University of Alberta

A pilot study investigating arm and leg FES-assisted cycling as an intervention for improving ambulation after Incomplete Spinal Cord Injury

by

Laura Alvarado

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Master of Science

Centre for Neuroscience

Spring 2013
Edmonton, Alberta

ABSTRACT

People with incomplete spinal cord injury (iSCI) have the potential for recovering walking through plasticity-induced changes in the remaining neural circuitry.Current rehabilitation for walking attempts to induce such changes by providing relevant sensory inputs and motor commands through repetitive practice.Current rehabilitation fails to actively incorporate arm movements despite being naturally involved in human walking. The overall goal of my thesis was to demonstrate that active arm involvement through arm and leg FES-assisted cycling improvesovergroundwalking afteriSCI. Specifically, my pilot studyevaluated the changes in walking after 12 weeks of the intervention in individuals with chronic iSCI. Arm and leg FES-assisted cyclingwas effective in improving walking speed and endurance. Balance, motorand sensory scores,and gait kinematics improved in most cases. The reflex modulation improved in every case suggesting that neuronal reorganization (plasticity)was involved. Hence, arm and leg FES-assisted cycling is worthy of further investigation.

ACKNOWLEDGEMENT

ToAlfredo for his enormous support during my masters studies.

To José Andrés and Maria Paulina for supporting me in their own little ways.

To my Mom and Dad for raising me with love and patience. For being always cheering for me.

To my sister, Ana Margarita, for being my best friend and an example of righteousness.

To Maria de los Angeles Thomassiny, Margarita Alvarado, and Alfonso Alvaradofor everything you gave me during your lifetime and these last years. I miss you.

To Carmen Pacheco for your example of fortitude while suffering from ALS. I miss you.

To the Lacroix family for their love and support.

To all my family and friends who encouraged me during my masters.

To my study participants for their patience, perseverance and for sharing with me their life experiences.

To Dr. Vivian Mushahwar for teaching me, for always believing that I could complete this work, and for always pushing for excellence in every project we shared.

To my co-authors: Robert Ogilvie, Su Ling Chong, AletheKabore, Jacques Bobet, and YahyaKinyogo for their contributions and friendship.

To all the members of the Mushahwar Lab for being friends and the best critics ever.

To my committee members: Dr. Jaynie Yang, Dr. Ming Chan and Dr. Richard Stein for their guidance during my degree.

To funding agencies that supported my work:

Canadian Bureau for International Education (CBIE),

Alberta Innovates Health Solutions (AIHS), the Spinal Cord Injury Treatment Centre Society-Northern Alberta (SCITCS),

the Rick Hansen Institute,

and the Alberta Paraplegic Foundation.

To God.

Thank you

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

List of Abbreviations

AD: Autonomic Dysreflexia

AIS: ASIA Impairment Scale

ASIA: American Spinal Injury Association

BBB: Blood-brain barrier

BWSTT: Body weight supported treadmill training

CDT: Coordination Dynamics Therapy

CNS: Central Nervous System

CPG: Central Pattern Generator

FES: Functional electrical stimulation

ISCI: Incomplete spinal cord injury

MCI: minimal clinically important

MN: Motor Neuron

MU: Motor unit

SCI: Spinal cord injury

ROM: Range of motion

Chapter 1. INTRODUCTION

1.1. SPINAL CORD INJURY (SCI)

The spinal cord plays an important role in the performance of motor, sensory and autonomic functions of the body below the neck. The innervations to motor nerves emerge from the spinal cord at different levels (Last, 1949; Sharrard, 1964). Likewise, the sensory afferents are innervated at the corresponding levels of the spinal cord(Eccles, Fatt, Landgren, & Winsbury, 1954). This information interacts in the spinal networks via synaptic connections of motorneurons, sensory neurons and interneurons, allowing it to reach to various sites of action (e.g. muscles, motor cortex in the brain)(M. E. Schwab, 2002). An injury to the spinal cord affects the person’s sensory and motor abilities which are critical for functions such as balance, hand movements, autonomic regulation, and locomotion. Depending on the level and severity of the injury some functions may be lost and some may be spared below the injury level. As a consequence of this loss of function, the insults to the spinal cord severely affect the quality of life of those who suffer from it(Tate, Kalpakjian, & Forchheimer, 2002). In addition to the motor, sensory and autonomic deficits that the injury itself originates, other health-related, psychological and economic complications arise after suffering a SCI.

1.1.1. CURRENT INCIDENCE AND PREVALENCE OF SCI

In Canada, the incidence of SCIhas been estimated to be 4,259 cases per year, of which 3,675 survive the initial insult.The prevalence has been estimated to be of approximately 86,000 people in Canada(Farry & Baxter, 2010) Two age groups stand out as the most affected by SCI: The young adult population due to violence and accidents and the older adult population, mainly due to falls. For instance, the incidence was highest in the 20-29 year old group in Alberta, Canada(Dryden et al., 2003)This group of individuals have many years ahead of living with the devastating effects of SCI. Not only personal but financial challenges accompany a SCI. The financial care requirement per individual with SCI over a lifetime ranges from 1.6 to 3 million dollars(Farry & Baxter, 2010). The costs involved vary depending on the level and severity of the lesion. The economic burden imposed on the families of those affected not only include the significantly higher costs for healthcare, but also lower income of their families compared to average families (Christopher and Dana Reeve Foundation, 2009). The impact of SCI goes beyond the economic aspect since it involves a significant reduction in the quality of life perceived by those affected (Tate, et al., 2002). Hence, there is an incentive for developing interventions that help prevent SCIs, but also ones that help improve the quality of life of the people with SCI.

1.1.2. CLASSIFICATION OF SPINAL CORD INJURIES

According to their etiology SCIs can be traumatic or non-traumatic. Traumatic injuries occur when an external object strikes the spinal cord causing compression, flexion, extension, rotation or distraction of the spinal cord(Dumont et al., 2001). The principal causes for this kind of injuries are motor vehicle accidents, falls, or violence(Dryden, et al., 2003; Raineteau & Schwab, 2001). Non-traumatic injuries may be caused by cancerous tumors, ischemic or hemorrhagic events within the spinal cord, malformations, and degenerative diseases such as multiple sclerosis(Bauchet et al., 2009; Citterio et al., 2004).

Spinal cord injuries can also be classified according to their outcome: Paraplegia or Quadriplegia. Quadriplegia involves the impairment of functions in the arms, trunk, legs and pelvic organs. Paraplegia involves the impairment of only trunk, legs and pelvic organs. In addition to that, injuries can be deemed complete when practically no sensory or motor functions from regions below the lesion are preserved or incomplete where some motor or sensory functions in regions below the injury are preserved. It has been estimated that approximately half of the spinal cord injuries are incomplete (Marino, Ditunno, Donovan, & Maynard, 1999).

The classification method that is most commonly used and that describes the injuries with more detail is the ASIA (American Spinal Injury Association) Impairment Scale (AIS). This scale classifies each injury by the resulting level of motor and sensory impairments. The AIS maps the body into regions called dermatomes according to their sensory innervations on each segment of the spinal cord. In a similar way, regions called myotomes are defined for the motor innervations. Each dermatome and myotome is graded according to the sensory and motor capacities that remain. Dermatomes can be graded on a 0 to 2 scale where 0 represents no sensation, 1 represents impaired sensation,and 2 represents sensation with normal intensity. Myotomesare evaluated with a 0 to 5 scale where 0represents total muscle paralysis and 5 represents active movement, full range of motion (ROM) against gravity and full resistance to be considered normal(Figure 1-1).According to the grades below the level of the lesion, each SCI is classified as:

A. Complete injury. No motor or sensory function preserved inthe sacral segments S4-S5.

B. Sensory Incomplete injury. Sensory but no motor function is preserved below the neurological level and includes the sacral segments S4-S5, and no motor function is preserved more than three levels below the motor level on either side of the body

C. Motor Incomplete injury. Motor function is preserved below the neurological level, and more than half of the key muscle functions below the single neurological level of injury have a muscle grade less than 3.

D.Incomplete injury. Motor function is preserved below the neurological level and at least half of the key muscles below the neurological level have a muscle grade 3 or more.

E. Normal. Motor and sensory function is normal. (ASIA, International Standards for Neurological Classification of SCI Revised, 2011).

In order to classify an injury as C or D it is also required that one of the following two conditions be present: 1) voluntary anal sphincter contraction or 2) sacral sensory sparing with sparing of motor function more than three levels below the motor function.

1.1.3. PROGRESSION OF SCI

Immediately following an insult to the spinal cord the blood-brain barrier (BBB) breaks and neutrophils enter the lesion site causing edema. The primary injury is caused by the direct disruption of spinal tissue and the events that take place during the first one to two hours after the initial insult (Norenberg, Smith, & Marcillo, 2004).The hemorrhage and blood flow interruption due to edema affect first the grey matter, but later expand to the white matter rostrally and caudally. This process continues into the chronic phase as one of the mechanisms for secondary SCI.

The progressive damage of the tissue surrounding the initial lesion is known as secondary injury(Bauchet, et al., 2009). This group of complex mechanisms produce vascular changes, electrolyte changes, biochemical changes, edema, and metabolic changes in the spinal tissue(Tator & Fehlings, 1991). First, two pathways lead to ischemic damage of the spinal tissue: the direct mechanical damage to microvasculature(Fairholm & Turnbull, 1971); and the decrease in sympathetic tone which may cause bradycardia and hypotension affecting the tissue perfusion(Dumont, et al., 2001; Guha & Tator, 1988). Meanwhile, the edema, hemorrhage and neutrophils infiltration continue. After ischemia and reperfusion events, the tissue around the injury site is damaged by the formation of reactive oxygen species that initiate the oxidation of proteins, lipids and nucleic acids, e.i., oxidative stress (Lewén, Matz, & Chan, 2000). The destruction of cell membranes triggers excitotoxicity(Faden & Simon, 1988).Excitotoxicity is defined as the extreme activation of excitatory neurotransmitter receptors (e.g. glutamate) that allow intracellular accumulation of Na^{+}(Agrawal & Fehlings, 1997) water, and Ca^{2+} along with extracellular K^{+}that alter the cell physiology and cause death(Schanne, Kane, Young, & Farber, 1979). In particular, accumulation of Ca^{2+} along with mechanical stress and inflammation affect mitochondria resulting in the release of apoptogenic proteins (Dumont, et al., 2001). Additionally, excitotoxicity releases reactive oxygen species resulting in more cell death. Cell death in the spinal cord activates microgliafor removal of necrotic debris.Although microglial activity prevents further damage, it has been demonstrated that microglia also releasesneurotoxins (Giulian, Vaca, & Corpuz, 1993). All this induces necrotic cell death which is worsened by the accumulation of macrophages and lymphocytes(Jones, McDaniel, & Popovich, 2005).

The accumulation of proteoglycans around the lesion creates a growth-inhibitory environment(Bradbury & Carter, 2011). Although the glial response is effective in resolving the edema and restoring the BBB, the microglia and macrophages leave a scar formed by connective tissue and fluid-filled cysts, the mesenchymal scar(Norenberg, et al., 2004). The action of Astrocytes generates the astroglial scar which isolates the lesion site and releases neuroinhibitory molecules. Axons retract, causing an influx of Ca^{+2}, release of caspases and cytochrome and more retraction. These processes continue and cells die due to apoptosis(Abe et al., 1999; Beattie, Shuman, & Bresnahan, 1998; Emery et al., 1998). Demyelination due to axonal damage and oligodendrocyte apoptosis causes further conduction impairment(Abe, et al., 1999). Finally, remyelination and plasticity take place during the chronic stage and their outcome depends on whether or not some neuronal networks were spared.The events that integrate the secondary injury may take place simultaneously. The exact progression of early events is unclear since different models of SCI present different responses with more or less intensity than human SCI and several mechanisms may lead to the same pathway for cell death (e.g. ischemic and excitotoxic events may lead to the liberation of reactive oxygen species) (Dumont, et al., 2001).

Clinically, during the first 1 to 6 weeks after SCI a complete loss of voluntary movement, sensation and reflexes below the lesion is observed. This stage is known as spinal shock(Bastian, 1890). The reason for spinal shock may be the interruption of descending inputs which normally maintains the level of excitability of spinal neurons. It has been demonstrated that alpha and gamma motor neurons (MNs) have a reduced excitability during this period (Hiersemenzel, Curt, & Dietz, 2000). After a few weeks, the flexor reflexes become excitable again and the muscle tone recovers for most patients. With time, these responses become more and more easily excitable up to a point (months later) when they can present exaggerated spasms(Dietz & Sinkjaer, 2007). Some subjects during this time present episodes of autonomic dysreflexia (AD): hypertension, intense perspiration and headache owing to a bladder or rectal stimulus. Electrical stimulation may induce AD as well. After the flexor responses are fully developed, the extensor reflexes become excitable again(Hiersemenzel, et al., 2000). As early as 6 months post injury, these extensor spared reflexes become exaggerated, allowing the legs to remain extended , thereby aidingin standing and stepping(Macht & Kuhn, 1948).

1.1.4. Treatments during the acute phase

The pathology of SCI is complex. Some of the processes following SCI have both destructive and regenerative effects (e.g. macrophage and microglial responses may generate the glial scar, but also aid regeneration) (Dumont, et al., 2001; Hagg & Oudega, 2006; Norenberg, et al., 2004; Oyinbo, 2011; Tator & Fehlings, 1991). Therefore, treatments to control the damage after SCI have to consider multiple approaches or consider carefully the time of intervention. Neuroprotective therapies are used in order to reduce the membrane breakdown and ameliorate the secondary injury. Some examples of neuroprotective therapies are glucocorticoids such as methylprednisolone, opiate antagonists such as naloxone, glial scar inhibitors such as Cethrin, Na^+ channel blockers such as Riluzole(Ates et al., 2007) and other substances that have combined effects like minocycline. Methylprednisolone reduces edema, inflammation, release of free radicals and glutamate(J. M. Schwab et al., 2006). Naloxone may counteract the depression of the central nervous system (CNS) after SCI (Olsson, Sharma, Nyberg, & Westman, 1995). Minocycline decreases microglial activity and thus reduces neuronal and glial apoptotic mechanisms (Beattie, 2004). All these interventions have been tested in animal models, but few have shown the same positive effects in humans. Methylprednisolone has been tested in clinical trials with humans. The improvements were small, but not significant and the benefits were better when it was administered within the first three hours after the injury (Bracken et al., 1997).

1.1.5. Treatments during the chronic phase: Repairing the injured spinal cord.

Recovery of the lost motor, sensory and autonomic functions is important for people with SCI. In a survey in 2004 people with SCI expressed what would most improve their quality of life and their integration into the community. The top three functions for people with quadriplegia were: regaining arm and leg function (47%), sexual function (13%), and upper body strength and balance (11.5%). The top three functions for people with paraplegiawere: sexual function (26.7%), bladder and bowel function (17%), and upper body strength and balance (16.5%). Walking movement was ranked fourth for people with paraplegia (15.9%) and fifth for people with quadriplegia (7.8%)(Anderson, 2004). Another approach to investigate the priorities for the SCI population was through patient and clinician panels. Eight out of nine patient panels and two clinician panels preferred walking as a recovery outcome over other elements of the mobility Functional Independence Measure (FIM)(P. L. Ditunno, Patrick, Stineman, & Ditunno, 2008). Hence, most rehabilitation strategies focus on these functions.I identified three different approaches to treat a SCI: Compensation, restoration and regeneration

Compensation refers to any training or therapy that promotes replacement of an ability lost after the injury by a different strategy using the remaining abilities of the subject. An example for this is the training focused on using crutches, walkers or wheelchairs for ambulation in people with paraplegia. Compensation strategies are preferred for individuals with complete injuries since their prospects for recovery or rehabilitation are very low.

Restoration aims to restore the functions of the individual affected by SCI as closely as possible to their state prior to the SCI. In other words, to reverse the disability (Banovac & Sherman). The extent to which restoration is effective depends much on the severity of the lesion. Individuals with iSCI may benefit from the early initiation of restoration strategies(Dobkin 2006).In particular, individuals with injuries classified as AIS C have obtained the greatest motor improvements after discharge and 1 year. Approximately 40% of them had injuries classified as A or B after their injury which shows the potential for recovery of this particular group(Marino, et al., 1999). The rehabilitation program that I completed in this thesis is aimed at improving walking through restoration of the locomotor function.

Regeneration aims to reestablish the original function of the spinal cord. The regeneration of the damaged tissue after SCI has been attempted by many research groups.

Although some authors use regeneration and restoration indistinctly to refer to therapies that aim to reverse the disability, I separated the regeneration and restoration strategies in order to differentiate between therapies that focus on the performance of the function without necessarily recovering the damaged tissue (restoration) and those that aim to recover the lost tissue or connectivity of the spinal cord (regeneration). The ideal is that both overlap in that restoration of function may produce anatomic regeneration (e.g. anatomic plasticity) and regeneration may bring about a functional restoration.

Schwab classified the strategies for repairing (including regeneration and restoration) the injured spinal cord into four categories(M. E. Schwab, 2002) :

1. Promoting the regrowth by enhancing the expression of neuronal regeneration proteins and the activation of neurotrophic factors. The largest effort in this area is focused on using antibodies to block growth-inhibitory molecules such as Neurite outgrowth inhibitor protein or Nogo-A (Brittis & Flanagan, 2001; Delekate, Zagrebelsky, Kramer, Schwab, & Korte, 2011). This therapy is already in clinical trials in humans. (Thuret, Moon, & Gage, 2006).

2. Bridging the lesion with a growth-permissive scaffold. Some of the materials used are olfactory ensheathing glia, Schwann cells, embryonic and adult stem cells, embryonic neural tissue and hydrogels with growth-enhancing substances. These techniques are currently under investigation in animal models,

but some have reached human clinical trials (Bradbury & Carter, 2011; J. M. Schwab, et al., 2006; Thuret, et al., 2006).

3. Remyelination by implanting Schwann cells and oligodendrocytes. The regrowth of the myelin in spared axons would reestablish the function of the neuronal networks involved(Liu et al., 2000).

4. Enhancing CNS Plasticity in two forms: synaptic plasticity or anatomical plasticity. The collateral sprouting is one of these mechanisms for anatomical plasticity. The challenge has been to guide these collaterals to their original targets or to some other target where they can reestablish a similar network and obtain improved function(Dunlop, 2008). Some research groups agree that repetitive practice of task-specific movements is essential to achieve plasticity. It has been demonstrated that rhythmic motor systems in animals and humans are capable of adapting after training or changes in external conditions(Pearson, 2000). An example of this is the incline walking versus horizontal walking. It has been postulated that the walking behavior is modified after adaptation, but is produced by the same rhythmic motor systems(E. Zehr et al., 2007). Within this framework, it could be argued that plasticity can be induced by non-specific training as well. This idea will be discussed in the following section of this introduction.Plasticity can have positive effects (e.g., rehabilitation with repetitive practice) and negative effects (e.g. reinforcement of spasticity, autonomic dysreflexia and pain) (Dietz, 2011; Hagg & Oudega, 2006). This section is only intended to provide a perspective of the current therapies offered for regeneration after SCI, but complete reviews on the topic can be found elsewhere (Gensel, Donnelly, & Popovich, 2011; M. E. Schwab, 2002; Thuret, et al., 2006).

1.2. INTERVENTIONS FOR IMPROVING WALKING AFTER SCI

Regaining walking function was the most important aspect of recovery for only 7.8 % of the people with spinal cord injury that were interviewed(Anderson, 2004). Despitethis, clinicians report that their SCI patients repeatedly ask them about their chances of walking (Subbarao, 1991). It is understandable that they desire independence in ambulation in order to have more access to the community and improve their quality of life. Consequently, an important focus of research in spinal cord injury is dedicated to independence in ambulation via the recovery of motor and sensory functions necessary for walking or compensatory ambulation strategies.

1.2.1. Compensatory ambulation strategies

During the chronic phase, physical rehabilitation therapy can be focused on compensation or restoration. A team of professionals including, but not limited to physicians, therapists, nurses and counselorschoose the approach for each function depending on the prognosis for each type of injuryand previous clinical experience (Banovac & Sherman; Kirshblum, Groah, McKinley, Gittler, & Stiens, 2002). It was thought that after damage to the adultCNS, the lost motor functions couldonly be recovered during the first one or two years post-injury but improvements have been reported in many individuals during the chronic stage after SCI(Piepmeier & Jenkins, 1988).The old paradigm caused rehabilitationto be focused on compensation, a strategy that intends to overcome the impairment by finding other means (e.g. using the uninjured parts of the body) for achieving the functional goal without directly restoring the lost function.The goal of this approach is to train the patient to be as independent as his/her condition allows at the moment as soon as possible. Compensation approaches includepassive weight bearing, passive stretching, balance training, standing and stepping with an emphasis on the effective use of assistive devices(Dobkin et al., 2003). The inpatient rehabilitation therapy is reduced to weeksfollowing the discharge from acute care(Banovac & Sherman). Despite growing evidence of motor recovery with training during the chronic stage after SCI, only a small percentage (approximately 12%) of people with SCI have access to regular exercise with a trained therapist (Anderson, 2004).This may be due to financial limitations since insurance companies have determined their policies of coverage based on a compensatory approach. In some cases, individuals with SCI are not provided with any rehabilitation program during the chronic stages despite having regular visits with the physiatrist.

Compensation strategies may beeffective in integrating the patients with SCI to the community although some researchers have proposed that they might actually hinder the restoration of walking because assistive devices change the gait kinematics by promoting the use of the arms for load bearing. This can cause secondary complications such as hip hiking during the swing phase (Visintin & Barbeau, 1994).

1.2.2. Animal studies supporting current locomotion rehabilitation paradigm

The development of rehabilitation protocols for movement disorders like SCI and stroke requires changing the interaction of the damaged neuronal networks related to locomotion. First it was necessary to obtain a level of understanding about such interactions. Electrophysiology methods in humans can be used to research such networks indirectly, but their results are influenced by many external factors difficult to eliminate without invasive techniques. Therefore, the specific configuration of the neural circuitry that produces the locomotor behavior can only be investigated throughmore basic scientific methods. Animal models allow access to their underlying neural circuitry and eliminate many external factors. The investigations of locomotion after deafferentation, spinal section and decerebration have given insight into the mechanisms and helped in the development of new rehabilitation interventions after stroke and SCI. They have also generated enough evidence to support the existence of CPGs: a neural network that presents a cyclic activity capable of producing rhythmic motor outputs (e.g. locomotion) without external inputs. CPGs in mammals are thought to exist in the spinal cord to control locomotor movements by alternating activation of the flexor and extensor muscles of the limbs (Grillner & Zangger, 1979). Since 1910, the "stepping reflex" was discovered indecerebratequadrupeds. Surprisingly, this "stepping reflex" suffered little to no alteration in the absence of cutaneous afferent inputs (Sherrington, 1910). Many others have described since then the capacity of the spinal cord to produce locomotor– likeoutput. Supraspinal commands can initiate (Gordon, Dunbar, Vanneste, & Whelan, 2008)and interfere (Gordon & Whelan, 2008) with the spinal locomotor pattern. Afferent inputs are responsible for changing parameters of this activity such as stance duration and speed, but the main alternation pattern remains the same(Carlson-Kuhta, Trank, & Smith, 1998; Smith, Carlson-Kuhta, & Trank, 1998). Lovely and colleagues demonstrated that cats with experimental SCI improved more their stepping capacities after they were trained to step on a treadmill with partial weight support rather than just to stand (Lovely, Gregor, Roy, & Edgerton, 1986) therefore highlighting the importance of appropriate afferent input during the training. The age at the time of injury influences the level of recovery as well(Smith, Smith, Zernicke, & Hoy, 1982).

Similarities between quadrupeds and humans in the ability to generate locomotor-like patterns in the absence of supraspinal input, the relationship between extensor and flexor motorneuron pools, and the capacity of interlimb coordination support the existence of similar CPGs in humans(Dietz & Harkema, 2004; S. J. Harkema, 2008). and make it possible to transfer findings in animal models to human SCI(Dietz, 2002). Evidence-based therapies use these findings to outline the parameters of new rehabilitation interventions.

1.2.3. Body weight supported overground or treadmill training

Animal studies have demonstrated that the adult CNS can, to a certain extent, recover walking and standing abilities by repetitive practice after iSCI(Lovely, et al., 1986). It is likely that activity-dependent plasticity in spinal networks is responsible for the recovery in these animals (De Leon, Hodgson, Roy, & Edgerton, 1999). Consequently, a variety of interventions have been evaluated that exploit this capacity and propose different ways in which to recover walking after SCI.

Body weight supported training is the rehabilitation technique most studied. It is based on findings that stepping after spinal cord injury can be achieved through intense practice with functionally-relevant sensory input such as load and stretch (Barbeau, 2003). Based on this principle, a rehabilitation protocol with kinematics very close to walking has been tested in people with incomplete spinal cord injury. Body weight supported treadmill training (BWSTT) is a rehabilitation technique that involves the use of a treadmill to regulate the stepping speed and a partial body weight support system which allows for upright stability. The rehabilitation program is designed to induce stepping with physical assistance in the lower limbs and increasing the loading through the legs progressively. It is delivered according to four basic principles:

1) Maximize weight bearing on the legs by unloading the arms with a body weight support system;

2) optimize sensory cues like cutaneous feedback in the soles of the feet and walking speed;

3) optimize the kinematics so that the movement of the joints resembles those previous to the injury; and

4) maximize recovery strategies while minimizing compensation strategies(Susan J. Harkema, Behrman, & Barbeau, 2011).

During BWSTT the arms should be unloaded and free from the use of assistive devices. Arm swinging is encouraged with the idea that this will help develop appropriate balance responses(Behrman & Harkema, 2000). Even though these indications are part of the BWSTT, the benefit of having simultaneous active arm swinging has not been demonstrated or quantified.After reviewing the literature in two databases: Pubmed and SciVerse (Scopus) with the keywords "arm swing" and "spinal cord injury" and "gait/walking/BWSTT" I found no published data that answers whether BWSTT with arm swing improves the outcome of gait rehabilitation. Body weight supported treadmill training has been successful in improving walking outcomes in people with iSCI since it was first proposed. Subjects with chronic SCI classified as ASIA C or D have improved their walking speed and endurance significantly after BWSTT(Field-Fote & Roach, 2011) and BWSTT with complementary overgroundtraining(S. J. Harkema, Schmidt-Read, Lorenz, Edgerton, & Behrman, 2011).

1.2.4. Robotic-assisted locomotor training

Robotic-assisted locomotor training was developed to reduce the intensity of physical work required by the physical therapists so that BWSTT sessions could be longer. Several systems have been developed that integrate a robotic gait orthosis or electromechanical foot plates in a treadmill. Examples of these systems that are commercially available and currently used in rehabilitation centres are the Gait Trainer GTI (RehaStim, Germany), the Lokomat (Hocoma AG, Switzerland) and the LokoHelp (Woodway GmbH, Germany).

The advantages of robotic-assisted BWSTT are that it reduces the intensity of the physical labor performed by the therapists, provides a more consistent pattern of movements and allows having longer sessions(Colombo, Joerg, Schreier, & Dietz, 2000). Studies using robotic-assisted locomotor training have demonstrated that it is effective in improving gait ability. The use of robotic devices has been criticized because they have failed to demonstrate an added advantage of longer sessions of BWSTT over manual locomotor training (Dobkin & Duncan 2012; Field-Fote & Roach, 2011). The disadvantage of robotic-assisted BWSTT is that the equipment is very expensive. For instance, the Lokomat's price is $400,000

USD approximately without considering maintenance costs (Neuroxcel, Palm Beach, Fl, USA). The cost of a physical therapy session in the United States varies from $75 USD to $350 USD, making from 20 to 6 years of daily sessions (5 times per week) with the cost of a Lokomat.The median annual salary for a physical therapist in the United States is 76,310 USD (Bureau of Labor Statistics, 2012-13), and only one physical therapist is required for Lokomat guidance and setup.From a rehabilitation centre administration perspective, if we compare the cost of the Lokomat with the cost of hiring only three physical therapists, then the Lokomat costs less and therefore its acquisition may be justified. The functional improvements obtained using robotic assistance during locomotor training did not exceed those obtained with manual assistance (Field-Fote& Roach, 2011). Therefore, the higher cost may only be justified by the number of clients served by a single robotic-assisted locomotor training device. Another critic to the first versions of robotic-assisted locomotor training devices was that they did not require that the subject activated their legs voluntarily, so the subject could be just passive during training sessions. Volition may be important for the plasticity in neuronal circuits to take place(Barsi, Popovic, Tarkka, Sinkjaer, & Grey, 2008). This issue has been solved by providing verbal encouragement during training sessions and by the development of a biofeedback function in the new version of the Lokomat (Lunenburger, Colombo, Riener, & Dietz, 2004).

1.2.5. Overground "skill training"

An alternative to BWSTT has been proposed which is termed skill training. It is based on the idea that rehabilitation training has to be task-specific. It incorporates ten walking tasks that the subjects encounter in real-life walking. Following alternating three month periods of either BWSTT or skill training, four subjects achieved results with skill training that go beyond the minimal clinically important (MCI) value of 0.05 to 0.06 m/s for the SCI population and their own improvement with BWSTT. Their result could be explained by the fact that overground skill training is more task specific than BWSTT. This study contributes to the debate about task specificity after iSCI and about treadmill training being really task specific for overground walking after iSCI. This rehabilitation strategy proved effective in a group of four individuals, but it still has to be tested for efficacy in a larger group of individuals (Musselman, Fouad, Misiaszek, & Yang, 2009).

1.2.6. Functional Electrical Stimulation

Neuromuscular Electrical Stimulation is a technique that allows the activation of the motor nerve using a train of pulses of electric current in order to produce a muscle contraction. As opposed to direct muscular stimulation, nerve stimulation requires considerably less current to produce the same strength of muscular contraction. This is owing to the difference in the threshold current for excitation between muscle and nerve tissue, given by the stimulation strength – duration curve. The strength – duration curve is characterized by its rheobase (the stimulation intensity required to produce a response given an infinitely long pulse) and chronaxie (the stimulation pulse duration required to obtain a response twice the rheobase). The rheobase and chronaxie for neural tissue are less than those of muscle tissue. For muscle, the chronaxie is approximately 0.01 ms and for muscle 2 ms.Functional electrical stimulation or FES is the application of neuromuscular electrical stimulation in order to produce movement for a specific function. Whenever the lower motor neuron is healthy, as it is common after SCI, the use of FES with lower current intensity is possible.Direct muscle stimulation has been used after SCI to reverse muscle atrophy in denervated muscles (Kern et al., 2005).

Functional electrical stimulation is used extensively after SCI. Some applications are for cardiac pacing, phrenic nerve pacing, and restoration of bladder, bowel and sexual function. FES is also used to restore movement in skeletal muscles of the trunk, the upper and the lower extremities (Gater Jr, Dolbow, Tsui, & Gorgey, 2011; P. Peckham & Knutson, 2005). Some authors include Transcutaneous Electrical Nerve Stimulation (TENS), the use of electrical stimulation for treating pain, as a form of FES (Gater Jr, et al., 2011), but since it does not involve movement it will not be considered as a form of FES in this review. The interest of my work is related to FES as a therapeutic tool to exercise and rehabilitate walking after SCI.

1.2.6.1. Electrical stimulation of excitable tissue

The cell's membrane acts electrically like a charged capacitor, having two different concentrations of ions inside and outside separated by a dielectric which generates a potential difference of about -70mV. If the membrane is depolarized in a small region past the threshold (-55mV), an influx of Na^+ ions will result inan Action Potential. This process happens normally for muscular activation, but it can also be triggered by the injection of an electrical current through the tissue. The electrodes can be arranged relative to the target tissue in three different ways which define the mode of stimulation: bipolar (both electrodes close to it), monopolar (only one electrode close to it) and field stimulation (both electrodes distant from it) which is the case for surface stimulation. The intensity of the response is determined by the axonal diameter of the target nerve, the stimulation pulse amplitude and the stimulation pulse duration. The larger the axonal diameter, the more excitable the axon will be due to the larger currents it may receive across its membrane. When an electric current is injected into a certain tissue, the axons with the larger diameter will reach the threshold for firing an Action Potential before the axons with smaller diameter. A motor unit (MU) is an alpha motor neuron (MN) and all the muscle fibers it innervates. Each muscle is a bundle of fibers of different types that are intermingled and give the muscle particular speed to react, strength and fatigability characteristics. Typically, the axons with larger diameter innervate the fast fatigable fibers. During voluntary muscle activation, slow acting fibers are recruited first, but FES activates fast fatigablemotor units first.This is known as reverse recruitment order. The recruitment of fatigable MUs of FES implies a challenge if the muscle force produced has to be maintained. The continued use of FES can induce long lasting changes in the composition of the muscle(P. H. Peckham, Mortimer, & Van Der Meulen, 1973).

There are several types of stimulators developed so far for FES.Depending on the purpose of FES, implanted, percutaneous or surface stimulation is preferred. Surface stimulation is the least invasive, although it has the disadvantages that deeper muscles are hard to stimulate and that the effect may not be isolated to a single muscle. Surface electrodes can be made of diverse materials, but self-adhesive hydrogel electrodes are the most common. Surface electrodes are placed above the “motor point” in order to produce the strongest and most isolated contraction with the least amount of current. The area of the electrodes depends on the target muscle, the strength of the desired muscle contraction and the sensation tolerance. Studies have confirmed that the same current applied through a larger electrode produces the same force output, but causes significantly less discomfort in the subject (Alon, Kantor, & Ho, 1994).

Functional electrical stimulation is usually delivered as a train of current pulses.The amount of electric current injected into the tissue (and therefore the resulting muscle contraction) is influenced by the stimulation frequency, amplitude and pulse duration.If the pulses are close enough the muscle does not return to resting potential and the twitches merge together causing a “fused” contraction. This means that the force produced by the muscle is maintained beyond the simple duration of each stimulation pulse. Therefore, increasing the frequency produces a smoother contraction, but since it implies that the muscle is responding with a sustained contraction, it will be susceptible to fatigue earlier. Variations in pulse width and amplitude influence the strength of the contraction within the limits of the muscle's capacity. For implanted electrodes, intensities of 1 to 10mA are used whereas for surface stimulation intensities of 10 to 150mA are required. Typically, a biphasic stimulus comprised of a train of pulses smaller than 1ms and with a frequency of less than 100 Hz(Prutchi & Norris, 2005) is used.

The first application of FES in humans was to correct foot drop, the inability to flex the ankle during the swing phase of gait, by stimulating the common peroneal nerve(Liberson, Holmquest, Scot, & Dow, 1961). Since then, the application of FES extended to other muscles and to multiple channels (Brandell, 1986). Currently, it is used for stimulating the upper extremities (Long 2nd, 1963; P. Peckham et al., 2001; Prochazka, Gauthier, Wieler, & Kenwell, 1997) and the lower extremities for standing and stepping (Graupe & Kohn, 1998; Hardin et al., 2007; Stein et al., 2006). Researchers and clinicians have dedicated a huge amount of effort in using FES to restore standing and stepping in the population with SCI, stroke, and multiple sclerosis. Despite the success they have had during the last decades with several systems available for clinical use, restoring standing and stepping has been very challenging given the kinematic complexity and metabolic requirement of these two tasks. FES systems for standing and walking often require a long period of conditioning and the use of bracing systems to avoid muscle fatigue due to constant stimulation(Gater Jr, et al., 2011).

1.2.6.2. FES-ASSISTED EXERCISE

Other research groups have used FES as a therapeutic tool to provide the health-related benefits of exercise to the people with SCI (Newham & Donaldson, 2007). This application is known as FES exercise and has been used since the 80's in different forms. Its first application was during cycling (Petrofsky, Phillips, & Heaton Iii, 1984). Later it was expanded to other forms of exercise. An online search for manufacturers of FES ergometers showed that the forms available are leg cycling, arm cranking, rowing, stepping and elliptical arm and leg movements. A new form of FES exercise termed "Hybrid" combines voluntary or FES arm cycling with FES leg cycling. Although some of these systems combine arms and legs, they are either mechanically coupled (i.e. RT200, Restorative Therapies) or disengaged completely (i.e. RT300, Restorative Therapies). There exists an opportunity for developing a system which engages both arms and legs in a coordinated fashion through FES of arm and leg muscles and not necessarily through a mechanical coupling. This coordination would have an advantage for the iSCI population: the voluntary control of both arms and legs would be strengthened since such an exercise would require a voluntary effort to coordinate them. This study is the first to apply such coordination through a visual feedback system.

Most of the equipment commercially available for FES exercise is designed with the complete SCI in mind. Nonetheless, subjects with iSCIcould also take advantage of FES exercise and use it for assisting rather than replacing the movement of the legs. The movement activates load and stretch receptors of the muscles involved. This activation mimics the normal proprioception and visual perception which reinforces the voluntary control over these muscles. This has been used by Page and colleagues in one subject with iSCI(Page, Levine, & Strayer, 2007)

The risks of FES-assisted exercise are minimal. These include skin burns if the electrodes do not make proper contact with the skin, bone fractures if a severe muscle spasm occurs and autonomic dysreflexia.Most of the equipment that is currently available for clinical use has built-in mechanisms for reducing the risk of the last two complications. Also precautions like periodic replacement of surface electrodes and skin inspection are necessary for burns prevention.

1.2.6.3. Benefits of FES after SCI

Functional electrical stimulationwith low intensity is applicable whenever there is a healthy motor neuron and an innervated muscle; hence its use after SCI is convenient.

There is a robust body of evidence that demonstrates the health benefits of FES in the SCI population. Functional electrical stimulation cycling slows down and reverses the loss of muscle mass (Baldi, Jackson, Moraille, & Mysiw, 1998; Heesterbeek et al., 2005) and improves significantly the fatigability and strength of some lower extremity muscles(Duffell et al., 2008). Moreover, FES cycling prevents muscle atrophy when initiated during the first year post SCI, which is the time when most of it occurs, but it is not as effective in reversing the disuse atrophy in chronic SCI(Baldi, et al., 1998).

The effects of FES cycling on bone mineral density (BMD) are not consistent since the results vary depending on which bone is studied (Dolbow et al., 2011). Some studies have demonstrated that an intensive program (more than 24 weeks, more than 30 min per week) of FES cycling significantly increases bone mass (Bélanger, Stein, Wheeler, Gordon, & Leduc, 2000; Frotzler et al., 2008; Mohr et al., 1997); but other groups under similar conditions found insignificant changes (Leeds, Klose, Ganz, Serafini, & Green, 1990). Chen and colleagues proposed that the effect of FES exercise on different bones is likely to be dependent on the loading that the exercise involves (Chen et al., 2005).

FES-assisted exercise, like any other form of aerobic exercise if conducted regularly, improves the cardiovascular health (Davis, Hamzaid, & Fornusek, 2008; Wheeler et al., 2002). Subjects with SCI have more sedentary lives than healthy individuals and they would benefit from any form of FES-assisted exercise.

Beyond the benefits of FES that I have already mentioned, there is a less obvious one. Since the first studies of FES training, researchers reported that after prolonged use, some subjects were able to perform the movements even without stimulation (Vodovnik, 1971). Later, several research studies have confirmed that this is the case for many forms of FES (Stein, et al., 2006). It has been proposed that this long lasting effect is a consequence of neuronal reorganization either at the cortical or spinal level induced by the electrical stimulation of both the motor and afferent nerves (Stein, et al., 2006).

1.2.7. Arm and leg FES-assisted cycling: a novel approach to rehabilitate walking

A combination of leg FES cycling and voluntary arm cycling known as FES hybrid exercise emerged with the intention of offering an exercise regimen that involves more muscles and maximizes the benefits of FES exercise. Several research groups proved its efficacy in improving cardiovascular health beyond FES leg cycling alone (Franken, Veltink, Ijzerman, Withaar, & Boom, 1997; Heesterbeek, et al., 2005; Mutton et al., 1997; Raymond, Davis, Fahey, Climstein, & Sutton, 1997). The arm and leg FES-assisted cycling approach that I propose is similar to hybrid FES cycling and to leg FES cycling. The difference is that the former involves the stimulation of both arms and legs as needed to assist with the cycling movement.

Rehabilitation strategies to recover ambulation after SCI range from regeneration of neuronal circuits to compensation. BWSTT is a widely applied therapy after iSCI. Its efficacy has been demonstrated and replicated in several studies. Functional electrical stimulation – assisted exercise has been used to improve cardiovascular health and muscle health. It has been proposed that these interventions could be combined to increase their effects. For instance, BWSTT has been used along with FES or with robotic assistance.Some research groups have concluded that important improvements can only be obtained by including pharmacological therapy along with locomotor training. Despite recent findings by Courtine and colleagues suggesting that BWSTT is more effective when combined with electrical stimulation or pharmacological approaches (Courtine et al., 2009), the effectiveness of such an approach in humans is yet to be demonstrated. In these rehabilitation protocols, the role of the arms is ignored.

1.3. ARM INVOLVEMENT DURING THE REHABILITATION OF WALKING

To any observer, it is obvious that humans swing their arms during walking. The arm swing is coordinated with the leg step cycle. For normal walking speed: the ipsilateral arm moves anti-phase while the contralateral arm moves in-phase with the legs (Webb, Tuttle, & Baksh, 1994). This relationship was not studied in detail until the 1960s. Recently, there has been a moderate interest in the role the arms play during human locomotion and the potential they have for affecting rehabilitation outcomes. This section summarizes the evidence that I have considered in proposing that arms be involved in the rehabilitation of walking through the arm and leg cycling paradigm.

1.3.1. ROLE OF ARMS DURING WALKING

Arm swinging increases the efficiency of gait. The swinging of the arms becomes more pronounced during running. During running, it helps to reduce excursion of the center of mass, improve the uniformity of running speedand contribute slightly to the lift (Hinrichs, Cavanagh, & Williams, 1987).

Contrary to the original conception of the arms moving as passive pendulums during walking, it is well established that the arm movement is a consequence of active muscle action. In 1939 Elftman demonstrated indirectly that arm swing is a consequence of muscular action since the pendular force involved was not strong enough to move the arms by itself (Elftman, 1939). Later, Fernandez-Ballesteros confirmed that arm swinging is an action of the shoulder and upper arm muscles by recording the activity of these muscles and defining an approximate pattern of muscle activation for the arms during the gait cycle. Even after constraining the movement of the arms, an involuntary step-related pattern of muscle activation persisted in four arm muscles. Thus, the basic arm muscular activity is independent of the biomechanics and may be part of a central pattern of activity in neuronal networks that involve both, arms and legs (Fernandez-Ballesteros, Buchthal, & Rosenfalck, 1965). Not only gravity, but also muscle force are the driving forces behind arm swinging during walking(Gutnik, Mackie, Hudson, & Standen, 2005). Recently, the view that anti-phase arm swing is due to muscle activity was challenged by two different studies. In the first study, Pontzer and colleagues found, on the one hand, correlations between the shoulder rotation due to the pelvis rotation and the arm swing therefore concluding that the arms must act as a mass damper to reduce such rotation. On the other hand, they recorded alternating muscle activity during walking in the anterior and posterior deltoids similar to that reported by Fernandez-Ballesteros (Pontzer, Holloway, Raichlen, & Lieberman, 2009). In the second study, Collins, Adamczyk and Kuo supported a passive dynamics model for arm swinging as opposed to active arm swing dynamics. They were able to reproduce the arm swing with passive elements hanging from the shoulders of healthy subjects (Collins, Adamczyk, & Kuo, 2009). Their results explain the movement in the arms, but not the presence or muscular activity in the arms and its relation to the leg muscle activity.

1.3.2. Arms and legs are coordinated via spinal neuronal network

Previous studiesin which muscle activity in the arms was recorded confirmed that, even if small, this activity is present during walking regardless of whether the arms are allowed or not allowed to swing and of changes in the mass of the arms. This suggests that the arm activity may be predetermined as part of walking. Beyond the different roles of the arms that are proposed by these studies, the consistency in the arm activity confirms that a higher level of control is in charge of producing this activity. The coordinated nature of the arm swinging which maintains a frequency relationship with the legs during stepping suggests that an internal oscillator for both arms and legs (presumably, the CPG) is involved in walking, swimming and creeping (Wannier, Bastiaanse, Colombo, & Dietz, 2001). As I have described in section 1.2.2 there is evidence supporting the existencein humans of CPGs that control the basic locomotor pattern similar to those found in quadrupeds. It is likely that such networks involve the arms and the legs given the evolutionary past of the human species (Dietz, 2002) and owing to the presence of long projecting interneurons from the leg to the arm motor neuron pools in the spinal cord (Nathan, Smith, & Deacon, 1996). An example of quadrupedal coordination in humans is baby crawling. Upon studying crawling in babies and adults it was concluded that they followed a lateral sequence similar to that of quadrupeds and that a gradual transition from gait to gallop may suggest sharing of neuronal networks between these two tasks (Patrick, Noah, & Yang, 2009).

The fact that arm and leg reflexes modulate each other during walking further confirms the existence of neuronal interactions between these two centers (i.e. arm controlling and leg controlling) in the spinal cord(Dietz, Fouad, & Bastiaanse, 2001). Based upon findings in the cat that networks of interneurons that mediate reflexes in the spinal cord are involved in the control of locomotion, researchers started looking for similar modulation mechanisms in the human. The function of the spinal interneuronal networks in humans can be studied through reflex activation (either via mechanical or electrical stimulation). By measuring the evoked electromyographic activity of the muscles involved relative to the onset of stimulation, researchers can study the correlation between reflex responses and the stimulation. Not only have responses in the muscles of the same leg (ipsilateral responses) been found, but also responses in muscles in the contralateral leg (contralateral reflexes). Dietz and colleagues found that cutaneous stimulation in the heel and mechanical perturbations in the leg also evoke responses in the arms (interlimb reflexes) if elicited during walking, but not during standing or sitting (Dietz, et al., 2001). In 2003, this was confirmed and expanded upon when Haridas and Zehr measured interlimb reflexes to cutaneous stimulation that crossed over from arms to legs and viceversa during walking(Carlos Haridas & E. Paul Zehr, 2003). In an effort to understand the functioning of the networks involved in the interlimb reflexes during locomotion, other rhythmic movements were then studied. In 2004, Frigon and colleagues reported that H-reflex responses in the legs were modulated during arm cycling but not when the arms were static at the same position. Interestingly, this modulation is independent of the motoneuronal excitability (Frigon, Collins, & Zehr, 2004).

Unlike people with intact spinal cord, more than half of the people with iSCI did not exhibit walking related arm swing during treadmill walking. Among other issues following a SCI, this absence may indicate that the interactions between arms and legs that normally promote arm swing during locomotion have been affected. The presence of arm swing coincides with the type of device used for ambulation (i.e. restrictive vs. promoter of arm movements during walking) (Tester et al., 2011). Hence, we could speculate that the daily practice of walking related arm movements in these individuals may result in the development of arm swing. Whether this feature is translated into better walking speed, efficiency or kinematics is still unknown.

1.3.2.1. THE COMMON CORE HYPOTHESIS

A robust group of interlimb reflex studies support the existence of neuronal networks linking arms and legs during several forms of locomotion such as walking, cycling and recumbent stepping(Frigon, et al., 2004; C. Haridas & E. P. Zehr, 2003; E. P. Zehr & Haridas, 2003). This evidence led Zehr to propose the common core hypothesis in 2005. After finding common factors that explain the phase-dependent modulation in response to cutaneous stimulation during walking, cycling and recumbent stepping, he proposed that a shared network of neurons located in the spinal cord is capable of reorganizing and producing the basic pattern of motor output for various forms of rhythmic movements in humans (Zehr, 2005). Leg cycling, incline walking and stair climbing share most of the interlimb modulation of walking (Lamont & Zehr, 2006; E. Zehr, et al., 2007; E. Paul Zehr, Klimstra, Johnson, & Carroll, 2007). Zehr first proposed the idea that another activity that engages this common core of neurons can be used for rehabilitation of a different pattern of movement. Klimstra and colleagues demonstrated that neural control paramenters are preserved among arm swinging and cycling despite mechanical differences(Klimstra, Thomas, Stoloff, Ferris, & Zehr, 2009).What if a different form of locomotion (such as arm and leg cycling) was used in rehabilitation after these neuronal networks were damaged due to injury? Would walking improve?Leg cycling alone was effective in improving walking speed and independence in an individual with chronic iSCI(Page, et al., 2007). Would arm and leg cycling have the same or better effect?

1.3.3. ROLE OF THE ARM AND LEG INTERACTIONS IN CURRENT REHABILITATION RESEARCH

Some research groups have explored the possibility of including the arms in the rehabilitation of walking after SCI. During BWSTT, for example, there is an indication of unloading the arms to allow for proper loading input to the legs. In a series of case studies, Behrman and Harkema went beyond the sole unloading and encouraged their subjects to swing the arms reciprocally during locomotor training (Behrman & Harkema, 2000). This has been done through poles that lead the arms in a reciprocal swing manually moved by the physical therapist. Interestingly, it was observed that after 9 weeks of BWSTT with arm swing assistance half of the people with iSCI who presented no walking related arm swing pre-training incorporated it post-training. Logically, it has been suggested that assistance for arm swing during locomotor training may induce walking related arm swing. One can speculate that this feature could be related to improvements in walkingas it was related to changes in the use of assistive devices (Tester, et al., 2011). The effect of arm involvement and the specific means through which it should be incorporated into the rehabilitation of walking is still unknown.

Arm cyclic activity can shape the legs' motor output through interlimb neural pathways between the cervical and lumbar segments of the spinal cord(N. Kawashima, D. Nozaki, M. O. Abe, & K. Nakazawa, 2008). In parallel to these studies, a therapy which consists of arm and leg coordinated movements like crawling, walking or running has been investigated.The Coordination Dynamics Therapy (CDT) consists of re-integrating the activation patterns of distributed neuronal networks that control different functions with a relative phase and frequency. A special device enforces time coordination between arm and leg movements in order to provide regulated afferent inputs to the spinal networks. It also involves other movements called "automatisms" that are supposed to reinforce such coordination like creeping, crawling, walking and running. This rehabilitation therapy has been effective to some extent in people with stroke and SCI (Schalow, 2003).Subjects with iSCI at sub C4/5 and L3/4, after at least 6 months of a very intense program of CDT (30 hrs per week) were able to walk independently and regain walking, running, jumping and even bladder function (Schalow, 2003). Although the effects of CDT are promising and it has been studied for over a decade, no published results demonstrate that it is effective in a large sample of subjects with SCI. Only a handful of case studies have been published using CDT and most of the subjects who participated received the therapy during the first three years after SCI. Unfortunately, the effect of the therapy versus a spontaneous recovery during this time is difficult to separate. The outcome measures used in the studies involving CDT are mainly magnetic resonance images of the spinal cord and a value for coordination dynamics as opposed to standard measures for independence of walking (e.g. WISCI or FIM) and walking speed (e.g. 6-minute walking test, 10-meter walking test). Their results are difficult to compare with other rehabilitation techniques due to the differences in duration and evaluation methods.

In the aforementioned studies, the arm involvement is regarded as important to improve the leg motor coordination for walking after SCI; and the fact that various forms of locomotion involving the arms and the legs can improve this coordination is emphasized. Nonetheless, it remains unclear which of the forms of locomotion available would be the best form of involving the arms and which is the benefit of including them in terms of walking improvement. Practical considerations must be taken into account so that the suggested therapy is not only effective, but also readily available to the iSCI population.

1.4. SUMMARY

A spinal cord injury is a serious condition that interruptsthe motor and sensory pathways in the spinal cord. Without having proper sensory input and motor control, the muscle activation patterns in people with iSCIbecome disorganizedto a certain extent depending on the level and severity of the SCI,resulting in gait impairments. Research has focused on compensation and rehabilitation techniques that have been somewhat successful in returning subjects with SCI to an acceptable level of independence and mobility. The difficulties encountered in functionally, rather than anatomically, regenerating spinal neuronal networks have led researchers to propose that a combination of therapies has better chances of improving walking capacity. With iSCI there is a potential for reorganizing remaining neuronal pathways in such a way that they function again with the coordination that locomotion requires. Locomotor training with partial body weight support and its variations provide regulated sensory input in order to reorganize the spinal neuronal networks. It has been successful for improving walking after iSCI, but it has not incorporated the arms beyond their unloading during training. FES exercise improves cardiovascular health, promotes muscle health and induces plasticity in spinal circuits. It is an excellent tool not only for assisting during rehabilitation in the movement of the limbs, but also for providing regulated sensory stimulation to the spinal circuitry. The specific form in which the sensory input must be delivered has not been determined. Nonetheless, the common elements between human walking and other forms of locomotion open the door for exploring the effects of non-specific rehabilitation of walking. Such rehabilitation should involve rhythmic and coordinated movements such as arm and leg cycling or recumbent stepping maintaining a relative phase and frequency between the arms and the legs.

A research therapy that promotes plasticity in spinal neuronal networks involved in walking through arm and leg cycling and taking advantage of the benefits of FES exerciseis proposed in this thesis. I identified several advantages in using the arm and leg cycling paradigm. First, it relieves the physical therapist of the extenuating job of moving the legs according to the stepping motion (as it is required for locomotor training). Second, it incorporates the arms smoothly through an activity that influences the leg motor output. Third, it eliminates the challenge for maintaining the subject in an upright position and the risks of falling involved becausethe cycling is performed while sitting. Finally, it takes advantage of the regulated sensory input provided by electrical stimulation.

1.5. MASTER'S THESIS OBJECTIVES

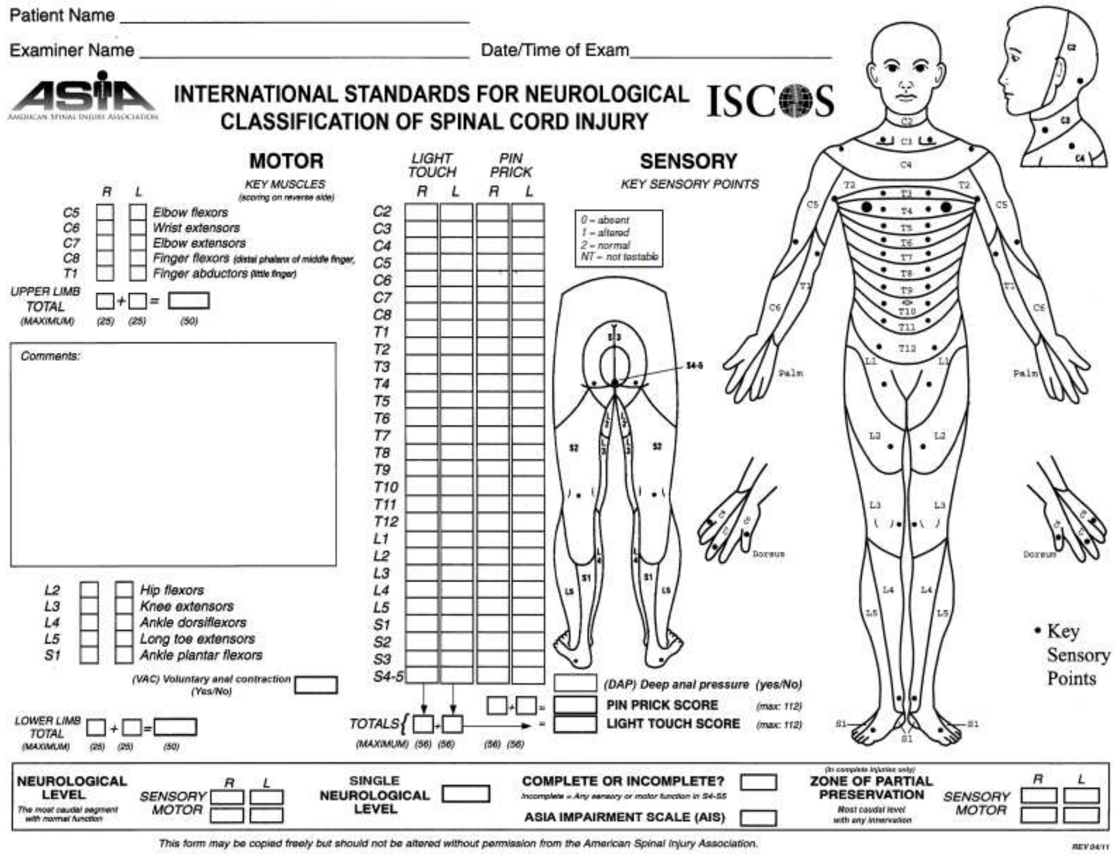
The main goal of my master's research was to evaluate the efficacy of a rehabilitation program for walking in the first pilot study that involvesFES-assisted arm and leg cycling after iSCI. Specifically, my working hypothesis was that FES-assisted arm and leg cycling therapy would be effective in improving walking speed and independence of walking after chronic iSCI. The null hypothesis is that FES-assisted arm and leg cycling will not improve walking in individuals with chronic iSCI. My thesis is part of a larger study that will compare the effects of FES-assisted arm and leg cycling with FES-assisted leg cycling in order to determine the effect of active arm involvement on the rehabilitation of walking.

To test my hypothesis, a group of five individuals with iSCI received FES-assisted arm and leg cycling therapy over the course of 12 weeks. I measured periodically their walking ability and gait kinematics along with balance, reflex excitability,and motor and sensory responses below the lesion in order to investigate the mechanisms of changes observed in walking ability.

In chapter 2, I describe the methodology of the experiments I performed to test my hypothesis, the results I obtained and their significance.

In chapter 3, I offer a general conclusion to my thesis; I place my results in the context of current rehabilitation research for walking; and propose some future directions for the research of arm and leg FES-assisted cycling.

1.6. FIGURES AND TABLES



Patient Name ____________________

Examiner Name ____________________ Date/Time of Exam ____________________

ASIA AMERICAN SPINAL INJURY ASSOCIATION

INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

ISCOS

MOTOR

KEY MUSCLES (scoring on reverse side)

	R	L	
C5			Elbow flexors
C6			Wrist extensors
C7			Elbow extensors
C8			Finger flexors (distal phalanx of middle finger)
T1			Finger abductors (little finger)

UPPER LIMB TOTAL (MAXIMUM) (25) + (25) = (50)

Comments:

	R	L	
L2			Hip flexors
L3			Knee extensors
L4			Ankle dorsiflexors
L5			Long toe extensors
S1			Ankle plantar flexors

(VAC) Voluntary anal contraction (Yes/No)

LOWER LIMB TOTAL (MAXIMUM) (25) + (25) = (50)

	LIGHT TOUCH R	LIGHT TOUCH L	PIN PRICK R	PIN PRICK L
C2				
C3				
C4				
C5				
C6				
C7				
C8				
T1				
T2				
T3				
T4				
T5				
T6				
T7				
T8				
T9				
T10				
T11				
T12				
L1				
L2				
L3				
L4				
L5				
S1				
S2				
S3				
S4-5				
TOTALS (MAXIMUM)	(56)	(56)	(56)	(56)

SENSORY

KEY SENSORY POINTS

0 = absent
1 = altered
2 = normal
NT = not testable

(DAP) Deep anal pressure (yes/No)

PIN PRICK SCORE (max: 112)

LIGHT TOUCH SCORE (max: 112)

NEUROLOGICAL LEVEL — The most caudal segment with normal function — SENSORY R L / MOTOR R L

SINGLE NEUROLOGICAL LEVEL

COMPLETE OR INCOMPLETE? — Incomplete = Any sensory or motor function in S4-S5

ASIA IMPAIRMENT SCALE (AIS)

ZONE OF PARTIAL PRESERVATION (In complete injuries only) — Most caudal level with any innervation — SENSORY R L / MOTOR R L

This form may be copied freely but should not be altered without permission from the American Spinal Injury Association.

REV 04/11

Figure 1-1: ASIA sensory and motor evaluation form (ASIA, International Standards for Neurological Classification of SCI Revised, 2011).

1.7. BIBLIOGRAPHY

Akay, T., McVea, D. A., Tachibana, A., & Pearson, K. G. (2006). Coordination of fore and hind leg stepping in cats on a transversely-split treadmill. *Exp Brain Res, 175*(2), 211-222. doi: 10.1007/s00221-006-0542-3

Allan H. Ropper, Martin A. Samuels. (2009). Chapter 44. Diseases of the Spinal Cord. In M. A. S. Allan H. Ropper (Ed.), *Adams and Victor's Principles of Neurology.* (9th ed.). New York: McGraw-Hill.

Alon, G., Kantor, G., & Ho, H. S. (1994). Effects of electrode size on basic excitatory responses and on selected stimulus parameters. *J Orthop Sports Phys Ther, 20*(1), 29-35.

Anderson, KD. (2004). Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma, 21*(10), 1371-1383.

Baldi, J. C., Jackson, R. D., Moraille, R., & Mysiw, W. J. (1998). Muscle atrophy is prevented in patients with acute spinal cord injury using functional electrical stimulation. *Spinal Cord, 36*(7), 463-469.

Ballion, B., Morin, D., & Viala, D. (2001). Forelimb locomotor generators and quadrupedal locomotion in the neonatal rat. *Eur J Neurosci, 14*(10), 1727-1738. doi: 1794 [pii]

Barbeau, Hugues. (2003). Locomotor Training in Neurorehabilitation: Emerging Rehabilitation Concepts. *Neurorehabilitation and Neural Repair, 17*(1), 3-11.

Behrman, Andrea L., & Harkema, Susan J. (2000). Locomotor Training After Human Spinal Cord Injury: A Series of Case Studies. *Physical Therapy, 80*(7), 688-700.

Berg, KO, Wood-Dauphinee, SL, Williams, JI, & Maki, B. Measuring balance in the elderly: validation of an instrument. *Can J Public Health, 83 Suppl 2*, S7-11.

Bracken, M. B., Shepard, M. J., Holford, T. R., Leo-Summers, L., Aldrich, E. F., Fazl, M., . . . Young, W. (1997). Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *JAMA, 277*(20), 1597-1604.

Brandell, B. R. (1986). The study and correction of human gait by electrical stimulation. *Am Surg, 52*(5), 257-263.

Butland, R. J., Pang, J., Gross, E. R., Woodcock, A. A., & Geddes, D. M. (1982). Two-, six-, and 12-minute walking tests in respiratory disease. *Br Med J (Clin Res Ed), 284*(6329), 1607-1608.

Bélanger, Marc, Stein, Richard B., Wheeler, Garry D., Gordon, Tessa, & Leduc, Bernard. (2000). Electrical stimulation: Can it increase muscle strength and reverse osteopenia in spinal cord injured individuals? *Archives of Physical Medicine and Rehabilitation, 81*(8), 1090-1098. doi: 10.1053/apmr.2000.7170

Charteris, J. (1982). Human gait cyclograms: conventions, speed relationships and clinical applications. *Int J Rehabil Res, 5*(4), 507-518.

Chen, Shih-Ching, Lai, Chien-Hung, Chan, Wing P., Huang, Mao-Hsiung, Tsai, Hsing-Wen, & Chen, Jia-Jin J. (2005). Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. *Disability and Rehabilitation, 27*(22), 1337-1341. doi: 10.1080/09638280500164032

Collins, Steven H., Adamczyk, Peter G., & Kuo, Arthur D. (2009). Dynamic arm swinging in human walking. *Proceedings of the Royal Society B: Biological Sciences*, -. doi: 10.1098/rspb.2009.0664

Courtine, G, Gerasimenko, Y, van den Brand, R, Yew, A, Musienko, P, Zhong, H, . . . Edgerton, VR. (2009). Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. *Nat Neurosci, 12*(10), 1333-1342.

Davis, GM, Hamzaid, NA, & Fornusek, C. (2008). Cardiorespiratory, metabolic, and biomechanical responses during functional electrical stimulation leg exercise: health and fitness benefits. *Artif Organs, 32*(8), 625-629. doi: AOR622 [pii]

10.1111/j.1525-1594.2008.00622.x

De Leon, R. D., Hodgson, J. A., Roy, R. R., & Edgerton, V. R. (1999). Retention of hindlimb stepping ability in adult spinal cats after the cessation of step training. *J Neurophysiol, 81*(1), 85-94.

Dietz, V. (2011). Neuronal plasticity after a human spinal cord injury: Positive and negative effects. *Exp Neurol*. doi: S0014-4886(11)00121-X [pii]
10.1016/j.expneurol.2011.04.007

Dietz, V., Fouad, K., & Bastiaanse, C. M. (2001). Neuronal coordination of arm and leg movements during human locomotion. E*uropean Journal of Neuroscience, 14(*11), 1906-1914.

Dietz, Volker. (2002). Do human bipeds use quadrupedal coordination? T*rends in Neurosciences, 25(*9), 462-467.

Dietz, Volker, & Duysens, Jacques. (2000). Significance of load receptor input during locomotion: a review. G*ait & Posture, 11(*2), 102-110.

Dittuno, P. L., Ditunno, J. F., & Dittuno, J. F. (2001). Walking index for spinal cord injury (WISCI II): scale revision. S*pinal Cord, 39(*12), 654-656. doi: 10.1038/sj.sc.3101223

Ditunno, J. F., Ditunno, P. L., Graziani, V., Scivoletto, G., Bernardi, M., Castellano, V., . . . Nance, P. (2000). Walking index for spinal cord injury (WISCI): an international multicenter validity and reliability study. S*pinal Cord, 38(*4), 234-243.

Ditunno Jr, J. F., Barbeau, H., Dobkin, B. H., Elashoff, R., Harkema, S., Marino, R. J., . . . Chung, J. (2007). Validity of the walking scale for spinal cord injury and other domains of function in a multicenter clinical trial. N*eurorehabilitation and Neural Repair, 21(*6), 539-550.

Ditunno, P. L., Patrick, M., Stineman, M., & Ditunno, J. F. (2008). Who wants to walk? Preferences for recovery after SCI: a longitudinal and cross-sectional study. S*pinal Cord, 46(*7), 500-506.

Dobkin, B. H. (2006). Short-distance walking speed and timed walking distance: Redundant measures for clinical trials? N*eurology, 66(*4), 584-586.

Dobkin, B. H., Apple, D., Barbeau, H., Basso, M., Behrman, A., Deforge, D., . . . Scott, M. (2003). Methods for a randomized trial of weight-supported treadmill training versus conventional training for walking during inpatient rehabilitation after incomplete traumatic spinal cord injury. N*eurorehabil Neural Repair, 17(*3), 153-167.

Dobkin, B. H., & Duncan, P. W. (2012). Should body weight-supported treadmill training and robotic-assistive steppers for locomotor training trot back to the starting gate? N*eurorehabil Neural Repair, 26(*4), 308-317. doi: 1545968312439687 [pii]
10.1177/1545968312439687

Dolbow, D. R., Gorgey, A. S., Daniels, J. A., Adler, R. A., Moore, J. R., & Gater Jr, D. R. (2011). The effects of spinal cord injury and exercise on bone mass: A literature review. Ne*uroRehabilitation, 29(3*), 261-269.

Duffell, LD, Donaldson, Nde N, Perkins, TA, Rushton, DN, Hunt, KJ, Kakebeeke, TH, & Newham, DJ. (2008). Long-term intensive electrically stimulated cycling by spinal cord-injured people: effect on muscle properties and their relation to power output. Mu*scle Nerve, 38(4*), 1304-1311.

Elftman, Herbert. (1939). The Function of the Arms in Walking. Hu*man Biology, 11(4*), 529-535.

Fernandez-Ballesteros, Maria L., Buchthal, Fritz, & Rosenfalck, Poul. (1965). The Pattern of Muscular Activity During the Arm Swing of Natural Walking. Ac*ta Physiologica Scandinavica, 63(3*), 296-310.

Field-Fote, E. C., & Roach, K. E. (2011). Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial. Ph*ys Ther, 91(1*), 48-60. doi: ptj.20090359 [pii]
10.2522/ptj.20090359

Field-Fote, E. C., & Tepavac, D. (2002). Improved intralimb coordination in people with incomplete spinal cord injury following training with body weight support and electrical stimulation. Phy*s Ther, 82(7)*, 707-715.

Franken, H. M., Veltink, P. H., Ijzerman, M. J., Withaar, F. S., & Boom, H. B. (1997). The influence of voluntary upper body exercise on the performance of stimulated paralysed human quadriceps. J E*lectromyogr Kinesiol, 7(1)*, 67-77. doi: S1050-6411(96)00017-X [pii]

Frigon, A, Collins, DF, & Zehr, EP. (2004). Effect of rhythmic arm movement on reflexes in the legs: modulation of soleus H-reflexes and somatosensory conditioning. J N*europhysiol, 91(4)*, 1516-1523.

Frotzler, A, Coupaud, S, Perret, C, Kakebeeke, TH, Hunt, KJ, Donaldson, Nde N, & Eser, P. (2008). High-volume FES-cycling partially reverses bone loss in people with chronic spinal cord injury. Bon*e, 43(1)*, 169-176.

Gater Jr, D. R., Dolbow, D., Tsui, B., & Gorgey, A. S. (2011). Functional electrical stimulation therapies after spinal cord injury. Neu*roRehabilitation, 28(3)*, 231-248.
Gordon, I. T., Dunbar, M. J., Vanneste, K. J., & Whelan, P. J. (2008). Interaction between developing spinal locomotor networks in the neonatal mouse. J N*europhysiol, 100(1)*, 117-128. doi: 00829.2007 [pii]
10.1152/jn.00829.2007
Gordon, I. T., & Whelan, P. J. (2008). Brainstem modulation of locomotion in the neonatal mouse spinal cord. J P*hysiol, 586(10*), 2487-2497. doi: jphysiol.2007.148320 [pii]
10.1113/jphysiol.2007.148320
Graupe, D, & Kohn, KH. (1998). Functional neuromuscular stimulator for short-distance ambulation by certain thoracic-level spinal-cord-injured paraplegics. Sur*g Neurol, 50(3)*, 202-207.
Grillner, S., & Zangger, P. (1979). On the central generation of locomotion in the low spinal cat. Exp*erimental Brain Research, 34(2)*, 241-261. doi: 10.1007/bf00235671
Gutnik, B., Mackie, H., Hudson, G., & Standen, C. (2005). How close to a pendulum is human upper limb movement during walking? Hom*o, 56(1)*, 35-49.
Hagg, T., & Oudega, M. (2006). Degenerative and spontaneous regenerative processes after spinal cord injury. Jou*rnal of Neurotrauma, 23(3*-4), 264-280.
Hardin, E, Kobetic, R, Murray, L, Corado-Ahmed, M, Pinault, G, Sakai, J, . . . Triolo, RJ. (2007). Walking after incomplete spinal cord injury using an implanted FES system: a case report. J R*ehabil Res Dev, 44(3)*, 333-346.
Haridas, Carlos, & Zehr, E. Paul. (2003). Coordinated Interlimb Compensatory Responses to Electrical Stimulation of Cutaneous Nerves in the Hand and Foot During Walking (Vol. 90, pp. 2850-2861).
Harkema, S. J., Schmidt-Read, M., Lorenz, D., Edgerton, V. R., & Behrman, A. L. (2011). Balance and Ambulation Improvements in Individuals With Chronic Incomplete Spinal Cord Injury Using Locomotor Training-Based Rehabilitation. Arc*h Phys Med Rehabil. d*oi: S0003-9993(11)00129-8 [pii]
10.1016/j.apmr.2011.01.024
Heesterbeek, P. J. C., Berkelmans, H. W. A., Thijssen, D. H. J., van Kuppevelt, H. J. M., Hopman, M. T. E., & Duysens, J. (2005). Increased physical fitness after 4-week training on a new hybrid FES-cycle in persons with spinal cord injury. Tech*nology and Disability, 17(2)*, 103-110.
Hiersemenzel, L. P., Curt, A., & Dietz, V. (2000). From spinal shock to spasticity: neuronal adaptations to a spinal cord injury. Neur*ology, 54(8)*, 1574-1582.
Hill, A. A., Masino, M. A., & Calabrese, R. L. (2003). Intersegmental coordination of rhythmic motor patterns. J Ne*urophysiol, 90(2)*, 531-538. doi: 10.1152/jn.00338.2003
90/2/531 [pii]
Hinrichs, Richard N., Cavanagh, Peter R., & Williams, Keith R. (1987). Upper Extremity Function in Running. I: Center of Mass and Propulsion Considerations. Inte*rnational Journal of Sport Biomechanics, 3(3)*, 222-241.
Institute, Rick Hansen, & Futures, Urban. (2010). The Incidence and Prevalence of Spinal Cord Injury in Canada. In A. B. Farry, David (Ed.), Over*view and estimates based on current evidence.*
*Ka*washima, N, Nozaki, D, Abe, MO, & Nakazawa, K. (2008). Shaping appropriate locomotive motor output through interlimb neural pathway within spinal cord in humans. J Ne*urophysiol, 99(6)*, 2946-2955. doi: 00020.2008 [pii]
10.1152/jn.00020.2008
Kawashima, Noritaka, Nozaki, Daichi, Abe, Masaki O., & Nakazawa, Kimitaka. (2008). Shaping Appropriate Locomotive Motor Output Through Interlimb Neural Pathway Within Spinal Cord in Humans (Vol. 99, pp. 2946-2955).
Klimstra, Marc D., Thomas, Evan, Stoloff, Rebecca H., Ferris, Daniel P., & Zehr, E. Paul. (2009). Neuromechanical considerations for incorporating rhythmic arm movement in the rehabilitation of walking. Chao*s: An Interdisciplinary Journal of Nonlinear Science, 19(2)*, 026102-026114.
Lamont, E. V., & Zehr, E. P. (2006). Task-specific modulation of cutaneous reflexes expressed at functionally relevant gait cycle phases during level and incline walking and stair climbing. Expe*rimental Brain Research, 173(1)*, 185-192.
Leeds, E. M., Klose, K. J., Ganz, W., Serafini, A., & Green, B. A. (1990). Bone mineral density after bicycle ergometry training. Arch *Phys Med Rehabil, 71(3)*, 207-209.

LIBERSON, W. T., HOLMQUEST, H. J., SCOT, D., & DOW, M. (1961). Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients. Arch *Phys Med Rehabil, 42, 10*1-105.

Long 2nd, C. (1963). AN ELECTROPHYSIOLOGIC SPLINT FOR THE HAND. Arch*ives of physical medicine and rehabilitation, 44, 49*9-503.

Lovely, R. G., Gregor, R. J., Roy, R. R., & Edgerton, V. R. (1986). Effects of training on the recovery of full-weight-bearing stepping in the adult spinal cat. Expe*rimental Neurology, 92(2),* 421-435. doi: 10.1016/0014-4886(86)90094-4

Lunenburger, L., Colombo, G., Riener, R., & Dietz, V. (2004, 1-5 Sept. 2004). Biof*eedback in gait training with the robotic orthosis Lokomat. Pap*er presented at the Engineering in Medicine and Biology Society, 2004. IEMBS '04. 26th Annual International Conference of the IEEE.

Marino, RJ, Ditunno, JF Jr, Donovan, WH, & Maynard, F Jr. (1999). Neurologic recovery after traumatic spinal cord injury: data from the Model Spinal Cord Injury Systems. Arch *Phys Med Rehabil, 80(11)*, 1391-1396.

Mohr, T., Pødenphant, J., Biering–Sørensen, F., Galbo, H., Thamsborg, G., & Kjær, M. (1997). Increased Bone Mineral Density after Prolonged Electrically Induced Cycle Training of Paralyzed Limbs in Spinal Cord Injured Man. Calc*ified Tissue International, 61(1),* 22-25. doi: 10.1007/s002239900286

Musselman, K. E., Fouad, K., Misiaszek, J. E., & Yang, J. F. (2009). Training of walking skills overground and on the treadmill: Case series on individuals with incomplete spinal cord injury. Phys*ical Therapy, 89(6),* 601-611. doi: 10.2522/ptj.20080257

Mutton, D. L., Scremin, A. M. E., Barstow, T. J., Scott, M. D., Kunkel, C. F., & Cagle, T. G. (1997). Physiologic responses during functional electrical stimulation leg cycling and hybrid exercise in spinal cord injured subjects. Arch*ives of Physical Medicine and Rehabilitation, 78(7),* 712-718.

NATHAN, P. W., & SMITH, M. C. (1955). Long descending tracts in man. I. Review of present knowledge. Brai*n, 78(2),* 248-303.

Nathan, P. W., Smith, M., & Deacon, P. (1996). Vestibulospinal, reticulospinal and descending propriospinal nerve fibres in man. Brai*n, 119 (Pt 6), 18*09-1833.

Newham, DJ, & Donaldson, Nde N. (2007). FES cycling. Acta *Neurochir Suppl, 97(Pt* 1), 395-402.

Page, Stephen J., Levine, Peter, & Strayer, Jonathan. (2007). An Electric Stimulation Cycling Protocol for Gait in Incomplete Spinal Cord Injury. Arch*ives of Physical Medicine and Rehabilitation, 88(6),* 798-800.

Patrick, S. K., Noah, J. A., & Yang, J. F. (2009). Interlimb coordination in human crawling reveals similarities in development and neural control with quadrupeds. Jour*nal of Neurophysiology, 101(2),* 603-613.

Pearson, K. G. (2000). Neural adaptation in the generation of rhythmic behavior. Annu *Rev Physiol, 62, 72*3-753. doi: 10.1146/annurev.physiol.62.1.723

Peckham, PH, Keith, MW, Kilgore, KL, Grill, JH, Wuolle, KS, Thrope, GB, . . . Wiegner, A. (2001). Efficacy of an implanted neuroprosthesis for restoring hand grasp in tetraplegia: a multicenter study. Arch *Phys Med Rehabil, 82(10)*, 1380-1388.

Peckham, PH, & Knutson, JS. (2005). Functional electrical stimulation for neuromuscular applications. Annu *Rev Biomed Eng, 7, 32*7-360.

Petrofsky, J. S., Phillips, C. A., & Heaton Iii, H. H. (1984). Bicycle ergometer for paralyzed muscle. Jour*nal of clinical engineering, 9(1),* 13-18.

Phadke, C. P., Thompson, F. J., Kukulka, C. G., Nair, P. M., Bowden, M. G., Madhavan, S., . . . Behrman, A. L. (2010). Soleus H-reflex modulation after motor incomplete spinal cord injury: effects of body position and walking speed. J Sp*inal Cord Med, 33(4),* 371-378.

Phadke, Chetan P., Flynn, Sheryl M., Thompson, Floyd J., Behrman, Andrea L., Trimble, Mark H., & Kukulka, Carl G. (2009). Comparison of Single Bout Effects of Bicycle Training Versus Locomotor Training on Paired Reflex Depression of the Soleus H-Reflex After Motor Incomplete Spinal Cord Injury. Arch*ives of Physical Medicine and Rehabilitation, 90(7),* 1218-1228.

Phadke, Chetan P., Wu, Samuel S., Thompson, Floyd J., & Behrman, Andrea L. (2007). Comparison of Soleus H-Reflex Modulation After Incomplete Spinal Cord Injury in 2 Walking Environments: Treadmill With Body Weight Support and Overground. Arch*ives of Physical Medicine and Rehabilitation, 88(12),* 1606-1613.

Pontzer, H., Holloway, J. H., Raichlen, D. A., & Lieberman, D. E. (2009). Control and function of arm swing in human walking and running. J Ex*p Biol, 212(Pt* 4), 523-534. doi: 212/4/523 [pii]
10.1242/jeb.024927
Prochazka, A, Gauthier, M, Wieler, M, & Kenwell, Z. (1997). The bionic glove: an electrical stimulator garment that provides controlled grasp and hand opening in quadriplegia. Arch *Phys Med Rehabil, 78(6),* 608-614.
Prutchi, David, & Norris, Michael. Design and Development of Medical Electronic Instrumentation - A Practical Perspective of the Design, Construction and Test of Medical Devices: John Wiley & Sons.
Raymond, J., Davis, G. M., Fahey, A., Climstein, M., & Sutton, J. R. (1997). Oxygen uptake and heart rate responses during arm vs combined arm/electrically stimulated leg exercise in people with paraplegia. Spina*l Cord, 35(10),* 680-685.
Schalow, G. (2002). Recovery from spinal cord injury achieved by 3 months of coordination dynamic therapy. Elec*tromyogr Clin Neurophysiol, 42(6),* 367-376.
Schalow, G. (2003). Partial cure of spinal cord injury achieved by 6 to 13 months of coordination dynamic therapy. Elec*tromyogr Clin Neurophysiol, 43(5),* 281-292.
Schalow, G., & Zach, G. A. (1998). Neuronal reorganization through oscillator formation training in patients with CNS lesions. J Per*ipher Nerv Syst, 3(3),* 165-188.
Schwab, Martin E. (2002). Repairing the Injured Spinal Cord. Scien*ce, 295(5557*), 1029.
Sherrington, C. S. (1910). Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. The J*ournal of Physiology, 40(1-2),* 28-121.
Skinner, F. K., & Mulloney, B. (1998). Intersegmental coordination in invertebrates and vertebrates. Curr *Opin Neurobiol, 8(6),* 725-732. doi: S0959-4388(98)80114-1 [pii]
Smith, J. L., Smith, L. A., Zernicke, R. F., & Hoy, M. (1982). Locomotion in exercised and nonexercised cats cordotomized at two or twelve weeks of age. Exper*imental Neurology, 76(2),* 393-413. doi: 10.1016/0014-4886(82)90217-5
Stein, R. B., Chong, S., Everaert, D. G., Rolf, R., Thompson, A. K., Whittaker, M., . . . Ihashi, K. (2006). A multicenter trial of a footdrop stimulator controlled by a tilt sensor. Neuro*rehabilitation and Neural Repair, 20(3),* 371-379.
Stevenson, T. J. (2001). Detecting change in patients with stroke using the Berg Balance Scale. Austr*alian Journal of Physiotherapy, 47(1),* 29-38.
Subbarao, J. V. (1991). Walking after spinal cord injury. Goal or wish? West *J Med, 154(5),* 612-614.
Tate, D. G., Kalpakjian, C. Z., & Forchheimer, M. B. (2002). Quality of life issues in individuals with spinal cord injury. Arch *Phys Med Rehabil, 83(12 S*uppl 2), S18-25. doi: S0003999302006214 [pii]
10.1053/apmr.2002.36835
Tepavac, D., & Field-Fote, E. C. (2001). Vector coding: A technique for quantification of intersegmental coupling in multicyclic behaviors. Journa*l of Applied Biomechanics, 17(3), 2*59-270.
Tester, N. J., Howland, D. R., Day, K. V., Suter, S. P., Cantrell, A., & Behrman, A. L. (2011). Device use, locomotor training and the presence of arm swing during treadmill walking after spinal cord injury. Spinal *Cord, 49(3), 4*51-456.
Thuret, S., Moon, L. D. F., & Gage, F. H. (2006). Therapeutic interventions after spinal cord injury. Nature *Reviews Neuroscience, 7(8), 6*28-643.
van Hedel, Hubertus J., Wirz, Markus, & Dietz, Volker. (2005). Assessing walking ability in subjects with spinal cord injury: Validity and reliability of 3 walking tests. Archiv*es of Physical Medicine and Rehabilitation, 86(2), 1*90-196.
Visintin, M., & Barbeau, H. (1994). The effects of parallel bars, body weight support and speed on the modulation of the locomotor pattern of spastic paretic gait. A preliminary communication. Parapl*egia, 32(8), 5*40-553. doi: 10.1038/sc.1994.86
Vodovnik, L. (1971). Information processing in the central nervous system during functional electrical stimulation. Med Bi*ol Eng, 9(6), 6*75-682.
Wannier, T., Bastiaanse, C., Colombo, G., & Dietz, V. (2001). Arm to leg coordination in humans during walking, creeping and swimming activities. Exp Br*ain Res, 141(3), 3*75-379. doi: 10.1007/s002210100875
Webb, D., Tuttle, R. H., & Baksh, M. (1994). Pendular activity of human upper limbs during slow and normal walking. Am J P*hys Anthropol, 93(4), 4*77-489. doi: 10.1002/ajpa.1330930407

Wheeler, G. D., Andrews, B., Lederer, R., Davoodi, R., Natho, K., Weiss, C., . . . Steadward, R. D. (2002). Functional electric stimulation-assisted rowing: Increasing cardiovascular fitness through functional electric stimulation rowing training in persons with spinal cord injury. Archiv*es of Physical Medicine and Rehabilitation, 83(8), 1*093-1099.

Wirz, M., Müller, R., & Bastiaenen, C. (2010). Falls in persons with spinal cord injury: validity and reliability of the Berg Balance Scale. Neuror*ehabil Neural Repair, 24(1), 7*0-77. doi: 1545968309341059 [pii]

10.1177/1545968309341059

Zehr, E. Paul, Klimstra, Marc, Johnson, Elizabeth A., & Carroll, Timothy J. (2007). Rhythmic leg cycling modulates forearm muscle H-reflex amplitude and corticospinal tract excitability. Neuros*cience Letters, 419(1), 1*0-14.

Zehr, EP, Balter, JE, Ferris, DP, Hundza, SR, Loadman, PM, & Stoloff, RH. (2007). Neural regulation of rhythmic arm and leg movement is conserved across human locomotor tasks. J Phys*iol, 582(Pt 1)*, 209-227. doi: jphysiol.2007.133843 [pii]

10.1113/jphysiol.2007.133843

Chapter 2. ACTIVE ARM INVOLVEMENT IN THE REHABILITATION OF WALKING AFTER SPINAL CORD INJURY

2.1. INTRODUCTION

Humans swing their arms in opposition to the legs while walking and running. Arm swinging significantly increases the efficiency of gait (Collins, et al., 2009; Umberger, 2008) especially at faster speed(Chang II Park, 2000; CI Park, 2000). During walking, arm and leg movements are coordinated and maintain a frequency relationship between their rhythmic motion (Wannier, et al., 2001).

Experiments in different species have demonstrated that vertebrates are capable of generating synchronized movements along the body axis that involve inter-segmental coordination within the spinal cord(Akay, McVea, Tachibana, & Pearson, 2006; Hill, Masino, & Calabrese, 2003; Skinner & Mulloney, 1998).Interactions between cervical and lumbar enlargements (likely through propriospinal neurons) in cats produce coordinated locomotor movements between fore- and hind- limbs (Akay, et al., 2006; Ballion, Morin, & Viala, 2001; NATHAN & SMITH, 1955).

Neuronal networks were positedto allow for cervico-lumbar coordination in quadrupeds and to be also present in humans,Longpropriospinal neurons may be responsible for such coordination(Nathan, et al., 1996; NATHAN & SMITH, 1955). Evidence for interlimb coordination and reflex modulation in humans during locomotion has been presented, and involves both arm and leg control centres in the spinal cord (Dietz, 2002). Leg H-reflexes are modulated during rhythmic arm movements (Frigon, et al., 2004) and cutaneous reflexes are modulated between the upper and lower limbs during walking, but not during standing (Lamont & Zehr, 2006).

After a spinal cord injury, the regulation of motor patterns becomes disorganizedincluding the coordination of arm and leg movements that are normally present during walking. Hence, we believe that the arms can play an important role in the rehabilitation of walking after a spinal cord injury.

A few research groups have explored this possibility through diverse approaches (Behrman & Harkema, 2000; N. Kawashima, D. Nozaki, M. Abe, & K. Nakazawa, 2008; Schalow, 2002; Schalow & Zach, 1998); however, none have evaluated the outcomes of their interventions for arm involvement on walking ability. Moreover, it is still unknown if arm and leg coordinated movements that provide rhythmic afferent input to the spinal networks would improve walking ability in people with iSCI.

We hypothesized,first, that phasic sensory input coordinated with phasic motor activation during rhythmic arm and leg FES-assisted cycling exercise will improve walking speed, endurance and the patterns of motor activation during walking in people with spinal cord injury. Our secondary hypothesis was that the improvement in walking ability would be owing to reorganization of the neuronal networks involved in locomotion. We proposed that such reorganization would manifest as improvements in sensation in the upper and lower extremities, reflex modulation, balance and the whole limb coordination rather than to pure muscle strengthening.In the present study, we used arm and leg cycling equipment that allows the generation of reciprocal movements between the arms and legs, mimicking the movement of the swinging arms during walking. FES was applied to the main flexor and extensor muscles of the arms and legs as needed in order to assist in the production of movement and deliver regulated sensory input to the spinal networks. Resistance to the movement was increased periodically through the training program while the cycling speed was held constant. The positive results of this novel intervention in the first group of subjects with chronic iSCI indicate that the training paradigm could be effective for improving walking in people with iSCI and should be further developed.

2.2. MATERIALS AND METHODS

2.2.1. SUBJECTS

Five adults (4 male, 1 female) with a chronic incomplete SCI acquired more than 2 years earlier were recruited to the study. We recruited subjects with injuries classified according to the ASIA (American Spinal Injury Association) impairment scale (AIS) as C (more than half of the key muscles below the neurological level graded 3 or less) or D (less than half of the key muscles below the neurological level graded 3 or less). The injury classification was self-reported during the screening process and confirmed later during the baseline assessments by the physical therapist. The study protocol and inclusion criteria were approved by the University of Alberta Human Research Ethics Board. The subjects ambulated with varying levels of assistance. Table 2-1 summarizes the characteristics of the subjects involved in the study. A list of each of the subjects' medication was obtained at baseline and any changes in dosage throughout the 12 week-training protocol were recorded. We also asked the subjects to maintain the same level of physical activity throughout the training period. All the participants had intact innervation of the main flexor and extensor muscles of arms and legs which allowed for the use of FES.

Before initiating the training and every 3 weeks thereafter, clinical, biomechanical and electrophysiological evaluations were performed. The pre-training (baseline) tests were repeated up to three times and the results were compared to ensure the stability of the baseline measures. The outcomes of the periodical evaluations were compared to the baseline measurements.

2.2.2. FES-ASSISTED ARM AND LEG CYCLING

We used a combined arm/leg FES ergometer to activate the arms and the legs simultaneously and generate arm/leg movements resembling the coordination present in natural walking. One of three different ergometers was used for training based upon participant comfort and equipment availability: 1) A custom-made combined arm/leg FES ergometer (ERGYS 2, Therapeutic Alliances, Inc. Fairborn OH, USA) and (THERAvital, MedicaMedizintechnik, Hochdorf, Germany), 2) RT200 "hybrid" FES system (Restorative Therapies, Maryland, USA), and 3) BerkelbikeImpuls (Berkelbike BV, Sint-Michielsgestel, Netherlands). In every case the flexion to extension intralateral and interlimb reciprocity was maintained despite some differences in the range of movement itself. For instance, the RT200 presents a more elliptical movement rather than a circular one. The subjects had one hour of training 5 times a week for 12 weeks. Electrical stimulation was delivered through surface electrodes targeting the main flexor and extensor muscles of the arms and legs as needed. Full use of the arms wasdetermined whenever every myotome in the arms received a score of at least 4 (active movement against some resistance) and the participant was able to move the arm crank by him/herself. If these conditions were met,no electrical stimulation was applied to the arms (refer to Table 2-2 for a list of the muscles stimulated for each subject). Settings for the stimulation intensity were determined based upon the muscle response as follows. A) The minimal intensity required to produce a twitch in the muscle, threshold stimulation (TH), was used by the leg ergometer as the minimal level of stimulation delivered. B) The maximal intensity of stimulation (MAX) was the level of stimulation that generated a muscle contraction that was strong enough to produce the desired movement without causing any uncomfortable sensations. We selected a target speed one level above the highest speed at which the volunteer was able to cycle without stimulation and held it constant during the training. The stimulation amplitude increased proportionally to the speed lag (difference between the target speed and the actual speed) up to MAX. Even when the participant was able to meet the target speed at times, at least TH level stimulation was delivered to the muscles. We increased the resistance manually on the ergometer as the training progressed to challenge the participant, maintain voluntary engagement in the exercise, and maintain a regular level of sensory feedback that the loading would apply to the spinal networks. All parameters regarding intensity of stimulation, speed, resistance and frequency of rest periods were monitored and entered in a daily log.

2.2.3. CLINICAL ASSESSMENTS

Most clinical assessments: sensory and motor changes according to the AIS, Walking Index for Spinal Cord Injury (WISCI), and Berg Balance Scale were performed after 6 and 12 weeks of arm and leg training. Walking speed and walking endurance were measured every 3 weeks. A trained physical therapist performed sensory (light touch and sharp/dull) and motor evaluations in association with the AIS. One limitation of our clinical assessments is that the same physical therapist who supervised the training performed the AIS evaluation. The sensory testing evaluated two aspects: 1) Light touch, performed by touching with a soft cotton swab each of the dermatomes and rating the person's ability to sense it; and 2) sharp/dull testing, performed using a sterile needle and the blunt end of a long Q-tip stick, respectively, and rating the participant's ability to differentiate between them. We applied the validated WISCI II clinical assessment method to evaluate the need for assistive devices during ambulation (Dittuno, Ditunno, & Dittuno, 2001; J. F. Ditunno et al., 2000; Ditunno Jr et al., 2007). We evaluated balance using the Berg Balance scale (Berg, Wood-Dauphinee, Williams, & Maki) which was recently validated for people with spinal cord injury (Wirz, Müller, & Bastiaenen, 2010).

To test walking endurance, the 6-minute walking test was performed on an oblong track, 18.54 m long, by asking each subject to walk as fast and as safely as possible. To test walking speed, we performed a timed 10-meter walking assessment on a straight line following the same instruction: to walk as fast as safely possible(Butland, Pang, Gross, Woodcock, & Geddes, 1982; Dobkin, 2006; van Hedel, Wirz, & Dietz, 2005). A distance between one and two meters was left before the actual 10-meter distance (the point where the stopwatch was started). Three measures were taken for each test.

2.2.4. BIOMECHANICAL ASSESSMENTS

To better describe the changes in walking ability, we evaluated the muscle activation patterns (electromyography), kinetics and kinematics during walking. We used a Vicon motion capture and analysis system with a full body model (PlugInGait, Vicon Motion System). These evaluations took place prior to the initiation of training and after 6 and 12 weeks of training. Muscle activity during walking was recorded using an AMT-8 EMG Wire Telemetry System (Bortec Biomedical Ltd.). The signals were amplified with a gain of 500, band pass filtered (10-1000 Hz) and sampled at a rate of 2400 Hz. A 3rd order low pass Butterworth filter (7Hz cutoff) was then applied to the rectified EMG data using Matlab'sfilt-filt function (The Mathworks, Natick, Massachusetts, U.S.A) then down-sampled by interpolation to 1000 samples. The number of steps obtained per assessment session varied depending on the subjects' ability to walk during the session. The number of steps considered for a particular dataset is reported on the corresponding figure. EMG and joint angle data obtained from each step were normalized to the percentage of gait cycle.

Gait cyclograms have been characterized for able-bodied individuals and proposed as a means for evaluating clinically the outcome of interventions affecting human walking (Charteris, 1982). In particular, the regularity of the hip vs. knee angle cyclogram has been related to improvements in walking after iSCI(Field-Fote & Tepavac, 2002). We followed the vector coding technique to calculate the regularity or coefficient of correspondence of the hip vs. knee angle cyclogram(Tepavac & Field-Fote, 2001). The regularity can have values from zero (no correspondence between cyclograms) to one (identical shape of cyclograms). We calculated the area inside the hip vs. knee angle cyclogram using the polygon function in Matlab (The Mathworks, Natick, Massachusetts,U.S.A) both as a measure of range of motion and the extent of the hip and knee excursion.

2.2.5. ELECTROPHYSIOLOGICAL ASSESSMENTS

Changes in the monosynaptic reflex response can be an indicator of reorganization of the neuronal networks at the spinal level and may be correlated with functional recovery(Phadke et al., 2010) We assessed the strength and modulation of the H-reflex of the most affected side of each subject while sitting with the leg fixed at 90 degrees knee flexion and the ankle at the neutral position. We used a 1 ms single pulse of electrical current to stimulate the posterior tibial nerve and measured the resulting M-wave (motor evoked response) and H-reflex in the soleus muscle through surface electromyography (e.g., figure 6A).

We obtained H-reflex peak-to-peak amplitudes relative to the M-wave peak-to-peak amplitudes, called H-M recruitment curves, by increasing the stimulus intensity gradually from a level below the H-reflex threshold to a level at which a stable maximal M-wave (Mmax) was elicited. In order to characterize and compare between the H-M recruitment curves at baseline and after 12 weeks of the intervention, we obtained the percentage of Mmaxthat corresponded toH max (%Mmax@Hmax) and the Hmax/Mmax ratio. Later, we set the stimulus intensity to a level producing an M-wave response of 10%Mmax(Phadke, Wu, Thompson, & Behrman, 2007)and acquired ten H-reflex responses for each of two conditions: with the muscle relaxed, and with the muscle contracted to 20% of its maximal voluntary contraction (MVC). To obtain the MVC we asked the subjects to perform three isometric contractions, measured the force with a transducer attached to the foot and used 20% of the highest one. At the baseline assessment, for one subject, the H-reflex with a stimulation intensity that produced a consistent 10%Mmax was not acquired systematically and could not be extrapolated from the H-M recruitment curves due to insufficient data points. Therefore, we compared the results to the 3-weeks data instead and did not include the results of this individual with the group results.

2.2.6. Statistical Analysis

We present a longitudinal study where the five subjects acted as their own controls for pre-training vs. post-training comparisons. According to our hypothesis, our goal was to investigate the effect that training using arm and leg FES-assisted cycling may have on each specific measure in individuals with iSCI.

We performed a Wilcoxon matched pairs test for the results of clinical non-parametric tests such as Berg Balance score and AIS. The p-value was calculated and a confidence interval of 95% was established to consider significance. For the 6-minute distance walked and 10-meter walking speed, 3 measurements were obtained at each assessment period (baseline, 3, 6, 9 and 12 weeks). We performed a repeated measures ANOVA for the raw walking speed data obtained for all participants at all assessment sessions (3 measurements per subject per assessment period). In order to identify if at any specific time point significant changes occurred, we contrasted the data from each assessment period with the data from the baseline assessment. We calculated the regularity and mean area of hip vs. knee cyclograms obtained at each assessment period (baseline, 6 and 12 weeks). We calculated the mean and standard deviations per assessment per subject and performed paired t-tests comparing the assessment means with the baseline means from all the participants. The p-value was calculated and a confidence interval of 95% was established to consider significance. After we calculated the mean of each group of 10 measurements per assessment of H-reflex peak to peak amplitudes at 10% Mmax, we normalized by obtaining the difference between each assessment mean to the baseline mean and dividing by the baseline mean. In order to find out whether the differences between H-reflex results from assessment sessions were significant, a one-way ANOVA and Fisher post-hoc tests were conducted in the normalized H-reflex data. Aiming to investigate whether the MVC and M-max values remained stable throughout the training, a one-way ANOVA and Fisher post-hoc tests were conducted in the normalized MVC and M-max data. All statistics analyses were conducted using Statistica (StatSoft, Tulsa, OK, USA, 2010). The kinematic and EMG data from the assessment sessions were averaged point by point and the standard deviation was calculated. The results were then plotted and visually compared to those obtained at baseline.

2.3. RESULTS

All the participants completed 60 sessions (at least three per week) of one hour of FES-assisted arm and leg cycling. Clinical, biomechanical and electrophysiological assessments were conducted to evaluate the effects of a novel FES-assisted arm and leg cycling training paradigm on overground walking of five subjects with iSCI. We present here descriptive analysis of the results. To the best of our knowledge, this presents the first systematic delivery of the effects of a combined arm and leg training paradigm for the improvement of ambulation in people with iSCI.

2.3.1. CLINICAL OUTCOMES FOLLOWING FES-ASSISTED ARM AND LEG CYCLING

Evaluation at baseline according to the AIS indicated severe impairments in light touch sensation and the differentiation of sharp/dull sensation for all subjects. The maximal total score was 104 points: 26 per assessment, per side. Interestingly, after 12 weeks of training, all but subject #3 improved their sensory scores, with differences ranging from -4 to 39 (figure 2-1A). We performed a Wilcoxon matched pairs test comparing baseline to post-training and found that these improvements were not significant (p=0.08). The mean improvements are similarly distributed for both sides and both aspects evaluated (figure 2-1C). Subject #3 presented improvements in the pin prick testing: 7 points for the right and 3 points for the left. We observed the reduced scores in this individual in the light touch testing: -5 points for the right and -9 points for the left (figure 2-1E). The improvements in sensory scores were unanticipated and may have been limited to the dermatomes around muscles receiving electrical stimulation. Hence, we classified each of the evaluated dermatomes by whether they received electrical stimulation or not for each subject. Surprisingly, the sensory scores improved in many dermatomes regardless of stimulated locations (figure 2-1D). We asked whether the changes post-training in stimulated dermatomes and in non-stimulated dermatomes were significantly higher. After analyzing the results with a Wilcoxon matched pairs test we found that these changes were not significant for either group.

The motor scores according to the AIS at baseline indicated impairments in specific muscles for each individual. Post-training, the motor scores improved in all but subject #1, with differences ranging from -3 to 27(figure 2-1B). We performed a Wilcoxon matched pairs test comparing baseline to post-training and found that improvements were not significant (p=0.14). For subject #1, out of a total possible motor score of 50 points per side (5 points per muscle), the volunteer scored 46 for the right (all muscles graded 5, except for the hip flexors with 4 and knee extensors with 2) pre-training, and 47 for the left (all muscles graded 5, except for the hip flexors with 3 and long toe extensors with 4) (figure 2-1F). Pronounced hyperactivity was observed in the left ankle plantarflexor during the baseline evaluation. Following 12 weeks of FES-assisted arm and leg cycling, no change was measured on the right side whereas on the left side a reduction to 44 points (3 points reduction) was observed. Along with this reduction, an improvement in range of motion in the ankle and hip was reported anecdotally due to a decrease in the contracture in ankle plantar-flexor and hip flexorwhich resulted in the inability to move through the new range with the same strength and a reduced score for these two muscle groups.

At baseline, the mean Berg Balance Scale score was 30 out of a total possible score of 56. After 12 weeks of arm/leg cycling, the mean Berg Balance Scale score was 35 with changes ranging from -2 to 15 (figure 2A). We observed individual results and found that four out of five subjects improved their balance. Without considering subject 5 who did not improve the balance score, we performed a Wilcoxon matched pairs test comparing baseline to post-training and found that improvements were not significant (p=0.07). Although it is not included in the Berg Balance Scale, we observed an improvement in the upright posture of subjects #1 and #3 while walking and standing. Figure 2B shows pre and post training pictures of one of the subjects.

We assessed the need for assistive devices using the WISCI II scale. At baseline, all five subjects were at least able to walk with two crutches, no brace and no physical assistance. After 12 weeks, only two subjects improved and required less assistance to ambulate. Before training, these individuals were capable and felt safe to walk for 10 m with no devices, no braces and with physical assistance of one person (score=17). After 12 weeks, they felt safe to try and walked for 10 m with just one crutch or cane, no braces and no physical assistance (score=19).Although the two points improvement according to the WISCI II is considered clinically significant (Musselman, 2007), the subjects who presented this change did not modify their regular mode of ambulation in the community.

At baseline, the mean walking speed over a 10 m track was 0.49±0.22 m/s and the distance walked for the 6-minute walking test was 175.48±62.46 m. After 3, 6, 9 and 12 weeks of training, we found improvements in the distance walked of a 6-minute walking test and in the walking speed of the 10-meter timed walking. We contrasted the data from each assessment period with the data from the baseline assessment. The changes were significant for each contrast (repeared measures ANOVA, p<0.0005). This suggests that significant changes in walking speed occurred as early as 3 weeks post-training. After 12 weeks of training, there was a significant improvement of 0.18 m/s (44±9%) ranging from 0.10 to 0.27 m/s in the 10-meter walking speed (repeated measures ANOVA, P<0.0005) and of 42.85 m (30±6%) ranging from 29.75 to 61.48 m in the walking endurance (repeated measures ANOVA, P<0.0005) (figures2-3). The change in the 10-meter walking speed was clinically significant, exceeding the minimally clinically important difference (MCID) of 0.06 m/s (Musselman, 2007). To the best of out knowedge, the MCID for the 6-minute walking test has only been estimated between 54 and 80 m for the population with pulmonary disease by obtaining the minimal change that the patients perceived as an improvement.Therefore, we calculated the standard error of the measurement (SEM) with the formula used by Musselman for the 10-meter walking test (2007):

$$SEM = s_x * \sqrt{1 - r_x}$$

Where s_x represents the baseline standard deviation (62.46 m) and $r_x$represents the reliability of the outcome measurewhich was previously calculated as 0.970 for a group of individuals with SCI (van Hedel, et al., 2005). The estimated SEM for the 6-minute walking test was 10.81 m. For all the subjects, the change in distance walked exceeded the SEM value.

2.3.2. Outcomes in the pattern of motor activation following FES-assisted arm and leg cycling

After 12 weeks of training, positive changes were observed in the pattern of muscle activation for all five subjects. We classified changes in two: 1) Improved intensity of the electromyography signal obtained during walking (figure 2-4A, 2-4B, 2-4D, 2-4E, 2-4G and 2-4H) and 2) improved pattern of activation of that specific muscle during walking better resembling what able-bodied gait produces (figures, 2-4B, 2-4D, and 2-4H).Although larger electromyography signal is not necessarily better, it can be interpreted as strengthening of the muscle. Our goal was to compare the pattern of muscle activation of the same individual after the training. Hence, we did not obtain any matched able bodied gait data and only display able bodied subjects' gait data obtained from Winter, D.A. (1991) as an example. By no means is this a standard for our participants. One limitation of using this data is the difference in the walking speed used by the healthy control subjects and our SCI participants. Furthermore, even if walking ability improved in our participants, they might be using a different strategy thanhealthy controls. Hence, the changes in the patterns in muscle activation can only be considered as positive in the light of other positive changes in the walking ability.

2.3.3. BIOMECHANICAL OUTCOMES FOLLOWING FES-ASSISTED ARM AND LEG CYCLING

We found diverse gait patterns within the group at baseline. As the training progressed, different strategies were adopted by each subject and shaped changes in their gait pattern. Therefore, we investigated whether there were any common elements in the improvements presented by the subjects. An interesting finding was that three subjects improved their foot clearance. In subjects 3, 4 and 5 the improvement in foot clearance coincides with increased muscle activity during the swing phase in leg muscles (figures 2-4C, 2-4F and 2-4I).

We classified the sides by more affected and less affected based upon their motor and sensory AIS scores. The mean regularity for the hip vs. knee angle cyclogram at baseline was 0.39 for both sides for all subjects. After 12 weeks of FES-assisted arm and leg cycling, the regularity improved significantly to 0.49 for the more affected side (paired t-test, p=0.0087) and 0.47 for the least affected (paired t-test, p=0.0038) (figures 2-5E &2-5F). The mean area of the hip vs. knee angle cyclogram at baseline was 0.20 deg^2 for the more affected and 0.21 deg^2 for the less affected. After 12 weeks of FES-assisted arm and leg cycling, the mean area improved to 0.25 deg^2 for the more affected side and 0.29 deg^2 for the less affected side. These changes were not significant according to a paired t-test (figures 2-5G &2-5H). Subject 4 had the largest improvement in area measurements for both sides and second largest in regularity for both sides (figures 2-5A to 2-5D).

2.3.4. Electrophysiological outcomes following FES-assisted arm and leg cycling

At baseline, the mean soleus H-reflex peak to peak amplitude at the stimulation intensity that produced a 10% of the maximal M-wave was 3.6 mV at rest and 4.2 mV with 20% MVC facilitation. At the 6-week assessment the H-reflex response was increased for three subjects at rest and for two with 20% MVC facilitation, this caused an increase in the mean. By the 12-week assessment, the H-reflex response was reduced significantly for all subjects under both conditions ranging from 0.3-2.2 mV reduction at rest and 0.4-2.1 mV reduction with facilitation (figures 2-6B and 2-6C). It can be concluded that the MVC remained stable throughout the training since it was only reduced by 0.06 mV ranging from -0.66 to 0.41 mV and this change was not significant (p=0.3747, ANOVA). On the contrary, the M-max measured at rest did not remain stable. Itwas significantly reduced by 0.0016 mV ranging from -0.0008 to -0.0020 mV (p<0.05, one-way ANOVA).In order to understand better the nature of the reduction in the H-reflex response at rest, we analyzed the change in two factors of the H-M recruitment curve: the H-max/M-max ratiowhich indicates changes in amplitude of the H-reflex relative to M-maxand the %Mmax@Hmaxwhich indicates a shift in the H-M recruitment curve (figure 2-6D). The H-max/M-max ratio was reduced significantly by 0.0979 mV ranging from -0.0760 to -0.1127 mV after 12 weeks of FES-assisted arm and leg cycling (p<0.05, ANOVA). The %Mmax@Hmax did not change significantly (p=0.2073, ANOVA).

2.4. Discussion

Our goal was to evaluate the efficacy of involving the arms along with the legs in a rehabilitation paradigm to improve walking after iSCI. We hypothesized that a new training paradigm which consists of FES-assisted arm and leg cycling would improve walking after chronic iSCI and investigated some of the mechanisms that led to the improvements. We found improvements in over ground walking speed, endurance, balance and the need for assistive devices. We also measured improvements in the foot clearance and the pattern of motor activation for leg muscles involved in walking. In addition, we measured reductions in the excessive excitability of H-reflex. Various mechanisms can account for the aforementioned improvements which will be discussed in the following section.

2.4.1. LIMITATIONS

There are several limitations to our study. First, we have a small number of participants and so our results cannot be generalized until they are replicated in a larger sample. Another important limitation of this study is the lack of blinding in general since the same researchers involved in the assessments were involved in the training sessions. We did not have a blinded physical therapist for the clinical testing which seems more susceptible to bias. The participants were aware that the goal of the research was to study walking and this might have influenced their expectations and motivation. We did not study the strength of other musclesinvolved in walking such as hip flexors.In the future, the same methodology used for MVC testing could be applied to other muscles. Finally, our comparisons were made within each subject. Therefore, we were not able to assess the effect of any exercise versus FES-assisted arm and leg cycling.

2.4.2. TRAINING PARADIGM

Humans engage in different forms of locomotion that involve the coordination of arms and legs (e.g. crawling, cycling, swimming, rowing, walking and running). Across walking, arm and leg cycling and arm-assisted recumbent stepping there is a strong correlation which supports the existence of a common neural network as the regulator of arm and leg rhythmic movements (E. Zehr, et al., 2007). Our goal was to activate this common neuronal network through an exercise that involved both the arms and the legs. Other forms of rhythmic movements like arm swing during walking, stair climbing, and recumbent stepping require an upright posture which is not possible for some individuals with iSCI. On the contrary, arm and leg cycling can be performed while sitting which is a secure, comfortable position for people with spinal cord injury. Furthermore, one session of leg cycling training significantly increased walking speed in incomplete spinal cord injured participants by 12%(Phadke et al., 2009). Therefore, we chose arm and leg coordinated cycling as the best intervention to involve arms and legs for the rehabilitation of walking after iSCI,

FES has been widely used to increase muscle mass (Baldi, et al., 1998), reduce bone density loss(Frotzler, et al., 2008), and improve cardiovascular health after SCI (Davis, et al., 2008). Page and colleagues reported that ten weeks of a cycling intervention assisted with electrical stimulation exclusively on the legs, helped a subject with iSCI improve motor scores, mean gait velocity, and WISCI II score (Page, et al., 2007). In this study, we used FES to assist five subjects with spinal cord injury in the generation of arm and leg cycling. The baseline mean walking speed of our participants is similar to the baseline walking speed of the subject in the former study (0.49±0.22 m/s vs. 0.47 m/s). The improvements in our group are smaller than the improvements in their subject (0.18 ±0.03 vs. 0.33), but this effect could be attributed to individual differences since their subject had a lower lesion than any of our participants.

2.4.3. Effect of FES-assisted arm and leg cycling on sensation.

The distribution of theimprovements in sensation was unexpected.Although the changes in sensation according to the AIS were not significant, the fact that they were present not only in those areas of the body over which stimulation was delivered, but also in non-stimulated dermatomes is interesting and worthy of further investigation. In participants with iSCI, the use of FES applied to the common peroneal nerve (fibular nerve) for assisting in dorsiflexion improved locomotor speed even after the cessation of stimulation, indicating that FES can induce long lasting changes in the nervous system (Stein, et al., 2006). This phenomenon may be attributed to the electrical stimulation of both, motor nerves causing a muscular contraction, as well cutaneous and proprioceptive sensory fibers. Sensory activation during FES-assisted exercise involves stretch and load receptors whose afferents project not only to cortical networks, but also synapse into propriospinal networks. These propriospinal networks may be responsible for a global response to the FES-assisted exercise and therefore an increase in sensory scores of non-stimulated regions of the body. Furthermore, the vigorous activity in the whole body resulting from the FES-assisted exercise not only induces a sensory input to the spinal cord from arm and leg regions, but to other regions as well.

2.4.4. Effect of FES-assisted arm and leg cycling on motor scores

The mean motor performance evaluated using the ASIA scale improved by 8 points. These improvements were not significant, suggesting that muscle strength according to AIS scale assessment cannot not be considered as the only mechanism for the improvements in walking speed. Especially considering the changes in reflex excitability and balance. In particular, for one subject, we found an apparent reduction of the score of the left ankle dorsiflexor (or L4 segment), and a reduction in the muscular contracture of the ankle plantarflexors which resulted in a larger range of motion (ROM). Testing for motor scores using a higher ROM of the ankle could have caused the dorsiflexor muscles to appear weaker and obtain a lower score. Unfortunately, the AIS motor score is inaccurate if an external condition, in this case, a change in the ROM, affects the muscle's ability to produce a normal (Grade 5) contraction. Bearing that fact in mind, we identify a limitation in the only use of the AIS for assessing motor performance. We propose that the ROM and isometric muscle contraction force be measuredadditionally.

2.4.5. Effect of FES-assisted arm and leg cycling on balance.

Interestingly, the balance improved substantially. Although the changes in balance were not statistically significant, for three subjects they exceeded the minimal clinically important difference for the Berg Balance Scale for stroke of 6 points (Stevenson, 2001)and reported noticeable changes in balance during their daily activities. This was an unanticipated finding since the training did not involve an upright posture. Increases in muscular strength could explain partially the improvements in balance, but we found that in the arm and leg muscles, these were not significant according to the AIS assessment. We did not evaluate changes in the strength of axial muscles which may have contributed to the improvement of balance and walking as well. The interaction within the cervical, thoracic and lumbar spinal neuronal networks of coordinated sensory inputs (e.g. load, stretch and electrical stimulation) provided by arm/leg FES-assisted cycling may have strengthened such networks and enhanced walking and postural responses. The effect of such coordinated sensory inputs is evident in the improvements in sensation that took place. In subject #1, the improvement in balance coincides with the reduction in plantarflexor hyperactivity which suggests another mechanism for the improvement in balance.

2.4.6. Effect of FES-assisted arm and leg cycling on walking speed.

Finally, the walking speed (10-meter walking) and distance walked (6-minute walking) improved. For this group of individuals, the improvement in muscular strength was not significant. This finding, together with the improvement in regulation of spinal reflexes (e.g., reduction in H-reflex hyperexcitability) suggests that walking improved due to a reorganization of spinal circuits triggered by the sensory inputs provided by the training. The mean walking speed improved consistently over the training period. The small improvements in walking speed during the first weeks of the intervention and the apparent reduction seen during the 9-week assessment may be due to the development of a new strategy for walking which required conditioning and strengthening of various muscle groups before it could translate into faster walking. Improvements in endurance were consistent over the assessment periods and may be the result of better cardiovascular health as a result of the FES-assisted exercise as has been shown elsewhere (Davis, et al., 2008).

The positive results in this group of individuals suggest that even years after SCI and active participation in walking-related interventions (e.g., treadmill training or overground walking exercises) a ceiling effect in walking ability has not been reached; and there is still an opportunity for improvement. This is particularly relevant in Subject #1 who was a very active individual and exercised daily at home by walking on a treadmill. The uniqueness of the training paradigm used in this study is that it systematically engages other networks (i.e., arms) that have not been involved in locomotor rehabilitation before.

Bearing in mind the encouraging results from this pilot study, a study with a larger number of participants with iSCI undergoing the same paradigm is needed to corroborate the efficacy of involving the arms along with the legs. The mechanisms underlying the improvements in walking are likely related to induced plasticity in spinal neuronal networks involved in walking due to changes in H-reflex excitabilityIf the positive changes in walking ability are confirmed by a larger study, we propose that this paradigm could also be beneficial for individuals with traumatic brain injury or stroke.

The results from this study suggest that involving the arms along with the legs in rehabilitation of walking is effective, but its advantage over interventions where only the legs are actively involved remains unknown. Other questions remain unanswered by this pilot study. For instance, is the efficacy of FES-assisted arm and leg cycling in improving walking better than FES-assisted leg cycling alone? Also, is FES-assisted arm and leg cycling as effectiveaslocomotor rehabilitation techniques currently in practice for improving walking? Despite the fact that we used validated clinical tests for spinal cord injury, we cannot compare our results to those from other interventions for rehabilitation of walking. This is due to differences in the duration of the intervention and in the methods used to evaluate outcomes between different interventions. In order to perform systematic comparisons with results from other rehabilitation strategies for walking after iSCI such as body weight-supported treadmill training and conventional overgroundlocomotor training (Dobkin et al., 2003), larger studies may be needed.

This training paradigm could be readily applied in the clinic because the equipment required is available in most rehabilitation centres. A key advantage of using FES-assisted cycling for the rehabilitation of walking is that it only requires one physical therapist for setting up and assistance compared to traditional locomotor training which requires three or even four therapists to deliver. Therefore, effective therapy could be delivered to more clients with the same staff resource.

2.5. FIGURES AND TABLES

Participant #	Age (yrs.)	Sex	Time post injury (yrs.)	Level of injury	ASIA impairment scale	Mode of ambulation
1	46	M	9	T10	D	Crutches
2	58	M	40	C5-C6	C	Walker
3	61	M	2	C3-C5	D	Wheelchair
4	50	M	13	C6-C7	C	Wheelchair
5	49	F	6	C2-C4	D	Wheelchair

Table 2-1: Study participants. Characteristics of the five subjects involved in the study. The mode of ambulation refers to the one used for daily activities prior to the participation in the study.

Participant #	Stimulated arm muscles	Stimulated leg muscles	Ergometer used
1	none	Quadriceps, Hamstrings, Gluteus	Custom-made ergometer
2	none	Quadriceps, Hamstrings, Gluteus	Custom-made ergometer
3	Biceps brachii, Triceps, Rhomboids	Quadriceps, Hamstrings, Tibialis Anterior	RT200
4	none	Quadriceps, Hamstrings, Gluteus	Berkelbike
5	none	Quadriceps, Hamstrings, Gluteus	Custom-made ergometer

Table 2-2: Characteristics of the training. Stimulation was delivered to different arm and leg muscles as needed per subject. Two commercially available arm and leg ergometers and one custom-made arm and leg ergometer were used to deliver the training.

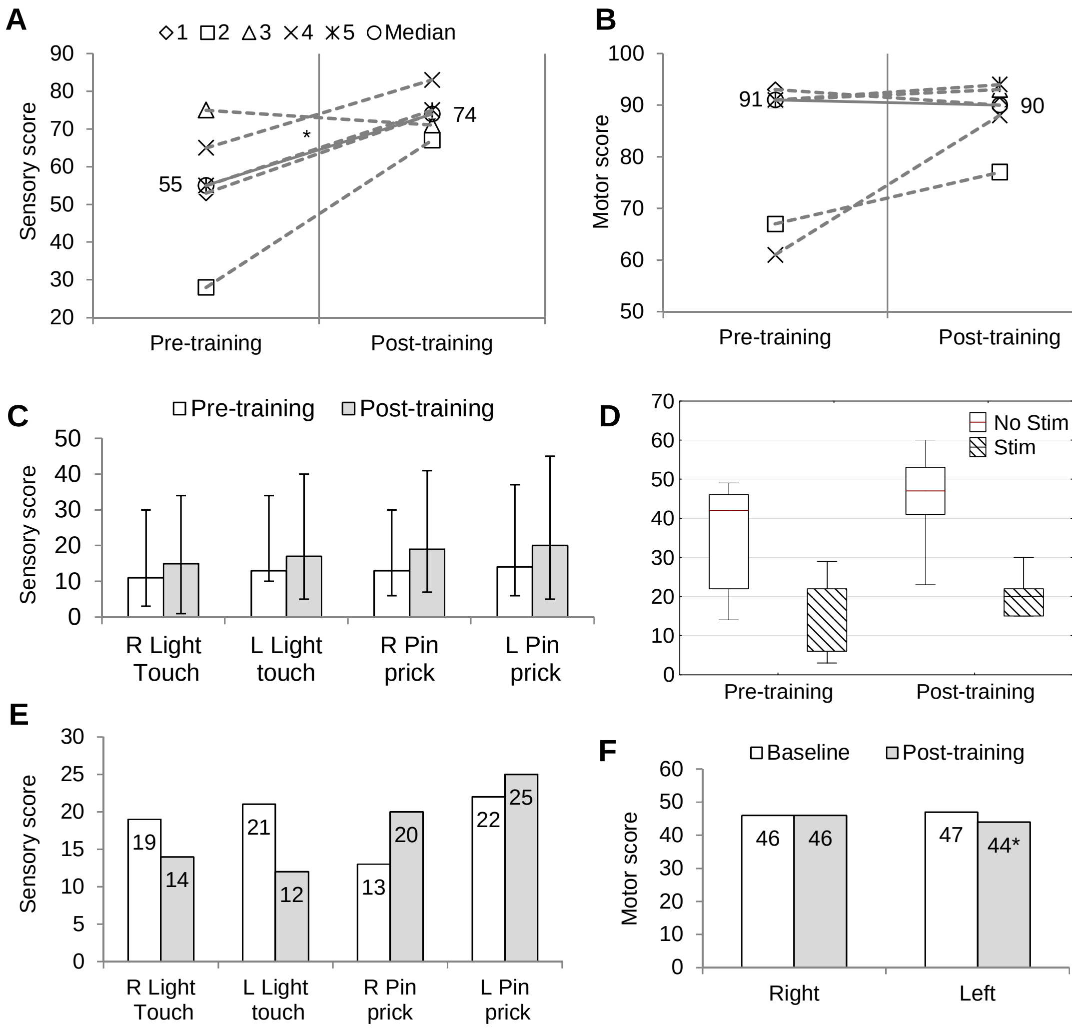


Figure 2-1: ASIA sensory and motor scores. A. Individual results from the ASIA sensory evaluation and group median indicated by solid line. N=5. Maximal score per subject = 104. B. Individual results from the ASIA motor evaluation and group median indicated by solid line. N=5. Maximal score per subject =100. C. ASIA sensory scores on both sides separated by the specific test and side. Bar height (median), error bars (range). D. ASIA sensory scores on both sides separated by stimulated and non-stimulated regions. Line (median), box (25%-75%), whiskers (range) N=5. Some of the dermatomes that improved in the sensory assessment were not in the stimulated areas. E. Subject #3. ASIA sensory evaluation indicates improvements on both sides for pin prick test, but a reduction in score for light touch test. F. Subject #1. ASIA motor evaluation. *Indicates contracture in left ankle plantarflexor.

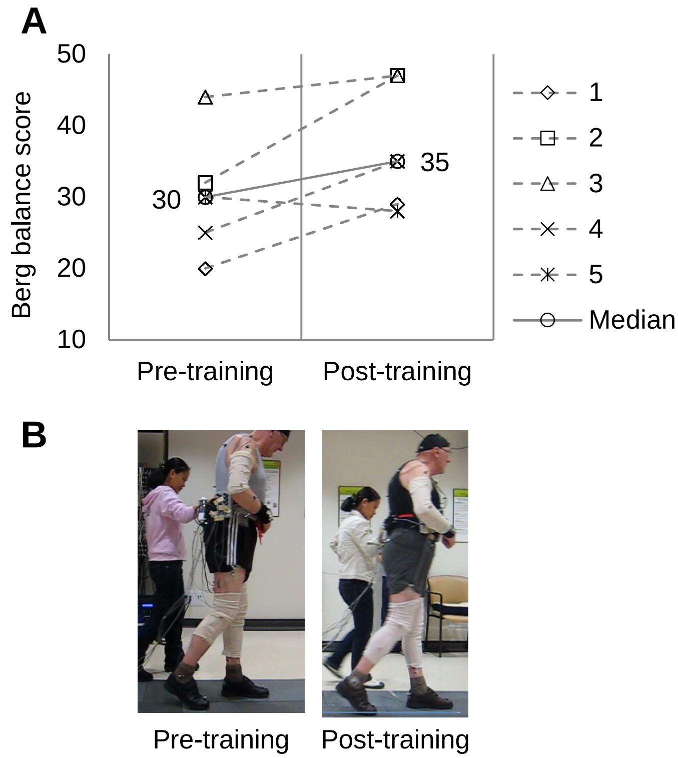


Figure 2-2: Balance. A. Individual balance measurements according to Berg Balance score. Group median indicated by solid line B. Pictures of one subject who improved his upright posture taken during kinematic gait analysis.

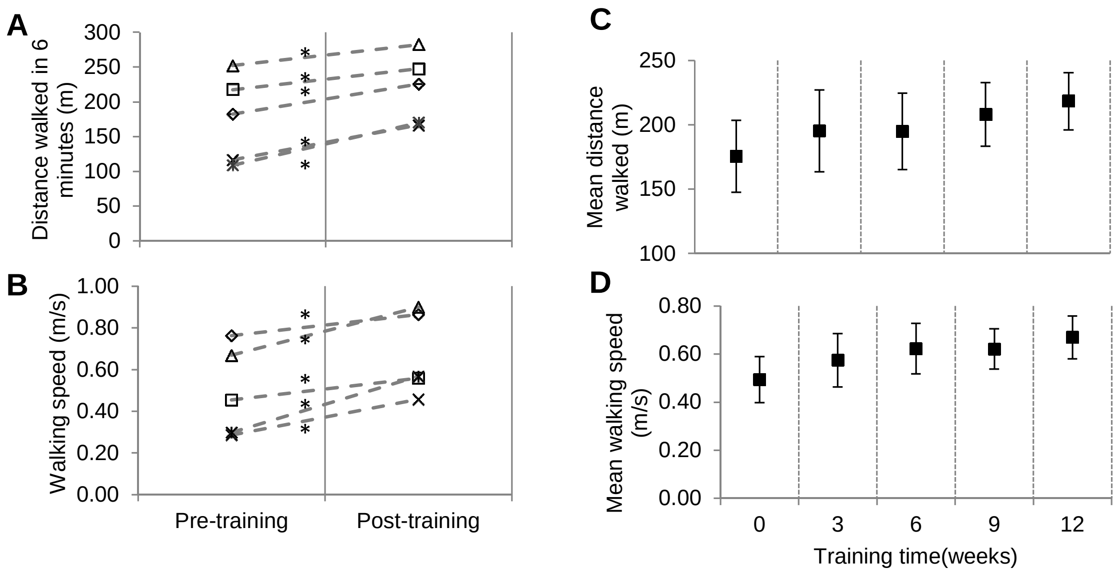


Figure 2-3: Walking speed. A. Individual distances walked measured during an endurance test of 6 minutes. All subjects improved significantly. B. Individual walking speeds measured during the 10-meter walking test. All subjects improved significantly. C. Mean distance walked ± s.e. measured during an endurance test of 6 minutes. Significant improvements of 30±6% after 12 weeks were measured. N=5. p<0.05 (paired t-test, P=0.00021). D. Mean walking speed ± s.e. measured during the 10-meter walking test. Significant improvements of 44±9% after 12 weeks were measured. N=5. p<0.05 (paired t-test, P=0.0063).

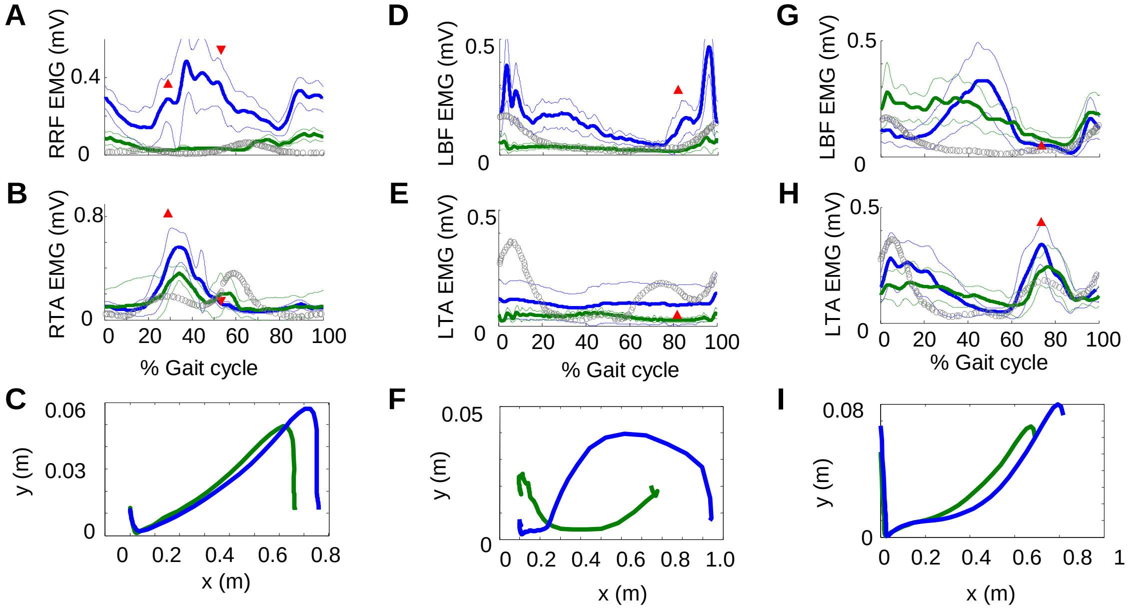


Figure 2-4. Muscle activation pattern and foot clearance. For all figures the green trace is the pre-training measurement and the blue trace indicates the post-training measurement. The grey trace indicates the able-bodied data (Winter, 1991).A. Subject # 5. Activity in the right rectus femoris improved post-training. B. Subject # 5. Activity in the right tibialis anterior improved post-training. C. Subject #5. Improvements in muscle activation patterns coincide with an improvement in the right foot clearance and step length. D. Subject # 4. Activity in the left biceps femoris improved post-training. E. Subject # 4. Activity in the left tibialis anterior improved post-training. F. Subject #4. Improvements in muscle activation patterns coincide with an improvement in the left foot clearance and step length. G. Subject # 3. Activity in the left biceps femoris improved post-training. H. Subject # 3. Activity in the left tibialis anterior improved post-training. I. Subject #3. Improvements in muscle activation patterns coincide with an improvement in the left foot clearance and step length.

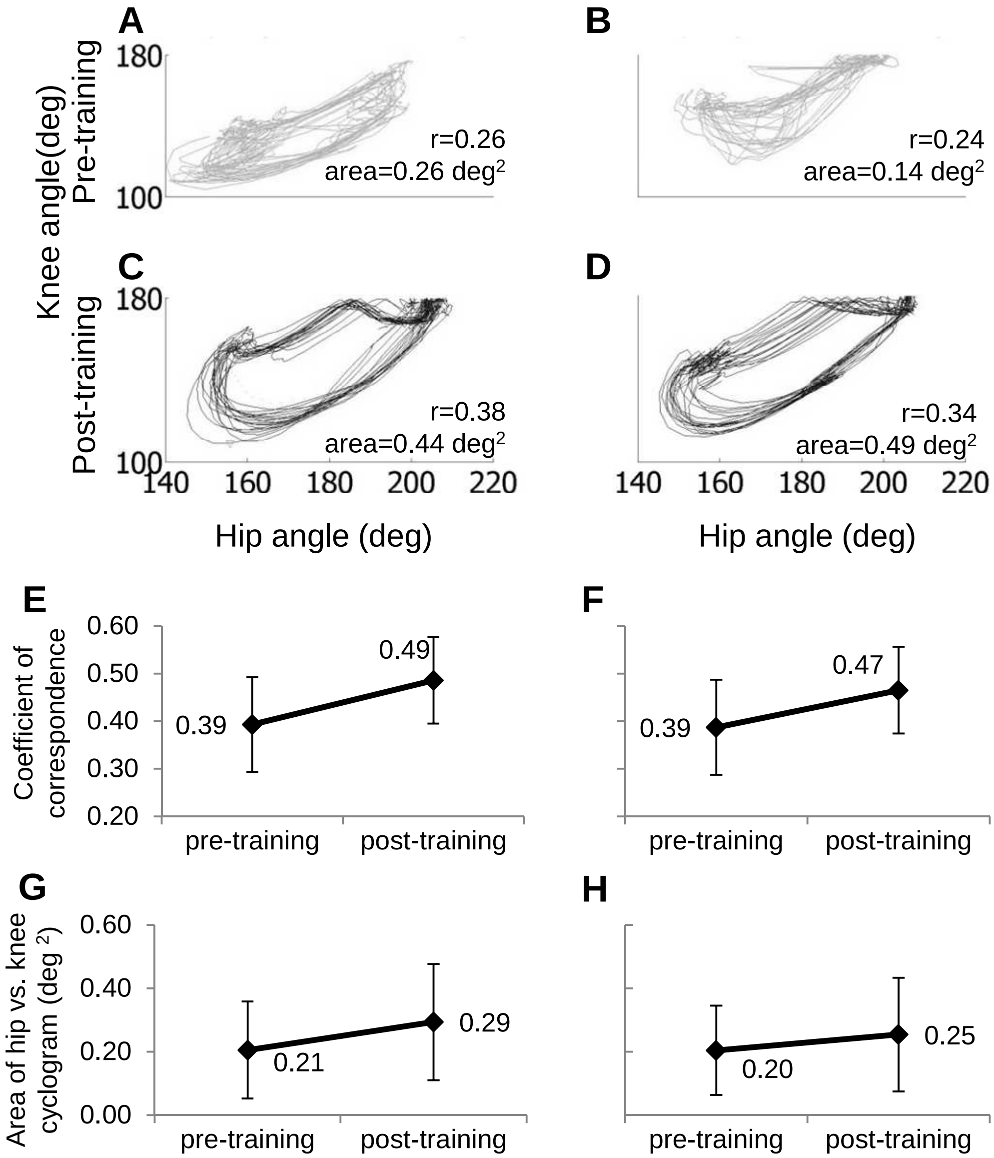


Figure 2-5: Walking regularity. A. Subject #4 Left hip vs. knee cyclogram for one participant walking with crutches at baseline. B. Subject #4 Right hip vs. knee cyclogram for one participant walking with crutches at baseline. C. Subject #4 Left hip vs. knee cyclogram for one participant walking with crutches post-training. D. Subject #4 Right hip vs. knee cyclogram for one participant walking with crutches post-training. r=coefficient of correspondence. E. Improved intersegmental coupling post training for the more affected side was measured. Mean±s.d. N=5. F. Improved intersegmental coupling post training for the less affected side was measured. Mean±s.d. N=5. G. Improved mean area of hip vs. knee cyclogram post

training for the more affected side was measured. Mean±s.d. N=5. H. Improved mean area of hip vs. knee cyclogram post training for the less affected side was measured. Mean±s.d. N=5.

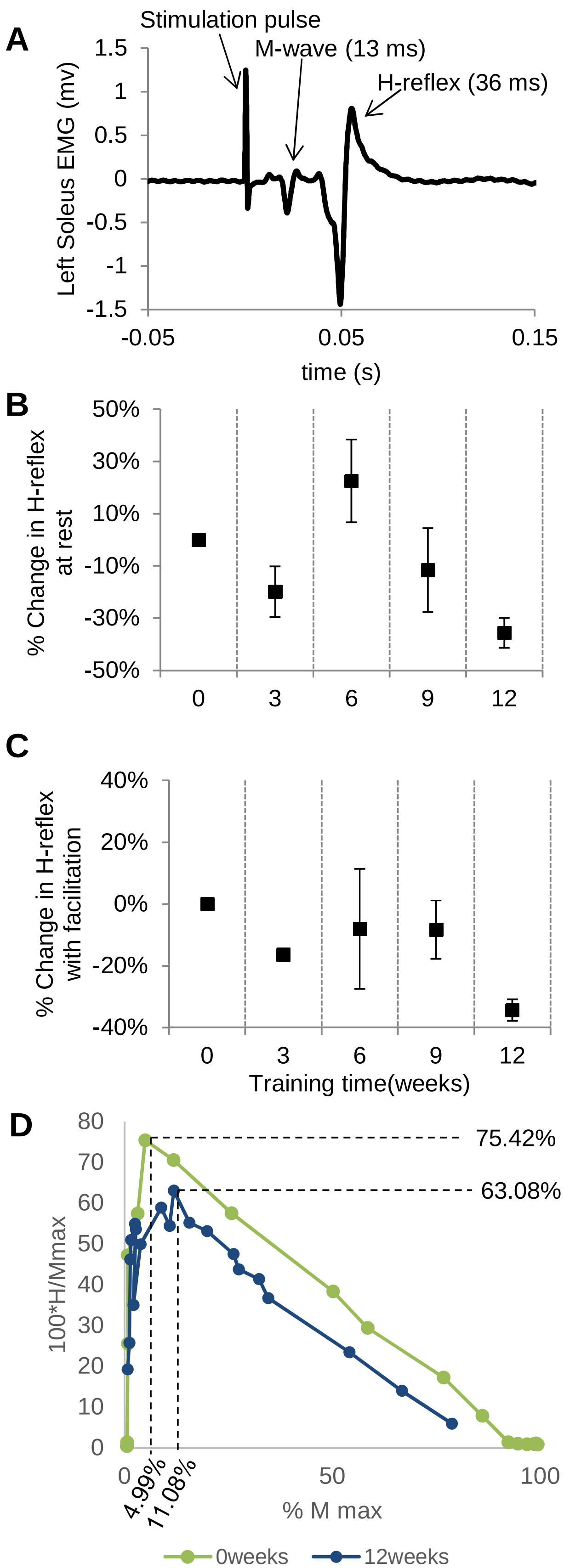

A
Stimulation pulse
M-wave (13 ms)
H-reflex (36 ms)
Left Soleus EMG (mv)
1.5
1
0.5
0
-0.5
-1
-1.5
-0.05
0.05
0.15
time (s)
B
% Change in H-reflex at rest
50%
30%
10%
-10%
-30%
-50%
0
3
6
9
12
C
% Change in H-reflex with facilitation
40%
20%
0%
-20%
-40%
0
3
6
9
12
Training time(weeks)
D
100*H/Mmax
80
70
60
50
40
30
20
10
0
75.42%
63.08%
0
50
100
4.99%
11.08%
% M max
0weeks
12weeks

Figure 2-6: H-reflex response. A. Subject#5. Raw EMG activity of left soleus muscle showing H-reflex response (latency indicated in parenthesis) and M-wave (latency indicated in parenthesis) at 10% of M – max. B. Significant reduction in H-reflex peak to peak amplitudes at rest normalized to baseline was observed. Mean±s.e., N=4. $p<0.05$ C. Significant reduction in H-reflex peak to peak amplitudes with muscle activation of 20%MVC normalized to baseline was observed. Mean±s.e, N=4. $p<0.05$. D. Subject#4. H/Mmax plotted against the corresponding percentage of Mmax. In this case, we observed a reduction in the Hmax relative to Mmax and a shift of the H-M recruitment curve to the right which suggests a reduction in the excitability of the H-reflex.

2.6. BIBLIOGRAPHY

Abe, Y., Yamamoto, T., Sugiyama, Y., Watanabe, T., Saito, N., Kayama, H., et al. (1999). Apoptotic cells associated with Wallerian degeneration after experimental spinal cord injury: a possible mechanism of oligodendroglial death. *J Neurotrauma, 16*(10), 945-952.

Agrawal, S. K., & Fehlings, M. G. (1997). The effect of the sodium channel blocker QX-314 on recovery after acute spinal cord injury. *J Neurotrauma, 14*(2), 81-88.

Akay, T., McVea, D. A., Tachibana, A., & Pearson, K. G. (2006). Coordination of fore and hind leg stepping in cats on a transversely-split treadmill. *Exp Brain Res, 175*(2), 211-222.

Alexander, M. S., Anderson, K. D., Biering-Sorensen, F., Blight, A. R., Brannon, R., Bryce, T. N., et al. (2009). Outcome measures in spinal cord injury: Recent assessments and recommendations for future directions. *Spinal Cord, 47*(8), 582-591.

Alon, G., Kantor, G., & Ho, H. S. (1994). Effects of electrode size on basic excitatory responses and on selected stimulus parameters. *J Orthop Sports Phys Ther, 20*(1), 29-35.

Anderson, K. (2004). Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma, 21*(10), 1371-1383.

Ates, O., Cayli, S. R., Gurses, I., Turkoz, Y., Tarim, O., Cakir, C. O., et al. (2007). Comparative neuroprotective effect of sodium channel blockers after experimental spinal cord injury. *Journal of Clinical Neuroscience, 14*(7), 658-665.

Baldi, J. C., Jackson, R. D., Moraille, R., & Mysiw, W. J. (1998). Muscle atrophy is prevented in patients with acute spinal cord injury using functional electrical stimulation. *Spinal Cord, 36*(7), 463-469.

Ballion, B., Morin, D., & Viala, D. (2001). Forelimb locomotor generators and quadrupedal locomotion in the neonatal rat. *Eur J Neurosci, 14*(10), 1727-1738.

Banovac, K., & Sherman, A. L. Spinal Cord Injury Rehabilitation *Rothman-Simeone The Spine* (6th ed.). St. Louis, MO: W.B. Saunders Company.

Barbeau, H. (2003). Locomotor Training in Neurorehabilitation: Emerging Rehabilitation Concepts. *Neurorehabilitation and Neural Repair, 17*(1), 3-11.

Barsi, G., Popovic, D., Tarkka, I., Sinkjaer, T., & Grey, M. (2008). Cortical excitability changes following grasping exercise augmented with electrical stimulation. *Exp Brain Res, 191*(1), 57-66.

Bastian, H. C. (1890). On the Symptomatology of Total Transverse Lesions of the Spinal Cord; with special reference to the condition of the various Reflexes. *Med Chir Trans, 73*, 151-217.

Bauchet, L., Lonjon, N., Perrin, F. E., Gilbert, C., Privat, A., & Fattal, C. (2009). Strategies for spinal cord repair after injury: A review of the literature and information. *Annals of Physical and Rehabilitation Medicine, 52*(4), 330-351.

Beattie, M. S. (2004). Inflammation and apoptosis: linked therapeutic targets in spinal cord injury. *Trends Mol Med, 10*(12), 580-583.

Beattie, M. S., Shuman, S. L., & Bresnahan, J. C. (1998). Apoptosis and spinal cord injury. *Neuroscientist, 4*(3), 163-171.

Behrman, A. L., & Harkema, S. J. (2000). Locomotor Training After Human Spinal Cord Injury: A Series of Case Studies. *Physical Therapy, 80*(7), 688-700.

Berg, K., Wood-Dauphinee, S., Williams, J., & Maki, B. Measuring balance in the elderly: validation of an instrument. *Can J Public Health, 83 Suppl 2*, S7-11.

Bracken, M. B., Shepard, M. J., Holford, T. R., Leo-Summers, L., Aldrich, E. F., Fazl, M., et al. (1997). Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *JAMA, 277*(20), 1597-1604.

Bradbury, E. J., & Carter, L. M. (2011). Manipulating the glial scar: Chondroitinase ABC as a therapy for spinal cord injury. *Brain Research Bulletin, 84*(4-5), 306-316.

Brandell, B. R. (1986). The study and correction of human gait by electrical stimulation. *Am Surg, 52*(5), 257-263.

Brittis, P. A., & Flanagan, J. G. (2001). Nogo domains and a Nogo receptor: implications for axon regeneration. *Neuron, 30*(1), 11-14.

Bureau of Labor Statistics. (2012-13). Occupational Outlook Handbook, 2012-13 Edition. from U.S. Department of Labor: http://www.bls.gov/ooh/healthcare/physical-therapists.htm

Butland, R. J., Pang, J., Gross, E. R., Woodcock, A. A., & Geddes, D. M. (1982). Two-, six-, and 12-minute walking tests in respiratory disease. *Br Med J (Clin Res Ed), 284*(6329), 1607-1608.

Bélanger, M., Stein, R. B., Wheeler, G. D., Gordon, T., & Leduc, B. (2000). Electrical stimulation: Can it increase muscle strength and reverse osteopenia in spinal cord injured individuals? *Archives of Physical Medicine and Rehabilitation, 81*(8), 1090-1098.

Carlson-Kuhta, P., Trank, T. V., & Smith, J. L. (1998). Forms of forward quadrupedal locomotion. II. A comparison of posture, hindlimb kinematics, and motor patterns for upslope and level walking. *J Neurophysiol, 79*(4), 1687-1701.

Chang II Park, J. C. S., Deog Young Kim. (2000). Role of arm swing on gait. *Gait and Posture, 11*(2), 164-165.

Charteris, J. (1982). Human gait cyclograms: conventions, speed relationships and clinical applications. *Int J Rehabil Res, 5*(4), 507-518.

Chen, S.-C., Lai, C.-H., Chan, W. P., Huang, M.-H., Tsai, H.-W., & Chen, J.-J. J. (2005). Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. *Disability and Rehabilitation, 27*(22), 1337-1341.

Christopher and Dana Reeve Foundation. (2009). One Degree of Separation: Paralysis and Spinal Cord Injury in the United States.

CI Park, J. S., DY Kim. (2000). Role of arm swing on gait. *Gait and Posture, 11*(2), 164-165.

Citterio, A., Franceschini, M., Spizzichino, L., Reggio, A., Rossi, B., & Stampacchia, G. (2004). Nontraumatic spinal cord injury: An Italian survey. *Archives of Physical Medicine and Rehabilitation, 85*(9), 1483-1487.

Collins, S. H., Adamczyk, P. G., & Kuo, A. D. (2009). Dynamic arm swinging in human walking. *Proceedings of the Royal Society B: Biological Sciences*, -.

Colombo, G., Joerg, M., Schreier, R., & Dietz, V. (2000). Treadmill training of paraplegic patients using a robotic orthosis. *Journal of Rehabilitation Research & Development, 37*(6), 693.

Courtine, G., Gerasimenko, Y., van den Brand, R., Yew, A., Musienko, P., Zhong, H., et al. (2009). Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. *Nat Neurosci, 12*(10), 1333-1342.

Davis, G., Hamzaid, N., & Fornusek, C. (2008). Cardiorespiratory, metabolic, and biomechanical responses during functional electrical stimulation leg exercise: health and fitness benefits. *Artif Organs, 32*(8), 625-629.

De Leon, R. D., Hodgson, J. A., Roy, R. R., & Edgerton, V. R. (1999). Retention of hindlimb stepping ability in adult spinal cats after the cessation of step training. *J Neurophysiol, 81*(1), 85-94.

Delekate, A., Zagrebelsky, M., Kramer, S., Schwab, M. E., & Korte, M. (2011). NogoA restricts synaptic plasticity in the adult hippocampus on a fast time scale. *Proceedings of the National Academy of Sciences, 108*(6), 2569-2574.

Dietz, V. (2002). Do human bipeds use quadrupedal coordination? *Trends in Neurosciences, 25*(9), 462-467.

Dietz, V. (2011). Neuronal plasticity after a human spinal cord injury: Positive and negative effects. *Exp Neurol*.

Dietz, V., Fouad, K., & Bastiaanse, C. M. (2001). Neuronal coordination of arm and leg movements during human locomotion. *European Journal of Neuroscience, 14*(11), 1906-1914.

Dietz, V., & Harkema, S. J. (2004). Locomotor activity in spinal cord-injured persons *J Appl Physiol* (Vol. 96, pp. 1954-1960). United States.

Dietz, V., & Sinkjaer, T. (2007). Spastic movement disorder: impaired reflex function and altered muscle mechanics. *The Lancet Neurology, 6*(8), 725-733.

Dittuno, P. L., Ditunno, J. F., & Dittuno, J. F. (2001). Walking index for spinal cord injury (WISCI II): scale revision. *Spinal Cord, 39*(12), 654-656.

Ditunno, J. F., Ditunno, P. L., Graziani, V., Scivoletto, G., Bernardi, M., Castellano, V., et al. (2000). Walking index for spinal cord injury (WISCI): an international multicenter validity and reliability study. *Spinal Cord, 38*(4), 234-243.

Ditunno Jr, J. F., Barbeau, H., Dobkin, B. H., Elashoff, R., Harkema, S., Marino, R. J., et al. (2007). Validity of the walking scale for spinal cord injury and other domains of function in a multicenter clinical trial. *Neurorehabilitation and Neural Repair, 21*(6), 539-550.

Ditunno, P. L., Patrick, M., Stineman, M., & Ditunno, J. F. (2008). Who wants to walk? Preferences for recovery after SCI: a longitudinal and cross-sectional study. *Spinal Cord, 46*(7), 500-506.

Dobkin , B. H. (2006). Short-distance walking speed and timed walking distance: Redundant measures for clinical trials? *Neurology, 66*(4), 584-586.

Dobkin, B. H. (2006). Short-distance walking speed and timed walking distance: Redundant measures for clinical trials? *Neurology, 66*(4), 584-586.

Dobkin , B. H., Apple, D., Barbeau, H., Basso, M., Behrman, A., Deforge, D., et al. (2003). Methods for a randomized trial of weight-supported treadmill training versus conventional training for walking during inpatient rehabilitation after incomplete traumatic spinal cord injury. *Neurorehabil Neural Repair, 17*(3), 153-167.

Dobkin, B. H., Apple, D., Barbeau, H., Basso, M., Behrman, A., Deforge, D., et al. (2003). Methods for a randomized trial of weight-supported treadmill training versus conventional training for walking during inpatient rehabilitation after incomplete traumatic spinal cord injury. *Neurorehabil Neural Repair, 17*(3), 153-167.

Dobkin , B. H., & Duncan , P. W. (2012). Should body weight-supported treadmill training and robotic-assistive steppers for locomotor training trot back to the starting gate? *Neurorehabil Neural Repair, 26*(4), 308-317.

Dolbow, D. R., Gorgey, A. S., Daniels, J. A., Adler, R. A., Moore, J. R., & Gater Jr, D. R. (2011). The effects of spinal cord injury and exercise on bone mass: A literature review. *NeuroRehabilitation, 29*(3), 261-269.

Dryden, D. M., Saunders, L. D., Rowe, B. H., May, L. A., Yiannakoulias, N., Svenson, L. W., et al. (2003). The Epidemiology of Traumatic Spinal Cord Injury in Alberta, Canada. *The Canadian Journal of Neurological Sciences, 30*(2), 113-121.

Duffell, L., Donaldson, N. N., Perkins, T., Rushton, D., Hunt, K., Kakebeeke, T., et al. (2008). Long-term intensive electrically stimulated cycling by spinal cord-injured people: effect on muscle properties and their relation to power output. *Muscle Nerve, 38*(4), 1304-1311.

Dumont, R. J., Okonkwo, D. O., Verma, S., Hurlbert, R. J., Boulos, P. T., Ellegala, D. B., et al. (2001). Acute spinal cord injury, part I: pathophysiologic mechanisms. *Clin Neuropharmacol, 24*(5), 254-264.

Dunlop, S. (2008). Activity-dependent plasticity: implications for recovery after spinal cord injury. *Trends Neurosci, 31*(8), 410-418.

Eccles, J. C., Fatt, P., Landgren, S., & Winsbury, G. J. (1954). Spinal cord potentials generated by volleys in the large muscle afferents. *J Physiol, 125*(3), 590-606.

Elftman, H. (1939). The Function of the Arms in Walking. *Human Biology, 11*(4), 529-535.

Emery, E., Aldana, P., Bunge, M. B., Puckett, W., Srinivasan, A., Keane, R. W., et al. (1998). Apoptosis after traumatic human spinal cord injury. *J Neurosurg, 89*(6), 911-920.

Faden, A. I., & Simon, R. P. (1988). A potential role for excitotoxins in the pathophysiology of spinal cord injury. *Ann Neurol, 23*(6), 623-626.

Fairholm, D. J., & Turnbull, I. M. (1971). Microangiographic study of experimental spinal cord injuries. *J Neurosurg, 35*(3), 277-286.

Farry, A., & Baxter, D. (2010). The Incidence and Prevalence of Spinal Cord Injury in Canada., *Overview and estimates based on current evidence*: Rick Hansen Institute & Urban Futures.

Fernandez-Ballesteros, M. L., Buchthal, F., & Rosenfalck, P. (1965). The Pattern of Muscular Activity During the Arm Swing of Natural Walking. [10.1111/j.1748-1716.1965.tb04069.x]. *Acta Physiologica Scandinavica, 63*(3), 296-310.

Field-Fote, E. C., & Roach, K. E. (2011). Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial. *Phys Ther, 91*(1), 48-60.

Field-Fote, E. C., & Tepavac, D. (2002). Improved intralimb coordination in people with incomplete spinal cord injury following training with body weight support and electrical stimulation. *Phys Ther, 82*(7), 707-715.

Franken, H. M., Veltink, P. H., Ijzerman, M. J., Withaar, F. S., & Boom, H. B. (1997). The influence of voluntary upper body exercise on the performance of stimulated paralysed human quadriceps. *J Electromyogr Kinesiol, 7*(1), 67-77.

Frigon, A., Collins, D., & Zehr, E. (2004). Effect of rhythmic arm movement on reflexes in the legs: modulation of soleus H-reflexes and somatosensory conditioning. *J Neurophysiol, 91*(4), 1516-1523.

Frotzler, A., Coupaud, S., Perret, C., Kakebeeke, T., Hunt, K., Donaldson, N. N., et al. (2008). High-volume FES-cycling partially reverses bone loss in people with chronic spinal cord injury. *Bone, 43*(1), 169-176.

Gater Jr, D. R., Dolbow, D., Tsui, B., & Gorgey, A. S. (2011). Functional electrical stimulation therapies after spinal cord injury. *NeuroRehabilitation, 28*(3), 231-248.

Gensel, J. C., Donnelly, D. J., & Popovich, P. G. (2011). Spinal cord injury therapies in humans: an overview of current clinical trials and their potential effects on intrinsic CNS macrophages. *Expert Opin Ther Targets, 15*(4), 505-518.

Giulian, D., Vaca, K., & Corpuz, M. (1993). Brain glia release factors with opposing actions upon neuronal survival. *J Neurosci, 13*(1), 29-37.

Gordon, I. T., Dunbar, M. J., Vanneste, K. J., & Whelan, P. J. (2008). Interaction between developing spinal locomotor networks in the neonatal mouse. *J Neurophysiol, 100*(1), 117-128.

Gordon, I. T., & Whelan, P. J. (2008). Brainstem modulation of locomotion in the neonatal mouse spinal cord. *J Physiol, 586*(10), 2487-2497.

Graupe, D., & Kohn, K. (1998). Functional neuromuscular stimulator for short-distance ambulation by certain thoracic-level spinal-cord-injured paraplegics. *Surg Neurol, 50*(3), 202-207.

Grillner, S., & Zangger, P. (1979). On the central generation of locomotion in the low spinal cat. *Experimental Brain Research, 34*(2), 241-261.

Guha, A., & Tator, C. H. (1988). Acute cardiovascular effects of experimental spinal cord injury. *J Trauma, 28*(4), 481-490.

Gutnik, B., Mackie, H., Hudson, G., & Standen, C. (2005). How close to a pendulum is human upper limb movement during walking? *Homo, 56*(1), 35-49.

Hagg, T., & Oudega, M. (2006). Degenerative and spontaneous regenerative processes after spinal cord injury. *Journal of Neurotrauma, 23*(3-4), 264-280.

Hardin, E., Kobetic, R., Murray, L., Corado-Ahmed, M., Pinault, G., Sakai, J., et al. (2007). Walking after incomplete spinal cord injury using an implanted FES system: a case report. *J Rehabil Res Dev, 44*(3), 333-346.

Haridas, C., & Zehr, E. P. (2003). Coordinated Interlimb Compensatory Responses to Electrical Stimulation of Cutaneous Nerves in the Hand and Foot During Walking (Vol. 90, pp. 2850-2861).

Haridas, C., & Zehr, E. P. (2003). Coordinated interlimb compensatory responses to electrical stimulation of cutaneous nerves in the hand and foot during walking. *J Neurophysiol, 90*(5), 2850-2861.

Harkema, S. J. (2008). Plasticity of interneuronal networks of the functionally isolated human spinal cord *Brain Res Rev* (Vol. 57, pp. 255-264). Netherlands.

Harkema, S. J., Behrman, A. L., & Barbeau, H. (2011). *Locomotor training : principles and practice*. Oxford ; New York: Oxford University Press.

Harkema, S. J., Schmidt-Read, M., Lorenz, D., Edgerton, V. R., & Behrman, A. L. (2011). Balance and Ambulation Improvements in Individuals With Chronic Incomplete Spinal Cord Injury Using Locomotor Training-Based Rehabilitation. *Arch Phys Med Rehabil*.

Heesterbeek, P. J. C., Berkelmans, H. W. A., Thijssen, D. H. J., van Kuppevelt, H. J. M., Hopman, M. T. E., & Duysens, J. (2005). Increased physical fitness after 4-week training on a new hybrid FES-cycle in persons with spinal cord injury. *Technology and Disability, 17*(2), 103-110.

Hiersemenzel, L. P., Curt, A., & Dietz, V. (2000). From spinal shock to spasticity: neuronal adaptations to a spinal cord injury. *Neurology, 54*(8), 1574-1582.

Hill, A. A., Masino, M. A., & Calabrese, R. L. (2003). Intersegmental coordination of rhythmic motor patterns. *J Neurophysiol, 90*(2), 531-538.

Hinrichs, R. N., Cavanagh, P. R., & Williams, K. R. (1987). Upper Extremity Function in Running. I: Center of Mass and Propulsion Considerations. *International Journal of Sport Biomechanics, 3*(3), 222-241.

Jones, T. B., McDaniel, E. E., & Popovich, P. G. (2005). Inflammatory-mediated injury and repair in the traumatically injured spinal cord. *Curr Pharm Des, 11*(10), 1223-1236.

Kawashima, N., Nozaki, D., Abe, M., & Nakazawa, K. (2008). Shaping appropriate locomotive motor output through interlimb neural pathway within spinal cord in humans. *J Neurophysiol, 99*(6), 2946-2955.

Kawashima, N., Nozaki, D., Abe, M. O., & Nakazawa, K. (2008). Shaping Appropriate Locomotive Motor Output Through Interlimb Neural Pathway Within Spinal Cord in Humans (Vol. 99, pp. 2946-2955).

Kern, H., Rossini, K., Carraro, U., Mayr, W., Vogelauer, M., Hoellwarth, U., et al. (2005). Muscle biopsies show that FES of denervated muscles reverses human muscle degeneration from permanent spinal motoneuron lesion... 3rd International Congress on the restoration of (wheeled) mobility in SCI rehabilitation: state of the art III, Amsterdam, April 2004. *Journal of Rehabilitation Research & Development, 42*(3), 43-53.

Kirshblum, S. C., Groah, S. L., McKinley, W. O., Gittler, M. S., & Stiens, S. A. (2002). 1. Etiology, classification, and acute medical management. *Archives of physical medicine and rehabilitation, 83*(3), S50-S57.

Klimstra, M. D., Thomas, E., Stoloff, R. H., Ferris, D. P., & Zehr, E. P. (2009). Neuromechanical considerations for incorporating rhythmic arm movement in the rehabilitation of walking. *Chaos: An Interdisciplinary Journal of Nonlinear Science, 19*(2), 026102-026114.

Lamont, E. V., & Zehr, E. P. (2006). Task-specific modulation of cutaneous reflexes expressed at functionally relevant gait cycle phases during level and incline walking and stair climbing. *Experimental Brain Research, 173*(1), 185-192.

Last, R. J. (1949). Innervation of the limbs. *J Bone Joint Surg Br, 31B*(3), 452-464.

Leeds, E. M., Klose, K. J., Ganz, W., Serafini, A., & Green, B. A. (1990). Bone mineral density after bicycle ergometry training. *Arch Phys Med Rehabil, 71*(3), 207-209.

Lewén, A., Matz, P., & Chan, P. H. (2000). Free radical pathways in CNS injury. *J Neurotrauma, 17*(10), 871-890.

Liberson, W. T., Holmquest, H. J., Scot, D., & Dow, M. (1961). Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients. *Arch Phys Med Rehabil, 42*, 101-105.

Liu, S., Qu, Y., Stewart, T. J., Howard, M. J., Chakrabortty, S., Holekamp, T. F., et al. (2000). Embryonic stem cells differentiate into oligodendrocytes and myelinate in culture and after spinal cord transplantation. *Proceedings of the National Academy of Sciences, 97*(11), 6126-6131.

Long 2nd, C. (1963). AN ELECTROPHYSIOLOGIC SPLINT FOR THE HAND. *Archives of physical medicine and rehabilitation, 44*, 499-503.

Lovely, R. G., Gregor, R. J., Roy, R. R., & Edgerton, V. R. (1986). Effects of training on the recovery of full-weight-bearing stepping in the adult spinal cat. *Experimental Neurology, 92*(2), 421-435.

Macht, M. B., & Kuhn, R. A. (1948). The Occurrence of Extensor Spasm in Patients with Complete Transection of the Spinal Cord. *New England Journal of Medicine, 238*(10), 311-314.

Marino, R., Ditunno, J. J., Donovan, W., & Maynard, F. J. (1999). Neurologic recovery after traumatic spinal cord injury: data from the Model Spinal Cord Injury Systems. *Arch Phys Med Rehabil, 80*(11), 1391-1396.

Mohr, T., Pødenphant, J., Biering–Sørensen, F., Galbo, H., Thamsborg, G., & Kjær, M. (1997). Increased Bone Mineral Density after Prolonged Electrically Induced Cycle Training of Paralyzed Limbs in Spinal Cord Injured Man. *Calcified Tissue International, 61*(1), 22-25.

Musselman, K. E. (2007). Clinical significance testing in rehabilitation research: what, why, and how? [Article]. *Physical Therapy Reviews, 12*(4), 287-296.

Musselman, K. E., Fouad, K., Misiaszek, J. E., & Yang, J. F. (2009). Training of walking skills overground and on the treadmill: Case series on individuals with incomplete spinal cord injury. *Physical Therapy, 89*(6), 601-611.

Mutton, D. L., Scremin, A. M. E., Barstow, T. J., Scott, M. D., Kunkel, C. F., & Cagle, T. G. (1997). Physiologic responses during functional electrical stimulation leg cycling and hybrid exercise in spinal cord injured subjects. *Archives of Physical Medicine and Rehabilitation, 78*(7), 712-718.

Nathan, P. W., Smith, M., & Deacon, P. (1996). Vestibulospinal, reticulospinal and descending propriospinal nerve fibres in man. *Brain, 119 (Pt 6)*, 1809-1833.

NATHAN, P. W., & SMITH, M. C. (1955). Long descending tracts in man. I. Review of present knowledge. *Brain, 78*(2), 248-303.

Newham, D., & Donaldson, N. N. (2007). FES cycling. *Acta Neurochir Suppl, 97*(Pt 1), 395-402.

Norenberg, M. D., Smith, J., & Marcillo, A. (2004). The pathology of human spinal cord injury: defining the problems. *J Neurotrauma, 21*(4), 429-440.

Olsson, Y., Sharma, H. S., Nyberg, F., & Westman, J. (1995). The opioid receptor antagonist naloxone influences the pathophysiology of spinal cord injury. *Prog Brain Res, 104*, 381-399.

Oyinbo, C. A. (2011). Secondary injury mechanisms in traumatic spinal cord injury: A nugget of this multiply cascade. *Acta Neurobiologiae Experimentalis, 71*(2), 281-299.

Page, S. J., Levine, P., & Strayer, J. (2007). An Electric Stimulation Cycling Protocol for Gait in Incomplete Spinal Cord Injury. *Archives of Physical Medicine and Rehabilitation, 88*(6), 798-800.

Patrick, S. K., Noah, J. A., & Yang, J. F. (2009). Interlimb coordination in human crawling reveals similarities in development and neural control with quadrupeds. *Journal of Neurophysiology, 101*(2), 603-613.

Pearson, K. G. (2000). Neural adaptation in the generation of rhythmic behavior. *Annu Rev Physiol, 62*, 723-753.

Peckham, P., Keith, M., Kilgore, K., Grill, J., Wuolle, K., Thrope, G., et al. (2001). Efficacy of an implanted neuroprosthesis for restoring hand grasp in tetraplegia: a multicenter study. *Arch Phys Med Rehabil, 82*(10), 1380-1388.

Peckham, P., & Knutson, J. (2005). Functional electrical stimulation for neuromuscular applications. *Annu Rev Biomed Eng, 7*, 327-360.

Peckham, P. H., Mortimer, J. T., & Van Der Meulen, J. P. (1973). Physiologic and metabolic changes in white muscle of cat following induced exercise. *Brain Res, 50*(2), 424-429.

Petrofsky, J. S., Phillips, C. A., & Heaton Iii, H. H. (1984). Bicycle ergometer for paralyzed muscle. *Journal of clinical engineering, 9*(1), 13-18.

Phadke, Flynn, S. M., Thompson, F. J., Behrman, A. L., Trimble, M. H., & Kukulka, C. G. (2009). Comparison of Single Bout Effects of Bicycle Training Versus Locomotor Training on Paired Reflex Depression of the Soleus H-Reflex After Motor Incomplete Spinal Cord Injury. *Archives of Physical Medicine and Rehabilitation, 90*(7), 1218-1228.

Phadke, Thompson, F. J., Kukulka, C. G., Nair, P. M., Bowden, M. G., Madhavan, S., et al. (2010). Soleus H-reflex modulation after motor incomplete spinal cord injury: effects of body position and walking speed. *J Spinal Cord Med, 33*(4), 371-378.

Phadke, Wu, S. S., Thompson, F. J., & Behrman, A. L. (2007). Comparison of Soleus H-Reflex Modulation After Incomplete Spinal Cord Injury in 2 Walking Environments: Treadmill With Body Weight Support and Overground. *Archives of Physical Medicine and Rehabilitation, 88*(12), 1606-1613.

Piepmeier, J. M., & Jenkins, N. R. (1988). Late neurological changes following traumatic spinal cord injury. *J Neurosurg, 69*(3), 399-402.

Pontzer, H., Holloway, J. H., Raichlen, D. A., & Lieberman, D. E. (2009). Control and function of arm swing in human walking and running. *J Exp Biol, 212*(Pt 4), 523-534.

Prochazka, A., Gauthier, M., Wieler, M., & Kenwell, Z. (1997). The bionic glove: an electrical stimulator garment that provides controlled grasp and hand opening in quadriplegia. *Arch Phys Med Rehabil, 78*(6), 608-614.

Prutchi, D., & Norris, M. (2005). Design and Development of Medical Electronic Instrumentation - A Practical Perspective of the Design, Construction and Test of Medical Devices: John Wiley & Sons.

Raineteau, O., & Schwab, M. E. (2001). Plasticity of motor systems after incomplete spinal cord injury. [10.1038/35067570]. *Nat Rev Neurosci, 2*(4), 263-273.

Raymond, J., Davis, G. M., Fahey, A., Climstein, M., & Sutton, J. R. (1997). Oxygen uptake and heart rate responses during arm vs combined arm/electrically stimulated leg exercise in people with paraplegia. *Spinal Cord, 35*(10), 680-685.

Schalow, G. (2002). Recovery from spinal cord injury achieved by 3 months of coordination dynamic therapy. *Electromyogr Clin Neurophysiol, 42*(6), 367-376.

Schalow, G. (2003). Partial cure of spinal cord injury achieved by 6 to 13 months of coordination dynamic therapy. *Electromyogr Clin Neurophysiol, 43*(5), 281-292.

Schalow, G., & Zach, G. A. (1998). Neuronal reorganization through oscillator formation training in patients with CNS lesions. *J Peripher Nerv Syst, 3*(3), 165-188.

Schanne, F. A., Kane, A. B., Young, E. E., & Farber, J. L. (1979). Calcium dependence of toxic cell death: a final common pathway. *Science, 206*(4419), 700-702.

Schwab, J. M., Brechtel, K., Mueller, C. A., Failli, V., Kaps, H. P., Tuli, S. K., et al. (2006). Experimental strategies to promote spinal cord regeneration--an integrative perspective. *Prog Neurobiol, 78*(2), 91-116.

Schwab, M. E. (2002). Repairing the Injured Spinal Cord. [Article]. *Science, 295*(5557), 1029.

Sharrard, W. J. (1964). THE SEGMENTAL INNERVATION OF THE LOWER LIMB MUSCLES IN MAN. *Ann R Coll Surg Engl, 35*, 106-122.

Sherrington, C. S. (1910). Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *The Journal of Physiology, 40*(1-2), 28-121.

Skinner, F. K., & Mulloney, B. (1998). Intersegmental coordination in invertebrates and vertebrates. *Curr Opin Neurobiol, 8*(6), 725-732.

Smith, J. L., Carlson-Kuhta, P., & Trank, T. V. (1998). Forms of forward quadrupedal locomotion. III. A comparison of posture, hindlimb kinematics, and motor patterns for downslope and level walking. *J Neurophysiol, 79*(4), 1702-1716.

Smith, J. L., Smith, L. A., Zernicke, R. F., & Hoy, M. (1982). Locomotion in exercised and nonexercised cats cordotomized at two or twelve weeks of age. *Experimental Neurology, 76*(2), 393-413.

Stein, R. B., Chong, S., Everaert, D. G., Rolf, R., Thompson, A. K., Whittaker, M., et al. (2006). A multicenter trial of a footdrop stimulator controlled by a tilt sensor. *Neurorehabilitation and Neural Repair, 20*(3), 371-379.

Stevenson, T. J. (2001). Detecting change in patients with stroke using the Berg Balance Scale. *Australian Journal of Physiotherapy, 47*(1), 29-38.

Subbarao, J. V. (1991). Walking after spinal cord injury. Goal or wish? *West J Med, 154*(5), 612-614.

Tate, D. G., Kalpakjian, C. Z., & Forchheimer, M. B. (2002). Quality of life issues in individuals with spinal cord injury. *Arch Phys Med Rehabil, 83*(12 Suppl 2), S18-25.

Tator, C. H., & Fehlings, M. G. (1991). Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. *J Neurosurg, 75*(1), 15-26.

Tepavac, D., & Field-Fote, E. C. (2001). Vector coding: A technique for quantification of intersegmental coupling in multicyclic behaviors. *Journal of Applied Biomechanics, 17*(3), 259-270.

Tester, N. J., Howland, D. R., Day, K. V., Suter, S. P., Cantrell, A., & Behrman, A. L. (2011). Device use, locomotor training and the presence of arm swing during treadmill walking after spinal cord injury. *Spinal Cord, 49*(3), 451-456.

Thuret, S., Moon, L. D. F., & Gage, F. H. (2006). Therapeutic interventions after spinal cord injury. *Nature Reviews Neuroscience, 7*(8), 628-643.

Umberger, B. R. (2008). Effects of suppressing arm swing on kinematics, kinetics, and energetics of human walking. *Journal of Biomechanics, 41*(11), 2575-2580.

van Hedel, H. J., Wirz, M., & Dietz, V. (2005). Assessing walking ability in subjects with spinal cord injury: Validity and reliability of 3 walking tests. [doi: DOI: 10.1016/j.apmr.2004.02.010]. *Archives of Physical Medicine and Rehabilitation, 86*(2), 190-196.

Van Hedel, H. J. A., Wirz, M., & Dietz, V. (2008). Standardized assessment of walking capacity after spinal cord injury: The European network approach. *Neurological Research, 30*(1), 61-73.

Visintin, M., & Barbeau, H. (1994). The effects of parallel bars, body weight support and speed on the modulation of the locomotor pattern of spastic paretic gait. A preliminary communication. *Paraplegia, 32*(8), 540-553.

Vodovnik, L. (1971). Information processing in the central nervous system during functional electrical stimulation. *Med Biol Eng, 9*(6), 675-682.

Wannier, T., Bastiaanse, C., Colombo, G., & Dietz, V. (2001). Arm to leg coordination in humans during walking, creeping and swimming activities. *Exp Brain Res, 141*(3), 375-379.

Webb, D., Tuttle, R. H., & Baksh, M. (1994). Pendular activity of human upper limbs during slow and normal walking. *Am J Phys Anthropol, 93*(4), 477-489.

Wheeler, G. D., Andrews, B., Lederer, R., Davoodi, R., Natho, K., Weiss, C., et al. (2002). Functional electric stimulation-assisted rowing: Increasing cardiovascular fitness through functional electric stimulation rowing training in persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation, 83*(8), 1093-1099.

Winter, D. A. (1991). *The Biomechanics and Motor Control of Human Gait: Normal, Elderly and Pathological*. Waterloo, Ontario: Waterloo Biomechanics Press.

Wirz, M., Müller, R., & Bastiaenen, C. (2010). Falls in persons with spinal cord injury: validity and reliability of the Berg Balance Scale. *Neurorehabil Neural Repair, 24*(1), 70-77.

Yang, J. F., & Musselman, K. E. (2012). Training to achieve over ground walking after spinal cord injury: a review of who, what, when, and how. *J Spinal Cord Med, 35*(5), 293-304.

Zehr, E., Balter, J., Ferris, D., Hundza, S., Loadman, P., & Stoloff, R. (2007). Neural regulation of rhythmic arm and leg movement is conserved across human locomotor tasks. *J Physiol, 582*(Pt 1), 209-227.

Zehr, E. P., & Haridas, C. (2003). Modulation of cutaneous reflexes in arm muscles during walking: further evidence of similar control mechanisms for rhythmic human arm and leg movements. *Exp Brain Res, 149*(2), 260-266.

Zehr, E. P., Klimstra, M., Johnson, E. A., & Carroll, T. J. (2007). Rhythmic leg cycling modulates forearm muscle H-reflex amplitude and corticospinal tract excitability. *Neuroscience Letters, 419*(1), 10-14.

Chapter 3. GENERAL CONCLUSION

The aim of my master's thesis was to demonstrate that arm and leg FES-assisted cycling improves walking after iSCI through a pilot study with subjects with iSCI.

I hypothesized that arm/leg FES-assisted cycling would improve walking speed and independence in a group of individuals with iSCI. by inducing plastic changes in the spinal networks involved in locomotion. To test my hypothesis, I evaluated a group of five individuals who were capable of talking some steps on their own, but needed significant assistance to walk years after suffering an iSCI. They participated in 12 weeks of arm and leg FES-assisted cycling. My hypothesis was supported by the significant improvements in walking speed and endurance that took place. The reduction in the excitability of the monosynaptic reflex pathwayis consistent with my hypothesis that such changes in walking were a consequence of plastic changes in the spinal networks although it is not sufficient since we did not find significant shifting of the H-M curve (i. e. changes in the percentage of Mmax that corresponded to Hmax). The quality of walking improved in the step to step regularity over a number of cycles, in the increased foot clearance, and in the change in the patterns of muscle activation that better resemble those of able-bodied individuals. Additionally balance improved in more than half of the study participants and in two of them an improvement in upright posture was evident.

Only one subject dropped out after 2 weeks of the program due to a preexisting neck pain, which was neither alleviated nor aggravated by the training. The fact that the remaining 5 subjects completed such an intense training program denotes its feasibility and the motivation they had for the training. I performed interviews at the end of the training and all subjects expressed their satisfaction and some mentioned that the effects of the training improved some aspects of their quality of life. Some of the participants even requested to be part of the next phase of this study which will involve only legs FES-assisted cycling. My research study is the first to show the benefits of an approach that includes the arms actively in the rehabilitation of walking. The positive results of this study demonstrate that an innovative training, arm and leg FES-assisted cycling, is feasible and effective in improving walking after iSCI and should be further developed.

3.1. MECHANISMS FOR IMPROVEMENT OF WALKING

Undoubtedly, arm and leg FES-assisted cycling was effective for the five individuals that participated in my study. I hypothesized that the improvements in walking would be due to plastic changes in the spinal neuronal circuits induced by the rhythmic sensory stimulation that the coordinated cycling movement itself plus the electrical stimulation provide to the CNS. Through this pilot study, I found evidence consistent with my hypothesis. First, I found significant improvements in walking butdid not observe significant improvements in the motor scores or the MVCs in this group of individuals. Therefore, changes in muscular strength likely played only a minor role in the process of improving walking. Second, I found a significant reduction in the excitability of the Soleus H-reflex. Several mechanisms may be responsible for the reduction in excitability of H-reflex: One could be the strengthening of the presynaptic inhibition pathways caused by the regulated activation of group 1a and 1b afferents of flexor muscles and the voluntary engagement of the subjects during the training. Both inputs can interact with spinal interneurons that are known to cause presynaptic inhibition of the stretch reflex.

Finally, I found that four out of five subjects improved balance, three of them over the minimal clinical importance difference (MCID) for stroke of 6 points(Stevenson, 2001). In order to understand specifically if the improvements in balance presented by three of the participants are clinically significant, the MCID in the Berg Balance Scale must be calculated. One limitation of this study is that we did not obtain any alternative measure of balance to use as an anchor scale for the MCID analysis. Conventional locomotor training techniques give critical importance to upright position during the rehabilitation and, consequently, have improved balance in subjects with chronic iSCI(S. J. Harkema, et al., 2011; Musselman, et al., 2009). In contrast, during arm/leg FES-assisted cycling sessions the subjects were not positionedupright and we did not give any indication about the trunk and head position. The clinically important improvementsin balance show indirectly that changes at the spinal neuronal networks that coordinate arms and legs for postural responses took place. Another explanation may be that changes in vestibulospinal and reticulospinal pathways took place, but we did not evaluate them. Muscle strengthening may also have contributed to the improvements in balance, but our motor scores and MVC data suggests that its contribution was not significant. Three sensory inputs trigger postural responses for balance: muscle proprioceptors, vestibular receptors (through vestibulospinal and reticulospinal tracts), and visual inputs. The vestibulospinal and reticulospinal pathways project directly to motor neurons, but also interact with interneurons and long propriospinal neurons that coordinate interlimb muscle responses (Ghez, 1991). The Arm/leg FES-assisted cycling provides the CNS with different kinds of coordinated sensory inputs such as load, stretch and electrical stimulation from arms and legs. The intense and vigorous activity engaged not only arms and legs, but the whole body, providing even more coordinated sensory inputs. Sensory inputs that relay into interneuronal networks, may strengthen them and affect positively walking and postural responses. In itself the improvement of balance is an important outcome since it implies safer mobility to perform activities of daily living and reduced risk of falls (Wirz, et al., 2010).

In conclusion, the reduced excitability of the H-reflex along with the improvements in balance demonstrate that the strengthening of interneuronal networks during arm and leg FES- assisted cycling may be responsible for the improvements in walking.

3.2. COMPARISON TO OTHER REHABILITATION INTERVENTIONS FOR ISCI

This is the first study of arm/leg FES-assisted cycling. One of my goals with this research was to be able to produce results clearly applicable to the reality of rehabilitation. An issue that is evident upon reviewing the literature in the rehabilitation of walking field is the lack of standardization of evaluation methods and study design for interventions after SCI. Recently, this issue was reviewed making evident that a consensus in the methods for studies investigating new forms of gait rehabilitation after iSCI must be met (Yang & Musselman, 2012). Studies in chronic SCI produce results that are not comparable among themselves due to different duration and intensity of the interventions and different outcome measurements. Although my study is a pilot one with a small number of participants, I chose evaluation standards that go according to current literature in the field that allow for comparison(Alexander et al., 2009; Dobkin , et al., 2003; Van

Hedel, Wirz, & Dietz, 2008). One aspect that is reported in all of them is the walking speed, balance and some variations of the walking endurance. I worked with several studies that served me as a frame of reference with which I could compare my results.

The first framework for comparison is the minimal clinically important difference, or MCID, as reported by Musselman for changes in 10-meter walking speed: 0.05 to 0.06 m/s for the SCI population (Musselman, 2007). The changes in walking speed that my subjects presented were above this level. My second source of comparison are other studies involving chronic iSCI subjects that have similar duration (12 weeks) and intensity of at least 30 minutes daily for at least 3 days per week. Recently, Field-Fote and colleagues reported improvements in walking in a group of individuals with chronic iSCI after 12 weeks of one of four different walking rehabilitation interventions: BWSTT, BWSTT with electrical stimulation, overgroundlocomotor training with electrical stimulation, and robotic training. Although both groups of volunteers were classified as C or D according to AIS, the mean walking speed at baseline was lower for their subjects than for my participants. They found the largest improvements in the group that trained overground with dorsiflexion assist device(Field-Fote & Roach, 2011). This type of training required more voluntary effort to initiate stepping than all the others that were performed in a treadmill. Improvements in endurance are consistent with evidence from other FES studies that suggest that FES improves cardiovascular health.

Intervention	Source	Subjects	n	Pre-test walking speed (m/s)	Change in walking speed (m/s)	Pre-test distance walked (m)	Change in distance walked (m)
BWSTT	Field-Fote, EC, et.al., 2011	Chronic SCI, ≥1yr. Post-injury, ASIA C or D	17	0.1 ±0.14	0.04 ±0.07 *	22.1±21.4 ‡	0.8 ±7.7‡
BWSTT + Stimulation	Field-Fote, EC, et.al., 2011	Chronic SCI, ≥1yr. Post-injury, ASIA C or D	18	0.18 ±0.18	0.05 ±0.09 *	20.6±23.1 ‡	3.8 ±6.3 * ‡
Overground locomotor training + stimulation	Field-Fote, EC, et.al., 2011	Chronic SCI, ≥1yr. Post-injury, ASIA C or D	15	0.19 ±0.20	0.09 ±0.11 *	24.0 ±35.3 ‡	14.2 ±15.2 * ‡
Robotic Training	Field-Fote, EC, et.al., 2011	Chronic SCI, ≥1yr. Post-injury, ASIA C or D	14	0.17 ±0.10	0.01 ±0.05	16.8 ±11.3. ‡	1.2 ±5.1 ‡
Leg cycling	Page, S.J., et.al., 2007	iSCI, 25mo. Post-injury	1	0.47	0.33	not reported	not reported
Skilled training	Musselman, KE, et.al., 2009	iSIC, >6mo. Post injury, ASIA C	4	0.24 ±0.25	0.11 ±0.09	76.28 ±77.18	27
BWSTT	Musselman, KE, et.al., 2009	iSIC, >6mo. Post injury, ASIA C	4	0.24 ±0.25	0.04 ±0.04	76.28 ±77.18	13
BWSTT	Harkema S, et.al. 2011	iSCI, ASIA C & D. ≥3 yrs. Post-injury	52	0.31 ±0.41 †	0.09±0.14	91 ±116 †	24 ±43
BWSTT	Harkema S, et.al. 2011	iSCI, ASIA C & D. 1-3 yrs. Post-injury	43		0.11 ±0.23		44 ±71
Arm/Leg FES-assisted cycling	this study	iSCI, ASIA C&D, ≥ 12yr. Post-injury	5	0.49 ±0.22	0.18 ±0.03	175.48 ±62.46	42.85 ±6.03

Table 3-1. Summary of recent studies for improving walking in iSCI population. ‡:2 min walking test. * : statistically significant †:The results were not published separately. This data is the mean change for both groups: 1-3 yrs. And ≥3yrs. post-injury. :Median values approximatedfrom Figure 2 in Musselman, K.E. et. al., 2009.

3.3. FUTURE DIRECTIONS

The main goal of my research study was to demonstrate that involving actively the arms through arm and leg FES-assisted cycling is an effective intervention to improve walking after iSCI. In order to further investigate the effects of active arm involvement a study of the effect of only leg FES-assisted cycling has to be conducted.

I propose that if the effects of Arm and leg FES-assisted cycling are larger than the effects of only leg FES-assisted cycling, a larger study that incorporates other rehabilitation interventions currently in clinical practice such as BWSTT and skill training should be conducted. This study should involve a larger sample of individuals with iSCI. One weakness of my pilot study is that I did not incorporate any blinding in the evaluation process. This may be important regarding clinical assessments where the responses of the participants have to be rated based upon rules given by the instrument but also by the perception of the rater. For the future studies involving other interventions and larger samples, I propose that training sessions direction and outcomes assessment should be carried out by a different trained physical therapists blinded to the intervention characteristics and milestones within the training.

Both coordination dynamics(Schalow, 2003) and only legs FES-assisted cycling(Page, et al., 2007)reported improvements in autonomic functions in their subjects. In my study, the subjects were asked not to change anything about their medications during the training. It would be interesting to test this training in a larger group and to inquire systematically at each assessment session whether any changes in autonomic functions were observed.

3.4. BIBLIOGRAPHY

Field-Fote, E. C., & Roach, K. E. (2011). Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial. PhysTher, 91(1), 48-60. doi: ptj.20090359

Harkema, S. J., Schmidt-Read, M., Lorenz, D., Edgerton, V. R., & Behrman, A. L. (2011). Balance and Ambulation Improvements in Individuals With Chronic Incomplete Spinal Cord Injury Using Locomotor Training-Based Rehabilitation. Arch Phys Med Rehabil. doi: S0003-9993(11)00129-8 [pii]

Musselman, K. E., Fouad, K., Misiaszek, J. E., & Yang, J. F. (2009). Training of walking skills overground and on the treadmill: Case series on individuals with incomplete spinal cord injury. Physical Therapy, 89(6), 601-611. doi: 10.2522/ptj.20080257

Page, Stephen J., Levine, Peter, &Strayer, Jonathan. (2007). An Electric Stimulation Cycling Protocol for Gait in Incomplete Spinal Cord Injury. Archives of Physical Medicine and Rehabilitation, 88(6), 798-800.

Schalow, G. (2003). Partial cure of spinal cord injury achieved by 6 to 13 months of coordination dynamic therapy. ElectromyogrClinNeurophysiol, 43(5), 281-292.

Stevenson, T. J. (2001). Detecting change in patients with stroke using the Berg Balance Scale. Australian Journal of Physiotherapy, 47(1), 29-38.

Wirz, M., Müller, R., &Bastiaenen, C. (2010). Falls in persons with spinal cord injury: validity and reliability of the Berg Balance Scale. Neurorehabil Neural Repair, 24(1), 70-77. doi: 1545968309341059 [pii]