20) [46,47] to solicit RPE values from participants every 2 min during training. We were interested in not only participants' general perceived training difficulty but also in which of the 9 skills would elicit the highest RPE values from participants in the HF + C group.

Recording total number of steps taken and distance covered per training session

For both groups, we recorded the total number of steps taken per session using a step watch (Orthocare Innovations), strapped around the participant's nonaffected ankle. We also recorded the total distance covered per training session using a Stanley distance wheel. We positioned and secured the wheel at the front of the treadmill belt and measured the distance of the moving belt while the participant walked during their training session.

Session duration, approach, and progressions

Although participants in both groups had to complete 30 min of training, each single session lasted for a total of 90 min. This included the time for baseline and post measurements/calculations (ie, blood pressure and HR), setting up the HR monitor, determination of BWS level for training, and intervention trials with/without rest breaks. Although we encouraged participants to continuously train for 30 min, we recognized that participants might not have the necessary cardiovascular endurance to continually train for 30 min. Hence, we divided each training session into six 5-min bouts. We gave participants the option to take a seated or standing rest break after completion of each 5-min bout or combine multiple bouts (ie, 10 or more continuous minutes) followed by a rest. Thus, participants could individualize their training sessions, according to their comfort and ability. We encouraged all participants, regardless of their starting point, to aggregate more bouts as they progressed with training. Research assistants, conducting the training session, verbally encouraged participants while training to maintain their CWS and finish each training bout. However, they did not provide any manual assistance or external support during training.

Criteria for successful training session completion

Although we encouraged all participants to complete their target 30 min of training per session, we used a threshold mark of 20 min to deem a session as “complete” and include it as a data point. If a participant did not achieve the minimum of 20 min, they had to repeat the session. At the completion of each session, we documented the above-described variables and entered them into a database. The PI and program coordinator monitored this database to ensure adequate study progress and safety of all participants.

Total time taken for each training session visit

Participants on an average spent 1 to 1.5 hours per training session. This included the time for evaluation and measurement of baseline parameters (blood pressure and HR), choosing appropriate BWS level, training for 30 min (including rest breaks), and final posttraining blood pressure, HR measurement, restroom breaks, and drop-off and pick-up wait. We, thus, instructed participants to keep aside 2 hours on the days they were training and up to 3 hours on the days they were assessed.

Participant compensation

We compensated participants (US $10 per hour) for the days we assess and trained them.

Participant adherence and missed session makeover

Our goal was to provide adequate rest by alternating training days with rest days per week. To support participant adherence, the program coordinator worked with participants to pick alternate training days (3 times a week) and time slots during those days that suited the participant's schedule. However, if a participant was not able to attend their session, we rescheduled it for 1 of the 2 free days of their training week. We requested participants to keep at least 2 hours aside for training on the days that they committed to come, and up to 3 hours aside for the days they would be assessed. We instructed participants that it was critical that they did not miss any training sessions and enrolled participants only after they had finished any travel obligations that would have interfered with their training. In addition, the program coordinator would also call and remind participants, a day before their training session, to come for training. If participants did not have a personal means of transport to come to the LocoLab for training, we arranged for alternate local public transport options, for example, local government run bus/van service. We also limited participants from rescheduling and extend their training sessions to a maximum of 7 consecutive weeks, to complete their 18 sessions, taking into account any rescheduled sessions because of personal commitments and/or national holidays. Participants were allowed a total of 5 rescheduled sessions.

Minimizing variability in application of procedures

We ensured that a minimum of 2 research staff members, one being a physical therapist, trained every participant during each training session. In total, we had 10 different research staff members, including 3 physical therapists, who regularly rotated and conducted all the training sessions to minimize expectation bias. The PI oversaw all training sessions and ensured strict adherence to all training protocols for both groups. The program coordinator and PI reviewed the progress of both training groups weekly and checked if all data were correctly documented. We ensured that no cointervention contamination occurred, by asking participants to refrain from attending any active lower limb physical therapy programs or participating in any walking intervention studies outside of our study.

Reporting of adverse events

We defined an adverse event as an event that occurred during or after the training session when the participant was at the training site and trained staff members to report any adverse event pertaining to -

1. Fall to the ground (defined as an unintentional loss of balance)
2. Any symptoms of angina or myocardial infarction
3. Any musculoskeletal injury during/after session training
4. New stroke or transient ischemic attack

5. Hospitalization for any cause
6. Death due to any cause.

Participants were also encouraged to report any symptoms (pain, soreness, numbness, etc) or signs of injury (inflammation, blisters, etc) that they experienced following training on returning home.

Standard precautions

We used the same standard precautions for both training groups and modified them for each individual participant, after evaluation and recommendation by the PI. These included the following:

1. Decrease in exercise intensity for systolic blood pressure greater than 200 mm Hg or diastolic blood pressure greater than 100 mm Hg.
2. Decrease in exercise intensity, if HR was greater than 75%.
3. Pause in training on observation of dyspnea or if blood pressure dropped below resting pressure.
4. Pause in training if participant reported symptoms of light-headedness.

Assessments

We used various functional mobility assessments at different time points - pretraining (baseline), midterm, posttraining (final), and 6-month follow-up, conducted by the physical therapist on our study at the LocoLAB. We used the 10-meter walk test to measure participants' CWS and fast walking speed (FWS) [48], and the 6-min walk test (6MWT) [49] to measure walking capacity using an 85-feet oval walkway. At baseline, participant's hemiparetic severity and ambulation category were classified using the lower extremity Fugl-Meyer, and functional ambulation category scale [50], respectively. We also used the Mini-Mental Scare Examination as a screening tool for participants' cognitive function (>24) [51]. We also used the Berg-Balance Scale (BBS) [52] and Dynamic Gait Index [53] to measure participants' balance function. We used the Activities-specific Balance Confidence (ABC) scale [54] to evaluate participants perceived balance function during activities of daily living, and the Geriatric Depression Scale (GDS) [55] and Stroke Impact Scale (SIS) [56] to assess participant's mental function and perceived impact of poststroke disability on their quality of life, respectively. Participants were assessed at baseline, midterm, final (after 6 weeks), and at 6-month follow-up. Table 3 describes the assessments performed during these periods.

Table 3. Timeline for assessments and collection of outcome variables at various study stages.

Baseline	**Midterm**	**Final**	**6-month follow-up**
Comfortable walk speed (CWS)	CWS	CWS	CWS
Fast walk speed (FWS) using	FWS	FWS	FWS
10-meter walk test (10MWT)	6MWT	6MWT	6MWT
6-min walk test (6MWT)	BBS	BBS	BBS
Fugl-Meyer lower extremity score	GDS	GDS	GDS
Functional Ambulation Category	-	DGI	DGI
Berg Balance Scale (BBS)	-	ABC	ABC
Dynamic Gait Index (DGI)	-	SIS	SIS
Geriatric Depression Scale (GDS)	-	-	-
Stroke Impact Scale (SIS)	-	-	-
Activities-Specific Balance Confidence (ABC)	-	-	-
Mini-Mental State Examination (MMS)	-	-	-

Primary outcome measure

As change in over-ground CWS is an important, valid, sensitive, and reliable measure of poststroke recovery and walking function [57], we chose difference in CWS between groups, from pre- to posttraining as our primary outcome measure [58,59]. On the basis of our power analysis, we planned to include baseline-walking speed as a covariate, if it was significantly related to CWS at pre- and posttraining.

Secondary outcome measures

We plan to report descriptive data on the following secondary exploratory outcome measures: FWS, 6MWT, BBS, GDS, SIS, and ABC scores, with mean and SDs. However, we will not include these variables in our main analysis, as we are not appropriately powered to include them.

Subgroup analysis

In addition to these main assessment measures, we also recorded BWS levels, HR, and RPE exertion changes, total number of steps, and distance covered during each session, for participants in both training groups. Descriptive data analysis along with subgroups comparative analysis will be performed on these variables, from pre- to postintervention and on a week-by-week basis, and will be reported in another manuscript. We will also assess feasibility and compliance of each group to either intervention, along with ability to maintain target HR intensity during training. These subgroup analyses will help in better understanding the impact of training on functional walking outcomes and impact on community ambulatory function.

Survey data analysis

Participants in both groups also completed our custom-designed study survey at the end of each training week. The survey consisted of questions on the 9 essential challenging mobility skills that we identified using the research criteria specified by Patla et al [26]. The survey questionnaire consisted of the following 3 subparts: (1) identify which of the 9 essential challenging mobility skills you have difficulty with in your daily life (using yes/no responses); (2) rank in order of importance (1-9), which of the 9 essential mobility skills is most important for you in improving walking function; and (3) respond to specific questions on your training experiences (using a Likert scale 1-7; see Multimedia Appendix 2). We will assess survey data responses for change in responses, ranking of task difficulty, and change in Likert scale scores, respectively.

Criteria for data analysis

We will only be considering those participants in our final analysis, as a data point, if they completed their first week of training. Participants will not be included in our final analysis if they were unable to complete the first week of training, for reasons such as personal time limitations, conflicting time commitments, family crises, and personal psychological factors such as depression and medical procedures.

Results

Total participants enrolled in our study

We assessed 77 individuals with chronic mild to moderate hemiparesis, and excluded 38 individuals who did not meet our inclusion criteria, from June 2012 to

January 2015. We enrolled and randomized a total of 39 individuals post stroke for our study, with 19 participants in the HF group and 20 participants in the HF+C group. Data collection along with 6-month follow-up continued until January 2016. Detailed results of this study will be presented in 2 subsequent manuscripts.

Proposed statistical methods

We will assess normality and homogeneity of data for all outcome measures in both groups. If possible, we plan to conduct an intention-to-treat analysis. We will compare our primary measure in both groups from pre- to postassessment using an ANCOVA at a significance level of $P<.05$, with the covariate being baseline CWS, if significantly related to change in CWS from pre- to posttraining. As all our secondary outcome measures are exploratory in nature, we will use a repeated measures design for comparing changes from baseline, midterm, final assessment, and at 6-month follow-up, at a significance level of $P<.05$, with post hoc analysis. For our survey data, we will compare changes between the first and last training sessions using Spearman correlation for the yes/no responses question, a Wilcoxon rank-sum test for the rank order question, and chi-square analysis for Likert scale responses. A subsequent manuscript will have detailed description of our data analysis methods and statistical tests.

Discussion

Locomotor disability post stroke continues to impede stroke survivors from engaging in active community participation and negatively impacts their quality of life. Given the prioritization of improvement in walking function by stroke survivors and the

2014 AHA exercise training recommendation report, it is all the more vital that poststroke gait interventions incorporate task-specific essential challenging mobility skills, akin to real-world scenarios, along with training at higher cardiovascular intensities to improve functional gains [60]. Through our study, we explored 2 unique gait interventions, ie, HF walking and HF+C walking, using a novel and safe gait training environment to investigate functional ambulation capacity after 6 weeks of training. Our study results will yield important insight on whether individuals post stroke can train at higher intensities, especially while walking without any external handrail support or passive manual assistance at their preferred self-selected BWS level (HF walking) or when practicing essential challenging mobility skills with HF walking (HF+C walking). Although our primary outcome measure is change over-ground CWS, we have also collected various secondary exploratory measures and survey data for both training paradigms. As our secondary measures are most commonly used in clinical settings to assess functional ambulatory capacity, we hope these variables will inform future poststroke studies that plan to use similar gait training paradigms. Our main study outcomes and week-by-week training analysis are being presented in 2 separate manuscripts, respectively. We hope that the results of this study will help in better informing clinicians and researchers on how real-world balance challenges can be incorporated to improve the selection of treadmill training protocols to improve functional walking capacity for individuals post stroke.

Acknowledgments

This study received funding from the National Institute of Disability Independent living and Rehabilitation Research (NIDLRR) 90IF0045-01-00. This grant was awarded to DAB. The authors would like to acknowledge the following LocoLAB members who helped with training and data collection: Deanna Rumble, MS; Sarah Graham, MA; Christopher Mullens, BS; Carmen Capo-Lugo, PT, PhD; Tara Pearce, PT; Valdeci Dionisio, PhD; Adam Wieckert, BS; Ender Ayvat, BS (Physiotherapy); Charlotte Wattes, MS; Katie Willis, BA; and Meghan O'Malley, BS.

Author's contribution

DAB and EJR conceived the study; DAB acted as the PI, and EJR was a coinvestigator. AN assisted in training protocols and data collection and drafted the manuscript. All authors contributed to editing the manuscript, read, and approved the final manuscript.

Conflicts of interest

DAB is a consultant to HDT Global, the company that markets and sells the device mentioned in this paper. DAB is also a named inventor on the intellectual property associated with the device and does receive royalties for any sales of the device. AN and EJR do not have any conflicts of interests to declare.

Abbreviations

6MT: 6-min walk test

10MWT: 10-meter walk test

ABC: Activities-Specific Balance Confidence scale

AHA: American Heart Association

ANCOVA: analysis of covariance

BBS: Berg Balance Scale

BWS: Body weight support

COM: center of mass

CWS: comfortable walking speed

DOS: degrees of freedom

FWS: fast walking speed

GDS: Geriatric Depression Scale

HF: hands-free

HF+C: challenge and HF walking

HR: heart rate

KA: KineAssist

KA interface: KineAssist treadmill interface

PI: principal investigator

RPE: rate of perceived exertion

SIS: Stroke Impact Scale

UAB: University of Alabama at Birmingham

References

1. Writing Group Members. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler 3rd ER,Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, ReevesMJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB, American Heart Association Statistics Committee. Stroke Statistics Subcommittee ExecutiveSummary: Heart Disease and Stroke Statistics--2016 Update: A Report From the American Heart Association. Circulation. 2016 Jan 26;133(4):447–54.

2. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol.2009 Aug;8(8):741–54.

3. Balaban B, Tok F, Yavuz F, Yaşar E, Alaca R. Early rehabilitation outcome in patients with middlecerebral artery stroke. Neurosci Lett. 2011 Jul 12;498(3):204–7.

4. Patterson KK, Mansfield A, Biasin L, Brunton K, Inness EL, McIlroy WE. Longitudinal changes inpoststroke spatiotemporal gait asymmetry over inpatient rehabilitation. Neurorehabil Neural Repair. 2015 Feb;29(2):153–62.

5. Chen G, Patten C, Kothari DH, Zajac FE. Gait differences between individuals with post-stroke hemiparesis and non-disabled controls at matched speeds. Gait Posture. 2005 Aug;22(1):51–6.

6. Tilson JK, Wu SS, Cen SY, Feng Q, Rose DR, Behrman AL, Azen SP, Duncan PW. Characterizing and identifying risk for falls in the LEAPS study: a randomized clinical trial of interventions to improve walking poststroke. Stroke. 2012 Feb;43(2):446–52.

7. Weerdesteyn V, de Niet M, van Duijnhoven HJ, Geurts AC. Falls in individuals with stroke. J Rehabil Res Dev. 2008;45(8):1195–213

8. Divani AA, Majidi S, Barrett AM, Noorbaloochi S, Luft AR. Consequences of stroke in communitydwelling elderly: the health and retirement study, 1998 to 2008. Stroke. 2011 Jul;42(7):1821–5.

9. Rimmer JH, Chen MD, McCubbin JA, Drum C, Peterson J. Exercise intervention research on persons with disabilities: what we know and where we need to go. Am J Phys Med Rehabil. 2010 Mar;89(3):249–63.

10. Bohannon RW, Horton MG, Wikholm JB. Importance of four variables of walking to patients with stroke. Int J Rehabil Res. 1991;14(3):246–50.

11. Bogey R, Hornby GT. Gait training strategies utilized in poststroke rehabilitation: are we really makinga difference? Top Stroke Rehabil. 2007;14(6):1–8.

12. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. J Speech Lang Hear Res. 2008

13. Nielsen JB, Willerslev-Olsen M, Christiansen L, Lundbye-Jensen J, Lorentzen J. Science-based neurorehabilitation: recommendations for neurorehabilitation from basic science. J Mot Behav.2015;47(1):7–17.

14. Hornby TG, Straube DS, Kinnaird CR, Holleran CL, Echauz AJ, Rodriguez KS, Wagner EJ, Narducci EA. Importance of specificity, amount, and intensity of locomotor training to improve ambulatory function in patients poststroke. Top Stroke Rehabil. 2011;18(4):293–307.

15. Macko RF, Ivey FM, Forrester LW. Task-oriented aerobic exercise in chronic hemiparetic stroke: training protocols and treatment effects. Top Stroke Rehabil. 2005;12(1):45–57.

16. Billinger SA, Arena R, Bernhardt J, Eng JJ, Franklin BA, Johnson CM, MacKay-Lyons M, Macko RF,
Mead GE, Roth EJ, Shaughnessy M, Tang A, American Heart Association Stroke Council. Council on Cardiovascular and Stroke Nursing. Council on Lifestyle and Cardiometabolic Health. Council on Epidemiology and Prevention. Council on Clinical Cardiology Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 Aug;45(8):2532–53.

17. Charalambous CC, Bonilha HS, Kautz SA, Gregory CM, Bowden MG. Rehabilitating walking speed poststroke with treadmill-based interventions: a systematic review of randomized controlled trials. Neurorehabil Neural Repair. 2013 Oct;27(8):709–21.

18. Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, Nadeau SE, Dobkin BH, Rose DK, Tilson JK, Cen S, Hayden SK, LEAPS Investigative Team Body-weight-supported treadmill rehabilitation after stroke. N Engl J Med. 2011 May 26;364(21):2026–36.

19. Swinnen E, Beckwée D, Meeusen R, Baeyens J, Kerckhofs E. Does robot-assisted gait rehabilitation improve balance in stroke patients? A systematic review. Top Stroke Rehabil. 2014;21(2):87–100.

20. Dobkin BH, Duncan PW. Should body weight-supported treadmill training and robotic-assistive steppers for locomotor training trot back to the starting gate? Neurorehabil Neural Repair. 2012May;26(4):308–17.

21. Mansfield A, Aqui A, Centen A, Danells CJ, DePaul VG, Knorr S, Schinkel-Ivy A, Brooks D, Inness EL, McIlroy WE, Mochizuki G. Perturbation training to promote safe independent mobility post-stroke:study protocol for a randomized controlled trial. BMC Neurol. 2015 Jun 06;15:87.

22. Mehrholz J, Pohl M, Elsner B. Treadmill training and body weight support for walking after stroke.Cochrane Database Syst Rev. 2014 Jan 23;(1):CD002840.

23. Hammer A, Nilsagård Y, Wallquist M. Balance training in stroke patients – a systematic review of randomized, controlled trials. Adv Physiother. 2009 Jul 11;10(4):163–172.

24. Dionisio VC, Brown DA. Collaborative robotic biomechanical interactions and gait adjustments in young, non-impaired individuals. J Neuroeng Rehabil. 2016 Dec 16;13(1):57.

25. Patla AE, Shumway-Cook A. Dimensions of mobility: defining the complexity and difficulty associated with community mobility. J Aging Phys Act. 1999 Jan;7(1):7–19.

26. Perry J, Garrett M, Gronley JK, Mulroy SJ. Classification of walking handicap in the stroke population. Stroke. 1995 Jun;26(6):982–9.

27. Haahr M. Random. 2010. Apr 02, [2018-03-30]. https://www.random.org/integers/ *webcite*.

28. Patton J, Brown DA, Peshkin M, Santos-Munné JJ, Makhlin A, Lewis E, Colgate EJ, Schwandt D.KineAssist: design and development of a robotic overground gait and balance therapy device. Top Stroke Rehabil. 2008;15(2):131–9. doi: 10.1310/tsr1502-131

29. Peshkin M, Brown DA, Santos-Munné JJ, Makhlin A, Lewis E, Colgate EJ, Patton J, Schwandt D.KineAssist: a robotic overground gait and balance training device. IEEE 9th International Conference on Rehabilitation Robotics; June 28-July 1, 2005; Chicago, US. IEEE; 2005. Jun 28,

30. Wang J, Hurt CP, Capo-Lugo CE, Brown DA. Characteristics of horizontal force generation for individuals post-stroke walking against progressive resistive forces. Clin Biomech (Bristol, Avon) 2015 Jan;30(1):40–5.

31. Hurt CP, Burgess JK, Brown DA. Limb contribution to increased self-selected walking speeds during body weight support in individuals poststroke. Gait Posture. 2015 Mar;41(3):857–9.

32. Capó-Lugo CE, Mullens CH, Brown DA. Maximum walking speeds obtained using treadmill and overground robot system in persons with post-stroke hemiplegia. J Neuroeng Rehabil. 2012 Oct 11;9:80.

33. Burgess JK, Weibel GC, Brown DA. Overground walking speed changes when subjected to body weight support conditions for nonimpaired and post stroke individuals. J Neuroeng Rehabil. 2010 Feb11;7:6.

34. Marchal-Crespo L, Reinkensmeyer DJ. Review of control strategies for robotic movement training after neurologic injury. J Neuroeng Rehabil. 2009 Jun 16;6:20.

35. Murray SA, Ha KH, Hartigan C, Goldfarb M. An assistive control approach for a lower-limb exoskeleton to facilitate recovery of walking following stroke. IEEE Trans Neural Syst Rehabil Eng. 2015 May;23(3):441–9.

36. Mehrholz J, Pohl M. Electromechanical-assisted gait training after stroke: a systematic review comparing end-effector and exoskeleton devices. J Rehabil Med. 2012 Mar 16;44(3):193–199.

37. Jezernik S, Colombo G, Keller T, Frueh H, Morari M. Robotic orthosis lokomat: a rehabilitation and research tool. Neuromodulation. 2003 Apr;6(2):108–15.

38. Hesse S, Werner C, Bardeleben A, Barbeau H. Body weight-supported treadmill training after stroke. Curr Atheroscler Rep. 2001 Jul;3(4):287–94. [PubMed: 11389793]
39. Hesse S, Werner C, von Frankenberg S, Bardeleben A. Treadmill training with partial body weight support after stroke. Phys Med Rehabil Clin N Am. 2003 Feb;14(1 Suppl):S111–23.

40. Chen G, Patten C. Treadmill training with harness support: selection of parameters for individuals with poststroke hemiparesis. J Rehabil Res Dev. 2006;43(4):485–98.

41. Berling J, Foster C, Gibson M, Doberstein S, Porcari J. The effect of handrail support on oxygen uptake during steady-state treadmill exercise. J Cardiopulm Rehabil. 2006;26(6):391–4.

42. Hofmann C, Dougherty C, Abkarian H, Fox M, Juris P. The reduction of metabolic cost while using handrail support during inclined treadmill walking is dependent on the handrail-use instruction. Int J Exerc Sci. 2014;7(4):10.

43. Karvonen J, Vuorimaa T. Heart rate and exercise intensity during sports activities. Practical application. Sports Med. 1988 May;5(5):303–11.

44. Tabet JY, Meurin P, Ben Driss A, Thabut G, Weber H, Renaud N, Odjinkem N, Solal AC. Determination of exercise training heart rate in patients on beta-blockers after myocardial infarction. Eur J Cardiovasc Prev Rehabil. 2006 Aug;13(4):538–43.

45. Noble BJ, Borg GA, Jacobs I, Ceci R, Kaiser P. A category-ratio perceived exertion scale: relationship to blood and muscle lactates and heart rate. Med Sci Sports Exerc. 1983;15(6):523–8.

46. Borg G, Hassmén P, Lagerström M. Perceived exertion related to heart rate and blood lactate during arm and leg exercise. Eur J Appl Physiol Occup Physiol. 1987;56(6):679–85.

47. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. Age Ageing. 1997 Jan;26(1):15–9.

48. Pohl PS, Duncan PW, Perera S, Liu W, Lai SM, Studenski S, Long J. Influence of stroke-related impairments on performance in 6-minute walk test. J Rehabil Res Dev. 2002;39(4):439–44.

49. Mehrholz J, Wagner K, Rutte K, Meissner D, Pohl M. Predictive validity and responsiveness of the functional ambulation category in hemiparetic patients after stroke. Arch Phys Med Rehabil. 2007 Oct;88(10):1314–9. doi: 10.1016/j.apmr.2007.06.764.

50. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189–98.

51. Blum L, Korner-Bitensky N. Usefulness of the Berg Balance Scale in stroke rehabilitation: a systematic review. Phys Ther. 2008 May;88(5):559–66.

52. An S, Jee YJ, Shin HH, Lee GC. Validity of the original and short versions of the dynamic gait index in predicting falls in stroke survivors. Rehabil Nurs. 2017;42(6):325–332.

53. Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) scale. J Gerontol A Biol Sci Med Sci. 1995 Jan;50A(1):M28–34.

54. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982;17(1):37–49.

55. Michaelsen M. Stroke Impact scale. In: Michalos AC, editor. Encyclopedia of Quality of Life and Well-Being Research. Dordrecht, Netherlands: Springer; 2014. pp. 6365–6368.

56. Schmid A, Duncan PW, Studenski S, Lai SM, Richards L, Perera S, Wu SS. Improvements in speedbased gait classifications are meaningful. Stroke. 2007 Jul;38(7):2096–100.

57. Bohannon RW, Andrews AW, Glenney SS. Minimal clinically important difference for comfortable speed as a measure of gait performance in patients undergoing inpatient rehabilitation after stroke. J Phys Ther Sci. 2013 Oct;25(10):1223–5.

58. Dickstein R. Rehabilitation of gait speed after stroke: a critical review of intervention approaches. Neurorehabil Neural Repair. 2008;22(6):649–60.

59. Dobkin BH. Training and exercise to drive poststroke recovery. Nat Clin Pract Neurol. 2008 Feb;4(2):76–85. doi: 10.1038/ncpneuro0709.

FORE-AFT RESISTANCE APPLIED AT THE CENTER OF MASS USING A NOVEL ROBOTIC INTERFACE TO PROPORTIONATELY INCREASE PROPULSIVE FORCE GENERATION IN NONIMPAIRED INDIVIDUALS WALKING AT A CONSTANT SPEED

by

NAIDU, A., GRAHAM, S.A., AND BROWN, D. A.

To be submitted to NeuroEngineering and Rehabilitation (JNER) journal

Format adapted for dissertation

ABSTRACT

Background

Proprioceptive limb-loading feedback during initial to mid stance facilitates limb-extensor mechanisms that enable propulsive force generation, appropriate to external requirements, during mid to terminal stance. Past studies have utilized external interfaces like resistive bands and motor-generated pulling systems to increase limb propulsion during treadmill walking at a constant speed. However, assessing limb propulsion against increasing resistance demands during self-controlled walking has not been undertaken.

Purpose

We assessed limb propulsion against increased fore-aft limb loading demands by applying graded fore-aft (FA) resistance at the center of mass (COM) during walking in a novel intent-driven treadmill environment that allowed participants to self-control their walking speeds. We hypothesized that to maintain a target speed; participants would proportionately increase their limb propulsion to applied resistance without increasing vertical forces. Additionally, we expected increases in propulsion would correspond with increases in training limb angle and positive joint work.

Methods

Seventeen nonimpaired participants (mean age 52 yrs, SD=11) walked at a target, self-controlled speed of 1.0 m/s, via treadmill-belt visual feedback, against 10%, 15%, 20%, and 25% (% body weight) fore-aft resistance levels. We primarily assessed linear slope values for mean propulsive impulse and secondarily analyzed mean propulsive force and vertical impulse of the dominant limb across all trials using one-sample *t*-tests. We further assessed changes in trailing and leading limb angles, stance times, and joint work

across all trials using one-way ANOVA's ($p \leq 0.05$) with Bonferroni corrections for post-hoc comparisons.

Results

Participants maintained target belt velocity of 1.0 m/s at most levels of applied FA resistance. They significantly increased propulsion proportional to FA resistance ($p<0.01$). Mean trailing limb angle increased ($p<0.05$), leading limb angle decreased ($p<0.05$), and positive joint work increased ($p \leq 0.01$) with higher levels of FA resistance.

Conclusions

These findings suggested that FA resistance applied during self-driven walking increases propulsive-force generation with accompanying biomechanical changes that facilitate greater limb propulsion. Rehabilitation interventions in neurological populations may utilize this principle to design task-specific interventions like progressive strength training and workload manipulation during aerobic training for improving walking function.

Index Terms— walking, fore-aft resistance, propulsion, biomechanics, treadmill-interface nonimpaired

INTRODUCTION

Walking is a complicated motor task that requires generation of lower-limb muscle forces that both propel and vertically support the body on a step-by-step basis [1]. During walking, proprioceptive limb-loading feedback via the Golgi-tendon organs (GTOs) and cutaneous sole receptors helps in regulating vertical support mechanisms (e.g., limb extension) during initial to mid stance and propulsive force generation during mid to terminal stance [2-4]. From a mechanical perspective, propulsive forces are the summation of the positive fore-aft component of the ground reaction force (GRF) vector, during mid to late stance, required to move the body's center of mass (COM) forward in the sagittal plane [5]. Similar generation of propulsive forces by each limb helps maintain interlimb symmetry, walking speed, and efficiency [6].

Considering the important role of stance-phase proprioceptive feedback on locomotor regulation, it is not surprising that various studies have investigated the effects of altering limb-loading dynamics on propulsive-force generation, walking speed, and walking energetics. Among these, some have focused on altering vertical-loading demands at constant and varying walking speeds using body-weight support (BWS)[7-12] or reduced gravity [13, 14]. These studies have highlighted how reducing body weight decreases propulsive-force generation while walking at constant speeds. Other studies have used both invasive and noninvasive procedures to demonstrate how reducing limb-loading proprioceptive feedback during walking decreases plantarflexor activity and propulsion generation during the second half of stance [4, 15]. Given that propulsive forces are generated in the fore-aft direction (anterior to posterior), remarkably few studies have explored the effects of altering stance phase fore-aft limb-loading demands without altering vertical-loading demands during walking [10]. These studies have mainly examined the effects of backward-directed resistance applied at the COM [10, 16-20] while walking at constant speeds, or on an uphill incline [10, 21-25] on increasing propulsion. However, participants in these studies walked on machine-driven treadmills programmed at constant speeds, which decrease requirements for muscle-force generation required to maintain speed, as evidenced by attenuated braking and propulsive force profiles.[26] Thus, investigation of walking function in such automated environments is not optimal to gauge the effects of altered proprioceptive limb-loading feedback on propulsive-force generation required to maintain speed.

Taking advantage of a unique robotic treadmill interface that allows individuals to control their self-selected walking speeds, we explored the effects of increasing fore-aft loading demands by using the interface to apply graded fore-aft (FA) resistance at the COM in specific percentages of vertical body weight (Newtons). We hypothesized that to maintain a target walking speed against increasing levels of FA resistance: 1) nonimpaired participants would proportionately increase propulsion without altering their vertical-force production; and 2) increases in propulsion would correspond with increases in trailing limb angle, stance time, and total positive limb work.

METHODS

Participants

Seventeen healthy, nonimpaired individuals (9 females), mean weight 179 lbs (SD=37), mean age 52 years (SD = 11) participated in this study after providing informed consent, approved by the Institutional Review Board of the University of Alabama at

Birmingham. We assessed safety for participation in low-to-moderate exercise using the Physical Activity Readiness Questionnaire (PAR-Q) form. We excluded participants with a history of severe cardiovascular, neurological, or musculoskeletal disorders that could affect their walking function or ability to perform mild physical activity. We assessed limb dominance by asking participants which limb they would use to stand on one leg, and baseline heart rate, blood pressure, and self-selected comfortable walking speed (10-meter walk test, mean speed=1.2 m/s (SD=0.03)) prior to study participation.

Experimental environment

We used the environment of an intent-driven robotic treadmill interface that consists of the KineAssist™ (KA) robotic device [27](HDT Global, Solon OH) synced to a dual-belt, force plate-instrumented Bertec treadmill (Figure 1) (BERTEC, Columbus, OH, USA).

We have previously published detailed descriptions of the control mechanics, walking biomechanics, and energetics in this device in both nonimpaired individuals and individuals poststroke [28-32]. Briefly, this interface consists of a pelvic mechanism with a pelvic harness that secures participants walking inside it through adjustable cloth straps around the waist and hips. The pelvic mechanism allows minimally impeded movement in the vertical, horizontal, and medio-lateral planes, providing a total of six degrees of freedom. However, for this study, we locked the pelvic mechanism to allow COM movement only in the fore-aft (relative to treadmill belts) and vertical directions of interest, to limit the effects of off-axis forces on propulsion generation.

A separate adjustable trunk harness, connected to the pelvic mechanism, secured the participant's trunk allowing forward-backward trunk tilting but preventing excessive forward lean. Two bidirectional force transducers located at the height of each hip (in the pelvic harness) sensed the net forces generated by the body and applied through the hip/pelvis interface, to control belt speed (as described in the next section). These optical encoders also track the vertical height of the mechanism and trigger a "safety-catch" feature, by sensing any drop in the pelvic mechanism height to "catch" the participant walking inside the device (at a preset height), thereby preventing a fall to the treadmill surface. Since the robotic system locked participants at a specific location on the treadmill belt, it prevented them from travelling forward or backward off the treadmill

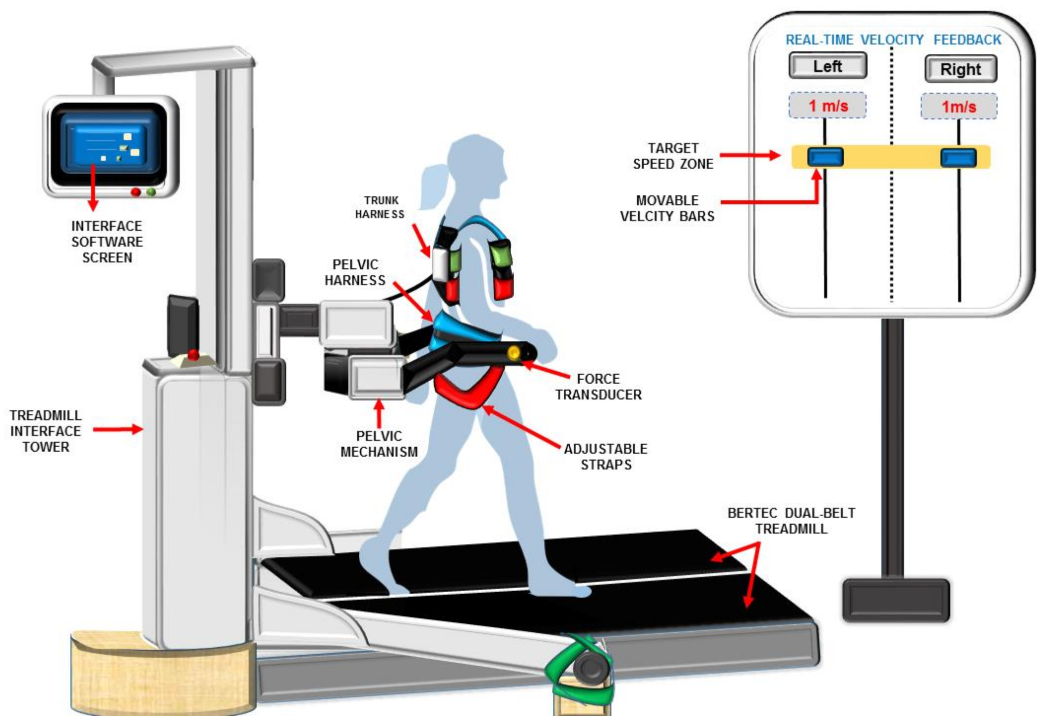


Figure 1: Participants walking inside the KineAssist (KA) split-belt treadmill interface using visual feedback via the interface's software output to target 1.0 +/- 0.2 m/s highlighted by a yellow target zone and, projected on a screen (at eye level)

belts. These collective features rendered our experimental environment safe for evaluation of self-selected walking speed function in different gait conditions.

Force-velocity relationship of KA split-belt treadmill interface

Participants walking inside the interface can control their walking speed using the interface's force-velocity relationship, which allows the investigator to set the required minimum net fore-aft force magnitude that participants must generate at the hip to initiate the treadmill belt motion. Once the belt starts moving, participants must increase their fore-aft force magnitude in order to attain and maintain a steady state walking speed. The two hip-force transducers record and relay these net forces to the main control system using a closed-loop haptic control algorithm, enabling participants to dictate the speed of each belt on a step-by-step basis, making the system "intent-driven" or "self-driven". We have previously shown that walking biomechanics in this environment are similar to typical treadmill walking [28, 31].

Application of different fore-aft resistance levels at target speed of 1.0 m/s

For this experiment, we selected a target walking speed of 1.0 m/s +/- 0.2 m/s i.e., target speed range, to account for the sinusoidal nature of normal walking. We felt that regardless of age or physical health, participants could safely target 1.0 m/s against increasing levels of FA resistance. Similar to the Gottschall and Kram study [16], we chose four FA resistance levels (10%, 15%, 20%, and 25%) taken as percentages of a participant's vertical body weight. We used an algorithm that took into account the participant's vertical body weight, interface control parameters, and the system's force-velocity relationship to calculate their target resistance levels. Thus, we normalized FA resistance by body weight for the same target speed using the equation:

$$\boldsymbol{b = y - mx}$$

Where **b** is the fore-aft resistance (Newtons) to move the belt at an intended speed, **y** is the percentage of vertical body weight (Newtons) needed to maintain treadmill belt movement at 1.0 m/s, **m** is the sensitivity constant of the interface (set for all participants at 50 N-sec/m that allows quick response of the belt with minimum delay (0.01 m/s)), and **x** is the target self-driven/self-controlled velocity of the tied-treadmill belts (1.0 m/s) (Example provided in supplemental section demonstrates FA resistance level calculations for one participant using the force-velocity relationship). In summary, we were able to calculate the proper magnitudes of FA resistance for each individual participant, regardless of body weight, that they had to overcome to maintain a target speed of 1.0 m/s.

Visual feedback

To ensure that participants maintained their target speed of 1.0 m/s, we provided real-time visual feedback of the tied treadmill-belt speed using the KA interface software. We projected the visual feedback onto a 5x6 foot projector screen, placed five feet from the treadmill interface (Figure 1). We highlighted the target-speed zone in a yellow block (displayed at eye level) and instructed participants to maintain their speed in the "yellow" zone i.e., 1.0 m/s ± 0.2 (SD), as walking is a cyclical motion and will fluctuate sinusoidally around a mean.

Data trials

After a suitable warm-up and familiarization period, participants completed four randomized FA resistance trials at a target speed of 1.0 m/s inside our interface. We collected data for each resistance level only after visually confirming that participants were able to achieve a steady-state gait pattern, by maintaining their target speed consistently for ten seconds. As we were mainly interested in short-term limb changes to FA resistance, each experimental trial was 40 to 60 seconds long, to enable participants to maintain target speed (initial few strides) and collect 30 strides (minimum) per limb. We continuously monitored heart rate using a GARMIN wrist monitor and provided participants with 30-second rest breaks after each resistance trial.

Overview of measures

We primarily assessed propulsive impulse i.e., the time integral of the positive fore-aft GRF during the second half of stance (Pimpulse (PI_{50}) = $\int$Fore-aft GRF × dt (50% stance)) i.e., period of propulsion (Fig.2.B). Secondarily, we also measured mean propulsive force (second half of stance) to ensure that changes in stance time were not affecting increases in propulsion along with stance time and stride time. Additionally, we also assessed vertical impulse during the entire stance phase to ensure that FA resistance was only affecting fore-aft loading and not modifying vertical loading or force generation in any way. As propulsion is associated with limb angle changes, we measured leading and trailing limb angle during stance. As supplementary measures, we calculated positive joint work for each joint and total positive work for the dominant limb, during the entire gait cycle, per FA resistance trial.

Data acquisition

We collected individual-limb GRFs via the Bertec instrumented treadmill, with kinetic data sampled at 1000 Hz. We also collected 3D kinematic data, sampled at 100 Hz, using an eight camera Qualisys motion capture system (Qualisys Inc., Gothenburg, Sweden) using 36 passive-reflective markers (1 cm diameter) placed bilaterally over anatomical landmarks (three markers per anatomical segment, and five markers over pelvis). We collected the real-time velocity of each treadmill belt and forces applied to the pelvic-mechanism force transducers (100 Hz) using our treadmill-interface's custom software.

Biomechanical data processing

We processed all data using custom MATLAB scripts (Mathworks®, version R2016b), and calculated all kinetic and kinematic variables either over the stance phase (ipsilateral heel strike to ipsilateral toe off) or over a complete gait cycle (ipsilateral heel strike to ipsilateral heel strike). We filtered all data using a low-pass Butterworth filter at a cutoff frequency of 15 Hz (kinetic) and 8 Hz (kinematic), respectively. We used Visual 3D (C-Motion, Germantown, MD, USA) to obtain joint powers for work calculations, but performed all kinematic data post processing via MATLAB using kinetic gait events (heel strikes and toe-offs with a threshold of 15 N) per limb. On an average, we included 30 complete strides per limb per participant for each FA resistance condition.

Kinetic gait variables

We normalized all kinetic (GRF) data to each participant's body weight (Newtons). We calculated all joint powers as the net muscle moment and joint angular velocity product ($P=M\times\omega$). For mechanical work, we normalized and integrated all joint powers (to body mass (W/kg)) during the entire gait cycle using the formula, $W = \int P \times dt$ (J/kg). All positive work values indicate power generation and negative work values indicate power absorption.

Statistical Analyses

We used SPSS (22 version) for all statistical analyses and checked that all primary and secondary dependent measures were normally distributed (Shapiro-Wilk's). For all kinetic GRF variables, to assess increasing or decreasing treads in propulsive- and vertical-force generation, we compared individual participant's (dominant limb) linear slope relationships across all FA resistance levels to zero using one-sample *t*-tests. We used separate one-way repeated measure's ANOVAs (repeated across resistance levels) for all secondary spatiotemporal variables, i.e., stance time, stride time, limb angles and individual belt speed (control variable), along with individual positive ankle, knee, and hip joint work and total positive lower–limb work across all joints. We used $p \leq 0.05$ to determine significance, with Greenhouse-Geisser corrections for violations of sphericity and Bonferroni corrections for multiple post-hoc comparisons. For visual aid and interpretation, we provide ensemble average profiles for vertical and fore-aft GRFs during stance and joint powers during the whole gait cycle.

Control over walking speed across FA resistance levels

We observed significant differences in tied-belt speed across FA resistance levels [F (3.45) =5.96, η^2=0.28, p<0.05)]. However, observed speeds were still within the expected target speed zone (1.0 ± 0.2 m/s) (Table 1). Thus, we did not consider these results practically significant as values were within the expected standard deviation range provided to participants.

Comparison of fore-aft and vertical GRF profiles during stance

The average ensemble vertical GRF profile remained relatively the same for 10%, 15% and 20% FA resistance trials. During the 25% trial, the first vertical peak decreased slightly with a more visible decrease in the second vertical GRF (Fig.2.A). On

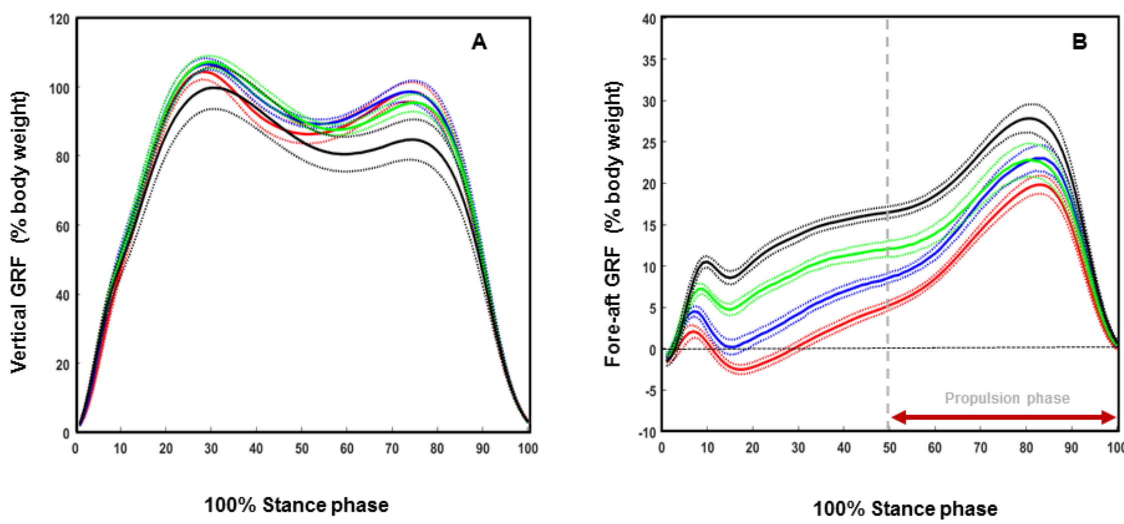


Figure. 2. Ensemble (average with standard error) vertical GRF profile (Fig. A) and ensemble average fore-aft GRFs profile (Fig .B) across all FA resistance conditions at 1.0 m/s target velocity for the dominant limb. Propulsion zone highlights stance period for propulsion calculation.

comparison of the fore-aft profiles (Fig.2.B), we found that participants decreased braking force production and had a larger propulsive phase at 10% FA resistance.

At subsequent FA resistance levels (15% to 25%), participants exhibited no braking-force generation and propelled during the entire stance phase, increasing their fore-aft ensemble average magnitudes. To account for the variation in timing of propulsion across FA resistance levels, we focused all propulsive-force calculations to the second half of stance i.e., the propulsion phase of walking.

Kinetic Variables

All participants increased their propulsive-force generation across all FA resistance levels, with significant increases in the slopes across mean propulsive impulses (M=0.42, SD=0.1, t (16) = 37.19, p<0.01) (Fig.3.A) and mean propulsive forces (M=0.63, R^2=0.99, p<0.01) (Fig.3.B)**.** However, the slopes across mean vertical impulses (M = -0.04, SD =0.17, p>0.05) (Fig.3.C) for the entire duration of stance did not significantly change across all FA resistance trials

.

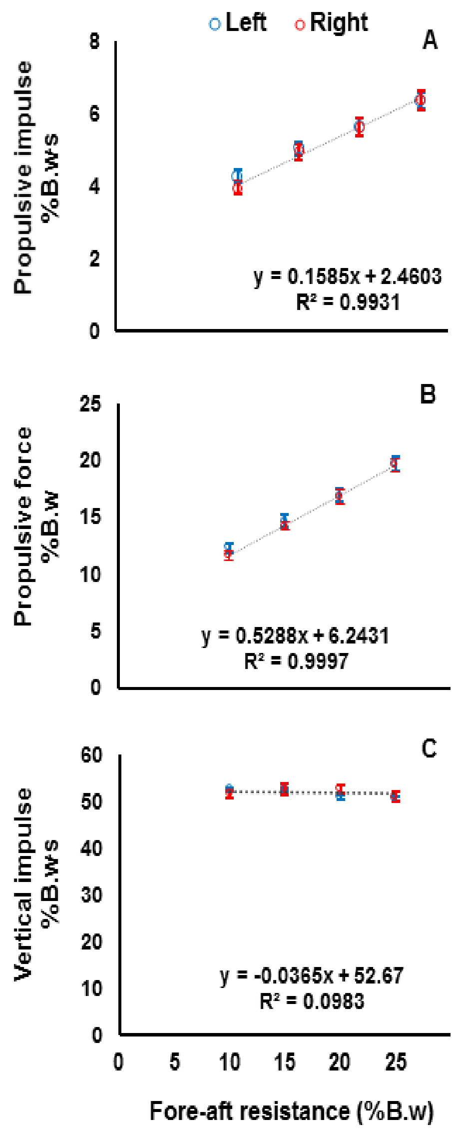


Figure 3: Mean propulsive impulse, propulsive force and vertical impulse with standard error bars (A) propulsive impulse and (B) mean propulsive force (both during 50 to 100% stance), and (C) vertical impulse (during 0 to 100% stance) for each fore-aft resistance trial normalized to body weight

Spatiotemporal Variables

We did not observe any significant changes in mean stance time or mean stride time across all FA resistance conditions. However, we found a main effect of FA resistance for mean trailing limb angle (F (1.97,27.7) = 7.6, p<0.05) and mean leading limb angle (F (1.37,19.25) = 5.85, $p<0.05$). Post-hoc comparisons revealed a significant increase in trailing limb angle for 20% and 25% FA resistance trials compared to 10% trials. In contrast, leading limb angle decreased significantly from 10% to 20% and 10% to 25% FA resistance trials respectively.

Table 1: Spatiotemporal variables for the dominant limb (Mean + 95% CI) across all four fore-aft (FA) resistance levels

FA resistance	10%	15%	20%	25%
Tied belt velocity(m/s)	1.13 [1.11 to 1.16]	1.06^{1} [1.02 to 1.11]	1.06^{1} [1.03 to 1.08]	1.06^{1} [1.02 to 1.09]
Stance time (s)	0.69 [0.66 to 0.72]	0.69 [0.66 to 0.72]	0.67 [0.64 to 0.70]	$0.65^{(2)}$ [0.63 to 0.68]
Stride time (s)	1.05 [1.00 to 1.09]	1.05 [1.00 to 1.11]	1.02 [0.96 to 1.08]	1.00 [0.95 to 1.06]
Trailing limb angle (°)	24.3 [22.9 to 25.69]	25.4 [23.98 to 26.7]	$26.7^{(1)}$ [24.9 to 28.5]	$27.4^{(1)}$ [24.9 to 29.7]
Leading limb angle (°)	-18.4 [-20.7 to -15.9]	-17.6 [-19.6 to -15.5]	$-15.6^{(2)}$ [-17.8 to -3.3]	$-12.6^{(4)}$ [-16.6 to -8.5]

NOTE: All superscripts represent significant post-hoc pairwise comparisons with Bonferroni corrections for each measure

Description of joint powers across all FA resistance levels

Magnitude of ankle power (Fig.4.A) absorption decreased at initial stance with increases in peak ankle power and ankle power generation during the propulsion phase. Knee power generation (Fig.4.B) was fairly consistent across all FA resistance levels. Regarding the hip joint, power generation magnitude markedly increased with the majority of power generation occurring during initial stance (Fig.4.C).

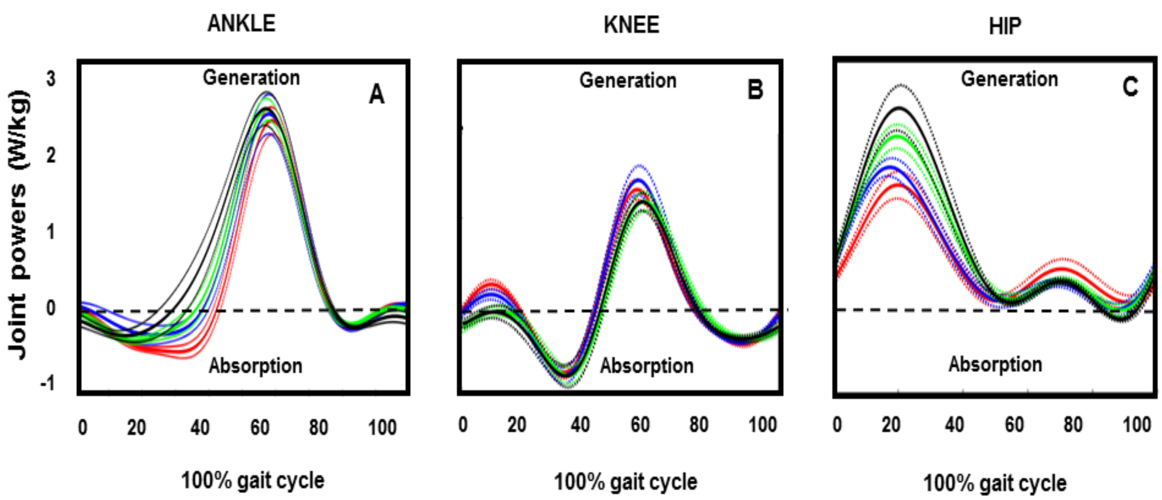


Figure 4. Ensemble average profiles of joint powers with standard error (dotted colored lines) for ankle (A), knee (B), and hip (C), respectively, at 10% (red), 15% (blue), 20% (green) and 25% (black) fore-aft (FA) resistance across 100% of the gait cycle

Work done across all individual joints against FA resistance

We assessed total positive work for each individual lower-limb joint and the total across joints (Figure 5). For positive ankle work, we found a main effect of resistance (F (3, 45) = 11.34, $p \leq 0.001$, η^2=0.7) (Fig.5.A). We found significant post-hoc differences at 15% (0.5 J/kg 95% CI [0.42-0.57]), 20% (0.58 J/kg 95%CI [0.49-0.66]), and 25% (0.6

J/kg 95% CI [0.5-0.69]) trials compared to 10% FA resistance (0.4 J/kg 95%CI [0.36-0.51]).

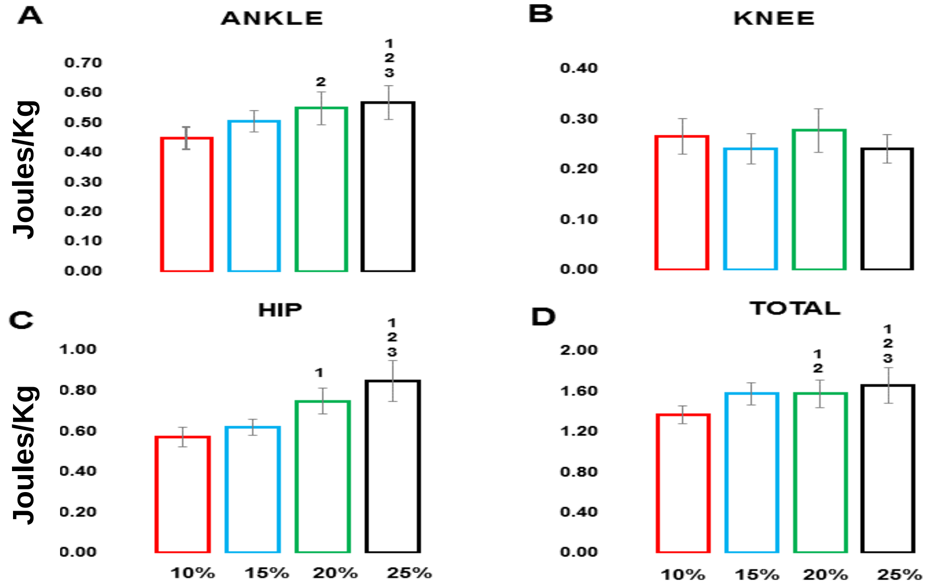


Figure 5: Mean ankle, knee and hip positive joint work. Mean and standard error values for ankle (Fig.5.A), knee (Fig.5.B) and hip joint (Fig.5.C) positive work (open bars), and total positive work across all three joints (Fig.5.D) for all four fore-aft (FA) resistance levels (10%=red, 15%=blue, 20%=green, 25%=black conditions, superscripts represents significant pairwise comparisons with Bonferroni corrections at p<0.01)

We did not find any significant increase in positive knee work across conditions (p >0.05) (Fig.5.B). For positive hip work (Fig.5.C), we found a main effect of FA resistance (F (3, 45) = 29.29, p≤0.001, η^2=0.66) with significant post-hoc differences between 10% FA (0.59 J/kg 95%CI [0.5-0.68]), 15% FA (0.64 J/kg 95%CI [0.56-0.72]), 20% (0.79 J/kg 95%CI [0.65-0.93]) FA, and 25% FA (0.94 J/kg 95%CI [0.79-1.09]) resistance levels.

On assessment of total positive work across all three joints (Fig.5.D), we found a main effect of resistance (F (1.7,26) = 16.88, p≤0.001, η^2=0.5). We found significant post-hoc differences between 10 % FA (1.3 J/K 95% CI [1.19-1.5]) and 20% FA (1.6

J/kg 95% CI [1.36-1.8]), and 10% and 25% FA resistance (1.77 J/kg 95%CI [1.53-2]) respectively. However, we did not find any significant post-hoc effects at 15% FA (1.6 J/kg 95% CI [1.37-1.83]) compared to 10% FA resistance.

DISCUSSION

Taking advantage of a unique robotic treadmill interface that allows individuals to control their self-selected walking speeds and can provide FA resistance at the COM, we explored the effects of increasing fore-aft limb loading during walking at a constant target speed. We hypothesized that participants would increase their interlimb propulsion to maintain a target speed against increasing FA resistance. These findings support our hypothesis, as nonimpaired participants proportionately increased intralimb propulsion, without altering vertical limb loading, in order to maintain walking speed in response to greater amounts of applied FA resistance. In addition, we also supported our hypothesis that walking against greater FA resistance would result in increased trailing limb angles and positive joint work.

Studies examining resistance and uphill walking at constant speeds have found nonimpaired individuals tend to scale their peak propulsion forces and duration of propulsion based on the amount of resistance or level of inclination against which they are walking [17, 20, 23, 25, 33]. This also suggests the requirements for maintaining a constant target speed against environmental factors that impede forward progression and walking function (example FA resistance) possibly facilitates increases in proprioceptive limb-extensor feedback along with feedforward mechanisms to increase propulsion generation. In addition to confirming these findings, we also observed little to no braking-force generation during initial stance, especially with greater levels of resistance [34, 35]. We also acknowledge that walking within our robotic interface environment provides some attenuation of braking-force generation [28, 31] due to the pelvic-mechanism holding participants in place and limiting forward-backward translation of the COM that occurs during typical walking. This effect coupled with requirements of walking against FA resistance may have further reduced braking, as walking against FA resistance is similar to uphill walking[24, 33], which has also shown reduction in braking-force generation, possibly due to increasing demands of raising the COM and earlier need for propulsion generation to maintain target speeds.

Regarding limb angle changes, participants increased their trailing limb angle and decreased their leading limb angle at higher FA resistance levels. Several studies have indicated that an increase in trailing limb angle is a strategy to increase propulsive-force generation, [36-39] while reduction in leading limb angle is also indicative of participants trying to quickly get the limb into a more posterior position to propel the COM forward. We believe that such a strategy enabled participants to increase rate and magnitude of propulsive-force generation to meet the demands of greater resistance and maintain walking speed, as stance time and stride time did not significantly change across conditions. These findings are consistent with studies that highlight how increases in trailing limb angle are associated with increases in propulsion needed to attain faster walking speeds [26[40].

At the individual joint level, walking against greater FA resistance resulted in increased ankle and hip power generation with little to no changes in knee power generation. Collectively, these changes indicated use of an ankle and hip strategy to attain target walking speeds against higher FA resistance levels. Visual analysis of joint moments (not reported here) also revealed increases in positive hip joint moments at higher resistance levels with minimal to little change in ankle and knee joint moments. This suggests that an increase in ankle joint angular velocity facilitated the increased ankle power generation, while an increase in hip joint force production (moment) facilitated the increased hip power production. This strategy implies that perhaps the larger hip muscles were best suited to lend themselves to the increased demands of fore-aft limb loading to maintain target speed inside the treadmill interface. It has been reported that positive hip joint powers are known to increase significantly over the ankle at faster walking speeds[[41, 42]. We found similar joint changes in our study, possibly to move the limb in a position directly underneath and behind the body to increase forward propulsion of the COM. Additionally, we visually noted an absence of hip joint power absorption that typically occurs in terminal stance and is associated with stretching of hip proprioceptors to facilitate offloading to initiate swing. This lack of negative hip work during terminal stance might indicate that walking against FA resistance created a different type of proprioceptive feedback to modulate limb offloading to enable propulsive-force generation to maintain target speed.

Limitations

In this study, we only explored walking function against FA resistance at one constant speed (1.0 m/s). However, prior published research from our lab has explored effects of FA resistance at different speeds, albeit in different experimental conditions, in both nonimpaired and poststroke populations [18, 28, 31, 32]. While kinetic and kinematic variables help in determining muscle-force generation strategies, they only provide pure mechanical measurements. Future studies should also measure EMG responses of plantarflexors (e.g., gastrocnemius, soleus), which are primarily associated with propulsion along with kinetic and kinematic changes to gain more complete insight into proprioceptive changes and the neuromechanical impact of FA resistance[10].

CONCLUSION

We demonstrated that walking against FA resistance, applied by a robotic system that allowed people to walk at a self-driven speed, proportionately increased fore-aft limb loading without significant changes in vertical limb loading. The experimental environment of the robotic treadmill interface enabled us to manipulate the fore-aft loading demands during stance while participants controlled their walking speeds. Our results suggested that FA resistance can be applied in environments that allow self-controlled walking ability and may be a useful rehabilitation application for assessment of walking function, designing progressive resistive strength training interventions, or regulating workloads during aerobic treadmill training, especially for individuals who cannot walk on inclines or at fast speeds.

Ethics: The UAB IRB approved this study, protocol number X150910010

Consent for publication: All participants provided written consent.

Availability of data and material: Available

Competing interests: Dr. Brown is a consultant to HDT Global, the company that markets and sells the device mentioned in this paper. Dr. Brown is also a named inventor on the intellectual property associated with the device and does receive royalties for any sales of the device. Ms. Naidu and Dr. Graham do not have any competing interests.

Funding: The UAB Center on Disability Health and Rehabilitation Science Internal Small Project Grant to Naidu supported this work.

Author's contributions: Ms. Naidu and Dr. Brown conceived the study. Dr. Brown acted as the principal investigator. Ms. Naidu is the primary author and Dr. Graham is the secondary author. Ms Naidu collected and analyzed data in this study collection, and drafted the manuscript with help from Dr. Graham and Dr. Brown. All authors contributed to editing the manuscript, and read and approved the final manuscript.

Acknowledgements: The authors acknowledge Rebecca Hennessy and Jennifer Uzochukwu for their assistance in data collection.

REFERENCES

1. Lacquaniti, F., Y.P. Ivanenko, and M. Zago, *Patterned control of human locomotion.* J Physiol, 2012. **590**(10): p. 2189-99.
2. Duysens, J., F. Clarac, and H. Cruse, *Load-regulating mechanisms in gait and posture: comparative aspects.* Physiol Rev, 2000. **80**(1): p. 83-133.
3. Dietz, V. and J. Duysens, *Significance of load receptor input during locomotion: a review.* Gait Posture, 2000. **11**(2): p. 102-10.
4. Grey, M.J., et al., *Positive force feedback in human walking.* 2007. **581**(1): p. 99-105.
5. Neptune, R.R., F.E. Zajac, and S.A. Kautz, *Muscle force redistributes segmental power for body progression during walking.* Gait Posture, 2004. **19**(2): p. 194-205.
6. Liu, M.Q., et al., *Muscles that support the body also modulate forward progression during walking.* J Biomech, 2006. **39**(14): p. 2623-30.
7. Lacquaniti, F., Y. Ivanenko, and M.J.A.i.d.b. Zago, *Kinematic control of walking.* 2002. **140**(4): p. 263-272.
8. Van de Crommert, H.W., et al., *Neural control of locomotion: sensory control of the central pattern generator and its relation to treadmill training.* 1998. **7**(3): p. 251-263.
9. Bachmann, V., et al., *Vertical perturbations of human gait: organisation and adaptation of leg muscle responses.* 2008. **186**(1): p. 123-130.
10. McGowan, C.P., R.R. Neptune, and R. Kram, *Independent effects of weight and mass on plantar flexor activity during walking: implications for their contributions to body support and forward propulsion.* J Appl Physiol (1985), 2008. **105**(2): p. 486-94.
11. Lewek, M.D.J.J.o.b., *The influence of body weight support on ankle mechanics during treadmill walking.* 2011. **44**(1): p. 128-133.
12. Wang, J., et al., *Characteristics of horizontal force generation for individuals post-stroke walking against progressive resistive forces.* Clin Biomech (Bristol, Avon), 2015. **30**(1): p. 40-5.
13. Sylos-Labini, F., F. Lacquaniti, and Y.P. Ivanenko, *Human locomotion under reduced gravity conditions: biomechanical and neurophysiological considerations.* Biomed Res Int, 2014. **2014**: p. 547242.
14. Ivanenko, Y.P., et al., *Gait transitions in simulated reduced gravity.* J Appl Physiol (1985), 2011. **110**(3): p. 781-8.
15. Sinkjær, T., et al., *Major role for sensory feedback in soleus EMG activity in the stance phase of walking in man.* 2000. **523**(3): p. 817-827.
16. Gottschall, J.S. and R.J.J.o.A.P. Kram, *Energy cost and muscular activity required for propulsion during walking.* 2003.
17. McGowan, C.P., R. Kram, and R.R. Neptune, *Modulation of leg muscle function in response to altered demand for body support and forward propulsion during walking.* J Biomech, 2009. **42**(7): p. 850-6.

18. Hurt, C.P., et al., *Effect of progressive horizontal resistive force on the comfortable walking speed of individuals post-stroke.* J Neuroeng Rehabil, 2015. **12**(1): p. 7.
19. Hurt, C.P., et al., *Comparison of Resistance-Based Walking Cardiorespiratory Test to The Bruce Protocol.* J Strength Cond Res, 2017.
20. Ellis, R.G., B.J. Sumner, and R. Kram, *Muscle contributions to propulsion and braking during walking and running: insight from external force perturbations.* Gait Posture, 2014. **40**(4): p. 594-9.
21. Janshen, L., et al., *Modular control during incline and level walking in humans.* 2017. **220**(5): p. 807-813.
22. Franz, J.R., M. Maletis, and R.J.C.b. Kram, *Real-time feedback enhances forward propulsion during walking in old adults.* 2014. **29**(1): p. 68-74.
23. Franz, J.R., R.J.G. Kram, and posture, *The effects of grade and speed on leg muscle activations during walking.* 2012. **35**(1): p. 143-147.
24. Noble, J.W. and S.D. Prentice, *Intersegmental coordination while walking up inclined surfaces: age and ramp angle effects.* Exp Brain Res, 2008. **189**(2): p. 249-55.
25. Gottschall, J.S. and T.R.J.P.T.o.t.R.S.B.B.S. Nichols, *Neuromuscular strategies for the transitions between level and hill surfaces during walking.* 2011. **366**(1570): p. 1565-1579.
26. Kautz, S.A., et al., *Comparison of motor control deficits during treadmill and overground walking poststroke.* Neurorehabilitation and neural repair, 2011. **25**(8): p. 756-765.
27. Patton, J., et al., *KineAssist: design and development of a robotic overground gait and balance therapy device.* Top Stroke Rehabil, 2008. **15**(2): p. 131-9.
28. Dionisio, V.C. and D.A. Brown, *Collaborative robotic biomechanical interactions and gait adjustments in young, non-impaired individuals.* J Neuroeng Rehabil, 2016. **13**(1): p. 57.
29. Capó-Lugo, C.E., C.H. Mullens, and D.A. Brown, *Maximum walking speeds obtained using treadmill and overground robot system in persons with post-stroke hemiplegia*. J Neuroeng Rehabil, 2012. **9**: p. 80.
30. Naidu, A., D. Brown, and E.J.J.r.p. Roth, *A Challenge-Based Approach to Body Weight–Supported Treadmill Training Poststroke: Protocol for a Randomized Controlled Trial.* 2018. **7**(5).
31. Graham, S.A., C.P. Hurt, and D.A. Brown, *Minimizing Postural Demands of Walking While Still Emphasizing Locomotor Force Generation for Nonimpaired Individuals.* IEEE Trans Neural Syst Rehabil Eng, 2018. **26**(5): p. 1003-1010.
32. Rumble, D.D., C.P. Hurt, and D.A. Brown, *Step-by-step variability of swing phase trajectory area during steady state walking at a range of speeds.* PLoS One, 2018. **13**(1): p. e0191247.
33. Franz, J.R. and R. Kram, *Advanced age and the mechanics of uphill walking: a joint-level, inverse dynamic analysis.* Gait Posture, 2014. **39**(1): p. 135-40.
34. Sawicki, G.S. and D.P.J.J.o.E.B. Ferris, *Mechanics and energetics of level walking with powered ankle exoskeletons.* 2008. **211**(9): p. 1402-1413.
35. Neptune, R.R., K. Sasaki, and S.A. Kautz, *The effect of walking speed on muscle function and mechanical energetics.* Gait Posture, 2008. **28**(1): p. 135-43.

36. Hsiao, H., et al., *Mechanisms to increase propulsive force for individuals poststroke.* J Neuroeng Rehabil, 2015. **12**: p. 40.
37. Hsiao, H., et al., *The relative contribution of ankle moment and trailing limb angle to propulsive force during gait.* Hum Mov Sci, 2015. **39**: p. 212-21.
38. Liu, M.Q., et al., *Muscle contributions to support and progression over a range of walking speeds.* 2008. **41**(15): p. 3243-3252.
39. Lovejoy, C.O.J.S.A., *Evolution of human walking.* 1988. **259**(5): p. 118-125.
40. Chen, H.L. and T.W. Lu, *Comparisons of the joint moments between leading and trailing limb in young adults when stepping over obstacles.* Gait Posture, 2006. **23**(1): p. 69-77.
41. Farris, D.J. and G.S. Sawicki, *The mechanics and energetics of human walking and running: a joint level perspective.* J R Soc Interface, 2012. **9**(66): p. 110-8.
42. Browne, M.G. and J.R.J.J.o.b. Franz, *The independent effects of speed and propulsive force on joint power generation in walking.* 2017. **55**: p. 48-55.

COMPARISON OF INTERLIMB CONTRIBUTIONS TO PROPULSION BETWEEN POSTSTROKE AND NONIMPAIRED INDIVIDUALS WALKING AGAINST FORE-AFT RESISTANCE

NAIDU A, GRAHAM. S.A., BROWN D.A.

To be submitted *Journal of Neurorehabilitation & Neural Repair (JNNR)* 2019

Format adapted for dissertation

ABSTRACT

Background

Perceived effort required to do an exercise task i.e., sense of effort is impaired in individuals poststroke. It is unclear how walking against increased effort demands (i.e., increasing fore-aft (FA) resistance while maintaining target speeds) affects relative propulsion contribution (i.e. % propulsion) between limbs in nonimpaired (NI) and poststroke (PS) individuals. We hypothesized that to maintain target speed against resistance; % propulsion of the NI (dominant limb) would be significantly higher than PS (paretic (P) limb) % propulsion due to a fixed propulsion relationship between P and nonparetic (NP) limbs, and that % propulsion or both groups would remain constant across all resistance levels.

Methods

21 PS participants (53.8 years, SD=12) targeted their CWS (group mean=0.5 m/s) and 15 NI participants (52 years, SD =11) targeted 0.5 m/s against six, graded FA resistance levels (6-21% body weight) while walking inside an intent-driven treadmill interface. We primarily assessed % propulsion between groups, and secondarily assessed trailing limb angle (TLA), stance time, and target-speed maintenance.

Results:

NI participants competed all FA resistance levels; 21 PS participants only completed 6-15% B.w, 13 PS completed up to 21% B.w, and 17 completed up to 18% B.w. Mean NI

% propulsion (48.1%, SD=13) was significantly greater than P limb PS % propulsion (28.8% SD=10, p<0.001), (. For both groups % propulsion remained constant across all levels (p>0.05).

Conclusion:

PS participants appear to have a fixed propulsion contribution between limbs for the same sense of effort against higher levels of resistance to maintain a target speed.

Keywords: Poststroke, sense of effort, walking, propulsion, fore-aft resistance,

INTRODUCTION

Hemiparesis significantly contributes to the growing burden of chronic poststroke disability in the US [1]. Altered paretic (P) limb loading dynamics and impaired muscle-force production decrease propulsive-force generation during walking [2-4]. Propulsive forces are the positive fore-aft component of the GRF vector that are essential for forward progression of the center of mass (COM) and modulation of walking speed [5,6]. Considering that hemiparesis mainly affects distal-limb muscle function, it is not surprising that impaired P limb propulsive-force generation ability is partially responsible for hemiparetic gait deficits [7,8]. To maintain walking speed, stroke survivors utilize compensatory strategies that favor greater non-paretic (NP) compared to P limb loading and propulsive-force generation. However, such compensatory mechanisms result in interlimb propulsion asymmetry, which corresponds with the level of hemiparetic severity, producing slow and energetically expensive gait patterns that limit functional mobility [9,10], and persist despite undergoing gait rehabilitation[11].

Among various theoretical frameworks concerning poststroke compensatory mechanisms, research examining the concept of learned “non-use” highlights how preferential use of the non-affected upper limb to perform activities of daily living leads to learned non-use of the paretic upper limb[12]. This premise extended to lower-limb function, suggests that stroke survivors develop a learned behavioral non-use of the P lower limb, with preferential use of the NP lower limb for meeting increased propulsion demands during walking (e.g., at faster speeds or against resistance)[12]. Another theoretical framework suggests that impaired central cortical discharge following stroke reduces recruitment and rate coding of available motor neurons of the P lower-limb muscles (plantarflexors and hip extensors), causes greater NP limb propulsion generation relative to the P limb during locomotion[13,14]. For example, Nadeau et al. used muscle utilization ratios and found that impaired P limb motor neuronal function, decreased propulsion-generation scalability in relation to a maximum force output during static and dynamic motor tasks (like walking), with the P limb working at a higher limit of its maximum force-generation ability compared to the NP limb [15-17]. Yet another possibility to consider is a miscalculation of actual perceived effort (sense of effort) and amount of force produced (sense of force) to perform a motor task [18-21] in the absence of appropriate central motor commands. Considering central control dysregulation occurs following stroke[2,22,23]; an altered poststroke internal-neuromechanical control model may cause miscalculations of P limb propulsion output, due to incorrect matching of the predicted force response compared to actual sensory feedback received during the movement. Thus, the same perceived ‘sense of effort’ can lead to different sense of force output (i.e., asymmetric limb propulsion) for each limb, with a relatively fixed propulsion calibration between the P and NP limbs [24-26]. Using an isometric force-matching task, Ferris et al. explored perceived lower-limb sense of effort between limbs in nonimpaired (NI) and poststroke (PS) participants, and found that PS participants had altered sense of force responses for the same effort demands compared to NI participants, [24,25,27]. Although not explicitly explored during walking, an altered sense of effort may explain why walking at faster speeds or against resistance causes greater NP propulsion contribution relative to the P limb.

One potential way of assessing P and NP limb sense of effort responses while walking, can be through applying fore-aft (FA) resistance either at the COM [28-32] or at specific joints [33,34] while poststroke participants maintain a constant speed. Studies that have explored these paradigms have found improvements in P limb propulsion (mean/impulse/peak) against greater resistance. Although informative, such singular limb-measures do not account for relative propulsion contribution of the P limb in relation is the NP limb, especially against the same sense of effort demands experienced by each limb. Instead, a measure like % P propulsion (defined as P propulsion impulse / P + NP impulse *100), which accounts for propulsion contribution by both limbs [35-37], and is also strongly associated with plantarflexor activity (primary propulsion, muscles) is better suited to explore relative propulsion changes between the P and NP limb [38]. Previously, we used an intent-driven treadmill interface [39] that allowed participants to control their walking speed, and found that PS participants increased net propulsion similar to NI participants against greater FA resistance; however, we did not quantify the % propulsion contribution for each limb or between groups [28,39,40].

In this current study, using the same intent-driven interface, our primary aim was to assess the relative P and NP limb propulsion contribution in PS, and age-similar NI participants, while maintaining a self-controlled target speed against increasing levels of FA resistance (applied at the COM) to provide similar sense of effort demands for each limb. Primarily, we hypothesized that when walking against similar increasing sense of effort demands, NI % propulsion (dominant limb) would be significantly greater than the P % propulsion, due to similar sense of force output by NI limbs (~50% per limb) and an altered PS sense of force output that fixes the relative propulsion relationship between limbs (NP>P). We further expected no change in % propulsion (for both groups) across FA resistance levels. Secondarily, we hypothesized that walking against increased FA resistance would correspond with respective increases in trailing limb angle (TLA) of P, NP, and NI limbs, as TLA is linked with increased limb propulsion in terminal stance [41].

METHODS

We included individuals poststroke with a history of unilateral stroke, ability to walk independently (overground) for 14 meters with/without an assistive device (e.g., cane, ankle-foot orthosis), and with physician approval to engage in mild-moderate physical activity, and age similar NI individuals. We excluded participants in both groups if they had history of severe cardiac, musculoskeletal, or neurological conditions that affected walking function. We assessed
all participants baseline heart rate, blood pressure, and self-selected CWS using a 10-meter walk test (10MWT). We enrolled 27 poststroke participants (53.8 years (SD=12), CWS=0.7 m/s (SD=0.3), weight=189lbs (SD=38)) based on our inclusion criteria, and 15 nonimpaired individuals (7 females, 53 years (SD = 11), weight =184(SD=37), CWS= 1.2 m/s (SD=0.3)) (Table 1). All participants provided informed consent, approved by the University of Alabama at Birmingham Institutional Review Board.

Table 1: Poststroke and nonimpaired participant demographics

Participant (ID)	Age (Yrs)	Sex (M/F)	Paretic side	Overground (CWS)	Interface (CWS)	Weight (Lbs)	Chronicity (Years)	FM LL
PS1	57	M	L	0.9	0.8	290	25	25
PS2	55	M	L	0.9	0.8	195	24	28
PS3	66	F	R	0.4	0.2	195	48	23
PS4	70	M	L(A)	0.7	0.4	190	27	25

PS5	43	M	R(A)	1.2	0.8	200	60	19
PS6	48	M	R	0.6	0.5	198	24	15
PS7	66	M	L	0.6	0.3	220	144	19
PS8	68	M	L(A)	0.9	0.8	173	27	24
PS9	62	F	L	0.8	0.4	200	312	25
PS10	67	F	L	0.6	0.4	170	327	25
PS11	27	F	R	0.9	0.5	162	144	18
PS12	41	M	L	1.3	0.7	178	36	26
PS13	55	M	L	1.1	0.8	145	36	23
PS14	34	M	R	0.5	0.4	236	26	19
PS15	36	M	R	0.6	0.4	240	22	24
PS16	54	M	R(A)	0.7	0.5	280	36	26
PS17	53	F	L	0.9	0.5	185	9	22
PS18	41	F	R(A)	0.9	0.5	128	48	20
PS19	52	F	R	0.8	0.6	165	49	26
PS20	62	F	R	0.6	0.5	135	9	29
PS21	66	F	R	0.9	0.8	174	120	30
Avg. PS n=21	**53.8 (11)**	**F:13**	**L:14**	**0.8 (0.2)**	**0.5 (0.2)**	**189 (38)**	**78.5(89)**	**21(6)**
Avg. NI n=15	**53 (12)**	**F:7**	N/A	**1.2 (0.3)**	**0.5 (Target)**	**184 (37)**	**N/A**	N/A

*** A = Ankle foot orthosis (AFO) assistive device**

Note: PS=poststroke, NI=nonimpaired, average + standard deviation. FM= Fugl-Myer lower limb (LL). Only those PS participants who could walk inside the interface (n=21) are represented in this table

Intent-driven split-belt robotic interface:

We used the walking environment of an intent-driven treadmill interface, which consists of the KineAssist robotic device connected to a split-belt force-instrumented treadmill (Bertec, Columbus, OH). An adjustable pelvic harness secures participants walking inside the interface at COM height. The pelvic harness attaches to a pelvic mechanism that connects to a vertical tower, and enables pelvic movement in all three planes with six degrees of freedom. However, for this study we locked the mechanism to prevent participants from hip movements like roll, pitch, and yaw during walking against FA resistance to allow movement in only the vertical and fore-aft directions (relative over the treadmill). Our lab has published details on walking mechanics inside this interface under various conditions, in a wide age range of nonimpaired and poststroke participants [39,40,42-44].

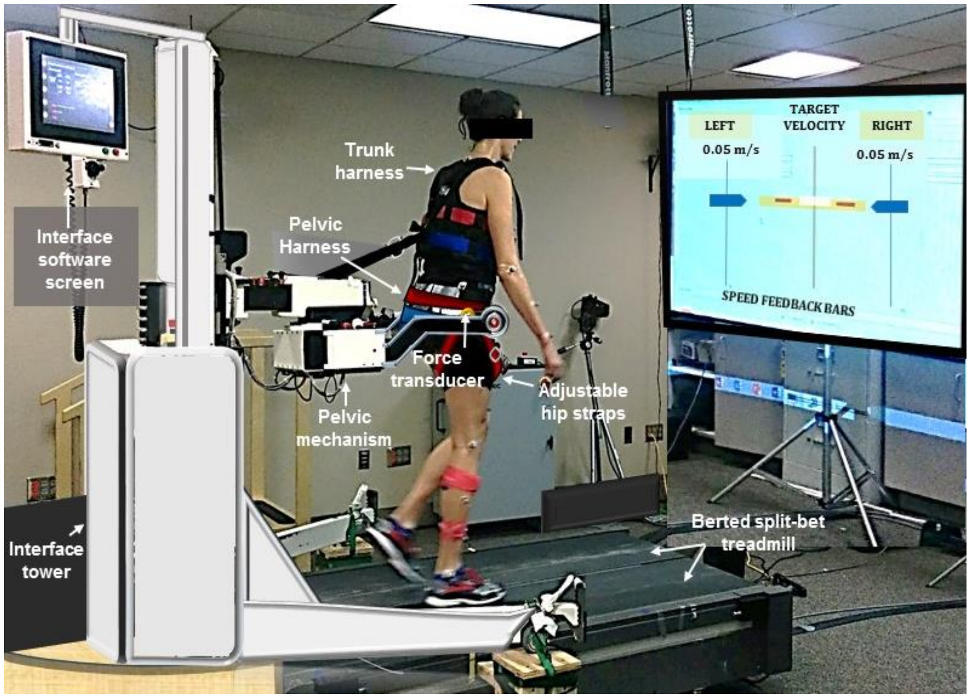


Figure 1: Nonimpaired individual walking inside the KineAssist (KA) robotic split-belt interface targeting a velocity of 0.5 m/s ± 0.1 using real-time visual feedback *Note: Tied belt velocity displayed as white bar on yellow target zone*

Application of FA resistance during walking

For this study, we used the force-velocity relationship of our interface to apply FA resistance. Essentially, to move and control each treadmill belt's speed, participants walking inside the interface must overcome a minimum force (Newton) in the fore-aft direction by generating sufficient net lower-extremity forces at the hip. The pelvic harness has two force transducers, embedded at each hip, which sense and relay these net forces to the interface operation system via haptic control algorithms. This closed-loop feedback system allows participants to control their self-selected treadmill speed by overcoming the FA resistance needed to start and keep the treadmill belts moving. Additionally, the force transducers can detect any sudden change in pelvic mechanism height triggered by a loss of balance or misstep and activate a safety-catch feature, which stops the mechanism from moving and prevents a fall.

Interface acclimatization and target speed selection

Prior to the beginning of each data collection, all participants had a five-minute acclimatization period to become familiar with the interface. For PS participants, we instructed them to "walk at a speed that they found comfortable inside the device", and checked if participants could maintain this speed for 30-seconds with visual feedback. If not, we decreased the speed by 0.1 m/s and tried again until we found a suitable speed. We then recorded this speed with a 10 MWT performed inside the device, and used it as the participant's target walking speed during data collection. Out of the 27 enrolled PS participants, six were not able to walk at a self-selected speed greater than 0.1 m/s without assistance, and hence were not included for data collection. To make similar speed comparisons between groups, we selected a target speed of 0.5 m/s for NI participants i.e., average interface CWS speed of PS participants.

Calculation of FA resistance levels

We used our interface's algorithm, which accounted for participant's weight (Newton), target speed (m/s), interface's force-velocity relationship, and control specifications to calculate six normalized FA resistance levels i.e., 6%, 9%, 12%, 15%, 18%, and 21% of vertical body weight (N). We used 21% B.w. as the highest resistance based on our previous exploration of FA resistance in nonimpaired participants (manuscript in review), which suggested that this value was challenging yet enabled participants to maintain target speeds. Other studies exploring walking against resistance have calculated resistance in a similar fashion using vertical body weight ([45,46]).

Real-time velocity feedback and maintenance of target speed

As walking speed has a sinusoidal characteristic and cannot be constant, we provided a range of target speed +/- 0.1 m/s (highlighted with a yellow block) and considered maintenance of speed within this target zone as acceptable for each participant (Figure 1). We used the interface's software to provide instantaneous visual feedback, projected as moving blue speed bars on a projector screen (5x6 foot) within the yellow target zone, placed in front of the interface.

Order of FA resistance trial presentation

We randomized the order of the FA resistance trials, and started collecting data for each trial only after visually confirming that participants matched their target speed for 10 initial steps. To account for the variability in poststroke participant's target speeds, and to ensure a minimum of 25 strides per limb, each trial was 50 to 80 seconds long. We did not collect data if participants could not (1) start the treadmill belt because of failure to overcome resistance, (2) maintain target velocity after two attempts, or (3) requested to stop. We constantly monitored heart rate and provided participants with 30-60 second rest breaks in between trials to minimize fatigue. All 21 poststroke participants completed 6 to 15% (four levels) of FA resistance, while seventeen completed 6 to 18% (five levels), and thirteen completed all six i.e., 6 to 21% FA resistance. Due to loss of pelvic markers and participant time constraints during data collection, we were unable to collect kinematic data for two participants.

Data acquisition

We used the instrumented dual-belt treadmill to collect GRF data (1000 Hz frequency) and an 8-camera Qualisys motion capture system (Qualisys Inc., Gothenburg, Sweden) for kinematic data (100 Hz) using a custom, bilateral, 36 passive-reflective marker setup (example shown in Fig. 2), and used Visual 3D (C-Motion, Germantown, MD, USA) to obtain marker trajectories. We used the interface's custom software to record treadmill belt speed (100 Hz frequency) for each resistance trial.

Kinetic measurements

We low-pass filtered kinetic GRF data using a 4^{th} order Butterworth filter (20 Hz cutoff), and normalized GRFs to body weight (i.e., % B.w) during the stance phase. Using custom MATLAB scripts (MathWorks®, version R2016b), we calculated all kinetic gait events (heel strikes and toe-offs) at a threshold of 15 N per limb for each FA resistance trial. As propulsion is mainly associated with the second half of stance, we carried out all propulsion-force analyses during this period to calculate propulsive impulse i.e., the time integral of the positive fore-aft GRF (i.e., ∫Fore-aft GRF × dt (50% stance)) for the P, NP, and NI dominant limb. We then used this value to calculate mean % propulsion i.e., % Paretic propulsion (%Pp) = P propulsive impulse / (P+NP) propulsive impulse; or, % Propulsion =Dominant / (Dominant + Nondominant) propulsive impulse, with 50% Propulsion = perfect symmetry between limbs, to determine the increasing or decreasing relationship of each limb's relative contribution to propulsion with respect to FA resistance. For visual inspection, we also provide ensemble average fore-aft GRF profiles for participants in both groups for each limb.

Stance duration during propulsion phase and trailing limb angle (TLA) measurements

We calculated stance duration during the propulsion phase from midstance to toe-off (i.e., 50% stance), as the second half of the time elapsed from ipsilateral heel strike to toe off[36]. We defined trailing limb angle (TLA) as the angle between the LAB's vertical axis and a line connecting the lateral toe marker of each limb to the ipsilateral ASIS marker at toe-off.

Statistical analysis

We used SPSS version 22 to conduct all statistical analyses, and assessed normality of all variables for both groups using Shapiro-Wilk's tests. If variables did not meet normality assumptions, we conducted their nonparametric equivalent. Since nonimpaired individuals symmetrically increased propulsion, we only used the dominant limb values for all statistical analyses. For FA resistance levels completed by all poststroke (PS) and nonimpaired (NI) participants, we compared % propulsion between groups using a repeated measures ANOVA design (group (PS, NI) X resistance condition) from 6 to 15% FA resistance. For all other measures, trailing limb angle, stance time, and target speed maintenance (control variable), we used separate one-way ANOVAs, as we were only interested in individual limb differences across resistance levels for participants that completed all six FA levels in each group. We performed all analyses at $p \leq 0.05$ with Greenhouse-Geisser corrections for sphericity violations (ANOVA), with Bonferroni corrections for post-hoc comparisons.

Control measurements

As all PS participants walked at different target speeds; thus, we converted their target speed to 100% and calculated their target-speed maintenance percentage (within a confidence interval of 10%) across all FA resistance trials to make comparisons with NI participants. For example: Target speed of 0.5 m/s =100%; if actual 6% FA resistance speed =0.47 m/s, Target-speed maintenance % = (100 x 0.47/0.5) = 94%. For all nonimpaired participants, we calculated their average target speed (0.5m/s ± 0.1) maintenance per trial.

RESULTS

Maintenance of target speed

Participants PS maintained their walking speed, evidenced by normalized values all within an acceptable range of 90% to 110% (Table 2). Although PS participants decreased their speed slightly at 21% B.w (n=13) the kinetic data at the 21% B.w level followed similar trends as previous FA levels (see Figure 3.C). All NI participants maintained their target speed of 0.5 m/s within their acceptable range of 0.4 to 0.6 m/s.

Table 2: Mean 95% CI for target speed of tied-treadmill belts for each fore-aft (FA) resistance trial for poststroke (PS) and nonimpaired (NI) participants

FA resistance level	**6% FA** ***PS n=21*** ***NI n=15***	**9% FA** ***PS n= 21*** ***NI n=15***	**12% FA** ***PS n= 21*** ***NI n= 15***	**15% FA** ***PS n=21*** ***NI n=15***	**18% FA** ***PS n=17*** ***NI n=15***	**21% FA** ***PS n=13*** ***NI n=15***
PS target	97.26	103.98	99	100	94.8	89.6
100±10%	[90.3-104.2]	[99.6-108.2]	[94.9-103.3]	[94-106.2]	[87.3-102.9]	[80.48-98.7]
NI target	0.52	0.57	0.55	0.56	0.54	0.53
0.5±0.1m/s	[0.52-0.58]	[0.54-0.6]	[0.52-0.6]	[0.52-0.6]	[0.5-0.58]	[0.49-0.56]

Fore-aft GRF profiles during stance between groups

All NI participants displayed little to no braking-force production and a large propulsive-force generation beginning as early as 20% stance and continuing until toe-off (100% stance) for both limbs (Fig.2 A & B). Regarding PS participants, the P limb displayed a considerably higher braking-force magnitude for PS participants with lower % propulsion, and the NP limb displayed little to no braking force during initial to mid-stance (Fig.2. D, F, and H) [39]. Both the P and NP limbs displayed early propulsive-force generation (around 20% stance), with a visible increase in magnitude across all resistance levels. However, the NP limb displayed a greater propulsion magnitude than the P limb (Fig.2.C, E, and G). For both groups, to account for the variation in early propulsion from initial to mid stance, we focused all propulsive-force calculations on the second half of stance i.e., the propulsion phase (red shaded area Fig.2)

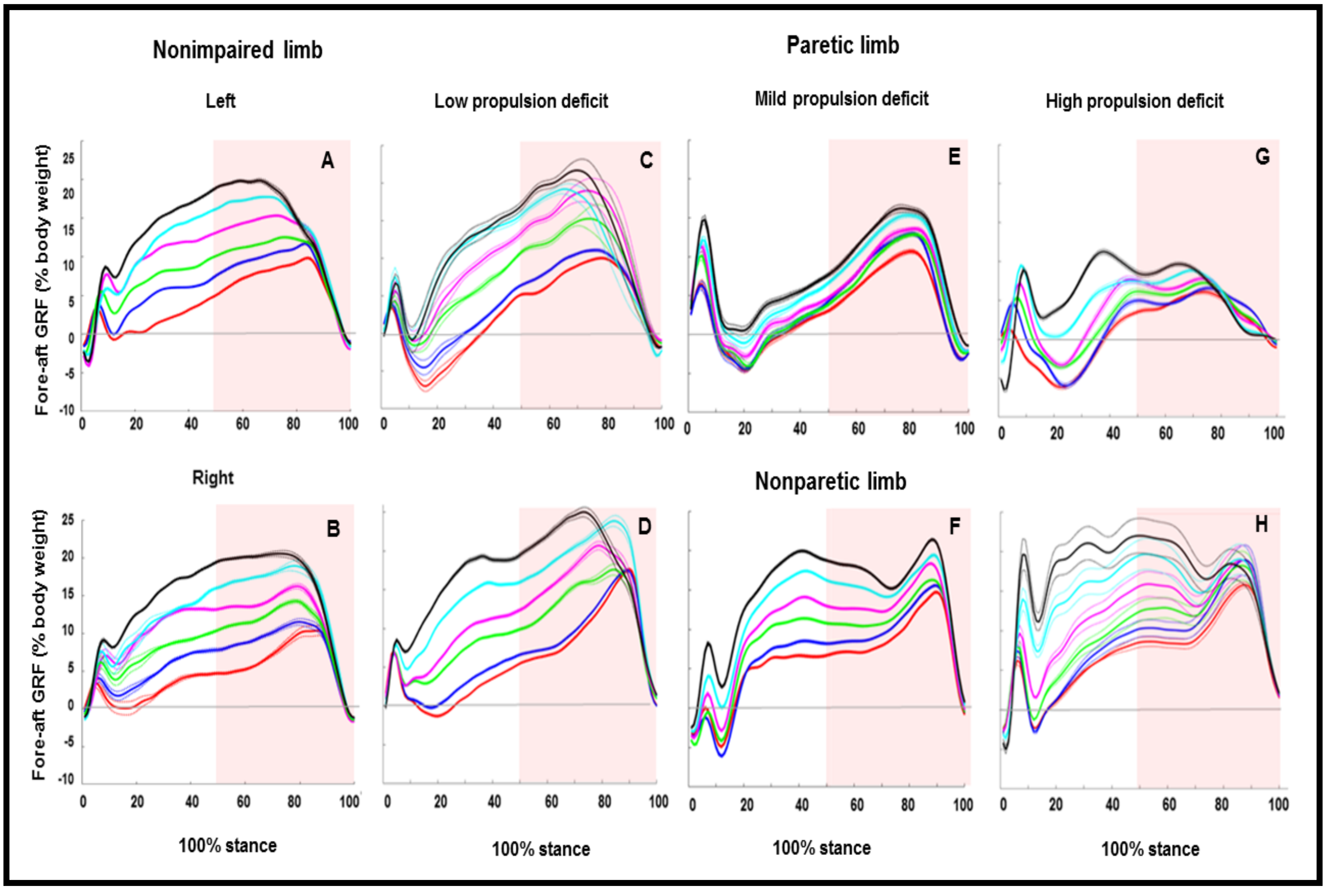


Figure. 2. Ensemble average fore-aft GRFs profiles (average with standard error) across all FA resistance levels (6%=red, 9%=dark blue, 15%=green, 15%=magenta, 18%=light blue, 21%=black). A nonimpaired participant (Fig 2.A & B) walking at 0.5 m/s, and three participants poststroke walking with different % paretic propulsion (%Pp) deficit at a target (interface) speed of 0.8 m/s i.e. low (PS21, Fig 2. C & D, Mean %Pp =50), mild (PS14, Fig 2. E & F, Mean %Pp =36) and high (PS5 Fig 2. G & H, Mean %Pp =19).

Percent propulsion between groups and at different FA resistance levels

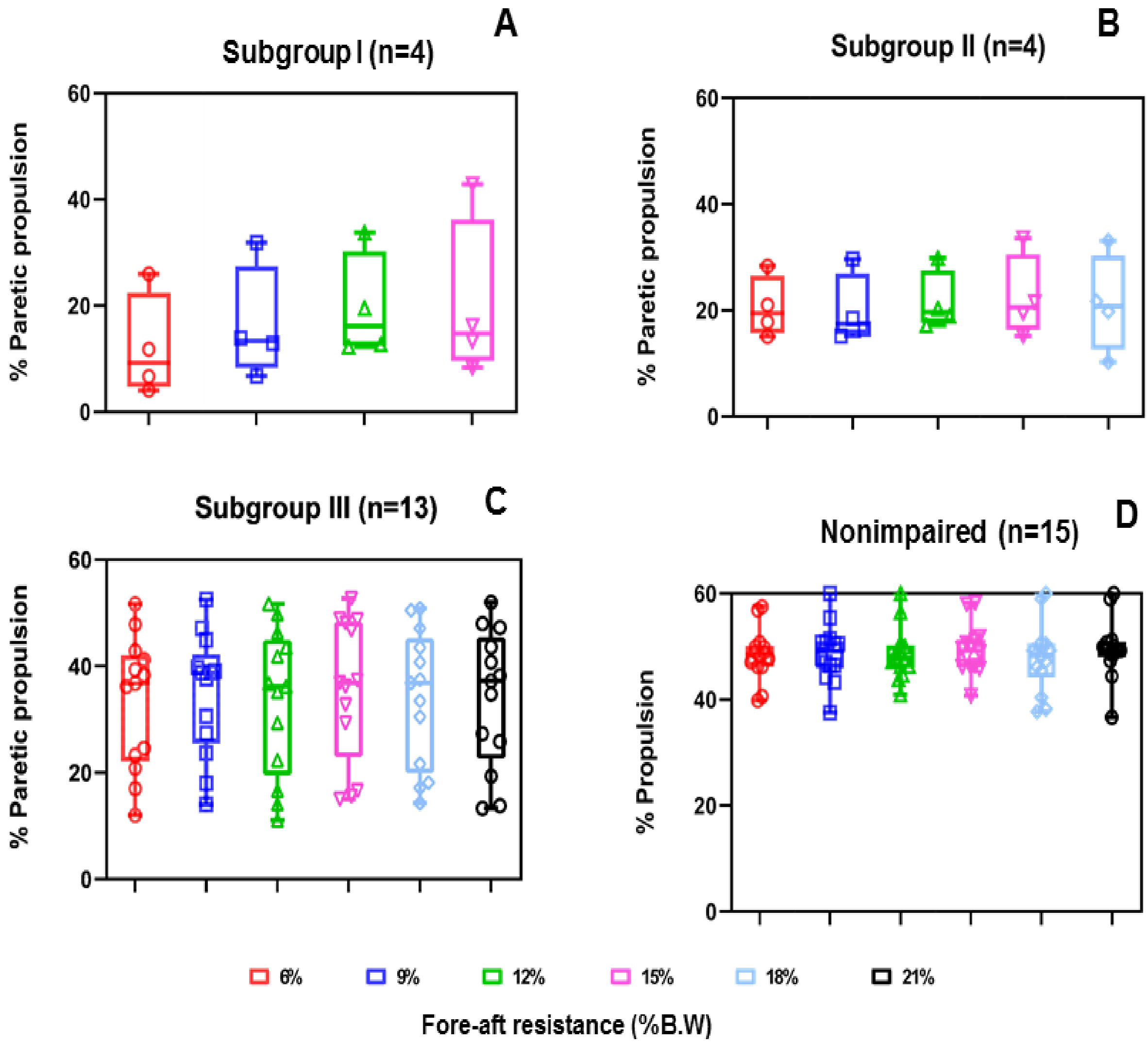


Figure 3: Box and whiskers plots for percentage of propulsion of the paretic limb at each FA resistance level completed by each poststroke participant (subgroup I to subgroup III) and all nonimpaired participants for their dominant limb (n=15).

Note: x represents mean and solid line represents median with interquartile range represented by whiskers.

NI % propulsion was relatively symmetric between limbs compared to asymmetric PS % propulsion between limbs. On comparison of % propulsion between groups from 6 to 15% B.w FA resistance, the mean NI limb (n=15) % propulsion (48.1%, 95% CI (42 to 55)) was significantly greater than the mean P limb (n=21) % propulsion (28.8%, 95% CI (23 to 33)), [F (1, 33) = 27.6, η^2= 0.7, *p*<0.001].

Across all resistance levels we found no main effect of resistance (*p*>0.05) for both groups. Additionally, due to heterogeneity within the PS group, we present the % propulsion of the P limb (Figure 3) based on the FA resistance levels that all PS participants were able to complete, using box and whiskers plots. We classified PS participants (n=21) into subgroups based on the highest FA resistance level they could tolerate i.e., subgroup I [6% to 15% (n=4) median walking speed=0.32 m/s (Figure 3A)]; subgroup II [6% to 18% (n=4), median walking speed=0.55 m/s, (Figure 3B)] and; subgroup III [6% to 21% (n=13), median walking speed=0. 82 m/s, (Figure 3C)]. As a comparison, we provide the consistent median % propulsion across resistance levels of NI participants (n=15 i.e., Figure 3D).

Stance time duration and TLA

Average stance time from midstance to toe-off (propulsion period) did not significantly change (*p*>0.05) for the P, NP, and NI limbs across all resistance levels. For TLA, since not all PS participants completed all FA resistance levels, we provided mean and 95% confidence intervals for participants who completed 6 to 15% B.w (n=21), 6 to 18% B.w (n=17), and 6 to 21% B.w (n=13) FA resistance respectively (Table2). However, from 6 to 21% B.w (n=13) we observed increases in TLA for the P limb [F

(1.9, 17) =4.7, $p<0.05$, $\eta2=0.5$], NP limb [F (1.5, 16) =9.52, $p<0.05$, $\eta2=0.5$], and NI limbs [F (5, 33) =6.12 $p<0.001$, $\eta2=0.32$]. (Table 3)

Table 3: Mean 95% CI for Trailing limb angle (TLA) across fore-aft (FA) resistance levels for paretic (P), Nonparetic (NP), and nonimpaired (NI) limbs

FA resistance	**Trailing limb angle (◦)**		
% B.w	**Paretic limb**	**Nonparetic limb**	**Nonimpaired limb**
6	*N=21*	*N=21*	*N=15*
Mean	**19.2**	**18.3**	**14.4**
95 % CI	[16.8-21.6]	[15.7-20.7]	[14.4-18.1]
9	*N=21*	*N=21*	*N=15*
Mean	**20.0**	**19.9**	**17.9**
95 % CI	[17.5-22.5]	[17.5-22.3]	[16.2-19.6]
12	*N=21*	*N=21*	*N=15*
Mean	**20.2**	**20.7**	**17.55**
95 % CI	[17.5-23.1]	[17.5-23.1]	[16-19.6]
15	N=21	N=21	N=15
Mean	**21.1**	**24.3$^{6.9.12\%}$**	**18.4**
95 % CI	[17.5-24.6]	[19.9-28.5]	[16.7-20.2]
18	*N=17*	*N=17*	*N=15*
Mean	**21.3**	**24.3$^{6.9.12\%}$**	**18.4**
95 % CI	[16.7-25.7]	[19.9-28.5]	[16.7-20.2]
21	*N=13*	*N=13*	*N=15*
Mean	**21.9$^{6.9.12\%}$**	**22.7$^{6.9\ \%}$**	**20.6$^{6,9\ \%}$**
95 % CI	[17.69-27.3]	[17.4-28.1]	[18.8-22.5]

Superscripts represent significant pairwise comparisons between all fore-aft (FA) resistance levels with Bonferroni corrections

DISCUSSION

The novel aspect of our current investigation centered on analyzing the relative propulsion contribution between limbs in poststroke (PS) and nonimpaired (NI) participants during walking against similar (for each limb) effort demands. We used the walking environment of a robotic-treadmill interface, which offered participants the ability to control and maintain their target speed against six, varying FA resistance levels (%B.w), normalized across all participants by body weight and target speed.

We found that both groups increased interlimb propulsion against resistance, with mean NI % propulsion significantly greater than the P limb to maintain a target speed across all resistance levels. However, both groups maintained the same relative-propulsion relationship between limbs i.e., % propulsion for each limb did not change across resistance levels. These findings support our primary hypothesis i.e., for the same effort requirements the P and NP limbs increase their propulsion while maintaining the same relative propulsion relationship, suggesting a fixed propulsion relationship between the limbs. The fact that % P propulsion did not change suggests that both the P and NP limbs maintained the same of force outs for similar effort demands, leaving the characteristic asymmetry between limbs unchanged. Contrary to the learned non-use framework, PS participants did not choose to limit engagement of their P limb due to greater NP limb utilization (i.e., the P limb also increased propulsion against resistance), but rather were unable to increase the P limb's contribution to match the NP limb's. Additionally, our findings show that an altered sense of force may cause the P limb to work at a higher level of its maximum force contribution than the NP limb, supporting the findings of Nadeau et al.

Most studies examining sense of effort have focused on exploring upper-limb function using bi-manual tasks, or lower-extremity, contralateral, isometric, force-matching tasks to explore perception of effort on muscle force production[19,25,49,50]. However, upper-limb function is not as tightly coupled as lower-limb function, and thus, it is more difficult to isolate sense of effort perception during walking. While it can be argued that poststroke studies exploring walking against resistance on motorized single/dual-belt instrumented treadmills (programmed to run at constant CWSs) can be used to study sense of effort, we believe such paradigms are not ideal. The momentum of the moving belts along with external support decrease muscle force-generation requirements, and have been shown to alter spatiotemporal parameters[51,52]. This may in turn affect ongoing proprioceptive feedback, and thus sense of effort perception, and propulsion calibration between limbs to maintain speed [51-53].

Contrary to our second hypothesis, other than 18% FA, the NP limb TLA was not relatively greater than the P limb and did not significantly change across FA resistance levels. This interesting finding suggests that participants were not necessarily placing their limb further back, at least during the initial few FA resistance levels, to increase propulsion against increased resistance demands, and that a more posterior limb position was not necessarily driving the larger propulsion contribution of the NP limb. Studies have associated increases in TLA with increases in ankle moment for improving propulsion generation at push-off to increase speed [47,48]. However, increases in TLA may not correspond with increases in plantarflexor activity, especially when walking at slower speeds and against resistance. This suggests that when maintaining a constant speed, increases in TLA are not the only strategy used by participants to increase propulsion generation, or that a constant sense of effort leads to consistent limb force responses, which might not significantly change across conditions.

Limitations

First, our sample size for poststroke participants was small and heterogeneous. The requirement for walking independently within our interface decreased our sample size from 27 to 21 participants and prevented inclusion of presumably lower-functioning individuals with greater propulsion deficits. Additionally, the majority of participants walked slightly slower than their overground CWS inside the interface. However, with our existing sample sizes we were still able to see important relationships between limbs. Second, we stopped FA resistance testing if participants could not maintain target speed / requested to stop, and only tested up to 21% B.w FA resistance. Hence, we may not have captured a true asymptote for propulsion reserve. However, we were interested in relative propulsion between limbs to maintain a target speed; thus, we feel that it was important to cease testing at levels above what participants could sustain. Third, we primarily focused on kinetic variables relating to propulsion to further investigate neuromechanical factors affecting sense of effort and relative propulsion between limbs. Future investigations should include lower-limb EMG activity, especially plantarflexors (e.g., gastrocnemius, soleus), along with additional biomechanical analyses (e.g., limb work). Lastly, by requiring each limb to overcome the same amount of FA resistance to maintain target speed inside our interface, we believe our paradigm was better able to capture how similar sense of effort affects relative propulsion during walking. However, since the treadmill belts were tied, we acknowledge that the NP limb was still in a position where it could compensate via greater propulsion magnitude to drive the treadmill-belt speed.

Conclusions

We demonstrated that walking at a self-controlled, constant speed against FA resistance applied at the COM can be used to study sense of effort and relative propulsion contributions between limb in PS and NI individuals. Our findings suggest that the relative propulsion contributions between the P and NP limbs remained constant with no change in % P limb propulsion across resistance levels, possibly due to a fixed propulsion calibration for the same sense of perceived effort. In future studies, we need to identify factors that can facilitate greater contribution of the P limb in relation to the NP limb during walking, like application of FA resistance in a differential manner, such that only the P limb can selectively experience greater sense of effort against resistance to maintain a constant speed. Such paradigms may provide insight on which factors can reduce NP limb compensation and selectively increase P propulsion.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Executive Summary: Heart Disease and Stroke Statistics--2016 Update: A Report From the American Heart Association. *Circulation.* 2016;133(4):447-454.

2. Raja B, Neptune RR, Kautz SA. Quantifiable patterns of limb loading and unloading during hemiparetic gait: Relation to kinetic and kinematic parameters. *J Rehabil Res Dev.* 2012;49(9):1293-1304.

3. Chen G, Patten C, Kothari DH, Zajac FE. Gait differences between individuals with post-stroke hemiparesis and non-disabled controls at matched speeds. *Gait Posture.* 2005;22(1):51-56.

4. Rogers MW, Hedman LD, Pai YC. Kinetic analysis of dynamic transitions in stance support accompanying voluntary leg flexion movements in hemiparetic adults. *Arch Phys Med Rehabil.* 1993;74(1):19-25.

5. Liu MQ, Anderson FC, Pandy MG, Delp SL. Muscles that support the body also modulate forward progression during walking. *J Biomech.* 2006;39(14):2623-2630.

6. Peterson CL, Kautz SA, Neptune RR. Braking and propulsive impulses increase with speed during accelerated and decelerated walking. *Gait Posture.* 2011;33(4):562-567.

7. Turns LJ, Neptune RR, Kautz SA. Relationships between muscle activity and anteroposterior ground reaction forces in hemiparetic walking. *Arch Phys Med Rehabil.* 2007;88(9):1127-1135.

8. Peterson CL, Hall AL, Kautz SA, Neptune RR. Pre-swing deficits in forward propulsion, swing initiation and power generation by individual muscles during hemiparetic walking. *J Biomech.* 2010;43(12):2348-2355.

9. Allen JL, Kautz SA, Neptune RR. Step length asymmetry is representative of compensatory mechanisms used in post-stroke hemiparetic walking. *Gait Posture.* 2011;33(4):538-543.

10. Lewek MD, Bradley CE, Wutzke CJ, Zinder SM. The relationship between spatiotemporal gait asymmetry and balance in individuals with chronic stroke. *J Appl Biomech.* 2014;30(1):31-36.

11. Dickstein R. Rehabilitation of gait speed after stroke: a critical review of intervention approaches. *Neurorehabil Neural Repair.* 2008;22(6):649-660.

12. Taub E, Uswatte G, Mark VW, Morris DM. The learned nonuse phenomenon: implications for rehabilitation. *Eura Medicophys.* 2006;42(3):241-256.

13. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. *Lancet.* 2011;377(9778):1693-1702.

14. Patten C, Lexell J, Brown HE. Weakness and strength training in persons with poststroke hemiplegia: rationale, method, and efficacy. *J Rehabil Res Dev.* 2004;41(3A):293-312.

15. Nadeau S, Gravel D, Arsenault AB, Bourbonnais D, Goyette M. Dynamometric assessment of the plantarflexors in hemiparetic subjects: relations between muscular, gait and clinical parameters. *Scand J Rehabil Med.* 1997;29(3):137-146.

16. Nadeau S, Gravel D, Arsenault AB, Bourbonnais D. Plantarflexor weakness as a limiting factor of gait speed in stroke subjects and the compensating role of hip flexors. *Clin Biomech (Bristol, Avon).* 1999;14(2):125-135.

17. Nadeau S, Betschart M, Bethoux F. Gait analysis for poststroke rehabilitation: the relevance of biomechanical analysis and the impact of gait speed. *Phys Med Rehabil Clin N Am.* 2013;24(2):265-276.

18. de Morree HM, Klein C, Marcora SM. Perception of effort reflects central motor command during movement execution. *Psychophysiology.* 2012;49(9):1242-1253.

19. Carson RG, Riek S, Shahbazpour N. Central and peripheral mediation of human force sensation following eccentric or concentric contractions. *J Physiol.* 2002;539(Pt 3):913-925.

20. Proske U, Gandevia SC. The proprioceptive senses: their roles in signaling body shape, body position and movement, and muscle force. *Physiol Rev.* 2012;92(4):1651-1697.

21. McCloskey DI, Ebeling P, Goodwin GM. Estimation of weights and tensions and apparent involvement of a "sense of effort". *Exp Neurol.* 1974;42(1):220-232.

22. Ko M, Bishop MD, Behrman AL. Effects of limb loading on gait initiation in persons with moderate hemiparesis. *Top Stroke Rehabil.* 2011;18(3):258-268.

23. Mercer VS, Freburger JK, Yin Z, Preisser JS. Recovery of paretic lower extremity loading ability and physical function in the first six months after stroke. *Arch Phys Med Rehabil.* 2014;95(8):1547-1555.e1544.

24. Simon AM, Kelly BM, Ferris DP. Preliminary trial of symmetry-based resistance in individuals with post-stroke hemiparesis. *Conf Proc IEEE Eng Med Biol Soc.* 2009;2009:5294-5299.

25. Simon AM, Kelly BM, Ferris DP. Sense of effort determines lower limb force production during dynamic movement in individuals with poststroke hemiparesis. *Neurorehabil Neural Repair.* 2009;23(8):811-818.

26. Milot MH, Nadeau S, Gravel D, Requião LF. Bilateral level of effort of the plantar flexors, hip flexors, and extensors during gait in hemiparetic and healthy individuals. *Stroke.* 2006;37(8):2070-2075.

27. Simon AM, Ferris DP. Lower limb force production and bilateral force asymmetries are based on sense of effort. *Exp Brain Res.* 2008;187(1):129-138.

28. Wang J, Hurt CP, Capo-Lugo CE, Brown DA. Characteristics of horizontal force generation for individuals post-stroke walking against progressive resistive forces. *Clin Biomech (Bristol, Avon).* 2015;30(1):40-45.

29. Hurt CP, Wang J, Capo-Lugo CE, Brown DA. Effect of progressive horizontal resistive force on the comfortable walking speed of individuals post-stroke. *J Neuroeng Rehabil.* 2015;12(1):7.

30. Lewek MD, Raiti C, Doty A. The Presence of a Paretic Propulsion Reserve During Gait in Individuals Following Stroke. *Neurorehabil Neural Repair.* 2018;32(12):1011-1019.

31. Blanchette A, Bouyer LJ. Timing-specific transfer of adapted muscle activity after walking in an elastic force field. *J Neurophysiol.* 2009;102(1):568-577.

32. Wu M, Landry JM, Yen SC, Schmit BD, Hornby TG, Rafferty M. A novel cable-driven robotic training improves locomotor function in individuals post-stroke. *Conf Proc IEEE Eng Med Biol Soc.* 2011;2011:8539-8542.

33. Awad LN, Bae J, O'Donnell K, et al. A soft robotic exosuit improves walking in patients after stroke. *Science Translational Medicine.* 2017;9(400):eaai9084.

34. Louie DR, Eng JJ. Powered robotic exoskeletons in post-stroke rehabilitation of gait: a scoping review. *J Neuroeng Rehabil.* 2016;13(1):53.

35. Allen JL, Kautz SA, Neptune RR. Forward propulsion asymmetry is indicative of changes in plantarflexor coordination during walking in individuals with post-stroke hemiparesis. *Clinical biomechanics (Bristol, Avon).* 2014;29(7):780-786.

36. Bowden MG, Balasubramanian CK, Neptune RR, Kautz SA. Anterior-posterior ground reaction forces as a measure of paretic leg contribution in hemiparetic walking. *Stroke.* 2006;37(3):872-876.

37. Roelker SA, Bowden MG, Kautz SA, Neptune RR. Paretic propulsion as a measure of walking performance and functional motor recovery post-stroke: A review. *Gait Posture.* 2019;68:6-14.

38. Bowden MG, Balasubramanian CK, Behrman AL, Kautz SA. Validation of a speed-based classification system using quantitative measures of walking performance poststroke. *Neurorehabil Neural Repair.* 2008;22(6):672-675.

39. Dionisio VC, Brown DA. Collaborative robotic biomechanical interactions and gait adjustments in young, non-impaired individuals. *J Neuroeng Rehabil.* 2016;13(1):57.

40. Naidu A, Brown D, Roth EJJrp. A Challenge-Based Approach to Body Weight–Supported Treadmill Training Poststroke: Protocol for a Randomized Controlled Trial. 2018;7(5).

41. Hsiao H, Knarr BA, Higginson JS, Binder-Macleod SA. The relative contribution of ankle moment and trailing limb angle to propulsive force during gait. *Hum Mov Sci.* 2015;39:212-221.

42. Graham SA, Hurt CP, Brown DA. Minimizing Postural Demands of Walking While Still Emphasizing Locomotor Force Generation for Nonimpaired Individuals. *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society.* 2018;26(5):1003-1010.

43. Hurt CP, Bamman M, Naidu A, Brown DA. Comparison of Resistance-Based Walking Cardiorespiratory Test to The Bruce Protocol. *J Strength Cond Res.* 2017.

44. Rumble DD, Hurt CP, Brown DA. Step-by-step variability of swing phase trajectory area during steady state walking at a range of speeds. *PLoS One.* 2018;13(1):e0191247.

45. McGowan CP, Neptune RR, Kram R. Independent effects of weight and mass on plantar flexor activity during walking: implications for their contributions to body support and forward propulsion. *J Appl Physiol (1985).* 2008;105(2):486-494.

46. Gottschall JS, Kram RJJoAP. Energy cost and muscular activity required for propulsion during walking. 2003.

47. Hsiao H, Awad LN, Palmer JA, Higginson JS, Binder-Macleod SA. Contribution of Paretic and Nonparetic Limb Peak Propulsive Forces to Changes in Walking Speed in Individuals Poststroke. *Neurorehabil Neural Repair.* 2016;30(8):743-752.

48. Awad LN, Binder-Macleod SA, Pohlig RT, Reisman DS. Paretic Propulsion and Trailing Limb Angle Are Key Determinants of Long-Distance Walking Function After Stroke. *Neurorehabil Neural Repair.* 2015;29(6):499-508.

49. McCloskey DI, Ebeling P, Goodwin GM. Estimation of weights and tensions and apparent involvement of a "sense of effort". *Experimental neurology.* 1974;42(1):220-232.

50. Christian R, Bishop D, GIRARD O, Billaut F. The role of sense of effort on self-selected cycling power output. *Frontiers in Physiology.* 2014;5(115).

51. Kautz SA, Bowden MG, Clark DJ, Neptune RR. Comparison of motor control deficits during treadmill and overground walking poststroke. *Neurorehabil Neural Repair.* 2011;25(8):756-765.

52. Chen G, Patten C, Kothari DH, Zajac FE. Gait deviations associated with post-stroke hemiparesis: improvement during treadmill walking using weight support, speed, support stiffness, and handrail hold. *Gait Posture.* 2005;22(1):57-62.

53. Goldberg EJ, Kautz SA, Neptune RR. Can treadmill walking be used to assess propulsion generation? *J Biomech.* 2008;41(8):1805-1808.

EXPLORING EFFECTS OF DIFFERENTIAL FORE-AFT RESISTANCE ON PROPULSIVE FORCE GENERATION DURING SPLIT-BELT TREADMILL WALKING IN NONIMPAIRED AND INDIVIDUALS POSTSTROKE

NAIDU A, GRAHAM S.A, HURT C.P, BROWN D.A

Prepared for Science translational medicine

Format adapted for dissertation

ABSTRACT

Background

Poststroke hemiparetic weakness impairs paretic (P) limb-loading dynamics and propulsion output causing greater propulsion contribution by the nonparetic (NP) limb to maintain walking speed. To design optimal rehabilitation strategies, exploration of factors that can selectively increase propulsive force contribution of one limb relative to the other in nonimpaired and individuals poststroke is required.

Purpose

We utilized a novel split-belt treadmill interface that allowed one belt to be automatically controlled (i.e. machine-driven or MD), while a force-velocity relationship enabled the user to control the other belt speed (i.e. self-drive or SD) by overcoming a set fore-aft resistance through lower-extremity force production on a step-by step basis. We hypothesized that when the SD limb targets slower speed and MD belt is set at a faster speed, the SD limb will generate relatively greater propulsion compared to the MD limb due to greater proprioceptive-limb loading time and force requirements to maintain SD belt speed that will engage limb-extensor propulsion mechanisms.

Methods

15 nonimpaired participants (mean age 51 years, SD=14), and 15 poststroke participants (mean age 53 years SD=12, left hemi=7) poststroke participants walked against six progressive levels of FA-resistance (i.e. 6-21%) applied to the SD belt in two separate conditions. *Nonimpaired condition I*, the left limb (SD belt) targeted 1m/s while the right limb (MD belt) was set at 0.5m/s. *Nonimpaired condition II*, the left SD limb target=0.5 m/s, right MD limb=1 m/s respectively. *Poststroke condition I*, the P limb targeting a

slow speed with the SD belt, while the NP limb moved faster on the MD belt. *Poststroke condition 2*, the P limb targeted a faster speed on the SD belt, while the NP limb moved slower. We primarily assessed mean propulsion output of each limb during the entire stance phase, and secondarily assessed mean stance time. We assessed differences between conditions in nonimpaired and poststroke groups using repeated measures ANOVA and comparisons of slope using one-sample *t*-test between limbs, respectively at $p<0.05$.

Results

All 15 nonimpaired participants performed most trails in both conditions. We found no significant results for condition 1 ($p<0.05$). However for condition 2, the slower SD limb significantly increased its propulsive force output over the faster MD limb ($p<0.05$). Of the 15 poststroke participants, 9 were able to walk in condition 1, and 14 were able to walk in condition 2, respectively. However, average slopes for percent paretic propulsion were significant only for condition 1 ($p<0.05$) and not condition 2 ($p>0.05$)

Conclusions

These findings highlight that rehabilitation interventions can utilize interface environments like ours to apply differential FA resistance as a means for strengthening the P limb and increasing its propulsion output while discouraging compensatory strategies during walking.

Index Terms— walking, fore-aft resistance, propulsion, biomechanics, treadmill-interface nonimpaired

BACKGROUND

An essential requirement for forward progression and regulation of speed during walking is symmetrical generation of propulsive forces on a step-by-step basis[1]. From a kinetic perspective, propulsive forces make up the positive fore-aft component of the ground reaction force (GRF) vector, which reflects the summation of lower extremity muscle force output by each limb[2]. However, hemiparetic weakness in chronic stroke survivors causes impaired limb loading and propulsive-force generation ability of the affected paretic (P) limb, reducing the P limb's contribution to body support and forward progression[3]. To maintain walking speed and forward progression, the nonparetic (NP) limb primarily generate propulsion, leading to interlimb propulsion asymmetry that correlates with the level of hemiparetic severity, and produces slow and energetically inefficient gait patterns[4-6]. Unfortunately, this use of such compensatory strategies continues despite gait rehabilitation efforts, which not only further exacerbates hemiparetic weakness, but also encourages adoption of sedentary lifestyles that negatively affect functional capacity and quality of life[7].

Numerous animal and human physiological studies have highlighted how limb-loading (proprioceptive) feedback during stance is critical to engage limb extensor mechanisms that prevent limb collapse at midstance, and facilitate propulsion generation from mid to terminal stance[8-10]. Considering hemiparesis decreases P lower-limb function and propulsion generation ability[11], various studies have explored the premise of applying resistance (at the center of mass (COM) or at various joints[12-18]) during walking and have found increase in P limb propulsion contribution, possibly due to greater engagement of limb-extensor mechanisms, indicating a strong rehabilitation potential. However, these studies have mainly focused on measurement of improvements in P limb propulsion alone and not necessarily compared its relative propulsion contribution to the NP limb, i.e., the NP limb might also be increasing its propulsion generation output to the external resistance demands along with the P limb with no change in the original compensatory strategy. Thus, symmetrically applied resistance (e.g., at the COM) may not affect/improve the relative propulsion contribution between limbs. To confirm this hypothesis, we previously explored interlimb contributions to propulsion generation in both poststroke and nonimpaired individuals walking against similar increasing levels of fore-aft (FA) resistance, applied at the COM at percentages of vertical body weight, while maintaining a target speed (In review). We used the walking environment of robotic split-belt treadmill interface[17,19-21 22] that allowed participants to control their walking speed (i.e., an intent-driven treadmill interface). We found that while poststroke and nonimpaired participants increased their individual limb propulsion generation against greater levels of FA resistance, the relative propulsion contribution between the limbs did not change. These findings highlight that although walking against resistance applied at the COM can be used as a modality to increase P limb propulsion, the NP limb will still take on the role of the primary propulsion driver. Thus, there is little to no change in utilization of the original compensatory strategy. Hence, there is still a strong need to investigate methods that can selectively increase P limb propulsion without encouraging the NP limb to dominate during walking.

One potential strategy to selectively emphasize greater relative propulsion of one limb over the other is by using split-belt treadmill paradigms [23-28]. Over the past few decades various split-belt treadmill paradigms have demonstrated how walking on two independently moving treadmill belts leads to distinct, and immediate spatiotemporal interlimb and intralimb parameter changes with different adaptation and post-adaptation (after) effects[29]. Both cross-sectional and training split-belt paradigms have used error augmentation to exaggerate step length asymmetry, by walking in a 2:1 speed ratio for an adaptation period (5-15 minutes), and have found improvements in step-length asymmetry when the belts are tied during the post-adaptation period (aftereffects) [23,24,30-34]. Unfortunately, the highly coupled nature of bipedal walking makes it difficult to target unilateral hemiparetic propulsion deficits without influencing the NP limb during walking via a manipulation of split-belt speeds alone. To improve poststroke kinetic outcomes, a kinetic perturbation during split-belt walking is required that involves provision of limb-loading resistance primarily to the P limb to increase its relative propulsion output over the NP limb. Although, studies have examined application of unilateral resistance during split-belt walking using various pulley systems[12,35,36], rubber tubing[18], and robotic interfaces[13], these studies primarily utilized split-belt environments where belt speed were pre-programmed or influenced by kinematic marker setups[37]. By taking advantage of a unique robotic-treadmill interface that allows users to control and drive treadmill belt speed (i.e. self-drive (SD)) via lower-extremity forces our lab has explored walking function against fore-aft (FA) resistance in individuals[17,38]. In our view, a split-belt version of such an environment would allow for separate manipulation of speed and FA resistance demands experienced by both limbs at the same time and perhaps increase engagement of the P limb propulsion relative to the NP limb. This would be possible is one belt is self-driven while the other while the other belt is automatically controlled. To our knowledge, biomechanical understanding of such a paradigm that involves asymmetrical manipulation of speed and resistance during self-controlled split-treadmill walking on relative interlimb propulsion output is still yet to be determined.

The main purpose in this study was to examine if we could alter the relative propulsion contribution of the P limb in relation to the NP limb during walking against fore-aft resistance by utilizing the walking environment of our intent-driven split-belt treadmill interface. We modified the software of our interface such that the velocity of one treadmill belt can be automatically set to a desired speed i.e., it is machine driven (MD)) or automatically control by the examiner. However, the velocity of the other treadmill-belt is controlled and driven control and driven by the user i.e. self-driven (SD) belt via the interface's force-velocity relationship. To initiate movement of the belt, this relationship requires user to produce lower-extremity forces to match and overcome a set (adjustable) fore-aft resistance on a step-by-step basis, with additional force production enabling users to reach and maintain a desired target speed similar to overground walking. Taking advantage of this software modification, in this study, we primarily assessed how differential application of FA resistance, by manipulation of relative force between limbs (SD vs MD belts) moving at a 2:1 speed ratio against progressive levels of FA resistance applied to the SD limb can selectively increase propulsion contribution of one limb over the other. We assessed this paradigm in chronic poststroke participants and age-similar nonimpaired individuals by dividing our study into two parts –

PART 1: Manipulation of speed (slow vs fast) on lower extremity force output when walking in different treadmill-belt modes (SD vs MD i.e. force modulation) to examine the effects on relative interlimb propulsion in nonimpaired participants to induce interlimb propulsion asymmetry. We assessed intent-driven maintenance of a target speed i.e., fast (1 m/s) or slow (0.5 m/s) by one limb on the SD belt, while the other limb was moving at a either a slow (0.5 m/s) or fast (1m/s)) speed on the automatic MD belt, against differential resistance, using the following two conditions –

Condition 1: Nonimpaired participants walked within the split-belt interface while targeting a speed of 1 m/s with their left (non-dominant limb) i.e., SD belt, while the right (dominant limb) belt was programmed to run at 0.5 m/s i.e., MD belt against differential resistance applied only to the SD belt. We hypothesized that the limb moving on the slower belt (i.e., 0.5 m/s MD or SD) would generate greater propulsive force than the faster moving belt (i.e., 1 m/s MD or SD). Additionally, due to increased time for proprioceptive limb-loading feedback as well as the fact that the slower limb will try to help meet the increased propulsion demands of the faster moving SD belt

Condition 2: Nonimpaired participants walked within the split-belt interface while targeting a speed of 0.5 m/s with their left (non-dominant limb) i.e., SD belt, while the right (dominant limb) belt was programmed to run at 1.0 m/s i.e., MD belt against differential resistance applied only to the SD belt. We hypothesized that the slower left SD limb (0.5 m/s) would generate greater propulsive force than the right faster right MD (1 m/s) speeds against differential resistance demands, due to increased proprioceptive limb-loading time and perception of force generation requirements during walking (due to self-drive function of the interface).

PART II: We separately manipulated speed (slow vs fast) and force (SD vs MD) of the P limb compared to the NP limb to evaluate relative interlimb propulsion in poststroke participants and determine if we could decrease interlimb propulsion asymmetry via this approach. We conducted Part II utilizing two specific walking conditions:

Condition 1: The P limb targeted a slower speed on the SD belt (i.e., ½ CWS) inside the interface against increasing levels of resistance, while the NP limb moved fast (twice P limb speed i.e., CWS) on the MD belt. We hypothesized that when the P limb was moving slower on the SD belt against resistance it would increase its propulsive contribution due to greater time for proprioceptive limb loading and force perception over the NP limb. Increase in P limb propulsion will correspond with increase in stance duration at progressively higher resistance levels.

Condition 2: The P limb on the SD belt targeted a faster speed (i.e., CWS) against increasing levels of resistance, while the NP limb moved on a slower (1/2 P limb speed) MD belt. . We hypothesized that when the P limb was moving faster on the SD belt against resistance it would not increase its propulsive contribution over the NP limb, as the NP limb will have greater proprioceptive limb-loading time and ability to compensate for force generation requirements of the P limb at progressively higher resistance levels. These changes will cause the P limb stance duration to not change or decrease at progressively higher resistance levels.

METHODS

Fifteen age-similar nonimpaired (NI) individuals (Mean=51 years, SD=14, F=7), all right dominant) and 15 chronic stroke survivors (Mean = 53 years, SD =13, F=7) participated in this study after providing informed consent obtained with approval from the institutional review board of our university. All poststroke (PS) participants had a history of unilateral stroke, were able to walk independently down a 14-meter hallway either with or without the help of an assistive device (e.g., cane, ankle-foot orthosis) with visible interlimb asymmetry, and permission from their physician to participate in light to moderate physical activity. We assessed comfortable and fast walking speed (CWS and FWS) of participants in both groups using a 10 meter-walk test (10MWT). In addition, all NI individuals completed a physical activity readiness questionnaire (PAR-Q) to rule out restrictions from being able to perform moderate physical activity, and tests to establish limb dominance i.e. which leg would they use to kick a ball, and which leg would they prefer to stand on for a single leg stance. We excluded participants with a history of uncontrolled cardiac, muscular, or neurological comorbid conditions that might have interfered with ability to perform mild to moderate physical activity in both groups.

Table 1: Participant demographics

ID	**Age Years**	**Sex M/F**	**Paretic side**	**Overground CWS**	**Interface CWS**	**Weight Lbs**	**Chronicity Years**	**FM LL**
PS1	55	M	L	0.9	0.8	195	24	28
PS2	66	F	R	0.4	0.2	195	48	23
PS3	70	M	L(A)	0.7	0.4	190	27	25
PS4	43	M	R(A)	1.2	0.8	200	60	19
PS5	48	M	R	0.6	0.5	198	24	15
PS6	68	M	L(A)	0.9	0.8	173	27	24
PS7	62	F	L	0.8	0.4	200	312	25
PS8	67	F	L	0.6	0.4	170	327	25
PS9	27	F	R	0.9	0.5	162	144	18
PS10	55	M	L	1.1	0.8	145	36	23
PS11	36	M	R	0.6	0.4	240	22	24
PS12	54	M	R(A)	0.7	0.5	280	36	26
PS13	53	F	L	0.9	0.5	185	9	22
PS14	41	F	R(A)	0.9	0.5	128	48	20

PS15	52	F	R	0.8	0.6	165	49	26
Avg. PS n=15	**53 (12)**	**F:7**	**L:7**	**0.8 (0.2)**	**0.54 (0.2)**	**188 (38)**	**80 (102)**	**23(3.5)**
Avg. NI n=15	**51 (14)**	**F:7**	N/A	**1.2 (0.3)**		**160 (30)**	**N/A**	N/A

*** A = Ankle foot orthosis (AFO) assistive device**

Note: PS=poststroke, NI=nonimpaired, average + standard deviation. FM= Fugl-Myer lower limb (LL). Only those PS participants who could walk inside the interface (n=21) are represented in this table

Spit-belt robotic treadmill interface:

We have previously described biomechanical comparisons across different walking conditions in both nonimpaired and poststroke populations walking inside the intent-driven environment of our KineAssist (KA) robotic (HDT Robotics) split-belt treadmill (Bertec, Columbus) interface. Briefly, the user interface of this device consists of an adjustable trunk harness and a pelvic mechanism (with six degrees of freedom) that connects to the device’s vertical tower, with an adjustable pelvic harness worn at the height of the COM. By locking the pelvic mechanism, we can prevent compensatory hip movements, like hip hiking or hip sway during walking, and only allow pelvic movements in the vertical and fore-aft direction (i.e., relative over the treadmill belt). The pelvic harness has two force transducers (located at each hip) that record and relay net hip forces through a custom haptic algorithm, which essentially forms the basis for the interface’s force-velocity relationship. This unique closed-loop feedback system allows participants walking inside the device to select and control their walking speed by overcoming a minimum resistance in the fore-aft direction through generation of net forces (recorded at the hip) to start the treadmill belts, while generation of additional lower-limb propulsion forces help maintain a self-selected treadmill speed during walking. The force-transducers can also sense any drop in the height of the pelvic mechanism and trigger a device stop that prevents the mechanism from moving, thus preventing a "fall" and rendering the environment safe for exploring walking function in nonimpaired and poststroke populations.

Differential fore-aft resistance

Previously, we used a custom algorithm that accounts for the user's body weight (Newton), desired target speed, device parameters, and force-velocity relationship to normalize and modulate FA resistance (at the COM) experienced by nonimpaired participants while targeting the same speed (1 m/s) with tied treadmill belts against increasing FA resistance (in review). We further extended this work to compare interlimb propulsion in individuals poststroke, using the algorithm to apply the same normalized FA resistance levels, accounting for their body weight and different target speeds (in review). In the present study, we modified the device software such that the user walking inside the device can control the velocity of one treadmill belt via the force-velocity relationship (i.e., self-drive) while the other belt's velocity was externally controlled (i.e., machine drive). This setup enabled participants to walk inside the interface with their limbs moving at two different speeds against FA resistance applied only to the SD limb (i.e., a differential resistance paradigm).

Device familiarization and selection of self-drive (SD) and machine-drive (MD) walking speeds for walking in the KA split-belt treadmill

All participants had a five-minute period to become familiar with walking inside the interface with both belts first tied and then split in a 2:1 speed ratio. NI participants practiced walking at tied and split speeds of 0.5 and 1 m/s with one speed programmed (MD) and the other controlled by the participant with visual feedback in SD mode. For PS participants, we evaluated their CWS inside the interface by instructing them to walk at a speed they were comfortable with for 30 seconds. We then assessed if participants could maintain this speed with visual feedback; if they could not, we reduced the speed by 0.1 m/s and reassessed their speed maintenance ability at the new speed. If they were able to comfortable maintain speed, we recorded their CWS with a 10MWT performed inside the device. We then divided this speed in a 2:1 ratio and allotted participants 60-seconds for practicing MD and SD speed combinations. For example: A participant's CWS at 0.6 m/s would yield a split speed of 0.3 and 0.6 m/s. PS participants practiced both split combinations for 60 seconds; if they were not able to maintain their split speeds, we reduced their speeds by 0.1 m/s and reassessed them.

Selection of differential FA resistance levels for nonimpaired (NI) and poststroke (PS) participants

For both groups, we selected treadmill-belt speeds in a 2:1 speed ratio. Considering NI individuals typically have CWS between 1.2 to 1.5 m/s, we selected 1 m/s and 0.5 m/s, as we have observed that these speeds are comfortable to walk at against resistance in our device in previous studies. We then used the interface's force-velocity relationship algorithm to calculate six progressive levels of FA resistance i.e., 6%, 9%, 12%, 15%, 18%, and 21% (% body weight) that required the same amount of intralimb propulsive-force generation for the SD belt, even though the speeds (1 and 0.5 m/s) were different. The force-velocity algorithm accounts of different speeds, by way of its resistance setting, such that even at slower speeds (i.e. 0.5 m/s) the amount of resistance that a particular individual experiences is the same if they were walking at faster speeds (i.e. 1 m/s) for the same calculated percentages of FA resistance. Our preliminary testing in NI and PS populations revealed that 21% FA resistance was the maximum resistance against which participants were able to comfortably walk while maintaining their target speed. Thus, we chose six-incremental resistance levels from 6-21% B.w. for application of FA resistance. All NI and PS participants performed two sets of differential FA resistance trials -

Part 1, conditions 1: We instructed NI participants to control and maintain a target speed of 1 m/s with the nondominant limb on the SD belt while experiencing FA resistance, while the MD was set to run at 0.5 m/s (Figure 1). C*ondition 2:* NI participants maintained a target speed of 0.5 m/s with the nondominant limb on the self-drive belt while experiencing FA resistance, while the MD belt was set to move at a speed of 1 m/s.

Part 2 conditions 1: We instructed PS participants to target and maintain their CWS (faster speed) on the SD belt with their P limb, while we set the NP limb speed to move at half this speed on the MD belt. *Conditions 2*: We instructed PS participants to target and maintain half their CWS on the SD belt with their P limb, while we set the NP limb speed to move at twice this speed on the MD belt.

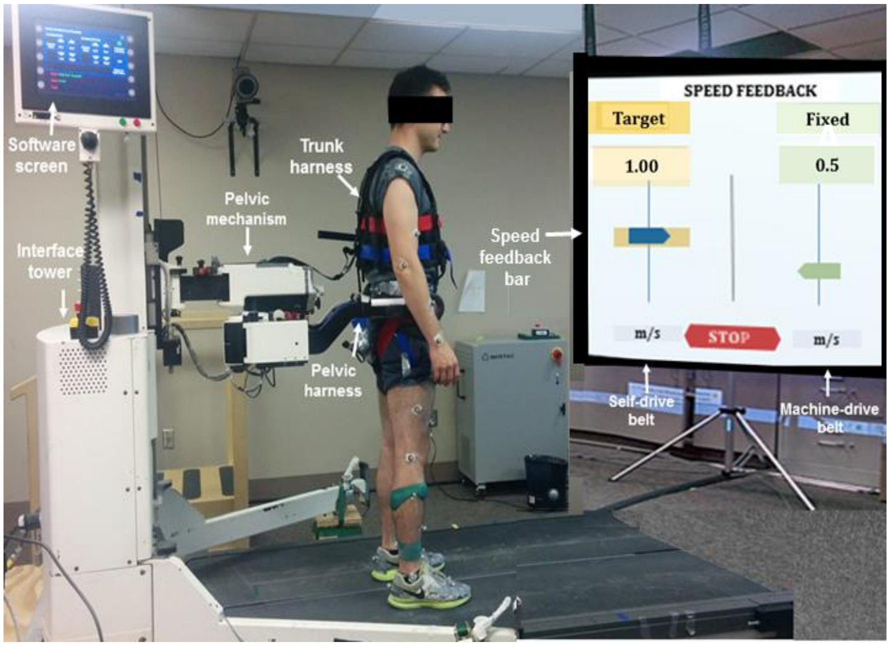


Figure 1A: Nonimpaired participant standing inside KineAssist (KA) split-belt treadmill interface. For experiment 1: Left belt was driven by participant (SD) with target speed of 1 m/s (yellow zone); right belt was fixed to move automatically (MD) at 0.5 m/s. Vice-versa for experiment 2.

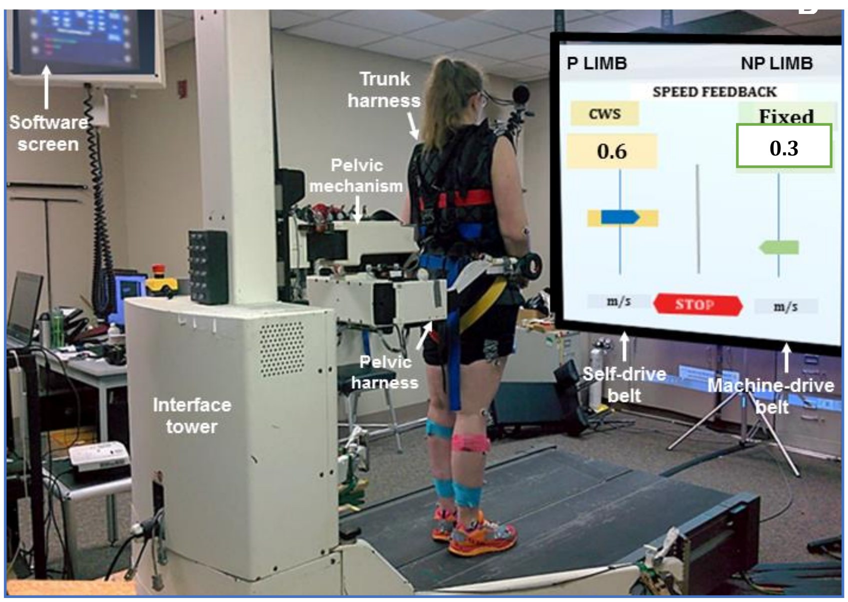


Figure 1B: Poststroke participant standing inside KineAssist (KA) split-belt treadmill interface. For Condition 2: Paretic (P) limb belt (left) was driven by participant (SD) with target CWS speed of 0.6 m/s (yellow zone); while the nonparetic (NP) limb belt (left) was fixed to move automatically (MD) at 0. 3 m/s. Vice-versa for condition 2.

Real-time velocity feedback and maintenance of target speed

We recognized that walking speed is characteristically sinusoidal in nature and is not constant. Hence, we provided participants in both groups with a target speed range highlighted by a yellow block. For NI participants their target zone was target speed with a range +/- 0.1 m/s. However, since PS participants had different CWS, we converted their speeds to 100% and then provided a +/- 0.1 m/s (e.g.,if target speed 0.5 m/s =100 % then target zone = 0.4-0.6 m/s = 80-120 %)and considered maintenance of speed within this target zone as acceptable for each participant (Figure 1). We used the interface's software to provide instantaneous visual feedback, projected as moving blue speed bars on a projector screen (5x6 foot) within the yellow target zone, placed in front of the interface.

Order of FA resistance trial presentation

For each condition in part 1 and part 2 for both groups, we randomized the order of presentation of differential FA resistance per trial. For each trial, we began collecting data only after visual confirmation that participants matched and maintained their target speed for 10 (initial) complete strides. Each data trial was 50 to 80 seconds long in order to account for the variability in NI and PS participant's target speeds, and to ensure a minimum of 25 strides per limb. However, if participants could not (1) start the treadmill belt because of an inability to overcome resistance, (2) maintain their target velocity even after two attempts, or (3) requested to stop and end experimental trials, we did not collect data. Throughout all experimental trials for both groups, we constantly monitored heart rate. In between all experimental trials, we provided participants with 30-60 second rest breaks to minimize fatigue.

Data acquisition

We collected all GRF data at 1000 Hz using the instrumented Bertec dual-belt treadmill and the interface's custom software to record treadmill belt speed (100 Hz) for each resistance trial.

Kinetic measurements

We normalized all GRF data to participant's body weight (%BW) after low-pass filtering using a 4th order Butterworth filter (20 Hz cutoff), and analyzed all data with custom MATLAB scripts (Mathworks®, version R2016b). We calculated kinetic gait events (heel strikes and toe-offs) at a threshold of 15 N per limb for each differential FA resistance trial. As both belts were moving at different speeds, we primarily focused on assessing mean propulsion force, i.e., positive component of fore-aft GRF during the stance phase, of each limb across all differential FA resistance trials. We then used this value to calculate mean % propulsion i.e., % Propulsion = Slow limb propulsive force/ (slow + fast limb) propulsive force and % Paretic propulsion (%Pp) = P limb propulsive force / (P+NP) propulsive force with 50% Propulsion = perfect symmetry between limbs. We used the % propulsion measure to determine the increasing or decreasing relationship of each limb's propulsion response with respect to FA resistance and to evaluate limb symmetry. We calculated stance time as the duration from ipsilateral heel strike to ipsilateral toe off for each limb. For visual inspection, we also provide ensemble average fore-aft GRF profiles for participants in both groups for each limb.

Statistical Analyses

We used SPSS (22 version) for all statistical analyses and checked that all primary and secondary dependent measures were normally distributed (Shapiro-Wilk's > 0.05). For part 1 conditions, we compared mean propulsion responses for each limb across all FA resistance levels using a repeated measures anova (limb x resistance). We also separately assessed the propulsion generation by each limb based on speed (slow vs. fast) and force (SD vs MD) using repeated measures ANOVAs. We compared stance time between limbs per conditions using independent samples *t*-tests. For part 2, to account for the variability in individual responses in the ability to walk at all differential levels in both conditions by the same participant, we separately compared individual slopes using one-sample t-tests for percent paretic limb propulsive force generation across all differential resistance trials achieved by the participant in condition 1 and condition 2. For those participants who could do both conditions, we compared their mean slope responses using paired samples t tests. We used $p \leq 0.05$ to determine significance, with Greenhouse-Geisser corrections for violations of sphericity and Bonferroni corrections for multiple post-hoc comparisons.

Results

Maintenance of self-drive (SD) belt target belt speed by nonimpaired and poststroke participants

On visual inspection, all nonimpaired participants maintained their SD belt target speed their acceptable range of 0.9 to 1.1 m/s for condition 1 and 0.4 to 0.6 m/s for condition 2, respectively. All PS participants maintained their target SD speed within the acceptable range of 100 ± 20 % for condition 1 and condition 2, respectively [*Note one-away ANOVA repeated measures statistic yet to be performed]*

Table 2: Mean 95% CI for self-drive (SD) belt target speed for condition 1 and condition 2 in nonimpaired (NI) and poststroke (PS) participants

Group	***Target speed***	***6% FA***	***9% FA***	***12% FA***	***15% FA***	***18% FA***	***21% FA***
NI	***Condition 1***	***N=9***	***N=15***	***N=15***	***N=15***	***N=15***	***N=14***
	1.0 ± 0.1m/s	1.03	0.95	0.96	0.94	0.93	0.93
	CI	[0.97-1.1]	[1-1.12]	[1-1.15]	[1-1.16]	[1-1.15]	[0.9-1.2]
NI	***Condition 2***	***N=15***	***N=15***	***N=15***	***N=15***	***N=15***	***N=15***
	0.5 ± 0.1m/s	0.55	0.52	0.51	0.50	0.50	0.48
	CI	[0.44-0.6]	[0.41-0.69]	[0.4-0.6]	[0.39-0.63]	[0.4-0.58]	[0.4-0.64]
PS	***Condition 1***	***N=9***	***N=9***	***N=9***	***N=9***	***N=7***	***N=3***
	100 ± 20%	101.01	101.28	102.35	89.89	100	93.6
	CI	[934-134]	[85.8-138]	[80-143.3]	[89-122.2]	[87-111.9]	[81-108]
PS	***Condition 1***	***N=14***	***N=14***	***N=14***	***N=13***	***N=7***	***N=5***
	100 ± 20%	91.93	92.96	89.83	*85.85*	81.54	82.12
	CI	[89-122]	[81-121]	[82-116]	[77.1-117]	[75.1-110]	[74-100]

Average fore-aft GRF for condition 1 and condition 2 comparison of fore-aft ground reaction force profiles for self-drive (SD) and machine drive (MD) belts in nonimpaired individuals

The average ensemble fore-aft GRF profile for each limb in both conditions for NI participants increased at each subsequent differential resistance level. For the same speed, fore-aft GRF profiles for the SD belt at 1 m/s (Fig.2.A) were relatively greater (i.e., propulsion increased more quickly and reached higher peaks) than those for the MD belt at 1 m/s (Fig.2.B) across resistance levels.

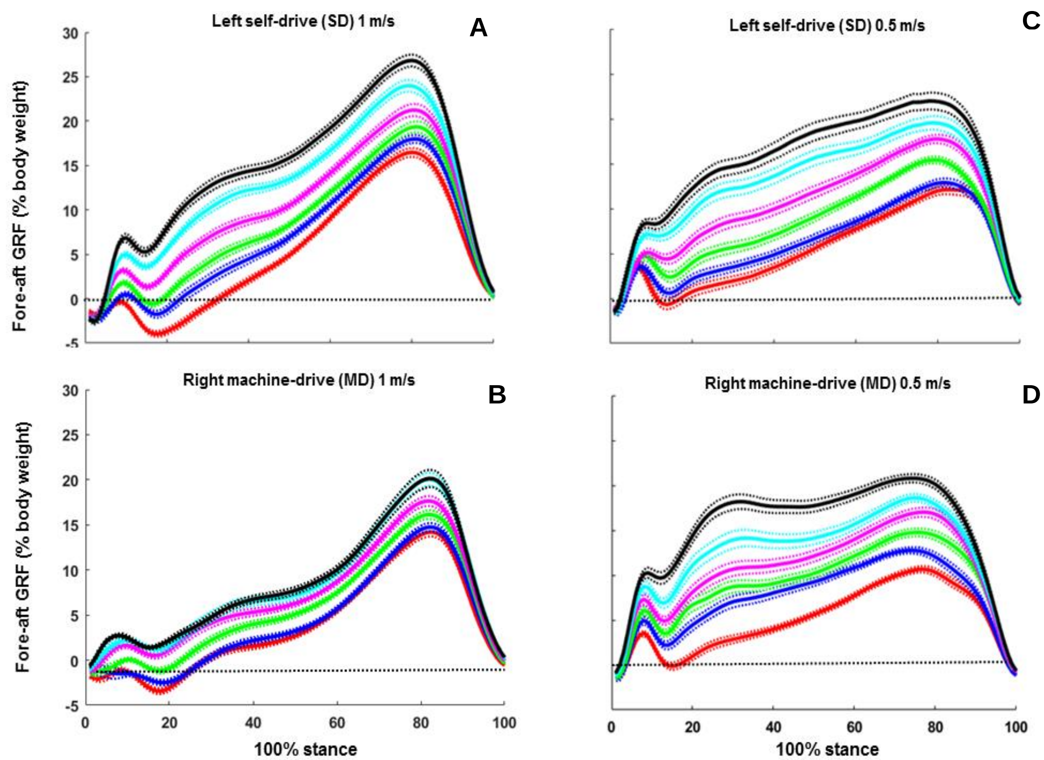


Figure. 2. Ensemble (average with standard error) fore-aft GRF profiles during condition 1 and condition 2 for left self-drive (SD) belt at 1 m/s (Fig.2.A) and right machine-drive (MD) belt at 1 m/s (Fig.2.B) with 0.5 m/s SD (Fig 2.C) and 0.5 m/s MD (Fig 2.D) across all FA resistance conditions. FA resistance levels – 6% (red), 9% (dark blue), 12% (green), 15% (magenta), 18% (light blue), and 21% (black).

However, at the slower speed of 0.5 m/s, average ensemble fore-aft GRF profiles for the SD (Fig.2.C) and MD limbs (Fig.2.D) appeared more similar in shape and magnitude.

Propulsive force for both limbs increased across resistance levels in both experiment

For condition 1, mean propulsive force for both the faster left limb SD belt (1 m/s) and slower right limb MD belt (0.5m/s) increased with greater differential FA resistance. We found a significant main effect of differential FA resistance [F (570, 9.4) =60.55, η^2= 0.68, *p*<0.001] with significant post-hoc effects (*p*<0.001) at each subsequent differential FA resistance level. We found with no significant main effect of limb or interaction effects between limb and resistance (Figure 3.A)

For condition 2, mean propulsive force for both limbs also increased across all differential resistance levels; however, the slower left limb SD belt (0.5 m/s) propulsive force was greater than faster right limb MD belt (1 m/s), particularly at higher resistance levels (18% & 21%). We found a significant interaction effect for differential FA resistance and limb [F (73.98, 1.68) =11.99, η^2= 0.27, *p*<0.001], with separate main effects of resistance [F (482,160) =78.23., η^2= 0.7, *p*<0.001] and limb [F (161.19, 32) =4.6, η^2= 0.12, *p*<0.05]. Post hoc comparisons revealed that the slower left limb (SD belt) had greater mean propulsive force compared to the faster right limb (MD belt) at 18% and 21% resistance levels (*p*<0.05.).

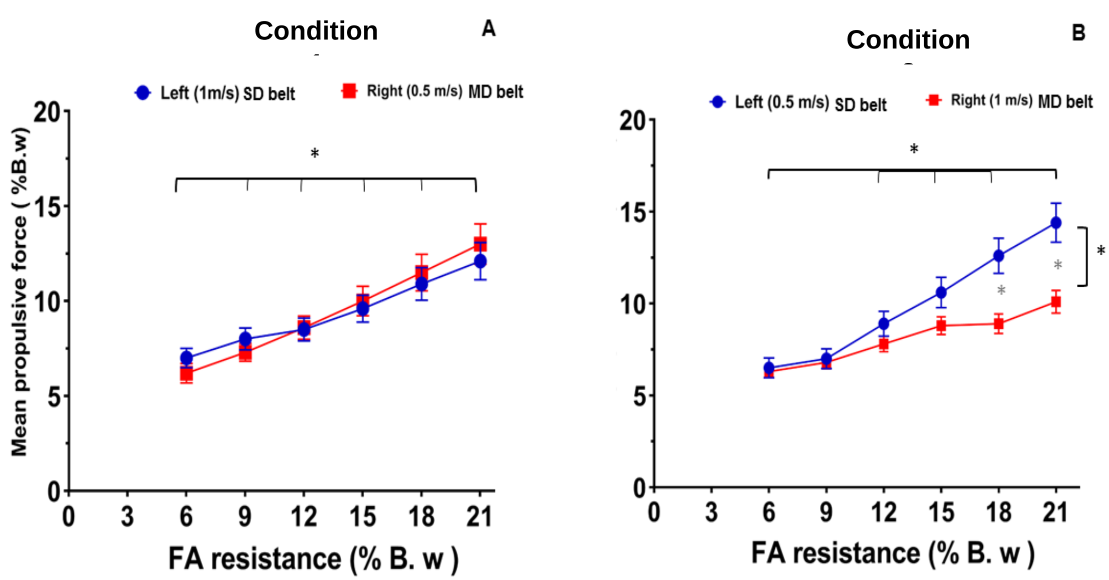


Figure 3: A. Mean propulsive force across all differential FA resistance levels in experiment 1 (left self-drive (SD)) belt at 1 m/s and right (machine-drive (MD)) belt at 0.5 m/s). B. Mean propulsive force across all differential FA resistance levels in experiment 2 (left self-drive (SD)) belt at 0.5 m/s and right (machine-drive (MD) belt at 1 m/s.
Note: Horizontal black bars represent significant main effects of resistance. Vertical black bars and black * represent significant interaction effects, while gray * represent significant post-hoc comparisons (*$p<0.05$)*

Effect of speed on propulsive force generation in self-drive (SD) and machine-drive (MD) across all differential resistance conditions

For the SD limb, mean propulsive force generation increased at each subsequent FA differential resistance level from 6 to 21% B.w. at 1 m/s and 0.5 m/s with a significant main effect of resistance level [F (703, 49) =90.05, η^2= 0.74, p<0.001, Figure 4] and significant post-hoc differences between all levels 6% to 21% B.w. We did not observe differences in propulsion generation between both SD limbs at the different speeds.

For the MD limb, mean propulsive force generation also increased at each subsequent FA differential resistance level from 6 to 21% B.w. (Figure 4). However, for the MD limbs we did observe differences in mean propulsion between limbs at higher resistance levels. Mean propulsion was greater at the higher resistance levels for the slower speed (18% and 21%) with a significant interaction effect of speed and resistance [F (14.4, 63) =3.23, η^2= 0.09, p<0.05]. We also found significant main effects of resistance [F (97, 63) =55, η^2= 0.63, p<0.001] (greater propulsion with increasing resistance) and speed [F (182, 32) =6.07, η^2= 0.65, p<0.05] (greater propulsion at the slower speed).

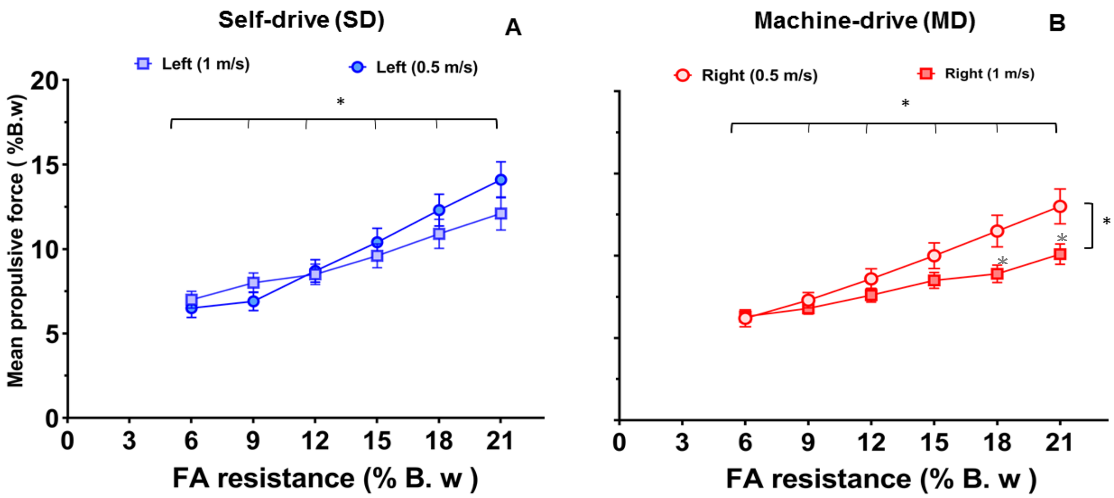


Figure 4: Mean propulsive force generation at different speeds by the left self-drive (SD) limb (Fig.3.A) and right machine-drive (MD) limb (Fig.3.B). Note: Horizontal black bars represent significant main effects, with smaller vertical black bars representing significant post-hoc effects and grey * representing between limb significant (p level) pairwise comparisons with Bonferroni corrections.

Comparisons of propulsive force generation against increasing FA resistance in the same mode (SDs MD) at the different speeds (0.5 vs 1 m/s)

At the slower speed of 0.5 m/s, we did not find any significant difference in mean propulsive force generation bewteen the SD and MD limbs. However, both the SD and MD limbs significantly increased their mean propulsive force generation from 6% to 21% B.w. of differential resistance with a main effect of resistance [F (1079, 1.3) =96.75, η^2= 0.75, p<0.001]. In comparison, at the faster speed of 1 m/s, we did find a significant difference in mean propulsive force generation between the SD and MD limb with a significant interaction effect of mode and resistance [F (14.4, 63) =3.23, η^2= 0.09, p<0.05]. We also found significant main effects of resistance [F (97, 63) =55, η^2= 0.63, p<0.001] and speed (SD mode) [F (182, 48) =6.07, η^2= 0.65, p<0.05F (1079, 1.3) =96.75, η^2= 0.75, p<0.001]. This suggests that both limbs increased mean propulsive force against greater resistance and that the SD limb generated greater propulsion than the limb on the MD belt, particularly at higher resistance levels (18% and 21%).

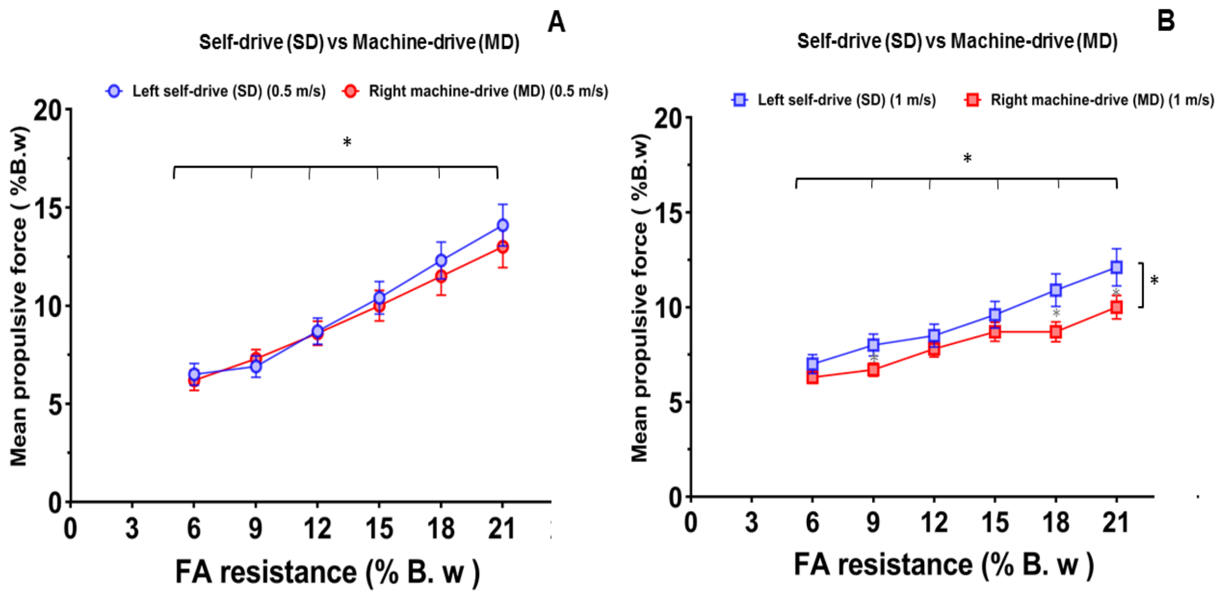


Figure 5: Mean propulsive force generation at the same speeds by the left self-drive (SD) limb and right machine-drive (MD) limb at 0.5 m/s (Fig.5.A) and at 1m/s (Fig.5.B). Note: Horizontal and vertical black bars represent significant main effects, with smaller black bars representing significant post-hoc effects, and grey * representing between-limb significant pairwise comparisons with Bonferroni corrections

Stance time changes between limbs for condition 1 and condition 2

For condition 1, Mean stance time for the faster left (1 m/s) SD limb resistance conditions (M=0.7 SD=0.03) and slower right (0.5m/s) MD limb (M=0.8, SD=0.001 m/s) condition 1. Independent sample *t*-test between limb at each resistance level was not significant ($p>0.05$). For condition 2, mean stance time for the slower left SD limb was M=0.9 SD=0.03, while that for the faster right MD limb (1 m/s) MD was M=0.7, SD=0.03 m/s. Comparison using independent-sample *t*-test was significantly greater for the slower (0.5m/s) right limb than the faster left limb (1m/s) at all resistance levels ($p<0.05$).

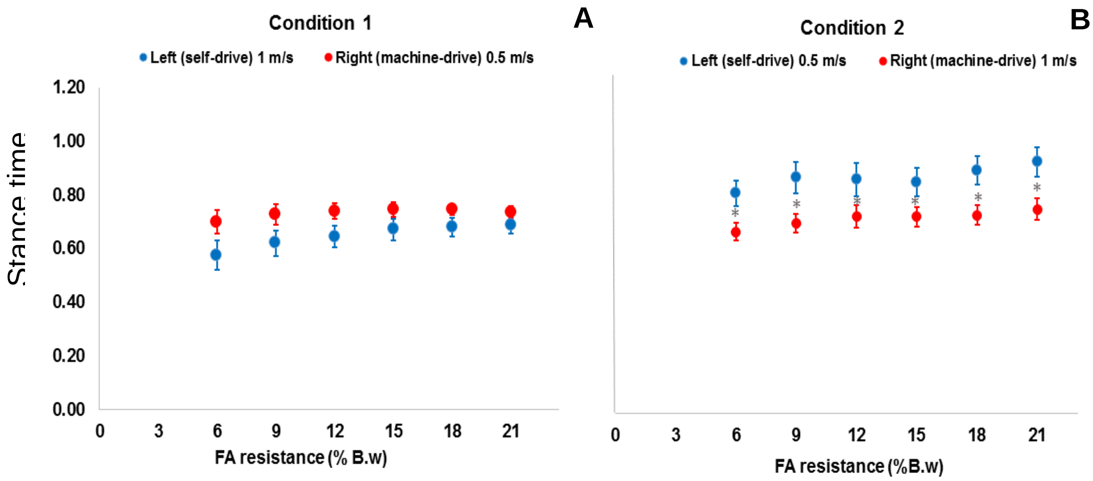


Figure 6: Mean stance time (seconds) with standard error bars for the self-drive (SD) and machine-drive (MD) limbs in condition 1 (Fig.6.A) and condition 2 (Fig.6.B) across all differential FA resistance levels. Note: Grey * represent significant pairwise comparisons using independent samples *t*-test at *p*<0.05.

Poststroke results

For condition 1, only 9 PS participants were able to successfully walk against resistance while maintaining a slower target speed with their P limb on the SD belt, while NP limb was set to move at a faster speed on the MD belt. For condition 2, only 14 out of the 15 PS participants walked successfully against resistance while maintaining a slower target speed with their P limb on the faster SD belt, while NP limb was set to move at a slower speed on the MD belt.

Percent paretic propulsion increased when the P limb was moving on the slower SD belt

For condition 1, on comparison of individual slopes for (n=9 participants) mean percent P limb propulsion across all differential FA resistance levels, one-sample *t* tests were significantly greater than zero (M=0.67 SD (0.73)) [t(8)=2.78, *p*<0.05)]. (Fig.7.A)

For condition 2, we found no significant difference when comparing the slopes (n=14 participants) for percent P limb propulsion across completed FA resistance levels with zero when the P limb was moving faster on the SD belt (M= -0.08, SD (0.77), p<0.05) (Fig.7.B)

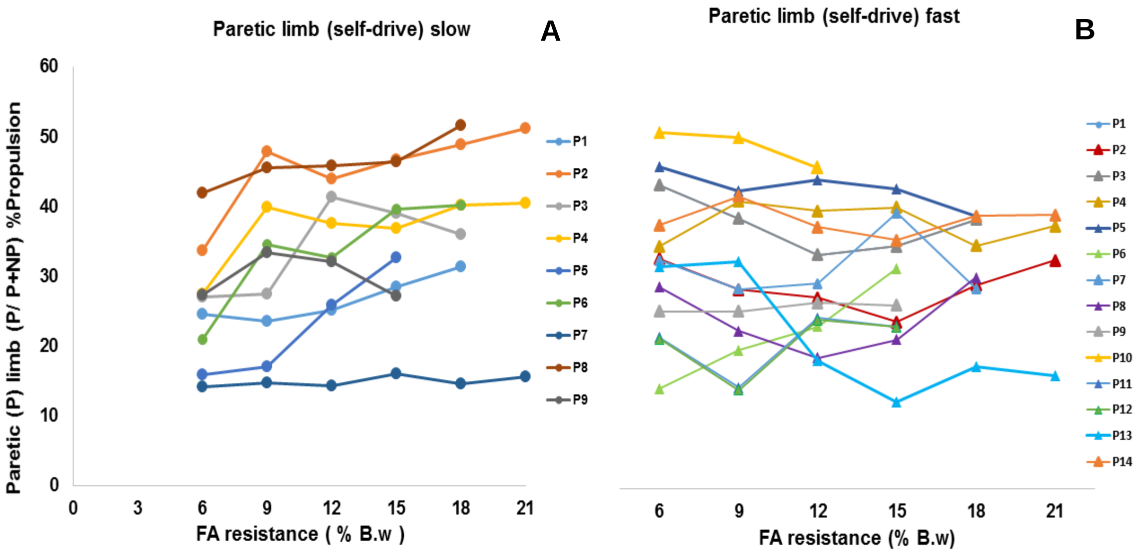


Figure 7: Percent paretic propulsive force across all differential FA resistance levels in condition 1 (P limb on slower self-drive (SD)) and faster NP machine-drive (MD)) belt, 1:2 ratio) (Fig.6.A), and condition 2 (P limb on faster self-drive (SD)) and slower NP machine-drive (MD)) belt, 2:1 ratio) (Fig.6.B).

Comparison of slopes for the 8 poststroke participants that could do condition 1 and condition 2

We compared the individual participant slopes for those poststroke participants who were able to successfully walk in both condition 1 and condition 2 (n=8), on comparison of mean slopes values for percent paretic propulsion in condition 1 (M=0.7 SD=0.72) (Fig.8.A) and condition 1 (M=0.05 SD=0.73) paired samples t-test was significant [t (7) =3.02, p<0.05)]. (Fig.8.B)

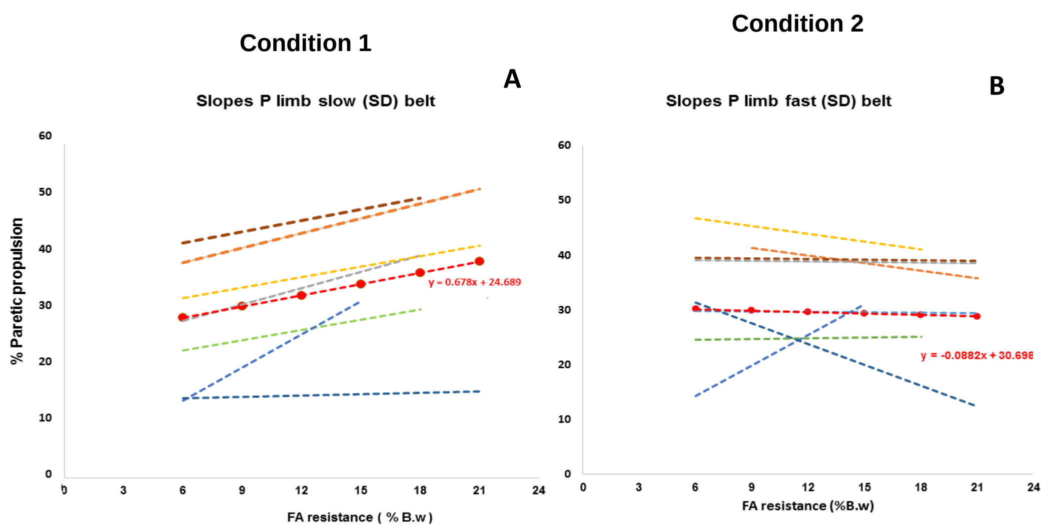


Figure 8: Individual % paretic propulsion slopes for all participants who completed (n=8) condition 1 (Fig.8.A) and condition 2 (Fig.8.B), red slope lines in the middle represent the average slope values for all participants in condition 1 and condition 2, using the average interpolated slope and intercept values of all participant in each condition, respectively.

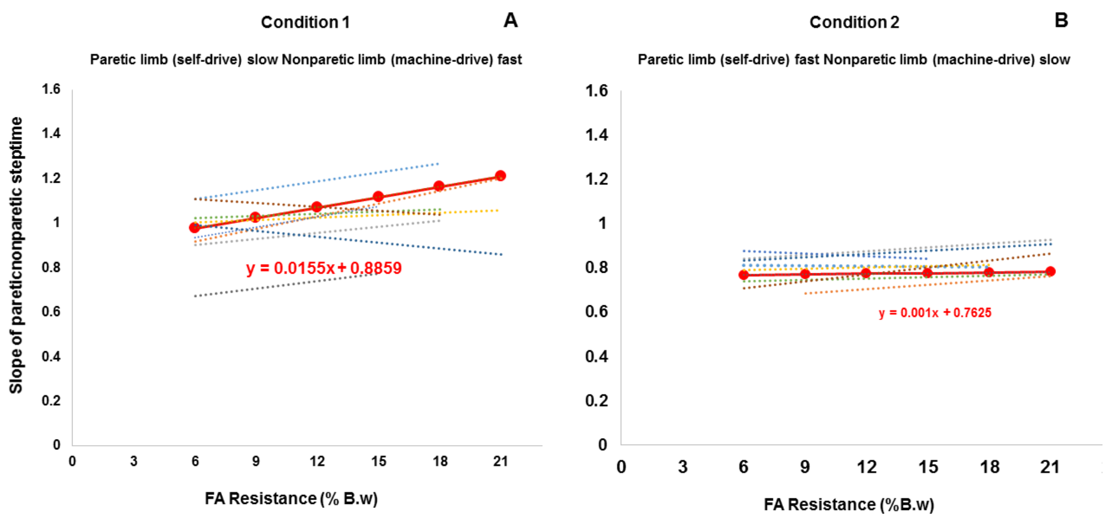
Stance time comparison of nonparetic limb in condition 1 and condition 2

In condition 1, all participants were able to walk at 6-15% FA resistance levels. Mean stance time of the nonparetic limb decreased from 1.03 seconds (SE=0.1) at 6% to 0.95 seconds (SE=0.1) at 15% B.W. FA resistance, indicating that P limb stance time increased. In condition 2, 13 of the 14 participants were able to complete 6-15% FA resistance levels. However, mean stance time of the nonparetic limb went from 1.3 seconds (SE=0.07) at 6% to 1.4 seconds (SE=0.1) at 15% B.W, indicating that it remained the same.

Stance time ratio of paretic limb and nonparetic limb in condition 1 and condition 2

We separately compared the individual participant slopes to zero for those poststroke participants who were able to successfully walk in both condition 1 and condition 2 (n=8) using one-sample t-tests. On comparison of mean slopes values for percent paretic propulsion in condition 1 was significant (M=0.02 SD=0.02, t (8) =2.37 *p*<0.05) and but not in condition 2 (M=0.004 SD=0.006) paired samples *t*-test was significant (*p*>0.05)

Figure 9: Individual % paretic propulsion slopes for all participants who completed (n=8) condition 1 (Fig.9.A) and condition 2 (Fig.9.B), red slope lines in the middle represent the average slope values for all participants in condition 1 and condition 2, using the average interpolated slope and intercept values of all participant in each condition, respectively.



DISCUSSION

In this study, our main purpose was to create a differential resistance paradigm using a split-belt robotic treadmill interface that allowed us to alter the relative propulsion output of one limb in comparison to the other. We divided our study into two parts to compare different combination of our differential resistance paradigm in both nonimpaired and poststroke participants.

For nonimpaired participants, our goal was to first understand if a differential resistance paradigm could be applied in a manner that causes asymmetric interlimb propulsive-force generation by altering the relative speed (slow vs fast) and force-generation requirements (SD vs MD) of one limb in comparison to the other while walking against increasing FA resistance. In part 1 condition 2, when the left SD belt moved at a 0.5 m/s and the right MD belt moved at 1m/s against, we found that initially the slower left SD limb produced similar propulsive force compared to the faster right MD limb at 6% and 9 % B.w. FA resistance levels. However, at higher resistance levels (12-15% B.w.) there is a noticeable increase in the slower SD limb propulsion output over the MD limb. At 18% and 21% B.w. levels the slower SD limb significantly increase its propulsion output over the the faster MD limb. These results highlight that the combination of the SD limb moving at slower speed i.e. force modulation and speed modulation compared to the MD being set at a faster speed allows for greater force generation percention and timing for proprioceptive limb-loading to engage extensor mechanisms and encourage a relatively greater propulsive force generation output, supporting our hypothesis for condition 2.

In contrast in condition 1, when the left SD belt moving at a faster speed (1 m/s) and the right MD belt moving at a slower speed (0.5 m/s) against increasing FA resistance, while mean propulsive force for each limb increase significantly at higher resistance levels there were no between limb differences. These results contradict our hypothesis, and indicate that the combination of force and speed modulation in this condition failed to cause a relatively greater propulsive generation output of the slower MD limb over the faster SD other.

However, comparison of both condition 1 and condition 2 results suggest that walking in the SD mode at a slower speed allowed for greater perception of FA resistance and lower extremity force output, as opposed to when the limb in in MD mode. Kautz et al. and others[39-41] on analysis of fore-aft forces during overground and treadmill walking at the same speed found that momentum of the moving belts along with external support can decrease muscle force-generation requirements, and alter spatiotemporal parameters. These results applied to our study, suggest that walking in the self-drive mode was more similar to overground walking allowing for better force perceptions, while the MD mode was similar to typical treadmill walking causing a reduction in force output for the same speed.

To better understand differences in condition 1 and 2 results, we further breakdown the results to isolate the effects of speed (slow vs fast) and force output requirement (SD vs MD). Regarding speed, we found that the when the machine-drive (MD) limb was moving at a slower speed (0.5m/s – condition 1) it generated significantly greater propulsive force compared to when the MD limb was moving at a faster speed (1 m/s – condition 2) against increasing levels of resistance. These results are interesting, as normally faster speeds are associated with increase in propulsive force generation. However, in our experimental setup we found the when the MD limb is moving slower it generated greater propulsion against increasing levels of resistance. This highlights that possibly by moving on at a slower speed against increasing resistance, the MD limb (right) at 0.5m/s had greater time for proprioceptive limb loading and thus, engagement of extensor mechanisms that enabled greater propulsive force generation. In contrast when the MD limb moving at a faster speed of 1m/s, had reduced time for proprioceptive limb-loading, especially with the belt velocity being externally controlled and hence was not able to generate greater mean propulsive force, even if the peak forces were similar. The fact that the slower MD limb also had a longer stance time in comparison to the fast MD limb strengthens this assumption.

Regarding force generation requirements, we found no difference in SD limb propulsion generation at 1m/s and 0.5 m/s. This is because we used our interface's force-velocity relationship to ensure that regardless of target speed, the force output for the resistance levels that the participant was walking against would produce the same propulsive force output. These results highlight that the SD limb was always producing the same propulsive force output regardless of target speed and MD limb's speed against progressive levels of resistance.

On comparison of force output between SD and MD limb at the same speed (0.5 m/s and 1m/s), we found that the slower SD limb at 0.5 m/s generated greater mean propulsive force than the MD limb at 0.5 m/s. In contrast, there was no difference in mean propulsive force generation between SD and MD limbs at 1 m/s. These results highlight the higher perceived force generation requirements by the SD limb when moving it is moving at a slower speed against resistance limb is moving at a faster speed against resistance. Stance time was also longer when the SD limb was targeting a slower speed. Together these findings highlight a greater time for proprioceptive limb-loading feedback and force perception when the SD limb moves at a slower speed against resistance.

For part 2, with regard to walking against differential resistance we found that only 9 of the 15 participants PS were able to walk in combination 1, where the P limb was targeting a slower speed on the SD belt while the NP limb was set to move at a faster speed. However, 14 of the 15 participants were able to walk in combination 2. We believe these results may be because PS participants found it more difficult to break away from their compensatory gait patterns, which may involve taking longer steps with their NP limb. Such compensatory patterns would also involve the NP limb moving at a slower speed with longer stance time in comparison to the P limb. Additionally, these participants might not have been able to generate the forces necessary to initiate movement of the SD belt at the desired target speed, which required generation of sufficient lower-extremity forces to match or overcome the resistance imposed by the force-velocity relationship in order to initiate treadmill belt movement.

However, for those PS participants (n=8) that were able to perform combination 1, we found that they increased their P limb propulsion output relative to the NP limb, as their slopes for mean % paretic propulsion were significant. In contrast PS participants who were able to do combination 2 (n=14) did not significantly increase their P limb propulsion output relative to the NP limb. This finding highlights that the combination of the P limb in self-drive moving at a slower speed against progressively highly resistance levels possibly enables greater proprioceptive limb-loading and force generation perception to engage extensor limb mechanisms that enable greater propulsion output. Additionally, by moving the NP limb at faster speed on the MD belt decreases its ability to compensate and produce greater propulsive force. This assumption is further strengthened on comparison of percent propulsion slopes between those participants who were able to do both condition 1 and condition 2. We found significant differences only in condition 1 and not in condition 2 for these participants, suggesting that when the P limb is moving faster the NP being on the slower MD belt is in a better position to compensate and take over propulsive force generation requirements. Additionally, on comparison of slopes for mean steptime ratio between the P and NP limbs, we found that in condition 1 participants had significant slope relationships. However, the same participants did not have significant slope relationships in condition 2. This finding states that when the NP limb stance time is reduced when it is made to move faster relative to the P limb, allowing the P limb greater opportunity to participate in propulsive force generation.

Limitations

While we attempted to create a novel split-belt application to apply FA-resistance in a differential manner during walking we acknowledge several limitation with our study. In this study, for part 1, we only explored walking function against differential resistance within our interface with the dominant in SD mode and non-dominant limb in MD mode. We also only assessed two speed combinations 0.5 m/s and 1 m/s in a selective range of resistance levels (6-21% B.w). To avoid participant fatigue, and in the interest of time, we only assessed P limb in SD mode and not the NP limb. Future studies should investigate this paradigm – (1) in different walking environments using intent-driven treadmills that allow the user to self-select their walking speed against different modes of resistance (either at the COM or individual joint level) with or without robotic interfaces, (2) different limb and speed combination at various increments of FA resistance. Additionally, (3) different selection of resistance levels to understand asymptotic effects of differential FA resistance, along with (4) further exploration of kinetic (joint power, work etc) and kinematic variables (moments, angles, etc) along with lower-limb electromyography is needed to help determine muscle-force generation strategies. The addition of these measures will help in further characterization of the neuromechanical strategies utilized during walking against differential fore-aft resistance in both nonimpaired and individuals poststroke.

Conclusions

Our results are the first to demonstrate that a differential application of resistance is possible within a split-belt environment. In the case of nonimpaired individuals, our results demonstrate selectively greater relative propulsion contribution of one limb over the other when the limb is moving at a slower speed in the SD against resistance. In the case individuals poststroke, our results highlight how differential application of resistance when the P limb in moving on the SD belt against resistance increases its relative propulsion contribution over the NP limb. The experimental environment of the robotic treadmill interface enabled us to manipulate the fore-aft loading demands during stance while participants controlled their walking speeds. Our results suggested that such applications of differential FA resistance have great rehabilitation potential and can be applied in as a means for progressive resistance strength training to increase P limb propulsion contribution during walking and discourage reliance on compensatory strategies.

Ethics: The UAB IRB approved this study, protocol number X150910010

REFERENCES

1. Liu MQ, Anderson FC, Pandy MG, Delp SL. Muscles that support the body also modulate forward progression during walking. *J Biomech.* 2006;39(14):2623-2630.

2. Neptune RR, Sasaki K, Kautz SA. The effect of walking speed on muscle function and mechanical energetics. *Gait Posture.* 2008;28(1):135-143.

3. Bowden MG, Balasubramanian CK, Neptune RR, Kautz SA. Anterior-posterior ground reaction forces as a measure of paretic leg contribution in hemiparetic walking. *Stroke.* 2006;37(3):872-876.

4. Awad LN, Palmer JA, Pohlig RT, Binder-Macleod SA, Reisman DS. Walking speed and step length asymmetry modify the energy cost of walking after stroke. *Neurorehabil Neural Repair.* 2015;29(5):416-423.

5. Hall AL, Peterson CL, Kautz SA, Neptune RR. Relationships between muscle contributions to walking subtasks and functional walking status in persons with post-stroke hemiparesis. *Clin Biomech (Bristol, Avon).* 2011;26(5):509-515.

6. Mansfield A, Inness EL, Lakhani B, McIlroy WE. Determinants of limb preference for initiating compensatory stepping poststroke. *Arch Phys Med Rehabil.* 2012;93(7):1179-1184.

7. Rimmer JH, Chen MD, McCubbin JA, Drum C, Peterson J. Exercise intervention research on persons with disabilities: what we know and where we need to go. *Am J Phys Med Rehabil.* 2010;89(3):249-263.

8. Duysens J, Clarac F, Cruse H. Load-regulating mechanisms in gait and posture: comparative aspects. *Physiol Rev.* 2000;80(1):83-133.

9. Pearson KG, Ramirez JM, Jiang W. Entrainment of the locomotor rhythm by group Ib afferents from ankle extensor muscles in spinal cats. *Exp Brain Res.* 1992;90(3):557-566.

10. Nielsen JB. How we walk: central control of muscle activity during human walking. *Neuroscientist.* 2003;9(3):195-204.

11. Turns LJ, Neptune RR, Kautz SA. Relationships between muscle activity and anteroposterior ground reaction forces in hemiparetic walking. *Arch Phys Med Rehabil.* 2007;88(9):1127-1135.
12. Savin DN, Tseng SC, Whitall J, Morton SM. Poststroke hemiparesis impairs the rate but not magnitude of adaptation of spatial and temporal locomotor features. *Neurorehabil Neural Repair.* 2013;27(1):24-34.
13. Awad LN, Bae J, O'Donnell K, et al. A soft robotic exosuit improves walking in patients after stroke. *Science Translational Medicine.* 2017;9(400):eaai9084.
14. Zhou Z, Sun Y, Wang N, Gao F, Wei K, Wang Q. Robot-Assisted Rehabilitation of Ankle Plantar Flexors Spasticity: A 3-Month Study with Proprioceptive Neuromuscular Facilitation. *Front Neurorobot.* 2016;10:16.
15. Yen SC, Schmit BD, Wu M. Using swing resistance and assistance to improve gait symmetry in individuals post-stroke. *Hum Mov Sci.* 2015;42:212-224.
16. Wang J, Hurt CP, Capo-Lugo CE, Brown DA. Characteristics of horizontal force generation for individuals post-stroke walking against progressive resistive forces. *Clin Biomech (Bristol, Avon).* 2015;30(1):40-45.
17. Hurt CP, Wang J, Capo-Lugo CE, Brown DA. Effect of progressive horizontal resistive force on the comfortable walking speed of individuals post-stroke. *J Neuroeng Rehabil.* 2015;12(1):7.
18. Lewek MD, Raiti C, Doty A. The Presence of a Paretic Propulsion Reserve During Gait in Individuals Following Stroke. *Neurorehabil Neural Repair.* 2018;32(12):1011-1019.
19. Dionisio VC, Brown DA. Collaborative robotic biomechanical interactions and gait adjustments in young, non-impaired individuals. *J Neuroeng Rehabil.* 2016;13(1):57.
20. Graham SA, Hurt CP, Brown DA. Minimizing Postural Demands of Walking While Still Emphasizing Locomotor Force Generation for Nonimpaired Individuals. *IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society.* 2018;26(5):1003-1010.
21. Patton J, Brown DA, Peshkin M, et al. KineAssist: design and development of a robotic overground gait and balance therapy device. *Top Stroke Rehabil.* 2008;15(2):131-139.
22. Naidu A, Brown D, Roth EJJrp. A Challenge-Based Approach to Body Weight–Supported Treadmill Training Poststroke: Protocol for a Randomized Controlled Trial. 2018;7(5).

23. Reisman DS, Wityk R, Silver K, Bastian AJ. Locomotor adaptation on a split-belt treadmill can improve walking symmetry post-stroke. *Brain.* 2007;130(Pt 7):1861-1872.

24. Reisman DS, Wityk R, Silver K, Bastian AJ. Split-belt treadmill adaptation transfers to overground walking in persons poststroke. *Neurorehabil Neural Repair.* 2009;23(7):735-744.

25. Choi JT, Bastian AJ. Adaptation reveals independent control networks for human walking. *Nat Neurosci.* 2007;10(8):1055-1062.

26. Vasudevan EV, Bastian AJ. Split-belt treadmill adaptation shows different functional networks for fast and slow human walking. *J Neurophysiol.* 2010;103(1):183-191.

27. Torres-Oviedo G, Vasudevan E, Malone L, Bastian AJ. Locomotor adaptation. *Prog Brain Res.* 2011;191:65-74.

28. Finley JM, Long A, Bastian AJ, Torres-Oviedo G. Spatial and Temporal Control Contribute to Step Length Asymmetry During Split-Belt Adaptation and Hemiparetic Gait. *Neurorehabil Neural Repair.* 2015;29(8):786-795.

29. Helm EE, Reisman DS. The Split-Belt Walking Paradigm: Exploring Motor Learning and Spatiotemporal Asymmetry Poststroke. *Phys Med Rehabil Clin N Am.* 2015;26(4):703-713.

30. Srivastava S, Kao PC, Reisman DS, Higginson JS, Scholz JP. Coordination of muscles to control the footpath during over-ground walking in neurologically intact individuals and stroke survivors. *Exp Brain Res.* 2016;234(7):1903-1914.

31. Reisman DS, Block HJ, Bastian AJ. Interlimb coordination during locomotion: what can be adapted and stored? *J Neurophysiol.* 2005;94(4):2403-2415.

32. Reisman DS, Binder-MacLeod S, Farquhar WB. Changes in metabolic cost of transport following locomotor training poststroke. *Top Stroke Rehabil.* 2013;20(2):161-170.

33. Reisman D, Kesar T, Perumal R, et al. Time course of functional and biomechanical improvements during a gait training intervention in persons with chronic stroke. *J Neurol Phys Ther.* 2013;37(4):159-165.

34. Knarr BA, Kesar TM, Reisman DS, Binder-Macleod SA, Higginson JS. Changes in the activation and function of the ankle plantar flexor muscles due to gait retraining in chronic stroke survivors. *J Neuroeng Rehabil.* 2013;10:12.

35. Blanchette A, Lambert S, Richards CL, Bouyer LJ. Walking while resisting a perturbation: Effects on ankle dorsiflexor activation during swing and potential for rehabilitation. *Gait Posture.* 2011;34(3):358-363.

36. Blanchette A, Bouyer LJ. Timing-specific transfer of adapted muscle activity after walking in an elastic force field. *J Neurophysiol.* 2009;102(1):568-577.

37. Roemmich RT, Bastian AJ. Two ways to save a newly learned motor pattern. *J Neurophysiol.* 2015;113(10):3519-3530.

38. Hurt CP, Burgess JK, Brown DAJG, posture. Limb contribution to increased self-selected walking speeds during body weight support in individuals poststroke. 2015;41(3):857-859.

39. Goldberg EJ, Kautz SA, Neptune RR. Can treadmill walking be used to assess propulsion generation? *J Biomech.* 2008;41(8):1805-1808.

40. Lee SJ, Hidler J. Biomechanics of overground vs. treadmill walking in healthy individuals. *J Appl Physiol (1985).* 2008;104(3):747-755.

41. Sullivan KJ, Knowlton BJ, Dobkin BH. Step training with body weight support: effect of treadmill speed and practice paradigms on poststroke locomotor recovery. *Arch Phys Med Rehabil.* 2002;83(5):683-691.

SUMMARY

Through the various investigations conducted throughout this dissertation, my main aims were to investigate the neuromechanical control mechanisms underlying propulsive force generation during walking in nonimpaired individuals and chronic stroke survivors against combined and differential fore-aft resistance. I was particularly interested in better understanding propulsive force generating mechanisms in both these groups, and whether the relative propulsive contribution of the paretic limb can be increased in relation to the without excessive utilization of compensatory mechanisms.

In chapter 1, I introduced the background and significance of force generation ability of each limb, in particular the importance of symmetric interlimb propulsive force generation ability from mid-terminal stance, in maintaining walking speed and forward progression of the COM [12–16,22]. I described a theoretical model that highlights the importance of proprioceptive limb-loading feedback during stance as an essential external sensory stimulus for appropriate engagement of Ib extensor mechanisms that prevent limb collapse at mid-stance and enable propulsive force generation from mid-terminal stance during walking [56,58] . I proposed that although hemiparesis causes reduction in cortical drive to distal lower-limb musculature, and may be a primary factor contributing to decreased propulsive-force generation, reliance on poststroke compensatory strategies causes inappropriate P limb loading and proprioceptive feedback during walking may also cause decreased engagement of Ib extensor mechanisms for propulsive force generation. Considering propulsive-forces represent the positive fore-aft component the

ground reaction force vector (GRF), which is a summation of lower-limb muscles forces, I suggested that even while stroke survivors utilizing compensatory strategies, walking against fore-aft resistance (applied at the COM) can act as a facilitator to promote greater proprioceptive P limb loading feedback and encourage greater propulsion. Taking this concept forward, I further suggested that application of fore-aft resistance in a differential manner during split-belt treadmill walking, such that the P limb has to walk against greater resistance demands compared the non-paretic (NP) limb can selectively encourage greater P limb propulsion relative to the NP limb. Such a method can be exploited to develop novel strength training interventions for individuals poststroke. To test these ideas, I developed a novel approach by utilizing the unique gait environment of a split-belt treadmill robotic to address my hypotheses.

Exploring the role of vertical limb-loading and locomotor challenges through two novel challenge based body-weight-support treadmill training paradigms for improving walking ability poststroke

Over the past several decades variations of BWSTT has been utilized to address balance and gait deficits in individuals poststroke. However, most of these interventions have been found to have limited transferability in improving improve poststroke community ambulatory function, with some studies reporting no significant outcome differences compared with over-ground training approaches. In chapter 2, I presented the outline of a 6-week BWSTT randomized controlled study that explored two novel paradigms designed to encourage greater active participation along with practice of 9 essential locomotor skills to help improve balance and gait outcomes for community ambulation in chronic stroke survivors. We recruited 29 participants, ≥ 5 months poststroke who exhibited slow CWS at baseline and randomized participants into either the BWSTT group which practiced walking without any handrail or external support (i.e. Hands-free (HF) group, N=15), while the other BWSTT group practiced HF walking along with 9 essential locomotor challenges (i.e. HF + challenge (C) group, N=15)). These challenges were narrow steps, long steps, walking with head turns, hurdles, backward walking, perturbations, speed up slow down, and variable speed. Participants in both groups trained in the unique walking environment of our robotic-treadmill that allowed participants to walk at their intended self-selected comfortable walking speed (CWS) i.e. intent driven via the device's force-velocity relationship. This chapter outlines the intent-driven treadmill environment of training environment of our device along with the rationale for designing the two BWSTT protocols used in this study together with how we measured pre-post training changes while ensuring all training parameters were similar between groups. We hypothesized that both groups to improve CWS pre to post training but expected that performing the nine locomotor challenging in addition to HF walking would lead to greater increase in overground CWS for the group HF+C group. While we selected nine specific locomotor challenges that we felt addressed locomotor skills required to improve community ambulatory function poststroke, one challenge did we failed to incorporate was walking with resistance. Considering hemiparetic weakness causes impaired paretic (P) limb propulsive-force generation, analysis of individual limb propulsion output during walking in an intent-driven treadmill environment against fore-aft resistance (as propulsion is generated in the fore-aft direction), applied at the center of mass (COM), can yield inside insight into the factors that can facilitate greater P limb propulsion. However, characterization of nonimpaired walking function in such an environment against FA resistance loads, normalized across body weight and speed, is first required.

Characterization of the KineAssist (KA) split-belt, intent-drive, robotic-treadmill interface and nonimpaired walking function at a target speed against increasing levels of fore-aft resistance.

In Chapter 3, I describe the walking environment of the KA split-belt treadmill in detail, which consists of the KA robotic device consisting of a pelvic harness attached to the pelvic mechanism and connected to a vertical tower that connects to a Bertec split-belt treadmill via sophisticated haptic control algorithm software. Individuals walking inside the interface interact with the pelvic mechanism via the pelvic harness (which has adjustable waist and hip straps) at the height of their COM. While the pelvic mechanism offers six degrees of freedom of movement, we restricted it to minimize external side-to-side translations and only allow COM translation only in the fore-aft and vertical direction for this study. Two bi-directional force transducers located at the height of each hip record and relay net forces at each hip to the treadmill belt via a positive feedback control algorithm that in turns dictates the treadmill belt speed. Once the individual has overcome a minimum set fore-aft resistance that can be controlled and adjusted the control algorithm will allow movement of treadmill belt. However, additional net hip forces are required to increase belt-speed to a desired speed on a step-by-step basis, thus making the treadmill "intent-driven". Taking advantage of this fore-velocity relationship, I explored how similar levels of graded FA resistance affects limb propulsion in nonimpaired individuals walking at the same target speed. To better characterize this fore-velocity relationship to calculate I developed an algorithmic relationship that accounts for the participants body weight, desired target speed, KA split-belt treadmills device parameters, and force-velocity relationship to calculate graded FA resistance levels that are equivalent to percentages of the participant's vertical body weight (Newton). I recruited N = 18 nonimpaired participants and assessed their individual propulsion against four graded levels of FA resistance (10%, 15%, 20%, 25% B.w.) while maintaining a target speed of 1m/s using visual feedback of the treadmill-belt speeds projected on a screen, placed at eye-level in front of the participant.

To characterize limb propulsion responses, I specifically focused on propulsive force generation during the second half of stance, as this period is commonly associated with overground propulsion generation. I primarily investigated propulsive impulse during this period as it accounts for propulsive force generation and the duration of propulsion. For additional secondary kinetic measurements, I also investigated mean propulsive force, and mean vertical impulse during the entire stance phase to assess if we were truly able to apply fore-aft resistance without changing vertical limb loading demands. I also assessed trailing limb angle, leading limb angle, stride time and step time to assess the spatiotemporal changes during walking against graded FA resistance. All participants maintained target belt velocity of 1.0 m/s at most levels of applied FA resistance, and significantly increased limb propulsion proportional to FA resistance ($p<0.01$) applied. Mean trailing limb angle increased ($p<0.05$), leading limb angle decreased ($p<0.05$), and positive joint work increased ($p\leq0.01$) with higher levels of FA resistance.

These findings suggested that we were able to successfully apply FA resistance at the COM in graded percentages of a participant's vertical body weight, while they maintained a target speed of 1m/s while walking within our intent-driven treadmill environment. Our results supplement that nonimpaired individuals respond to greater FA resistance demands by proportionally increasing their mean propulsive force generation (mean propulsive impulse and propulsive force) with accompanying biomechanical changes that facilitate greater limb propulsion, with no change in vertical forces. These results also validate our algorithm for calculation of FA resistance levels based on the participant's body weight and intended target speed. Additionally, these results also support our theoretical framework that walking against FA-resistance at a target speed increases proprioceptive limb loading and engages limb-extensor mechanisms that increases propulsive force generation. This study also provides rationale for design of rehabilitation interventions in neurological populations that may utilize application of FA resistance during walking at a target speed to design task-specific interventions like progressive strength training and workload manipulation during aerobic training for improving walking function. Lastly and most importantly, this study essentially laid the foundation for the next step in my dissertation, which was to explore and compare individual limb propulsion responses in poststroke and nonimpaired participants walking against similar FA resistance levels to better understand relative-limb propulsive differences between groups.

Walking against increasing levels of fore-aft resistance increases paretic limb propulsion but does not alter its relative propulsion contribution in relation to the nonparetic limb

Taking advantage of the KA-split-belt, intent-driven, treadmill interface experimental environment and the algorithm that allowed for provision of similar FA-resistance across all participants regardless of body weight and target speed. Chapter 5 explores an investigation into the relative propulsion contribution between limbs in both poststroke and nonimpaired individuals while walking inside our intent driven treadmill interface. In addition to exploring our theoretical model of proprioceptive limb loading this study also explored that possibility that an altered sense of effort affects propulsive-force generation in individuals poststroke. As one possibility for reduced P limb propulsive force generation following a stroke an altered sense of effort, which may occur due to a miscalculation of actual perceived effort (sense of effort) during ongoing movement that in turn affects the amount of force produced (sense of force) to perform a motor task in the absence of appropriate central motor commands. Previous using an isometric force-matching task, Ferris et al. found that an altered sense of effort affects P limb force generation especially in comparison to nonimpaired individuals. However, this concept has not been explored during walking as it is difficult to provide similar force-effort values to both nonimpaired and indiviudals poststroke for comparisons.

Fortunately, our unique KA-split-belt interface offers the opportunity of providing similar levels of FA-resistance (similar effort) to both nonimpaired and individuals poststroke walking at a target speed inside the interface. Equipped with this interface and the knowledge that its force-velocity relationship is able to provide similar FA resistance levels, regardless of their body weight and target speed, I investigated how walking against similar effort demands (i.e. FA-resistance) at a target speed affects propulsion contributions of each limb in nonimpaired individuals (N=15) and chronic stroke survivors (N=21with residual hemiparesis). All poststroke participants walked while targeting their CWS inside the interface, with average speed across all participants being 0.5 m/s. To make similar force and biomechanical comparisons, nonimpaired participants targeted walking at 0.5 m/s. We also focused on investigating % P propulsion (defined as P propulsion impulse / P + NP impulse *100), which accounts for propulsion contribution by both limbs, and is also strongly associated with plantarflexor activity (primary propulsion, muscles) is better suited to explore relative propulsion changes between the P and NP limb. All participants walked inside the interface while maintaining their target speed (using visual feedback) against six randomized and progressive levels of FA resistance i.e. 6%, 9%, 12%, 15%, 18% & 21% B.w. applied at the COM. Our primary hypothesis was that walking against similar increasing FA resistance demands will lead to a significantly greater NI % propulsion (dominant limb) over P % propulsion, due to similar sense of force output by NI limbs (~50% per limb) and an altered PS sense of force output that fixes the relative propulsion relationship between limbs (NP>P). Additionally, we hypothesized that there would be no change in % propulsion (for both groups) across FA resistance levels. Secondarily, we hypothesized that walking against increased FA resistance would correspond with respective increases in trailing limb angle (TLA) of P, NP, and NI limbs, as TLA is linked with increased limb propulsion in terminal stance.

We found that to maintain target speed both groups increased their interlimb propulsion across all resistance levels, with mean NI % propulsion significantly greater than the % P limb propulsion. Although, both groups increased their individual limb propulsion contribution they both maintained the same relative-propulsion relationship between limbs i.e., % propulsion for each limb did not change across resistance levels. These findings support our primary hypothesis i.e., for the same effort requirements the P and NP limbs increase their propulsion but maintain the same relative propulsion relationship between limbs, suggesting a 'fixed-interlimb propulsion relationship' for both groups. While this finding makes sense for nonimpaired participants who typically have interlimb force symmetry. In the case of PS participants, the fact that % P propulsion did not change even through both the P and NP limbs increased their propulsion contribution suggests that for similar effort demands the P and NP limb have different same of force output. This highlights a fixed relative propulsion relationship between limbs, with greater contribution of the NP limb over the P limb producing characteristic asymmetry interlimb propulsion output typical of compensatory gait.

Contrary to our second hypothesis, other than 18% FA, the NP limb TLA was not relatively greater than the P limb and did not significantly change across FA resistance levels. This interesting finding suggests that participants were not necessarily placing their limb further back, at least during the initial few FA resistance levels, to increase propulsion against increased resistance demands, and that a more posterior limb position was not necessarily driving the larger propulsion contribution of the NP limb. Studies have associated increases in TLA with increases in ankle moment for improving propulsion generation at push-off to increase speed [47,48]. However, increases in TLA may not correspond with increases in plantarflexor activity, especially when walking at slower speeds and against resistance. This suggests that when maintaining a constant speed, increases in TLA are not the only strategy used by participants to increase propulsion generation, or that a constant sense of effort leads to consistent limb force responses, which might not significantly change across conditions.

We demonstrated that walking at a target speed that is self-controlled within an intent-driven treadmill interface (like ours) against FA resistance, applied at the COM, can be used to assess similar effort requirements across NI and PS participants and be used to characterized the relative propulsion contributions of each limb. Our findings suggest that the walking against FA resistance at a constant speed supports that theoretical premise of greater proprioceptive limb loading to engage limb-extensor mechanisms for increasing propulsion generation. Additionally, our results reveal that even though individual limb propulsion increased against resistance for the PS participants, the relative propulsion contributions between the P and NP limbs remained constant with no change in % P limb propulsion across resistance levels. This might be due to a fixed propulsion calibration between limbs for the similar sense of effort perceived by each limb. While application of resistance at the COM during walking can be used as potential strength training method, it is not ideal as individuals PS will still rely on compensatory strategies with the NP limb being the main contributor to propulsion.

However, these results do raise the important question that to decrease NP limb propulsion participation during walking and encourage greater P limb propulsion contribution, perhaps application of FA resistance in a differential manner is required, such that only the P limb can selectively experience greater sense of effort demands against resistance applied to both limbs during walking. Such paradigms may provide insight on which factors can reduce NP limb compensation, and selectively increase P propulsion.

Walking against increasing differential fore-aft resistance asymmetrically increases propulsion output in nonimpaired individuals and selectively increase P limb propulsion relative to the nonparetic limb in individuals poststroke

In chapter 6, I worked with the system engineers who originally designed the KA-split-belt treadmill robotic device to design a software modification that enabled users walking within the split-belt environment of the interface to experience FA resistance in a differential manner. This modification allowed the speed of one treadmill belt to be set automatically by an external examiner i.e. machine-driven (MD) (similar to a typical treadmill belt), while the other treadmill belt speed was programed to be intent drive or self-driven (SD) by the user walking inside the interface. Essentially, the SD belt utilizes the interface's force-velocity relationship to allow users walking inside the interface to dictate the velocity of the belt, by overcoming a minimum (adjustable) fore-aft resistance via lower-extremity force generation on a step-by step basis to start the belt moving while additional forces enable participants to reach and maintain a desired target speed making the belt. Thus, by making users walk within the modified split-treadmill interface in a 2:1 speed ratio, by either programing the MD belt to run faster or slower than the SD belt target speed against increasing levels of FA-resistance (applied via the SD belt) we can apply FA resistance to each limb in a differential manner.

To characterize and understand how walking within this novel differential resistance environment affects walking function in nonimpaired individuals and individuals postroke. I broke down my study into two parts, part 1 explored walking in nonimpaired individuals in two different FA resistance conditions. In condition 1, Fifteen (N=15) nonimpaired participants (mean age 51 yrs, SD=14) walked with their left (non-dominant) limb on the SD belt at a target speed of 1m/s, while the right (dominant) limb was on the MD belt set at a slower speed of 0.5m/s. In condition 2, I reversed the speed combination for the same participants (N=15) who now walked with their left SD limb targeting 0.5 m/s while the right MD limb was set at 1 m/s. In both conditions participants walked against six progressive levels of FA-resistance (i.e. 6-21%) that were designed to elicit the same propulsive force output responses from the SD belt by using the device's force-velocity relationship. I hypothesized that the limb moving slower in both conditions

In part 2, I assessed (N=15) chronic poststroke survivors with residual hemiparesis (mean age 53 yrs SD=12, left hemi=7) in two separate conditions. In condition 1, participants walked with the P limb targeting a slow speed with the SD belt, while the NP limb moved faster on the MD belt at twice the speed. In condition 2, the P limb targeted a faster speed on the SD belt, while the NP limb moved slower against progressive FA resistance. For part 1 &2, we primarily assessed mean propulsion output of each limb during the entire stance phase, and secondarily assessed mean stancetime.

Our nonimpaired condition 1 results contradicted our hypothesis. We found that differential combination of force and speed modulation in this condition failed to cause a relatively greater propulsive generation output of the slower MD limb over the faster SD other. In contrast in condition 2 when the left SD belt moving at a slower speed (0.5 m/s) and the right MD belt moving at a faster speed (1m/s) against increasing FA resistance. These results highlight that the combination of the SD limb moving at slower speed i.e.

force modulation and speed modulation compared to the MD being set at a faster speed allows for greater force generation percention and timing for proprioceptive limb-loading to engage extensor mechanisms and encourage a relatively greater propulsive force generation output.

For part 2, we found that only 9 of the 15 participants PS were able to walk in combination 1, where the P limb was targeting a slower speed on the SD belt while the NP limb was set to move at a faster speed. However, 14 of the 15 participants were able to walk in combination 2. We believe these results may be because PS participants found it more difficult to break away from their compensatory gait patterns, which may involve taking longer steps with their NP limb. Such compensatory patterns would also involve the NP limb moving at a slower speed with longer stance time in comparison to the P limb. Additionally, these participants might not have been able to generate the forces necessary to initiate movement of the SD belt at the desired target speed, which required generation of sufficient lower-extremity forces to match or overcome the resistance imposed by the force-velocity relationship in order to initiate treadmill belt movement.

However, for those PS participants (n=8) that were able to perform combination 1, we found that they increased their P limb propulsion output relative to the NP limb, as their slopes for mean % paretic propulsion were significant. In contrast PS participants who were able to do combination 2 (n=14) did not significantly increase their P limb propulsion output relative to the NP limb. This finding highlights that the combination of the P limb in self-drive moving at a slower speed against progressively highly resistance levels possibly enables greater proprioceptive limb-loading and force generation perception to engage extensor limb mechanisms that enable greater propulsion output.

Additionally, by moving the NP limb at faster speed on the MD belt decreases its ability to compensate and produce greater propulsive force. This assumption is further strengthened on comparison of percent propulsion slopes between those participants who were able to do both condition 1 and condition 2. We found significant differences only in condition 1 and not in condition 2 for these participants, suggesting that when the P limb is moving faster the NP being on the slower MD belt is in a better position to compensate and take over propulsive force generation requirements. Additionally, on comparison of slopes for mean stance time ratio between the P and NP limbs, we found that in condition 1 participants had significant slope relationships. However, the same participants did not have significant slope relationships in condition 2. This finding states that when the NP limb stance time is reduced when it is made to move faster relative to the P limb, allowing the P limb greater opportunity to participate in propulsive force generation.

Future investigations

While this important work has yielded some interesting discoveries and provided insight on proprioceptive limb-loading mechanisms during walking in both nonimpaired and individuals poststroke. However, this important work still requires future investigation to characterize the neuromechanistic strategies adopted by both nonimpaired and poststroke individuals at combined and differential fore-aft resistance. In particular, future studies should explore these paradigms in - (1) different treadmill environments like standard treadmill environments or intent-driven treadmill environments that allow the user to self-select their walking speed. Different modes of FA resistance applied either at the COM or individual joint level using simple external apparatuses (e.g. pulley system, elastic tubing, motor system) or more sophisticated robotic or non-robotic interfaces (e.g. individual limb robotic resistance device or exoskeletons)), (2) different limb and split-speed combinations at different FA resistance levels should be explored. Additionally, (3) further exploration of kinetic (joint power, work etc) and kinematic variables (moments, angles, etc.) along with lower-limb electromyography is needed to help determine muscle-force generation strategies.

Clinical implications associated with this dissertation work

Experimental results and work from this dissertation highlights the rehabilitation potential of utilizing fore-aft resistance during walking at a constant speed to engage limb-extensor mechanisms and increase propulsive force generation in both nonimpaired and impaired neurological populations with lower-extremity weakness, such as individuals poststroke stroke. Both researcher and clinicians can incorporate this work to design task specific gait-rehabilitation strategies utilizing combined or differential application of fore-aft resistance during walking in walking environments similar to our interface. Alternatively, combined fore-aft resistance can be applied at the center of mass using resistance tubing or a motorized pulley system during walking on a standard intent or non-intent driven treadmill interfaces while participants walk at a constant speed. Various research groups have undertaken this venture and successfully demonstrated that combined fore-aft resistance can be applied in this manner. Additionally, simpler robotic interface attachments or exoskeletons can be used during split-belt treadmill walking to apply differential resistance.

Utilizing either our KA split-belt interface or any of the above methods to apply combined and differential FA resistance, as a next step to carry these research forward, future studies should explore the potential of using combined and differential fore-aft resistance as a progressive strength-training modality/regimen during walking in chronic stroke survivors. Such an exploratory study would likely be a 10-week randomized clinical study trial. Based on previous poststroke clinical studies exploring gait rehabilitation interventions previous clinical lab studies, we would recruit an estimated 40 chronic stroke survivors with residual hemiparesis, visible steplength asymmetry, with the ability to walk 14 meters independently with or without an assistive device (e.g. Cane, AFO), randomize them to two groups (n=20 each). Prior to training initiation, we will assess walking speed and interlimb propulsive force generation ability of participants against combined fore-aft resistance to determine their target speed and calculate their progressive resistance training levels. Group I participants, would participate in progressive resistance exercise regimen involving walking against combined fore-aft resistance applied at the COM. While group II participants, would participate in progressive resistance exercise regimen involving walking against differential resistance such that the P limb will walk at a slower target speed while the NP limb will walk at twice the speed (1:2 speed ratio) against fore-aft resistance. We hypothesize that participants in both groups will increase their P limb propulsion contribution. However, participants in group II will demonstrate increase in relative P limb propulsion output over the NP limb i.e. % paretic propulsion increase due to selective engagement and strengthening of P limb proprioceptive limb-loading extensor mechanisms that will promote greater P limb participation, with reduction in NP limb propulsion contribution. We will primarily evaluate mean propulsive force, percent propulsion contribution of the paretic-limb. Secondarily we will evaluate kinetic (joint powers, net joint work), kinematic (stance time, trailing limb angle, joint moments), energetics (Vo2 max) and treadmill and overground comfortable walking speeds (Pre-post measurements). Participants in both groups will train three times per week, 30 minutes per session (with a separate 10-minute warm up and cool down). A regular target speed and resistance assessment along with collection of kinetic (mean propulsive force generation, joint powers and net joint work for each limb), kinematic (stance time, trailing limb angle, joint moments) and energetic (Vo2 max) measures will be undertaken every two weeks. This will help determine progression of training with regard to either increase in target speed or resistance level for training, and help chart changes in biomechanical intralimb and interlimb parameters, and walking energetics. Results obtained from such a study will help determine the true rehabilitation potential of fore-aft resistance applied during walking to help improve P limb propulsion contribution.

LIST OF GENERAL REFERENCES

1. Mozaffarian, D., et al., *Executive Summary: Heart Disease and Stroke Statistics--2016 Update: A Report From the American Heart Association.* Circulation, 2016. **133**(4): p. 447-54.

2. Mozaffarian, D., et al., *Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association.* Circulation, 2016. **133**(4): p. e38-60.

3. *Post-stroke rehabilitation: assessment, referral, and patient management. U.S. Department of Health and Human Services Public Health Service. Agency for Health Care Policy and Research.* Clin Pract Guidel Quick Ref Guide Clin, 1995(16): p. i-iii, 1-32.

4. Ovbiagele, B., et al., *Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association.* Stroke, 2013. **44**(8): p. 2361-75.

5. Teasell, R., et al., *The next revolution in stroke care.* Expert Rev Neurother, 2014. **14**(11): p. 1307-14.

6. Langhorne, P., F. Coupar, and A. Pollock, *Motor recovery after stroke: a systematic review.* Lancet Neurol, 2009. **8**(8): p. 741-54.

7. Mayo, N.E., et al., *Disablement following stroke.* Disabil Rehabil, 1999. **21**(5-6): p. 258-68.

8. Mayo, N.E., et al., *Activity, participation, and quality of life 6 months poststroke.* Arch Phys Med Rehabil, 2002. **83**(8): p. 1035-42.

9. Tilson, J.K., et al., *Characterizing and identifying risk for falls in the LEAPS study: a randomized clinical trial of interventions to improve walking poststroke.* Stroke, 2012. **43**(2): p. 446-52.

10. Perry, J., et al., *Classification of walking handicap in the stroke population.* Stroke, 1995. **26**(6): p. 982-9.

11. Perry, J. and J.R. Davids, *Gait analysis: normal and pathological function.* Journal of Pediatric Orthopaedics, 1992. **12**(6): p. 815.

12. Bowden, M.G., et al., *Anterior-posterior ground reaction forces as a measure of paretic leg contribution in hemiparetic walking.* Stroke, 2006. **37**(3): p. 872-6.

13. Neptune, R.R., C.P. McGowan, and S.A. Kautz, *Forward dynamics simulations provide insight into muscle mechanical work during human locomotion.* Exerc Sport Sci Rev, 2009. **37**(4): p. 203-10.

14. Neptune, R.R., D.J. Clark, and S.A. Kautz, *Modular control of human walking: a simulation study.* J Biomech, 2009. **42**(9): p. 1282-7.

15. McGowan, C.P., R. Kram, and R.R. Neptune, *Modulation of leg muscle function in response to altered demand for body support and forward propulsion during walking.* J Biomech, 2009. **42**(7): p. 850-6.

16. Liu, M.Q., et al., *Muscles that support the body also modulate forward progression during walking.* J Biomech, 2006. **39**(14): p. 2623-30.

17. Ivanenko, Y.P., R.E. Poppele, and F. Lacquaniti, *Five basic muscle activation patterns account for muscle activity during human locomotion.* J Physiol, 2004. **556**(Pt 1): p. 267-82.

18. Balaban, B., et al., *Early rehabilitation outcome in patients with middle cerebral artery stroke.* Neurosci Lett, 2011. **498**(3): p. 204-7.

19. Chen, G., et al., *Gait differences between individuals with post-stroke hemiparesis and non-disabled controls at matched speeds.* Gait Posture, 2005. **22**(1): p. 51-6.

20. Patterson, K.K., et al., *Longitudinal changes in poststroke spatiotemporal gait asymmetry over inpatient rehabilitation.* Neurorehabil Neural Repair, 2015. **29**(2): p. 153-62.

21. Peterson, C.L., S.A. Kautz, and R.R. Neptune, *Braking and propulsive impulses increase with speed during accelerated and decelerated walking.* Gait Posture, 2011. **33**(4): p. 562-7.

22. Allen, J.L., S.A. Kautz, and R.R. Neptune, *Step length asymmetry is representative of compensatory mechanisms used in post-stroke hemiparetic walking.* Gait Posture, 2011. **33**(4): p. 538-43.

23. Peterson, C.L., S.A. Kautz, and R.R. Neptune, *Muscle work is increased in pre-swing during hemiparetic walking.* Clin Biomech (Bristol, Avon), 2011. **26**(8): p. 859-66.

24. Peterson, C.L., et al., *Pre-swing deficits in forward propulsion, swing initiation and power generation by individual muscles during hemiparetic walking.* J Biomech, 2010. **43**(12): p. 2348-55.

25. Hall, A.L., et al., *Biomechanical variables related to walking performance 6-months following post-stroke rehabilitation.* Clin Biomech (Bristol, Avon), 2012. **27**(10): p. 1017-22.
26. Olney, S.J., T.N. Monga, and P.A. Costigan, *Mechanical energy of walking of stroke patients.* Arch Phys Med Rehabil, 1986. **67**(2): p. 92-8.
27. Olney, S.J., et al., *Work and power in gait of stroke patients.* Arch Phys Med Rehabil, 1991. **72**(5): p. 309-14.
28. Divani, A.A., et al., *Risk factors associated with injury attributable to falling among elderly population with history of stroke.* Stroke, 2009. **40**(10): p. 3286-92.
29. Ramsay, J.W., et al., *Paretic muscle atrophy and non-contractile tissue content in individual muscles of the post-stroke lower extremity.* J Biomech, 2011. **44**(16): p. 2741-6.
30. Divani, A.A., et al., *Consequences of stroke in community-dwelling elderly: the health and retirement study, 1998 to 2008.* Stroke, 2011. **42**(7): p. 1821-5.
31. Rimmer, J.H., et al., *Exercise intervention research on persons with disabilities: what we know and where we need to go.* Am J Phys Med Rehabil, 2010. **89**(3): p. 249-63.
32. Dickstein, R., *Rehabilitation of gait speed after stroke: a critical review of intervention approaches.* Neurorehabil Neural Repair, 2008. **22**(6): p. 649-60.
33. Hartigan I., O.C., E., McCarthy, G., & O'Mahony, D., *First time stroke survivors' perceptions of their health status and their goals for recovery* International Journal of Nursing and Midwifery, 2011. **3**(2141-2499): p. 22-29.
34. Nadeau, S., et al., *Dynamometric assessment of the plantarflexors in hemiparetic subjects: relations between muscular, gait and clinical parameters.* Scand J Rehabil Med, 1997. **29**(3): p. 137-46.
35. Nadeau, S., et al., *Plantarflexor weakness as a limiting factor of gait speed in stroke subjects and the compensating role of hip flexors.* Clin Biomech (Bristol, Avon), 1999. **14**(2): p. 125-35.
36. Parvataneni, K., S.J. Olney, and B. Brouwer, *Changes in muscle group work associated with changes in gait speed of persons with stroke.* Clin Biomech (Bristol, Avon), 2007. **22**(7): p. 813-20.
37. Nadeau, S., M. Betschart, and F. Bethoux, *Gait analysis for poststroke rehabilitation: the relevance of biomechanical analysis and the impact of gait speed.* Phys Med Rehabil Clin N Am, 2013. **24**(2): p. 265-76.

38. Nadeau, S., et al., *Analysis of the clinical factors determining natural and maximal gait speeds in adults with a stroke.* Am J Phys Med Rehabil, 1999. **78**(2): p. 123-30.

39. Hsiao, H., et al., *Mechanisms to increase propulsive force for individuals poststroke.* J Neuroeng Rehabil, 2015. **12**: p. 40.

40. Awad, L.N., et al., *Paretic Propulsion and Trailing Limb Angle Are Key Determinants of Long-Distance Walking Function After Stroke.* Neurorehabil Neural Repair, 2015. **29**(6): p. 499-508.

41. Vasudevan, E.V. and A.J. Bastian, *Split-belt treadmill adaptation shows different functional networks for fast and slow human walking.* J Neurophysiol, 2010. **103**(1): p. 183-91.

42. Torres-Oviedo, G., et al., *Locomotor adaptation.* Prog Brain Res, 2011. **191**: p. 65-74.

43. Reisman, D.S., et al., *Locomotor adaptation on a split-belt treadmill can improve walking symmetry post-stroke.* Brain, 2007. **130**(Pt 7): p. 1861-72.

44. Reisman, D.S., H.J. Block, and A.J. Bastian, *Interlimb coordination during locomotion: what can be adapted and stored?* J Neurophysiol, 2005. **94**(4): p. 2403-15.

45. Reisman, D.S., A.J. Bastian, and S.M. Morton, *Neurophysiologic and rehabilitation insights from the split-belt and other locomotor adaptation paradigms.* Phys Ther, 2010. **90**(2): p. 187-95.

46. Reisman, D.S., et al., *Repeated split-belt treadmill training improves poststroke step length asymmetry.* Neurorehabil Neural Repair, 2013. **27**(5): p. 460-8.

47. Reisman, D.S., H. McLean, and A.J. Bastian, *Split-belt treadmill training poststroke: a case study.* J Neurol Phys Ther, 2010. **34**(4): p. 202-7.

48. Reisman, D.S., S. Binder-MacLeod, and W.B. Farquhar, *Changes in metabolic cost of transport following locomotor training poststroke.* Top Stroke Rehabil, 2013. **20**(2): p. 161-70.

49. Helm, E.E., et al., *The presence of a single-nucleotide polymorphism in the BDNF gene affects the rate of locomotor adaptation after stroke.* Exp Brain Res, 2016. **234**(2): p. 341-51.

50. Helm, E.E. and D.S. Reisman, *The Split-Belt Walking Paradigm: Exploring Motor Learning and Spatiotemporal Asymmetry Poststroke.* Phys Med Rehabil Clin N Am, 2015. **26**(4): p. 703-13.

51. Torres-Oviedo, G. and A.J. Bastian, *Natural error patterns enable transfer of motor learning to novel contexts.* J Neurophysiol, 2012. **107**(1): p. 346-56.

52. Reisman, D.S., et al., *Split-belt treadmill adaptation transfers to overground walking in persons poststroke.* Neurorehabil Neural Repair, 2009. **23**(7): p. 735-44.

53. Awad, L.N., et al., *Targeting paretic propulsion to improve poststroke walking function: a preliminary study.* Arch Phys Med Rehabil, 2014. **95**(5): p. 840-8.

54. Savin, D.N., et al., *Poststroke hemiparesis impairs the rate but not magnitude of adaptation of spatial and temporal locomotor features.* Neurorehabil Neural Repair, 2013. **27**(1): p. 24-34.

55. Blanchette, A. and L.J. Bouyer, *Timing-specific transfer of adapted muscle activity after walking in an elastic force field.* J Neurophysiol, 2009. **102**(1): p. 568-77.

56. Duysens, J., F. Clarac, and H. Cruse, *Load-regulating mechanisms in gait and posture: comparative aspects.* Physiol Rev, 2000. **80**(1): p. 83-133.

57. Dietz, V., R. Müller, and G. Colombo, *Locomotor activity in spinal man: significance of afferent input from joint and load receptors.* Brain, 2002. **125**(12): p. 2626-2634.

58. Duysens, J. and K.G. Pearson, *The role of cutaneous afferents from the distal hindlimb in the regulation of the step cycle of thalamic cats.* Exp Brain Res, 1976. **24**: p. 245-55.

59. Orlovskiĭ, G.N., T. Deliagina, and S. Grillner, *Neuronal control of locomotion: from mollusc to man*. 1999, Oxford University Press.

60. Dietz, V., W. Zijlstra, and J. Duysens, *Human neuronal interlimb coordination during split-belt locomotion.* Experimental brain research, 1994. **101**(3): p. 513-520.

61. Zehr, E.P., et al., *Cutaneous stimulation of discrete regions of the sole during locomotion produces "sensory steering" of the foot.* BMC Sports Sci Med Rehabil, 2014. **6**: p. 33.

62. Malone, L.A., A.J. Bastian, and G. Torres-Oviedo, *How does the motor system correct for errors in time and space during locomotor adaptation?* J Neurophysiol, 2012. **108**(2): p. 672-83.

63. Milot, M.H., et al., *Bilateral level of effort of the plantar flexors, hip flexors, and extensors during gait in hemiparetic and healthy individuals.* Stroke, 2006. **37**(8): p. 2070-5.

64. Milot, M.H., et al., *Effect of increases in plantarflexor and hip flexor muscle strength on the levels of effort during gait in individuals with hemiparesis.* Clin Biomech (Bristol, Avon), 2008. **23**(4): p. 415-23.

65. Milot, M.H., S. Nadeau, and D. Gravel, *Muscular utilization of the plantarflexors, hip flexors and extensors in persons with hemiparesis walking at self-selected and maximal speeds.* J Electromyogr Kinesiol, 2007. **17**(2): p. 184-93.

APPENDIX A

IRB APPROVAL

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration on Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301
|irb@uab.edu

APPROVAL LETTER

TO: Naidu, Avantika

FROM: University of Alabama at Birmingham Institutional Review
Board Federal wide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 10-Dec-2018

RE: IRB-150910010
Effects of Variables Resistance Forces on Horizontal Force Genera on in Non-Impaired Individuals and Individuals Poststroke

---

The IRB reviewed and approved the Continuing Review submitted on 16- Nov-2018 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review: Expedited
Expedited Categories: 4
Determination: Approved
Approval Date: 19-Nov-2018
Approval Period: One Year
Expiration Date: 18-Nov-2019

The following apply to this project related to informed consent and/or assent:

- Waiver (Partial) of HIPAA

Documents Included in Review:

- Renewal (consent.clean).181115.doc
- ipr.181115.pdf

Investigator's Progress Report

Form version July 30, 2015

☒Continuing Review (Complete Items 1-12)
—OR—
☐Final Report—all protocol-related activities are complete, including data analysis (Complete Items 1-11, and Item 13)

—FOR—

☒Expedited Review
—OR—
☐Convened (Full) Review

1. Dates		
Today's Date	11/15/2018	To help avoid delay, respond to all required items in the format provided, and include requested materials.
Starting Date of Project	11/24/2015	If previous approval expires before approval is officially re-issued by the Office of the IRB, all work on the protocol must cease.
Current IRB Expiration Date	11/27/2017	The IRB recommends applying for continuing review *4-6 weeks* before expiration of current approval. (See schedule.)

2. Principal Investigator (PI)			
Name (with degree)	Avantika Naidu, PT	**Blazer ID**	Avnaidu
Department	Physical Therapy & Occupational Therapy	**Division**	
Office Address	Building 516 6th Ave 20th Street South Birmingham 35233	**Office Phone**	
E-mail	avnaidu@uab.edu		
PI Contact who should receive copies of IRB correspondence (Optional)			
Name	Jennifer Uzochukwu	**E-mail**	jennyu@uab.edu
Phone	5-3592		

3. UAB IRB Protocol Identification	
Protocol Number	X150910010
Protocol Title	Effects of variable resistive forces on horizontal force generation in nonimpaired individuals
Study Sponsor(s)	UAB Department of Physical therapy and Occupational therapy
OSP Assigned Number (9 digits)	
Note. *If the source or amount of funding for this project has changed or a new OSP # has been assigned to the protocol, include the new or revised funding application and/or provide the new OSP Assigned Number:*	

4. Purpose

In two or three sentences, briefly summarize the purpose of this protocol, and related studies if applicable. Please use non-technical language, and write for adults with general knowledge rather than for specialists.

▶ The purpose of this study is to understand how nonimpaired individuals and individuals poststroke react to variable levels of horizontal resistance forces in relation to their individual limb muscle forces during walking.

5. Screened, entered, or otherwise accessed by the UAB Investigator(s). Include numbers for individuals, specimens, data records, charts, etc., as applicable to the protocol.	
5.a. Number screened for study entry since the start of the project?	69
5.b. Number entered in study since the start of the project? (See Total in 5.e.)	69
5.c. Number entered in study since the last IRB review?	51
5.d. What is the age range for all participants entered in the study since the start of the project (e.g., 18-65)?	20-67

5.e. Complete the table below for cumulative enrollment for each racial and ethnic category. Copy/paste the entire table for additional groups (e.g., controls, sub-studies) if needed.

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native										
Asian	2	1								3
Native Hawaiian or Other Pacific Islander										
Black or African American	11	12								23
White	17	24								41
More Than One Race	1	1								2
Unknown or Not Reported										
Total	31	38								69

☐ Check the box at the left if demographic information is not available (e.g., not collected for screening; collecting only specimens or data records and did not have access to the information).

6. Conflict of Interest Review Board (CIRB)

Does the Principal Investigator, the institution, or any other person listed on this protocol have a financial conflict of interest, as defined by the UAB CIRB, related to this research? **If No, continue with Item 7.** **If Yes, in the space below, provide the names of the individuals who have a conflict and indicate whether or not a management plan is in place for each person listed.**	☒Yes ☐No

▶ Dr. Brown is a co-inventor of the KineAssist robotic system used in the device and is a consultant to HDT robotics. He receives royalties on the sale of the KineAssist robotic device.

7. Information Since the Date of Last IRB Review

- Mark at least one checkbox to indicate the type(s) of information received since the Date of Last IRB Review.
- Please summarize each type of information, and provide details and copies as requested.

7.a. You received multi-center trial reports that you have not previously forwarded to the IRB. Attach a copy and, in the space below, provide the date and	☐Yes ☒No Multi-Center Trial Report

source of the report, and summarize the findings and any recommendations:	
▶	
7.b. You received data and safety or other monitoring reports (e.g., DSMB, sponsor site visit). Even if you have already forwarded a copy to the IRB, attach a copy and, in the space below, provide the date and source of the report, and summarize the findings and any recommendations:	☐Yes ☒No Data Safety or Other Monitoring Report
▶	
7.c. You learned of literature published about this research. Attach the publication or provide its web address, and summarize the published findings here:	☐Yes ☒No Published Literature
▶	
7.d. You learned of other relevant information regarding this research, especially about risks associated with the research. Attach a copy of the source and/or summarize below, and check "Other Information" at right. Also check "Affects Willingness" if this information might affect a participant's willingness to continue in the research, and describe the effects on participants here:	☐Yes ☒No Other Information ☐Yes ☒No Affects Willingness
▶	
7.e. You have received another type of information. Summarize the information, including details relevant to participants here:	☐Yes ☒No Other Type of Information
▶	

8. Reportable and Non-reportable Problems	
8.a. Have there been any "reportable events" since the IRB's last continuing review of the project? "Reportable events" are those that may constitute unanticipated problems involving risks to participants or others. If yes, attach the UAB Problem Report (even if already reported to the IRB); also attach the UAB Problem Summary Sheet completing Table A; Provide brief narrative summary (2-3 sentences) of any trends or increases in frequency or severity noted for all events over the life of the project, or enter "None noted" here:	☐Yes ☒No Reportable Events since last continuing review (Table A)
▶	

8.b. Have participants experienced harms (expected or unexpected, serious or not serious) that do not meet the UAB IRB criteria for "reportable events" since the IRB's last continuing review of the project? Attach UAB Problem Summary Sheet completing Table B; provide brief narrative summary (2-3 sentences) of any trends or increases in frequency or severity noted for all events over the life of the project, or enter "None noted" here:	☐Yes ☒No Other Events since last continuing review (Table B)
▶	
8.c. Have there been any reportable or non-reportable events over the life of the project? Attach UAB Problem Summary Sheet completing Table A and/or B as appropriate. Note the UAB Problem Summary Sheet is a cumulative report for all events over the life of the project. Provide brief narrative summary (2-3 sentences) of any trends or increases in frequency or severity noted, or enter "None noted" here:	☐Yes ☒No Any reportable or non-reportable events over the life of the project
▶	

9. Events Since the Date of Last IRB Review

Mark at least one checkbox to show event(s) that have occurred since the Date of Last IRB Review. Please summarize all events, and provide specific details and/or copies as requested.

9.a. You have had one or more problems obtaining informed consent. Briefly describe the problem(s) here:	☐Yes ☒No Consent Problems
▶	
9.b. You have received complaints about the research. Briefly describe the number and nature of the complaints:	☐Yes ☒No Complaints
▶	
9.c. One or more participants withdrew, or were withdrawn from, the research. Indicate here the number of withdrawals and the reason for each:	☐Yes ☒No Withdrawals
▶	
9.d. Participants have experienced research-related benefits. For example, "60% of participants in the treatment group appear to have reduced symptoms or reduced severity of symptoms, compared with 10% in the placebo group." Briefly describe the benefits here:	☐Yes ☒No Benefits
▶	
9.e. The risks, potential benefits, or both of this research have changed. Briefly describe the changes here:	☐Yes ☒No Change in Risk or Benefit
▶	

9.f. Does the research involve minors (<18 years of age)? If the study is still open to accrual or the participants are still receiving protocol driven intervention, the PI must either (a) confirm the previously assigned Children's Risk Level (CRL) number or (b) reassign a new CRL and give the reason it has changed in the space provided below:	☐Yes ☒No
▶	
9.g. Events have occurred that relate to participant safety but do not fit into the categories listed above. Briefly describe the events here:	☐Yes ☒No Other Events
▶	

10. Protocol and/or Informed Consent Modifications **Check the applicable boxes to indicate modifications made since Date of Last IRB Review (Yes to 9.a.) or requested with this renewal (Yes to 9.b. or 9.c.). Please provide the details and materials requested.**	
10.a. Previous Modifications	
Since the last IRB review, have you made modifications to the protocol, consent process, consent document or change in personnel?	☒Yes ☐No
If Yes, have the modifications been approved by the IRB?	
☐Yes—Provide a copy of each amendment form stamped "Approved" by the IRB during this approval period. ☐No—In the space below, justify making the modification without prior IRB approval:	
▶	
10.b. Modifications To Protocol Requested With This Renewal	
Are you requesting IRB review of changes to the protocol (e.g., procedures, personnel, recruitment)? If so, check "Yes" and describe them in the space below. If adding personnel, (1) provide full name and UAB department/division, (2) indicate role in research, (3) and address whether the personnel has a financial conflict of interest. If removing personnel, please provide name(s) of personnel being removed. Indicate beside the name whether you are adding or removing each individual.	☒Yes ☐No Protocol Changes
▶ **We would like to increase the total number of participants for the study to 100**	
10.c. Modifications To Consent Requested With This Renewal	
Are you requesting IRB review of changes to the consent process and/or form(s)? If so, check the applicable "Yes" box and, in the space below, describe the changes.	☐Yes ☒No Consent Process Changes ☐Yes ☒No Consent Document Changes

If the changes affect the consent form(s), indicate the number of consent and/or assent forms used for this protocol, and describe the changes to each form: **(a) describe all changes to IRB-approved forms and the reasons for them;** **(b) describe the reasons for the addition of any materials (e.g., addendum consent); and** **(c) indicate either (1) how and when you will reconsent enrolled participants or (2) why reconsenting is not necessary.** **Also, indicate the number of forms changed or added. For new forms, provide 1 copy. For revised documents, provide 3 copies:** **• a copy of the currently approved document (showing the IRB approval stamp, if applicable),** **• a revised copy highlighting all proposed changes with "tracked" changes, and** **• a revised copy for the IRB approval stamp.**
▶

11. Gene Therapy, Gene Transfer, Recombinant DNA				
If this study involves	☐Gene therapy	☐Gene transfer	☐Recombinant DNA	☒N/A – go to item 12.
	Complete this item, and include memorandum with original signatures of Gene Therapy Review Panel addressing the risk-benefit ratio, any recommendations, and the CRL if applicable.			
11.a. Has the Panel's assessment of the risk-benefit ratio of this project changed? If yes, please explain below.				☐Yes ☐No Risk-Benefit Change
▶				
11.b. Does the Panel have any recommendations regarding the protocol or the consent form? If yes, please explain below.				☐Yes ☐No Panel Recommendations
▶				

12. Continuing Review—Complete only if you want to renew IRB approval so that protocol-related activities can continue.	
12.a. Accrual Status—Indicate whether the study is "NOT YET OPEN," "OPEN," or "CLOSED" (described below) **and provide the details requested for that accrual status.**	
NOT YET OPEN: No individuals have been screened or entered.	☐Not Yet Open
OPEN: The study could still enroll more individuals, add more specimens, review more records, etc. **• Attach a copy of the most recently approved consent form(s) OR note in the space below that the IRB has waived informed consent and/or use of a consent form (waiver of documentation of informed consent).** **• Describe plans for future accrual, enrollment, or recruitment here:**	☒Open

▶ We are currently in the process of enrolling participants from the Birmingham metropolitan area.

CLOSED: No more individuals will be enrolled, no more specimens or records will be added.	☐Closed
If the study is closed, is a consent form being submitted for review? If "Yes," explain why in the space below.	☐Yes ☒No Closed & Consent Form
▶	
• **Indicate the date closed to accrual:**	Date Closed:
• **Choose one status to describe accrued participants, specimens, records:**	Check **ONE** Status Below:
One or more is/are still receiving procedures as defined in the protocol (therapy, intervention, follow-up visits, etc.)	☐On protocol procedure
All are off protocol-driven procedures, in long-term follow-up only	☐In long-term follow-up
All are off protocol-driven procedures, in data analysis only	☐In data analysis
12.b. Describe any interim findings from this research. Please note that the IRB expects to receive findings on any protocol approved for 5 years.	
▶	

13. Final Report—Complete only if you want to end IRB approval after all protocol-related data analyses are complete and no further work on the protocol will be done.	
13.a. On what date were the final data analyses completed?	Final Date:
13.b. Summarize the final findings from this protocol <u>and</u> provide copies of any publications:	
▶	
13.c. Who will be responsible for managing and storing the data records, including any and all research-related electronic files and paper documents?	
Name	
UAB Dept/Div, or Employer	
Work Address	
Daytime Telephone	
13.d. Describe the storage plan. How will data records be stored—on paper, computers, or both? How will they be protected from damage, unauthorized release, loss, and theft? How long will the data be stored? Where will the records be stored?	
▶	
13.e. At the end of the storage period, will the data records be destroyed, archived, or transferred? Describe the plan in detail.	☐Destroy ☐Archive ☐Transfer

▶

Note. **Specimens may be stored only if/as described in the IRB-approved protocol. Data records must be stored as described in the sponsor's protocol or contract if applicable, and/or in the UAB Health System Record Retention Policy. Anyone wishing to use these data or specimens for secondary research purposes or for purposes preparatory to secondary research must obtain prior IRB review and approval.**

Signature of Principal Investigator: _________________ **Date: 11/15/2018**

FOR IRB USE ONLY – Expedited Review

Change to Expedited Category Y / N

No change to IRB's previous determination of approval criteria at 45 CFR 46.111 or 21 CFR 56.111 ☐

____

Signature (Chair, Vice-Chair, Designee)

Date