Does continuous passive motion of the ankle applied with a pneumatic robot alter spinal cord excitability?

by

Steven A. Noble
Bachelor of Science (Honours), University of Victoria, 2015

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in the School of Exercise Science, Physical and Health Education

Supervisory Committee

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Abstract

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Background: Spasticity of the ankle can occur in multiple sclerosis and stroke, and can significantly reduce quality of life by impeding walking and other activities of daily living. Robot driven continuous passive motion (CPM) of the ankle may be a beneficial rehabilitation strategy for lower limb spasticity management, but, objective measures of decreased spasticity and improved locomotion remains uncertain. Additionally, the acute and chronic effects of CPM on spinal cord excitability are unknown. **Objectives:** To evaluate: 1) the acute changes in spinal cord excitability induced by 30 min of CPM at the ankle joint, in neurologically intact individuals and in those with lower limb spasticity; and, 2) chronic training-induced effects of 6 weeks of bilateral CPM training on reflex excitability and locomotion in those with lower limb spasticity. **Methods:** Spinal cord excitability was assessed using Hoffmann (H-) reflex recruitment curves, collected immediately before and following 30 min of CPM of the right (neurologically intact) or more affected (clinical) ankle. A multiple baseline repeated measures study design was used to assess changes following 18 bilateral CPM training sessions. Spasticity and locomotion were assessed using the Modified Ashworth Scale, the 10 m Walk test, and the Timed Up and Go test. **Results:** Twenty-one neurologically intact (6 female, 15 male, mean age 24.5 ± 1.7y) and 9 participants with spasticity (3 female, 6 male, mean age 58.9 ± 9.7y) due to various neurological

conditions including stroke (n=4), MS (n=3), spinal cord injury (n=1), and cerebral palsy (n=1). In the neurologically intact group, CPM produced a bi-directional modulation of H-reflex creating 'facilitation' (n=12) (31.4 ± 20.9% increase in H-reflex amplitude) and 'suppression' (n=9) (32.9 ± 21.0% decrease in H-reflex amplitude) groups. In the clinical participants, acute CPM before training significantly increased H-reflex recruitment curve variables H@Thres and H@50; but there was no significant effect of acute CPM post-training. Baseline reflex excitability following training was reduced on the MA side for H@Thres, H@50 and H@100 by 96.5 ± 7.7%, 90.9 ± 9.2%, and 62.9 ± 21.1%, respectively. On the less affected side there was a significant decrease in H@Thres and H@50 by 83.4 ± 29.0% and 76.0 ± 28.3%. Time to complete the 10 m Walk Test was not different (5.2 ± 7.9% change, $p = 0.06$), and time to complete the Timed Up and Go was decreased (9.5 ± 12.3% change, $p = 0.05$). Spasticity of the ankle plantar flexor muscles, assessed by the Modified Ashworth Scale, was reduced in 4 participants with spasticity.

Conclusion: Acute and chronic CPM of the ankle can significantly alter spinal cord excitability. CPM training may be a useful strategy to decrease spasticity of the ankle plantar flexors.

Keywords: continuous passive movement; spasticity; spinal cord excitability

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List of Abbreviations

CPM: continuous passive movement

MA: more affected

LA: less affected

MS: multiple sclerosis

SCI: spinal cord injury

ROM: range of motion

IaPSI: primary afferent fibre (Ia fibre) presynaptic inhibition

IaPSiIN: Ia presynaptic inhibitory interneuron

PAD: post-activation depression

MAS: Modified Ashworth Scale

10MWT: 10 m Walk Test

TUG: Timed Up and Go Test

SOL: soleus

TA: tibialis anterior

VL: vastus lateralis

MG: medial gastrocnemius

H-reflex: Hoffmann reflex

EMG: electromyography

Mmax: maximum compound action potential

Hmax: maximal H-reflex response

H@Thres: the amplitude of the H-reflex from the fitted sigmoidal curve of a test condition at the relative stimulus intensity which evoked a threshold response at baseline

H@50: the amplitude of the H-reflex from the fitted sigmoidal curve of a test condition at the relative stimulus intensity which evoked an H-reflex amplitude 50% of maximal H-reflex amplitude at baseline

H@100: the amplitude of the H-reflex from the fitted sigmoidal curve of a test condition at the relative stimulus intensity which evoked a maximal H-reflex amplitude at baseline

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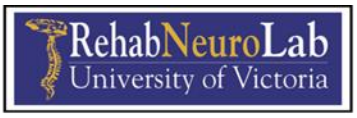

Chapter One : Review of Literature

1.1 Passive Movement as a Rehabilitation Technique

Passive muscle stretching is a technique commonly used in sport to increase or maintain joint range of motion (ROM) necessary for performing athletic maneuvers. In a rehabilitation setting, repetition of passive movements, such as passive muscle stretching, is one physical rehabilitation strategy often used to help manage symptoms of chronic neurological conditions such as stroke or multiple sclerosis (MS) [1–5].

Passive movement and passive muscle stretching although similar are not synonymous. Passive stretching typically involves using an external force, rather than muscle activity, to move a joint towards its maximal ROM and evoke a stretch in a muscle or muscle group. The joint position and stretch is typically maintained for a period of time [6]. Passive stretching is one type of passive movement, however other types of passive movement (e.g. passive arm cycling), although still using an external force to move a joint, might not evoke a significant stretch because the joint is not moved towards the end of its ROM, and typically involve much higher movement repetitions. While passive stretching is common in sport, the application of passive movement independent of muscle stretch, passive arm cycling or passive stepping in an exoskeleton, for example, is typically only used in a rehabilitation setting for those with a chronic neurological condition such as stroke.

Passive muscle stretching and passive movement independent of stretch can each influence anatomical structures and systems. During stretching, tension is applied to soft-tissue structures including: skin, muscles, tendons, joint aponeurosis, joint capsules, boney structures and ligaments [6]. Muscle stretching can also influence the central nervous system by changing

the activity neurons within the spinal cord (reflex pathways) that control muscle activity [7]. Passive movements independent of stretch might not put significant tension into soft-tissues, however they can also modulate reflex pathways due to the increase in afferent feedback (impulses in sensory neurons traveling from the moving limbs to the spinal cord).

The modulation of reflex pathways by passive movement is of interest because of there is an important clinical application. A common manifestation of neurological conditions such as stroke and MS is *spasticity*, which is most widely defined as 'a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes ('muscle tone') with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex [8]. In simpler terms, spasticity interferes with the reflex pathways that control muscles, which can lead to difficulty with walking. Although the precise mechanisms are unknown, it is generally accepted that spasticity involves a loss of modulation of reflex pathways [9,10]. It is suggested afferent feedback evoked by moving limbs during passive movement, or from static limbs during a held muscle stretch, can promote spinal adaptations (neural plasticity) to help restore some of this modulation in neurologically impaired individuals [11–13].

There is a lack of literature carefully examining passive movement as a rehabilitation technique. Many neural and peripheral responses to passive movement, especially in spasticity, remain unclear [7]. The available literature can be divided into 3 categories: investigation of primarily passive muscle stretch, investigation of repeated passive movement independent of stretch, and investigations which include both repeated continuous movement and muscle stretch. Interventions using high repetitions of continuous passive movement independent of muscle stretch to reduce spasticity, including passive arm cycling [14,15], passive leg cycling [16,17], and

passive stepping [18], have shown temporarily reduced measures of spasticity in clinical populations. The importance of this research is highlighting how afferent feedback independent produced independent of muscle stretch can influence spasticity.

With regard to interventions providing primarily passive muscle stretch, there is some clear evidence for clinical benefit - it is established that passive muscle stretching can increase the ROM of a joint [6]. This is important because one goal of passive muscle stretching in rehabilitation is to maintain or improve the ROM of a joint, which may be necessary to perform movements of daily living including standing and walking. For example, if 'foot-drop' while walking is occurring in part due to limited dorsiflexion ROM, then an increase in the ROM at the ankle might increase foot clearance during walking and lead to a more efficient gait pattern. Although passive muscle stretch has been shown to improve ROM, it is less clear if it can improve spasticity. Few studies have been published examining the efficacy of prevention or treatment of spasticity using passive stretching in the lower extremity, despite the fact that it is a commonly prescribed treatment [19–21] . Physical therapists often provide passive muscle stretch with the intent of reducing spasticity and contracture (the permanent shortening of a muscle), and restoring movement function [22]. Although, it is suggested that high-dose training is important for optimal benefit, which can make rehabilitation in spasticity a labor-intensive process [23] and a patient may receive infrequent sessions due to accessibility and cost [7].

Although most stretching activities involve soft-tissues being held at a particular length, it has been suggested that cyclic stretching can be more effective at reducing joint stiffness [7,24]. Cyclic stretching is also referred to as a form of continuous passive motion (CPM), and is often provided by a motorized device rather than a therapist. Robotics allows for a unique type of

passive movement involving both high repetitions of continuous passive movement *and* periods where a joint is held near its maximal ROM to provide passive muscle stretch. In theory, this form of CPM can produce the afferent feedback of both static muscle stretch and dynamic passive movement shown to modulate reflex pathways.

Two common types of robotic passive motion devices used in rehabilitation include end-effector-type devices and exoskeleton-type devices. End-effector devices work by applying mechanical forces to the distal segments of limbs to produce CPM at a joint [23]. Various studies have shown acute sessions of CPM in spastic joints can be beneficial [25–29] and a recent review on the use of this therapy in stroke found that five out seven studies demonstrated that robot-assisted therapy in combination with conventional physiotherapy produced greater improvement in gait function than conventional therapy alone [23]. Robotic devices have been developed specifically to provide both passive movement and muscle stretch to the human ankle in rehabilitation [30–32].

One research group has conducted many studies on an CPM ankle stretching device to treat the spastic or contractured ankles of neurologically impaired patients [1,33–36]. The device rotates the ankle joint safely throughout the ROM to extreme positions until a specified peak resistance torque is reached, the ankle stretch is then held at maximal dorsiflexion for 5 seconds [37] before moving towards maximal plantarflexion. The movement is slow near maximal ROM positions and fast (12°/sec) [37] in the middle ROM [22]. The intervention in addition to CPM also included an active muscle training component. In one of their early investigations, 10 stroke survivors completed 60 min of CPM, which resulted in reduced passive resistance torque (the amount of resistance provided at a given joint angle) [38], joint stiffness (the shape of the torque angle curve

which demonstrates the relationship between passive torque and joint angle) [39] , and increased ankle ROM [37]. In longitudinal studies, the device has been used in similar training protocols (typically 18 sessions of 20-30 min CPM duration over a period of 6 weeks) in individuals with spasticity due to cerebral palsy,[33,40] stroke [1,41] and MS [36]. Outcome measures from these studies include increased ankle ROM, decreased passive resistance torque, decreased joint stiffness, decreased spasticity as measured by the Modified Ashworth Scale, and improved locomotion. The results of these studies indicate that CPM of the ankle, with a passive muscle stretching component, can decrease spasticity and provide functional benefit to those with neurological conditions. The mechanisms responsible for the observed decrease in spasticity are uncertain, although literature on passive movement provides some insight.

1.2 Mechanisms

1.2.1 Soft Tissue Properties

The mechanisms behind any benefit from CPM training can be central (i.e. neural changes in the spinal cord) or peripheral within the soft tissues of the limb. With regard to peripheral structures, it is conceivable that the training might help reverse some of the adverse biomechanical changes that occur in these neurological conditions. Various connective tissues exist in a joint (e.g. tendon, aponeurosis); changes in these structures could contribute to hypertonia (an excessive level of muscle tone at rest and during activity) [42]. For example, immobilization could lead to increased tension in the joint aponeurosis [43]. The Achilles tendon length is shortened in children with spasticity due to cerebral palsy [40]. Changes to intramuscular connective tissues are also known to occur following immobilization [44–46]. Muscle atrophy is the reduction in the size or number of muscle fibres due to denervation or disuse [47]. Reduced

muscle mechanical activity leads to reduced gene expression and protein synthesis and consequently atrophy [48]. At the ankle the dorsiflexor tibialis anterior is commonly weak. Maximal dorsiflexion on the MA side in a poststroke population has been reported to be reduced to be 38% of the LA side [49]. It has been previously suggested that passive muscle stretching may alter connective tissue properties and muscle strength [1,42].

1.2.2 Afferent Feedback from Passive Movement

Passive movement of the limbs evokes sensory neurons to send afferent feedback about the movement to the spinal cord. This has been studied in many form of passive movement including passive stretching [22], passive arm cycling [14,15], passive leg cycling [16,17], and passive stepping [18]. Sensory feedback from passive movement includes cutaneous afferents and proprioceptive afferents. The Ia fibres of muscle spindle receptors, which help indicate the position of the limbs, have a particularly interesting role with regard to robotic CPM with muscle stretch [50]. During the CPM cycle there are dynamic periods where the length of muscle fibres is changing, and there is also a static phase while the muscle stretch is being held. Muscle spindle receptors contain specialized structures to send afferent feedback about the state of the muscle for each of these phases. Specifically, within a muscle spindle receptor, a *dynamic* nuclear bag fiber signals muscle fibre length change while *static* nuclear bag fiber signals the magnitude of muscle stretch [51]. The sensory pulses from both fibres are transmitted to the spinal cord along group Ia afferent fibres [51]. Consequently, afferent feedback from Ia afferents to the spinal cord likely occurs throughout the entire CPM movement cycle.

1.2.3 The Stretch Reflex Circuitry and Mechanisms of Spasticity

The Ia afferent fibre is part of a reflex pathway known as the stretch reflex pathway, which causes a muscle contraction in response to muscle stretch. They are mediated by mainly monosynaptic pathways where Ia afferent fibres from muscle spindles make excitatory connections onto alpha motor neurons that innervate the same muscle from which they arise. Passive stretch of the muscle excites the muscle spindles, leading Ia fibres to discharge and send inputs to the alpha motoneurons, which then send an efferent pulse to the muscle, causing it to contract [9].

Spasticity is defined as an exaggerated stretch reflex [8], which in part is due to a loss of modulation of this pathway. Descending (from the brain and brain stem) modulation of the stretch reflex pathway can be disrupted in stroke, spinal cord injury (SCI), MS, and cerebral palsy. Two major balancing descending systems exist that influence stretch reflex activity. The dorsal reticulospinal tract has an inhibitory influence, while the medial reticulospinal and vestibulospinal tracts are facilitatory [9]. Brain lesions cause spasticity when they disrupt the dorsal reticulospinal tract, due to the loss or reduction of the inhibitory influence [52] leading to prevalence of the facilitatory system and a state of disinhibition of the stretch reflex [9].

This imbalance of descending modulation is likely only the initiation of a more complicated process, because in the case of stroke or SCI, spasticity does not begin immediately following the lesion, suggesting long-term plastic changes occur in the spinal cord which bring about spasticity gradually [9]. Potential gradual changes within the spinal cord include a reduction of presynaptic inhibition and reciprocal inhibition, which also contribute to hyperexcitable stretch

reflexes [9]. Much of the research on passive movement targets modulation of these neural networks.

1.2.4 Ia Presynaptic Inhibition

The release of the neurotransmitter glutamate from the terminal of the Ia afferent fibre onto the alpha motoneuron pool evokes an excitatory post-synaptic potential which raises the excitability of motoneurons towards their threshold of activation. The excitability of this pathway can be regulated by inhibition of the release of glutamate from the Ia terminal, which is termed Ia presynaptic inhibition (IaPSI) [53]. This occurs due to activation of GABAergic interneurons near the Ia terminal within the spinal cord referred to as *Ia presynaptic inhibitory interneurons* (IaPSiIN) [54]. The release of the neurotransmitter GABA from IaPSiIN's inhibits the release of glutamate from the Ia terminal by binding to $GABA_A$ and $GABA_B$ receptors which alter ion currents into the terminal [55].

This represents a strong pathway for which both sensory and descending input can modulate excitability of the stretch reflex [56,57]. There are many known sources of input onto IaPSiIN's including descending supraspinal sources [58], spinal rhythmic movement generating networks [57], Ia afferents from various heterogenous muscles [59,60], autogenic Ia pulses [61,62], and cutaneous afferents [57,63]. One known example of cutaneous input is the stimulation of the sural nerve to facilitate the stretch reflex pathway by reducing IaPSI via another inhibitory interneuron [63,64]. Regulation of IaPSI is often impaired in spasticity of both the upper and lower body [65,66]. Although all muscles contain Ia afferent fibres, the majority of research conducted on IaPSI of the lower body is conducted in the soleus muscle. It is suggested part of the loss of modulation of the stretch reflex in spasticity is due to disruption of the descending influences onto the

IaPSiIN causing loss of IaPSI [65]. Passive movement interventions which increase excitatory transmission to IaPSIiN's [60,67] may be of benefit because of potential to restore lost modulation of the stretch reflex pathway which contributes to spasticity.

Although there are multiple approaches to determine change to IaPSI following an experimental intervention, one indirect method involves an experimentally induced phenomenon termed post-activation depression (PAD) [65]. PAD is a form of neural fatigue, where following repetitive afferent firing there is depletion of the neurotransmitters available at the Ia axon presynaptic terminal, thereby reducing the amplitude of the monosynaptic reflex response observed in the homonymous muscle up to 10 s [68] . PAD has been found significantly decreased in individuals with spasticity from various neurological conditions'; a positive correlation has been reported between the diminished PAD and the severity of spasticity following stroke and cerebral palsy [69]. Therefore, studies reporting augmentation of PAD following an intervention may be indicating an upstream change in IaPSI.

One research group found 60 min sessions of CPM training of the ankle over a 4 week period (5 sessions per week) was effective in restoring PAD and reducing clinical scores of spasticity in humans with chronic SCI [70]. The authors suggests alterations in IaPSI and interneuronal activity as a result of CPM underlie the restored PAD [70].

In terms of duration, discharge from Ia afferents during passive movement has been shown to decrease reflex excitability, after movement ceases, due to increased IaPSI [16,71]. Some work on passive cycling found decreased reflex excitability for up to 60 min following movement [16,72]. Similarly, reflex amplitudes were still reduced 30 min following passive stepping [18]. These

findings suggest passive movement can induce short-term plasticity, although there is a lack of literature suggesting long-term changes to IaPSI.

Passive movement can evoke IaPSI of both the ipsilateral and *contralateral* soleus Ia afferent [60]. The authors suggest that a significant role of muscle spindle discharge is to modulate heterogenous Ia pathways in the legs during movement. It was determined that during passive leg cycling the primary source of the afferent input to the soleus Ia pathway was the activation of muscle spindles of the quadriceps during phases of cycling which evoked stretch in these muscles [67].

Although the focus of above work was to suggest soleus Ia pathway modulation by quadriceps Ia afferents during passive movement, the authors also found soleus reflex amplitudes could be reduced when passive movement was created at the ankle alone [73]. Other studies provide support for this concept; passive lengthening of the soleus and gastrocnemius muscles decreased the Ia reflex excitability in both muscles, which was proposed to be caused by changes in resting spindle discharge rate from soleus and gastrocnemius altering IaPSI [74–76]. In reduced animal work it was determined that following sinusoidal changes in the length of the lateral gastrocnemius, IaPSI occurred in medial gastrocnemius fibres [77,78]. This work suggests sensory feedback evoked by movement of the ankle alone can modulate IaPSI of the soleus Ia pathway.

1.2.5 Reciprocal Inhibition

In addition to IaPSI, there is another neural pathway in the spinal cord which may be influenced by CPM. Voluntary muscle contraction requires descending input from supraspinal regions in the corticospinal tract and other descending pathways which increases the excitability of the

agonist alpha motor neuron pool [79]. In contrast, descending input during antagonist contraction causes the opposite effect at the same location via excitation of inhibitory interneurons, such as the Ia inhibitory interneuron [58], via collateral axons structurally organized to allow higher centers to send a single command for a voluntary movement [79]. This phenomenon is termed *reciprocal inhibition*; this neural organization prevents a prime mover from working against an opposing muscle [79]. The Ia inhibitory interneurons of this pathway also receive input from Ia afferents, which is why CPM may influence this pathway – it is expected that Ia afferents are highly active during the CPM cycle.

It is suggested cocontraction of opposing muscle groups, which can inhibit the desired movement or force production, in part occurs due to impaired reciprocal inhibition [80–83]. The negative consequence of altered muscle activation is a loss of dexterity and mechanical efficiency at the joint. This can result in excessive muscle activity that hinders movement control and causes fatigue [83].

Consequently, the development of interventions that may augment reciprocal inhibition in individuals with spasticity could lead to functional benefits. Some research groups have examined the efficacy of using chronic muscle stretching as a means to increase reciprocal inhibition from Ia afferents of tibialis anterior onto the soleus-gastrocnemius motoneuron pool [84,85]. It is therefore possible that CPM with muscle stretch could improve walking by restoring reciprocal inhibition.

1.3 Application of CPM

Neurological conditions including cerebral palsy, MS, SCI, or an acquired brain injury such as stroke are associated with changes in the spinal cord and also peripherally within soft tissues. A

common spinal manifestation of these conditions is spasticity. Spinal and peripheral changes together contribute to hypertonia and in severe cases can lead to the development of contracture [86,87] which greatly inhibits function [88]. Additional complications of these conditions can include muscle weakness and altered muscle activation patterns during locomotion. These symptoms can significantly lower quality of life by limiting mobility and independence.

1.3.1 Epidemiology

There are approximately 62,000 cerebrovascular incidents, or strokes, in Canada each year [19]. Stroke is the 3rd leading cause of death in North America, and the leading cause of disability [89]. After the acute phase of stroke, patients often continue to require rehabilitation for persisting deficits related to spasticity [19]. An estimated 60% of stroke survivors discharged from in-patient rehabilitation require an ankle orthosis due to spasticity to help improve mobility [90] while an estimated 34% develop ankle contracture.[90]

MS is a chronic, progressive, degenerative neurological disease, which causes axonal damage within the central nervous system as a result of demyelination [91] . MS is the leading cause of non-traumatic disability in young and middle-aged adults [92]. Canada has the highest rate of MS in the world, with an estimated 100,000 Canadians living with the disease [93]. An estimated 84% of individuals with MS reported spasticity, and that spasticity was associated with worse disability and quality of life [94].

Cerebral Palsy describes a group of disorders, affecting body movement and muscle co-ordination [95] characterized by persistently disordered posture and movement, often with muscle spasticity, due to a non-progressive disorder of the developing brain [96]. Currently there are over 50,000 Canadians with cerebral palsy [95].

There are currently over 85,000 Canadians with partial paralysis from SCI [97]. Spasticity is common with 65–78% of sample populations of individuals with chronic SCI (>1 year post injury) showing symptoms of spasticity [4].

1.3.2 Influence on Mobility

Although neurological conditions including stroke, MS, SCI and cerebral palsy involve impairments to the upper and lower body, the lower body will be the focus of this review. Spasticity, hypertonia, and contracture can manifest as equinovarus foot deformity, a condition characterized by reduced ankle dorsiflexion and foot inversion, which contributes a lesser base of support and therefore negatively impacts balance and gait [98].

Difficulty with locomotion often results in a sedentary lifestyle, which can then lead to further alterations including muscle atrophy - the reduction in the size or number of muscle fibres due to denervation or disuse [47] which is typically accompanied by muscle weakness [99] especially in distal muscle groups [100]. There is also typically an asymmetry of hemiparesis (weakness to a side of the body), producing more affected (MA) and less affected (LA) sides [101].

These deficits ultimately manifest as impaired mobility [22]. The gait pattern is often characterized by a low velocity, different stride lengths between the MA and LA sides, short stance, and relatively long swing phases on the MA side [102].

Hypertonia interferes with ankle dorsiflexion during the first phase of standing from a seated position [103] or during the late stance phase of walking [104]. The increased tone in calf muscles [42], weakness of the tibialis anterior [49], and limited ROM caused by contracture [105] can lead to "foot-drop", the inability to raise the foot during the swing phase of walking which can cause the foot to scuff the floor and add further difficulty to walking.

In summary, conditions discussed above can cause immobilization, especially if it creates great difficulty with walking, which can predispose individuals with spasticity to spend all or almost their entire time sitting. This posture results in the plantarflexor muscles being immobilized in a shortened position, precisely the conditions shown to exacerbate ankle stiffness [105] and muscle contracture,[106] creating a downward spiral of impairment. Any intervention which could prevent this immobilization would likely be of benefit.

1.3.3 Spasticity Management

Rehabilitation and symptom management for individuals with spasticity is important for maintaining or improving motor control and preventing secondary complications including cardiovascular disease [107]. In the case of stroke, rehabilitation can occur beyond 6 months post-infarct as studies [108–110] have shown neural adaptation can be induced well beyond typical post-stroke motor rehab timelines and highlight the usefulness of home-based rehabilitation strategies long after a patient has been discharged from a hospital. In the process of the functional recovery, improving or maintaining gait ability becomes the prime purpose of physical therapy, because gait is an important factor in realizing functional independence [111]. There are currently various approaches to decreasing spasticity to improve gait including pharmaceuticals [19], aerobic exercise [112], resistance training [108], and physical therapy [3]. Providing passive muscle stretch is a common technique in physical therapy [3], although this can be a labor-intensive process [23] and a patient may receive infrequent sessions due to accessibility and cost [7].

A robotic device that provides CPM (with muscle stretch) to the ankle has been developed. A unique feature of the device is it provides CPM at a very slow speed of 0.5-2^{o}/second from the

ankles resting position into maximal dorsiflexion. It also provides passive muscle stretch with a maximal torque of 18 Nm which is held for 5 seconds before releasing back to resting position. This specific slow CPM strategy is being implemented at spasticity clinics around Canada. However, the clinical benefit of long-term slow CPM training at the ankle joint as a therapy to decrease spasticity and improve locomotion remains uncertain. Additionally, a comprehensive neurophysiological assessment including measurement of spinal cord excitability following long-term CPM training of the ankle has not been conducted.

Therefore, the purpose of this thesis was to investigate the use of slow CPM of the ankle in neurologically intact individuals, and in those with lower limb spasticity, to determine potential clinical benefit of this emerging therapy and to assess the influence of acute slow CPM and chronic slow CPM training on spinal cord excitability.

1.4 Experimental Techniques to Evaluate CPM Outcomes

1.4.1 Clinical Evaluations

Clinical evaluations commonly used in health care can be used in an experimental setting to evaluate the effects of a rehabilitation intervention. Many of these evaluations are relatively quick to perform, a benefit to both the clinician and the participant.

Spasticity can be evaluated using the Modified Ashworth scale (MAS), an evaluation performed by a health care professional involving passive movements and a score representing the hyperexcitability of the response to stretch in a muscle group [113]. A benefit of this scale is its applicability across a wide range of movements and reliability [113]. Although, because it employs a gross scale subtle changes in spasticity over time may not be detected.

Clinicians also using walking tests to determine the level of functional independence an individual has, for example their ability to stand, mobility, and capability to perform activities of daily living. The 10 m Walk Test is a quick, highly objective, and easy to administer test of gait velocity, which is considered to be an effective indication of the degree of gait impairment [114,115]. A clinician can also use the Functional Ambulation Categories Scale [116] which ranges from 0 (non-functional ambulation) to 5 (independent ambulation on level and non-level surfaces). Another quick timed assessment is the Timed Up and Go Test [117] where a participant rises from a standard arm chair and walks 3 m, turns around, and returns to a seated position in the chair. In addition to the extra demand of standing from a seated position, this activity also requires unique demands on neural processes involved in the control of medial-lateral stability for the purpose of turning around which are not required for the 10 m walk test [118].

The above clinical assessments, although providing information on any large changes, may not be precise enough to detect smaller changes in function. Further, both of the walking tests may be incapable of detecting change in gait quality. Therefore to accurately assess the effects of CPM training on spasticity and locomotion, more complex neurophysiological assessment techniques are required.

1.4.2 The Hoffmann Reflex to Evaluate Spinal Cord Excitability

To assess spinal cord reflex excitability, the stretch reflex neural circuit can be electrically stimulated to create a reflex known as the Hoffmann reflex (H-reflex), an electric analogue to the stretch reflex [119]. Many studies choose to use the H-reflex rather than the stretch-reflex because it has the advantage of precise quantification and application of stimulus intensities [71].

The soleus H-reflex is induced by the stimulation of the Ia fibres of the tibial nerve in the popliteal fossa which bypasses the muscle spindle receptor [120]. The stimulus current is applied to a mixed nerve, consequently an action potential is also created in alpha motoneuron axons. Due to the greater diameter of Ia afferents, the H-reflex is generated at lower stimulus intensities with depolarization of Ia axons, while greater stimulus required to depolarize the smaller motor axons [119]. The afferent action potentials travel to the Ia terminal and evoke the release of glutamate to the alpha motorneuron pool. If sufficient excitatory input to an alpha motoneuron allows the membrane depolarization to reach threshold, an efferent action potential then travels to the neuromuscular junction to generate a muscle action potential which shows in the EMG trace as a waveform. As the stimulus intensity is increased, the H-reflex amplitude increases, and the depolarization of the motor axons leads to the appearance of the M-wave in the EMG trace [121]. Due to the ortho- and antidromic signals generated with electrical stimulation of a of nerve [122] an antidromic action potential generated in the motor axon travel towards the soma and collides with the incoming orthodromic signal responsible for the H-reflex. Consequently, as stimulus intensity is increased further the H-reflex amplitude decreases while the M-wave continues to increase until the maximum compound action potential of the soleus muscle (M_{max}) is reached. This process of steadily increasing stimulus intensity creates a H-reflex recruitment curve with ascending and descending limbs and a M-wave recruitment curve that rises up to a plateau [119].

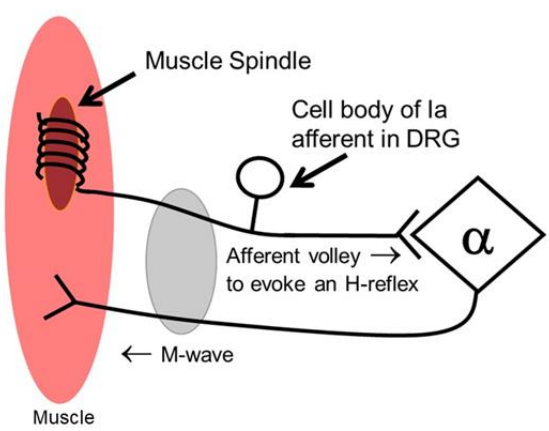

Figure 1. The H-Reflex pathway (Figure adapted from Zehr, 2002) [119].

One way to use the H-reflex to investigate the excitability of the stretch reflex pathway is to record H-reflexes at a constant M-wave size. Studies have shown a linear relationship between the magnitude of the afferent volley and the magnitude of the electrically induced efferent volley (M-wave), therefore the M-wave size can be used as a biocalibration for the stimulus condition when using the H-reflex [123]. An important consideration when using this method is to ensure the M-wave is small, so that H-reflexes recorded at a size approximately midway along ascending limb of the recruitment curve and antidromic action potentials have not begun to significantly impact the H-reflex [124].

An H-reflex methodology that may detect a broader scope of changes to the excitability of the pathway is to use a wide range of stimulus intensities to collect a recruitment curve. H- and M-wave peak-to-peak amplitudes are determined across this range and the H-reflex is normalized by comparing its size to M_{max} or to the level of stimulation current required to evoke M_{max} [124]. Different experimental protocols or neurological conditions might affect the excitability of

distinct populations of motor units, and this protocol allows for detection of changes in this full range of populations by measuring from H_{Thres}, i.e. the relative current where the first H-reflex response occurs, up the ascending limb to the maximal H-reflex response, H_{max} [119]. The relative stimulation current (i.e. normalized to current for M_{max}) for these measures can be used to compare recruitment curves collected before and after an intervention, with the latter referred to as a test condition. For example, the current required to evoke an H-reflex 50% of the amplitude of H_{max} during a baseline recruitment curve is applied to the test condition recruitment curve and the corresponding H-reflex amplitude, termed $H_{@50}$, determined. This process allows for assessment of change in H-reflex excitability at similar stimulus levels across conditions, with these comparisons termed 'fitted curve' variables [124].

H-reflex amplitude can be conditioned by volleys in peripheral cutaneous afferents such as the sural nerve. Stimulation of the sural nerve at the foot facilitates the soleus H-reflex by reducing IaPSI [63,64]. Therefore, one way to assess changes in IaPSI is to use this method to condition the H-reflex and determine if the effect of conditioning changes following an intervention hypothesized to influenced IaPSI. Neural signaling that elicits IaPSI may reduce the H-reflex recorded from the muscle, and because EMG level remains constant, altered IaPSI can be inferred over a post-synaptic effect of the intervention [119].

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Chapter 2: Manuscript

2.1 Introduction

Spasticity is a common manifestation of neurological conditions including cerebral palsy, multiple sclerosis (MS), spinal cord injury (SCI), or an acquired brain injury such as stroke. Lower limb spasticity involves hyperexcitable reflexes which can contribute to excessive muscle tone in the ankle [1]. Hypertonia can interfere with movement of ankle joint by impeding dorsiflexion during the first phase of standing from a seated position [2] or during the late stance phase of walking [3]. In severe cases of ankle spasticity this can significantly lower quality of life by limiting mobility and functional independence and inhibiting participation in rehabilitation programs. A bridging mechanism would be useful to move individuals with severe spasticity to a level of function where they can begin other rehabilitation techniques proven to be effective such as arm cycling [4–6], leg cycling [7–10], resistance training [11] and treadmill walking [12]. Studies investigating repetitive passive movements such as passive leg cycling have shown temporarily decreased spasticity [8,10]. Passive muscle stretching is commonly prescribed rehabilitation technique for individuals with severe spasticity [13,14] which is often provided by a physical therapist. However, this is a labor-intensive process [15] and a patient may receive infrequent sessions due to accessibility and cost [14].

Robot driven devices which provide both slow continuous passive motion (CPM) and passive muscle stretch of the ankle may be a beneficial rehabilitation strategy for spasticity [16–20]. However, the clinical benefit of long-term slow CPM training at the ankle joint as a therapy to decrease spasticity and improve locomotion remains uncertain. Additionally, a comprehensive

neurophysiological assessment including measurement of spinal cord excitability following long-term CPM training of the ankle has not been conducted.

The objectives of this study were: 1) to evaluate the effect of 30 min of CPM at the ankle joint in neurologically intact individuals on spinal cord reflex excitability and range of motion (ROM) 2) to provide evidence for the mechanisms behind any change to reflex excitability 3) to evaluation the effect of 6 weeks of bilateral CPM training on reflex excitability, strength, and mobility in those with severe lower limb spasticity.

2.2 Common Methods

2.2.1 CPM during Laboratory Evaluations

Participants performed 30 min of CPM of the right leg (Experiment One) or more affected (MA) leg (Experiment Two) using a pneumatic robot (*Kintech Orthopaedics, ATD-375 TPC Iso-T Motion System*).

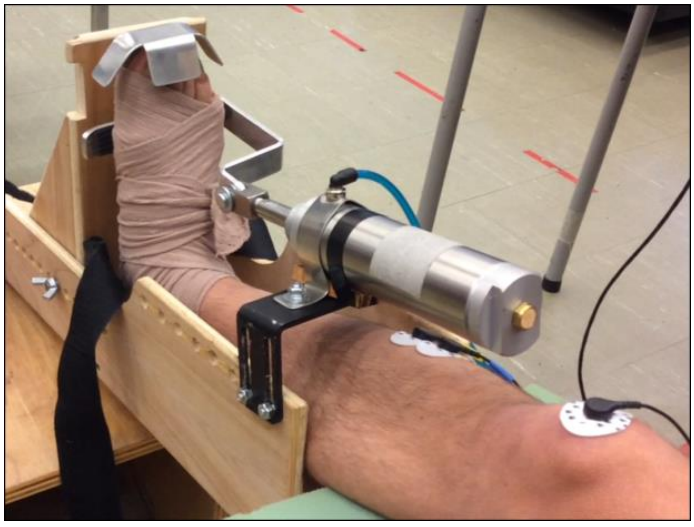

Figure 2. *Kintech Orthopaedics, ATD-375 TPC Iso-T Motion System*

A customized and comfortable fit of the robot to the ankle was provided for each individual. Slow CPM occurred at 0.5-2°/s from the ankles resting position into maximal dorsiflexion. The

device has a maximal torque of 18 Nm to hold ankle stretch for 5 seconds before releasing back to the ankle to resting position. The entire movement cycle had a frequency of 0.022Hz, yielding 42 cycles for a 30 min session. All sessions were conducted under the supervision of research team members at the Rehabilitation Neuroscience laboratory at the University of Victoria.

2.2.2 Electromyography (EMG)

Surface electrodes (Thought Technology Ltd., Montreal, QC, Canada) were placed in bipolar configuration over the muscle bellies of interest. Electrodes were placed on the skin, oriented longitudinally along the predicted fiber direction, in accordance with SENIAM procedures [21]. EMG signals were preamplified (x5000), band-pass filtered (100-300 Hz), converted to a digital signal (GRASS P511, AstroMed, West Warwick, RI, USA), and sampled at 1000 Hz using a custom-built continuous acquisition software (LabVIEW, National Instruments, Austin, TX, USA). Offline using custom-written software programs (Matlab, The Mathworks, Inc., Natick, MA, USA), EMG data were full-wave rectified and low-pass filtered at 100 Hz using a fourth-order Butterworth filter.

2.2.3 Spinal Cord Reflex Excitability Assessed by Hoffmann (H-) Reflexes

For H-reflexes, the tibial nerve was stimulated at the popliteal fossae using 1 ms square wave pulses to evoke reflexes in the soleus muscle. Bipolar surface electrodes were used for stimulation delivered pseudo randomly 3 to 5 seconds apart for all trials using a Digitimer (Medtel, NSW, Australia) constant current stimulator (model DS7A). Stimulation current was measured using a mA-2000 Noncontact Millimeter (Bell Technologies, Orlando, FL) in all trials. M-wave and H-reflex (M-H) recruitment curves consisting of 40 stimulations were collected for

each trial. These curves were used to determine the maximum compound action potential of the soleus muscle (Mmax) amplitudes to normalize data. Mmax was determined within the recruitment curves both before and after stretching and for recruitment curves with and without cutaneous stimulation to control for any change in muscle excitability throughout the experiment [22].

Many variables can influence the soleus H-reflex including: body posture [23], ipsi- and contra-lateral leg movements or muscle activity [24,25], upper limb movement [9], movements of the head [26], and talking [27]. These variables were controlled during both experiments.

2.2.4 Evaluation of Change in Reflex Excitability

Change in reflex excitability was in part determined by calculating the H_{max}/M_{max} ratio. M_{max} values used in this ratio were calculated from taking the mean of the three largest M-waves from the recruitment curve. If the 3rd largest M-wave amplitude was not within 10% of the amplitude of the largest M-wave, a mean of the 2 largest M-waves was used. H_{max} was calculated as the single largest H-reflex from the recruitment curve.

A more comprehensive evaluation of change in reflex excitability was determined using a curve fit analysis as described in previous work [28]. Briefly, the current intensities coincident with the H-reflex variables taken from the pre-training recruitment curves were used as inputs to the equations describing the post-intervention recruitment curves (where the intervention was either acute 30 min of CPM or 6-weeks of CPM training). This procedure allowed for comparison of reflex amplitudes at the same relative current intensities pre- and post-intervention, which has the largest sensitivity for detecting training-induced plasticity. That is, the presence or absence of shifts in the recruitment curve at different normalized stimulus

intensities could be investigated, and therefore motor units with different recruitment thresholds evaluated for change in sensitivity. To differentiate the description of the reflex variables taken from the fitted curves from the standard recruitment curve variables, they are described as "@" the value from control. The following predicted values were analyzed: H@thresh, reflecting recruitment of the lowest threshold motor units; H@max, reflecting recruitment of the highest threshold motor units; and H@50%, reflecting intermediary threshold units [29].

2.3 Methods – Experiment One

2.3.1 Participants

Twenty-one neurologically intact individuals (15 male, 6 female, age 24.5 ± 4.5 years) were recruited. A lab member explained the experimental protocol, including the risks and benefits of participation. These explanations were typically provided as the subject was prepared for the experiment (i.e. electrode placement onto muscles and nerves, goniometer placement). Participants were compensated for their time (approximately 75 minutes) with a lab t-shirt upon completion of the experiment. Participants provided informed written consent for this protocol, which was approved by the University of Victoria Human Research Ethics Committee and performed according to the Declaration of Helsinki.

2.3.2 EMG

EMG was used to record 3 minutes of ongoing muscle activity of the right leg from the soleus (SOL), tibialis anterior (TA), and vastus lateralis (VL) during CPM at the beginning, middle, and end of the 30 minute stretching session to determine any change in muscle activity during the CPM cycle.

2.3.3 H-Reflexes

H-reflexes were collected as described in the *Common Methods* with aspects specific to Experiment One described here.

Recruitment curves with and without cutaneous stimulation were recorded before and after CPM. Additionally, H-reflexes at constant M-wave amplitude, with and without cutaneous stimulation, were recorded before and after stretching. Reflexes were recorded by maintaining a constant M-wave amplitude at an intensity corresponding to midway along the ascending limb of the H-reflex recruitment curve, to allow both excitatory and inhibitory effects to be readily observed while also allowing for a stable Mmax [26]. Baseline and post-CPM H-reflex amplitude were calculated as the mean of 10 peak-to-peak amplitudes for each participant. A summary of the CPM, ROM, and reflex data collection protocol is provided in Appendix A.

2.3.4 Cutaneous Conditioning of H-reflexes

Stimulation of the cutaneous sural nerve was conducted using surface electrodes placed 1-2cm posterior and posterior-inferior to the lateral malleolus of the fibula of the right leg. Similar to previous studies [2,11,30] a Grass S88 stimulator with SIU5 stimulus isolation and a CCU1 constant current unit (Astro-Med Grass Instrument, West Warwick, RI, USA) were used to deliver stimulations with a single 150 ms duration train consisting of 5 x 1.0 ms square pulses at 300 Hz (P511 Astro-Med Grass Instrument). Perceptual and radiating thresholds (RT) were determined as the stimulation intensity to produce a perceptible stimulation and the point at which a stimulation produced radiating paresthesia in the entire cutaneous receptive field (lateral margin and heel). Non-noxious intensities (2 x RT) were found for each participant. The

cutaneous stimulation was delivered at 100 ms prior to the tibial nerve stimulation for the H-reflex, because this time point was determined to be optimal for reflex facilitation.

2.3.5 Evaluation of Change in Reflex Excitability

The changes in reflex excitability after CPM were evaluated using both the H_{max}/M_{max} ratios and test file variables from curve fitting as described in the *Common Methods.* H-reflexes were analyzed by comparing the effect of cutaneous conditioning, CPM, and cutaneous conditioning after CPM, to the baseline unconditioned reflexes using percent change from baseline.

2.3.6 Range of Motion

To detect joint kinematics during CPM, goniometers (Biometrics Inc., Ladysmith, VA) were used for the joints of interest. These devices were calibrated, output in degrees was determined, and data were sampled at 1000 Hz. Kinematic data were low-pass filtered at a cut-off frequency of 6 Hz with a fourth-order dual-pass Butterworth filter and were quantified by determining the range of motion by calculating the maximum and minimum angular excursions recorded throughout CPM.

2.4 Experiment Two Methods

2.4.1 *Clinical Participants*

Participants were recruited using posters displayed at the Queen Alexandra Spasticity Clinic in Victoria, BC. Inclusion criteria included having some level of ambulation and presence of severe lower limb spasticity. The initial clinical group (n=11) was composed of individuals with spasticity caused by stroke (n=6) multiple sclerosis (n=3) cerebral palsy (n=1) and spinal cord injury (n=1). For the chronic stroke group, participants were required to be a minimum six months after infarct, after spontaneous poststroke changes are thought to have occurred [31].

Participants were screened with the Physical Activity Readiness Questionnaire to determine eligibility to participate in physical activity [32]. If a response of "yes" was given for any of the questions in the questionnaire, indicating the presence of bone or joint problems or dizziness, medical permission was obtained for that participant. A list of current medications including Botulinum Toxin-A treatment schedule was obtained for each participant. Exclusion criteria included self-report of comorbidities such as any cardiovascular, musculoskeletal, respiratory or other chronic diseases. To assist with determining a participant's functional status and the clinical features of this population, clinical assessments were performed by a licensed physiatrist before continuation of the assessments. All exercise sessions were supervised by a CSEP (Canadian Society for Exercise Physiology) certified exercise physiologist and several laboratory assistants to ensure proper monitoring. Blood pressure (BP), measured with a digital blood pressure cuff over the less affected arm was taken following a rest period after arrival to the lab. If BP exceeded 140/90 mmHg, additional 5 min rest periods were given before retaking BP. Informed written consent was obtained for the protocol approved by the University of Victoria Human Research Ethics Committee and Vancouver Island Health Authority Ethics board and performed according to the Declaration of Helsinki.

Table 1: Participant Data and Clinical Assessment Parameters

N	Neurological Condition	Sex/age/MA	FACS (/6)
1	stroke, 8 years post-infarct	M/68/L	6
2	stroke, 8 years post-infarct	M/54/L	6
3	stroke, 17 years post-infarct	M/60/R	5
4	stroke, 15 years post-infarct	F/68/R	1
5	multiple sclerosis, secondary progressive	M/60/L	6
6	multiple sclerosis, relapsing remitting	F/65/R	6
7	multiple sclerosis, relapsing remitting	F/38/R	6
8	incomplete spinal cord injury, 13 years post-incident	M/65/R	5
9	cerebral palsy	M/52/L	6

MA, more affected; M, male; F, female; L, left; R, right; FAC, Functional Ambulation Category Scale.

2.4.2 Summary of Experimental Evaluations

Table 2. Summary and Order of Pre- & Post-Test Data Collection Protocol

Order	**Assessment**	**Evaluator**	**Duration**	**# of trials**
1	Introduction, consent forms & PAR-Q , HR & BP, medical history, 6-pt FACS	Lab Staff & Physiatrist	10-30 min	1
2	Modified Ashworth Scale	Physiatrist	20 min	1
4	Timed Up and Go Test	Lab Staff	5 min	2
5	10m Walk Test	Lab Staff	5 min	2
6	Strength (dorsiflexion & plantarflexion)	Lab Staff	15 min	2
7	Harness support treadmill walking with EMG	Lab Staff	30 min	1
8	H-Reflexes & 30min CPM	Lab Staff	50 min	1

2.4.3 Study Design

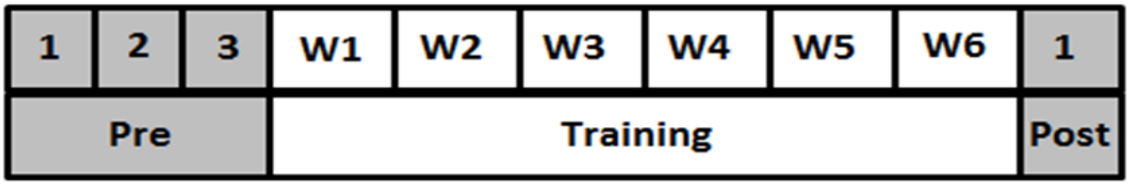

Figure 3: Illustration of the testing and training protocol. A multiple baseline within-subject control design was used for this study (individuals with spasticity)(W1=week one).

A multiple baseline within-subject control design was used for this study [9,33–35]. Multiple baseline measurements were obtained from participants in three baseline sessions over a period of 2 weeks, with a minimum of 24h between sessions. The post-test following training was performed in the same environmental conditions (i.e. temperature, noise, lighting, participant position) and session time of day was kept as constant as possible. This design allowed for the creation of a reliable and consistent pretest measure against which changes were evaluated. These measures have been previously shown to have high reliability across multiple baseline points [33] These sessions were conducted at the Rehabilitation Neuroscience Laboratory at the University of Victoria, Victoria BC.

2.4.4 Clinical Evaluations

Muscle tone on the more affected (MA) and less affected (LA) side was evaluated during following movements: ankle dorsiflexion and plantar flexion, knee flexion and extension, hip flexion, extension, adduction, and abduction. Tone was measured by a licensed physiatrist using the Modified Ashworth Scale with a graded rating of spasticity scored from 0 (flaccid) to 4 (rigid) [36]. A measure of the basic motor skills necessary for functional ambulation was derived using the 6-point Functional Ambulation Categories Scale (FACS), where a level 0 indicates that a patient is non-ambulatory and a level 5 indicates a patient is fully independent [37].

Clinical assessment of walking was performed by trained laboratory personnel. The Timed Up and Go Test [38] and timed 10 m walk test [39] were used to assess over-ground walking mobility, speed, and endurance. The Timed Up and Go Test, in addition to the extra demand of standing from a seated position, also required unique demands on neural processes involved in the control of medial-lateral stability for the purpose of turning around which are not required for

the 10 m walk test [40]. These tests were evaluated by the same individual as much as possible to limit inter-rater variability and in cases where this was not possible careful instruction on the timing protocol was delivered. Participants used the same gait aids (e.g. ankle orthosis, cane) normally used to assist with walking for these tests.

2.4.5 EMG & Strength Tests

EMG was recorded as described in the *Common Methods*. For Experiment Two, during strength, treadmill walking, CPM, and reflex collection the activity of 7 muscles were recorded: soleus (SOL), tibialis anterior (TA), and medial gastrocnemius (MG) bilaterally as well as the vastus lateralis (VL) from the MA side.

Maximal voluntary isometric contractions (MVIC) were assessed for ankle dorsiflexion and plantarflexion measured bilaterally while force and muscle activity of SOL, TA, and MG muscles were recorded with EMG. Similar to previous studies [15,16] participants were assessed while seated in a custom-fit chair designed to minimize extraneous movement. Maximum forces produced during dorsiflexion and plantarflexion contractions were established via strain gauge (Omegadyne Ltd. Model 101-500) and converted to torque using a moment arm length of 0.15 m (measured from the heel block to the center of the strain gauge). In 10-second trials, following a silent period of 5 seconds, contractions were held for each limb separately for 3 seconds. Participants completed two trials of maximum contraction for each condition. Ankle orthosis were removed for the strength tests. For analysis, maximum values were taken as the greatest reading generated within each trial by obtaining the mean value over 500 ms when force and EMG signals were highest.

2.4.6 H-Reflexes

H-reflex collection was completed as described in the *Common Methods* with specifics to Experiment Two described here. H-reflex recruitment curves were collected from both the MA and LA sides. Cutaneous stimulation and constant M-wave reflexes were not used in this experiment to manage the total duration of the evaluations. A summary of the reflex data collection protocol is provided in Appendix A.

2.4.7 Evaluation of Change in Reflex Excitability

Change in reflex excitability was compared across three conditions: 1) to assess the acute effects of CPM from the pre-training evaluation, reflexes recorded pre-CPM were compared to post-CPM; 2) to assess changes in acute effects arising from training, from the post-training evaluation, reflexes recorded pre-CPM were compared to post-CPM; and, 3) to assess global changes in reflex excitability arising from training, pre-CPM reflexes from pre-training were compared to pre-CPM reflexes post-training.

As described in the *Common Methods*, H_{max}/M_{max} ratio and curve fitting was done to determine changes in reflex excitability across conditions. Different from Experiment One is the fact that reflexes were recorded in both limbs, and there were 3 pre-tests. Therefore a mean H_{max}/M_{max} ratio was calculated from the 3 pre-training evaluations, for both pre-stretching and post-stretching recruitment curves, for the MA and LA sides.

The data from the H-reflex recruitment curves from the three pretests (each normalized to the maximal M-wave from each respective test) were pooled together to form a 120 sweep pre-CPM combined recruitment curve. This was also done for the three post-CPM recruitment curves. The combined curves account for variability in reflex excitability of each individual. To

determine the goodness of fit between the recruitment curve data collected and the generated sigmoid curve, Pearson product–moment correlation coefficient (r) values were calculated for each trial, and data sets were required to meet or exceed a criterion value of r = 0.312 for inclusion (the critical value of the correlation coefficient for a two-tailed test with level of significance at 0.05 and 38 degrees of freedom (i.e. *n-2* from 40 recruitment curve sweeps)). All trials recorded met this criterion, although some trials (n = 7) needed to be excluded from the combined curve due to failure of the current monitor during data collection. For this reason, for some participants the combined recruitment curves were composed of only 80 sweeps from 2 pretests.

2.4.8 Treadmill Walking

Similar to previously reported methods [2,9] participants walked at a self-selected ("comfortable") speed on a motorized treadmill (Woodway USA, Waukesha, WI) while wearing an overhead safety harness (Pneu-Weight, Pneumex Inc., Sandpoint, ID, USA). All participants wore the safety harness without body weight support both before and after the intervention and most wore an ankle foot orthosis. Participants were free to use hand-held railings in front or beside them during the trial and arm position did not change between pre- and the post-test. The self-selected treadmill speed (0.01 - 0.8 mph) was held constant for that participant for pre- and post-training tests to control for the effects of change in treadmill speed with change in EMG [41]. Similar to other studies [42–45] custom-made force sensing resistors (FSR) (model 1027-1001-ND, Digi-Key, Thief River Falls, MN, USA) were inserted into both shoes under the heel and first metatarsal head of each foot. FSR signals from the heel strike were used to determine stride duration and stride frequency (the average number of strides taken in one second).

2.4.9 CPM during Laboratory Evaluations

A description of CPM was provided in the Common Methods. The three pre- and single post-intervention evaluations involved CPM of the MA limb.

2.4.10 CPM Training Intervention

Participants performed CPM three times a week, with 30 min of total activity time per session, for a total of 6 weeks. Most participants completed training on Monday, Wednesday, and Friday at the same time each day. For training, the same CPM device as described in the *Common Methods* was used, with the exception that both ankles rather than just the MA side were stretched. The CPM training was well-tolerated. All training sessions were supervised by research team members at the Queen Alexandra Centre Spasticity Clinic in Victoria, BC.

2.4.11 Statistics

Using commercially available software (SPSS 18.0, Chicago, IL), pre-test and post-test data were compared. To evaluate the extent to which 6 weeks of CPM altered walking ability, post-test data were compared to the 95% confidence interval (CI) created from three pretest sessions and compared to a pre-test average, individually, for each participant. To establish the 95% CI for each measure, variability was computed from 3 pre-test sessions and used to create a data range with which the post-test value was compared. If data were missing from one of the pre-tests, the CI was created from 2 pre-test sessions. If the post-test value fell outside the 95% CI range, it was considered significant for that participant. The total number of participants with a significant test outcome is reported in Table 3.

For pretest data of walking tests and parameters, strength tests, and H_{max}/M_{max} ratio's, a repeated measure's ANOVA was performed to assess difference across the three pretest

sessions. Pre-test data were pooled together to create an average pretest value and compared to post-tests values with paired-samples t-tests with significance (*p)* reported. The observed effect for post-test differences is also reported as Cohen's effect size (*d)*, where a small effect size is $d = 0.2$, a medium effect is $d = 0.5$, and a large effect is $d = 0.8$ [46]. Statistical significance was set at $p \leq 0.05$. Paired t-tests were conducted to determine difference between variables of the pre-test combined recruitment curve and the post-test recruitment curve variables. A 2-way repeated measure's ANOVA with pooled data from the MA and LA sides was also conducted to determine significant changes to recruitment curve variables following acute unilateral CPM.

2.5 Results – **Experiment One**

2.5.1 CPM and Reflex Excitability

The main finding of Experiment 1 was 30 min of CPM of the ankle joint significantly altered spinal cord excitability, as shown by changes in the H-reflex amplitude, in 19 of 21 neurologically intact participants. The average change in reflex amplitude among all participants following CPM was insignificant: 3.3 ± 37.3% (mean ± standard deviation) increase in H-reflex amplitude, for the reflexes recorded at constant M-wave amplitude (n=21). However, CPM produced a bi-directional modulation of H-reflex amplitude in different subjects creating 'facilitation' (n=12) and 'suppression' (n=9) groups, each with significant change from baseline ($p<0.05$). There was no significant difference between these two groups in age, sex, baseline ankle range of motion, range of motion during CPM, muscle activity during CPM (i.e. of soleus, tibialis anterior, and vastus lateralis), or baseline H_{max}/M_{max} ratio.

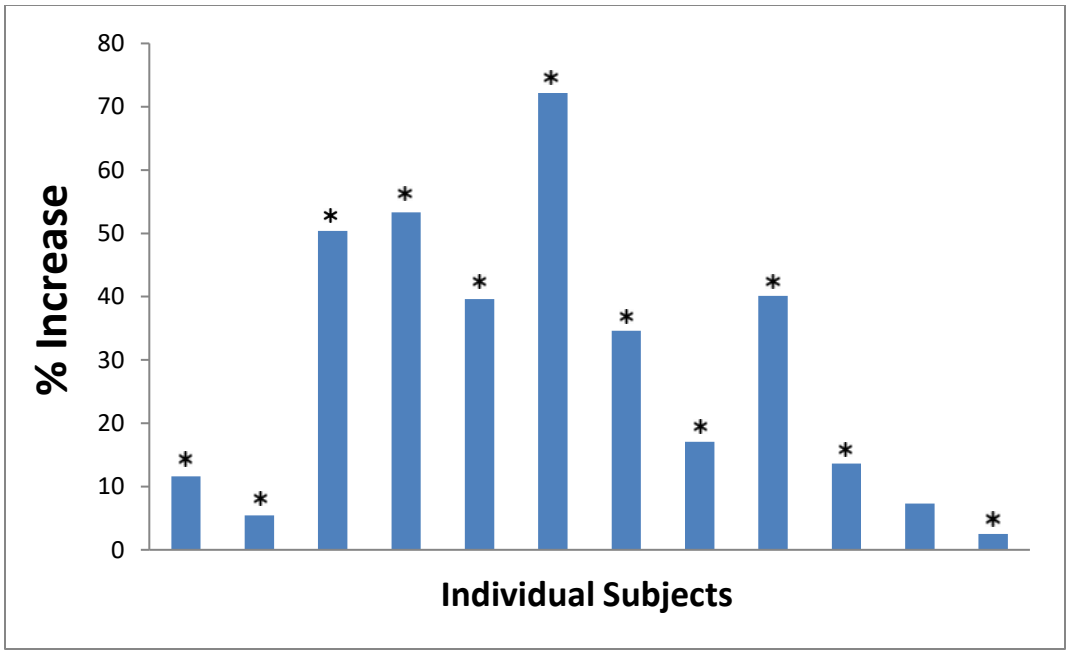

Figure 4. 'Facilitation' group showing increase in size of the soleus H-reflex amplitude following 30 min of CPM in 12 subjects (neurologically intact). Asterisk indicates significant difference ($p<0.05$).

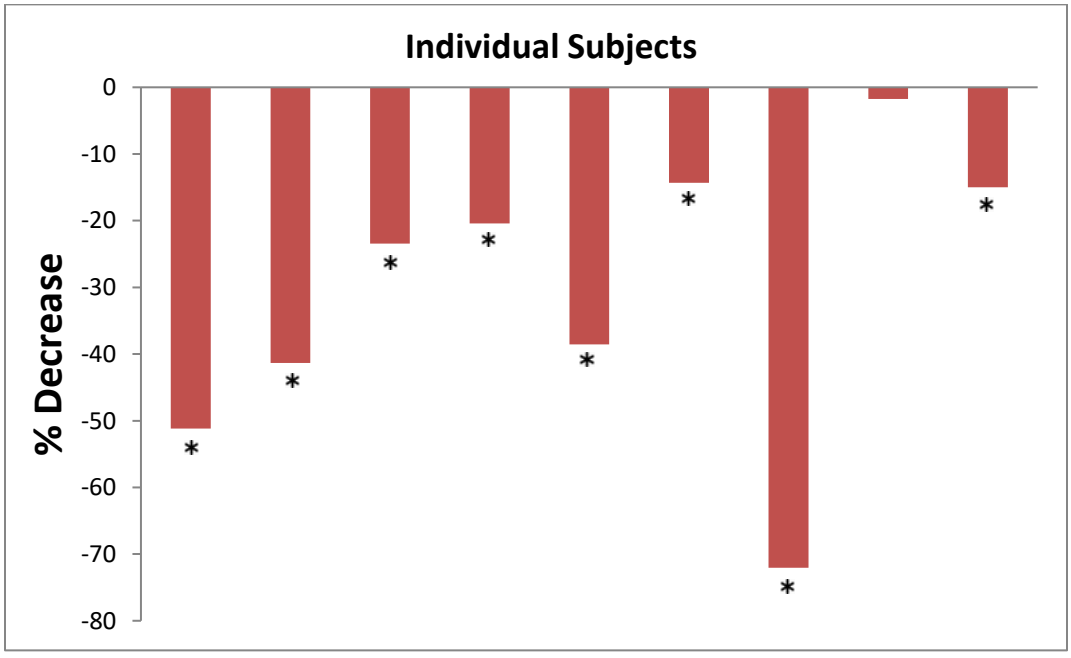

Figure 5. 'Suppression' group showing decrease in size of the soleus H-reflex following 30 min CPM in 9 subjects (neurologically intact). Asterisk indicates significant difference ($p<0.05$).

As shown in Figure 4, amongst participants in the 'facilitation' group, there was a 31.4 ± 20.9% increase in H-reflex amplitude immediately following 30 min of CPM. As shown in Figure 5, amongst participants in the 'suppression group', there was a 32.9 ± 21.0% decrease in H-reflex amplitude from baseline.

2.5.2 Effects of Cutaneous Stimulation

Sural conditioning significantly increased H-reflex amplitude in 15 of 21 participants, with a group effect of 13.1 ± 14.6% increase in amplitude at constant M-wave amplitude for the baseline recordings. Following CPM, sural conditioning significantly increased H-reflex amplitude by 11.0 ± 32.8% (not significantly different from baseline effect).

A separate analysis for the 'facilitation' and 'suppression' groups was done to determine potential different conditioning effects between the groups. At baseline, sural conditioning increased H-reflex amplitude by 11.8 ± 11.8% and 14.3 ± 15.9% for the facilitation group and suppression group, respectively, indicating no difference in conditioning effect between groups before CPM. After CPM, conditioning increased reflexes by 5.6 ± 13.1% and 32.7 ± 28.7% for the facilitation group (see Figure 4) and suppression group (see Figure 5), respectively. Paired *t*-tests revealed the effect of conditioning for both groups was not significantly different from the conditioning effect at baseline.

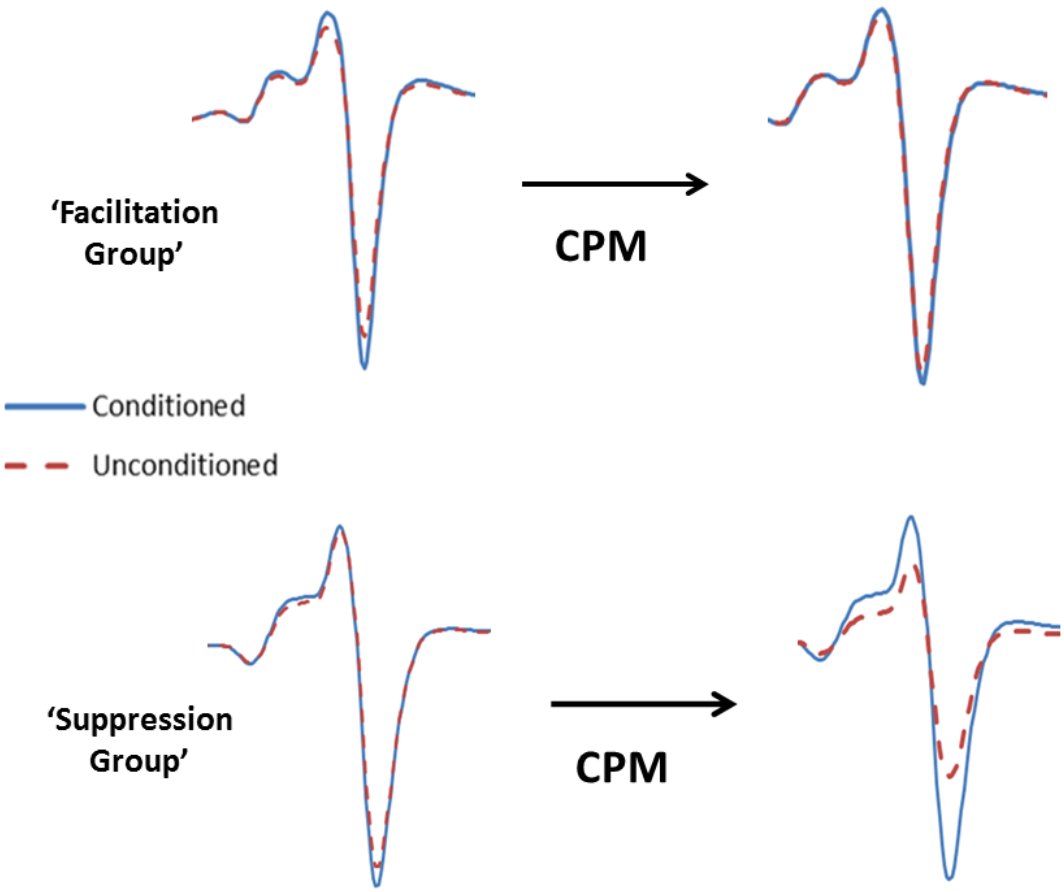

Figure 6. Example of the effect of sural conditioning of the H-reflex before and after CPM in neurologically intact subjects. One example of a participant from the 'facilitation' group and one example of a participant from the 'suppression' group.

Following 30 min of CPM the effect of sural conditioning was significantly increased for 5/9 individuals from the 'suppression' group and significantly decreased for 5/12 participants in the 'facilitation' group, see single subject samples in Figure 6. Cohens effect size was determined as d= 0.05 (trivial) and d= 0.50 (moderate) for these changes in conditioning for the 'suppression' and 'facilitation' groups, respectively.

2.5.3 Range of Motion

The ankle joint ROM did not change during or following CPM from baseline.

2.6 Results – Experiment Two

A total of 11 participants were recruited. Following the pre-tests, two participants withdrew from the research due to injuries obtained outside of the study which prevented further participation. Baseline and demographic data are reported for the remaining 9 participants who completed the study (see Table 1).

2.6.1 Training Results

The training protocol included a total of 18 bilateral CPM training sessions taking place over 6 weeks. Some sessions were missed due to illness or inaccessible transportation to the spasticity clinic: 4 participants completed all 18 sessions, 3 participants completed 17, and 2 participants completed 16 sessions. CPM of the LA ankle provided a mean ± standard deviation of 21.6 ± 3.3 degrees of movement, while the MA ankle was moved through 14.9 ± 4.4 degrees. The minimum movement within the group was 9 degrees of the MA ankle for one participant with significant contracture. ROM provided by CPM did not significantly change throughout the 30 min sessions.

2.6.2 Single-Participant Analysis

Table 2 summarizes results of from the single-participant statistical tests discussed below. The number of participants with a significantly increased or decreased post-test outcome is reported for each variable in the table. The 3 pretest measures for each variable were used to create a 95% confidence interval. If the post-test result fell outside the confidence interval, it was determined to be a significant change.

Table 3. Single-Subject Analysis (n = 9) (participants with spasticity)

Measure	Number of participants with significant decrease in variable post-CPM training	Number of participants with significant increase in variable post-CPM training
Timed Up and Go	4	1
10m Walk test	5	1
MA plantarflexion force	3	4
MA dorsiflexion force	1	2
LA plantarflexion force	3	4
LA dorsiflexion force	1	3
LA stride duration	3	3
LA stride frequency	2	3
MA stride duration	2	3
MA stride frequency	3	3

2.6.3 Clinical Measures

8 participants completed the clinical walking tasks (one participant could not safely participate). The time to complete the 10 m Walk Test decreased with a small effect size (5.2 ± 7.9% change, $p = 0.06$, and $d = 0.22$). Participants completed test in 10.5 ± 3.0 seconds before training and 9.8 ± 2.4 seconds after training. The repeated measures ANOVA determined a significant difference between pretest 1 and pretest 2. Time taken for the TUG test also decreased (9.5 ± 12.3% change, $p < 0.05$, and $d = 0.50$) with a moderate effect size. Participants completed the test in 14.6 ± 3.0 sec before training and 13.0 ± 1.9 sec after training. There was a significant difference between pretest 1 and pretest 3.

Table 4. Modified Ashworth Scale Scores: Dorsiflexion with Knee Extended

	P1	P2	P3	P4	P5	P6	P7	P8	P9
Pre 1	1	2	1+	4	2	0	3	3	0
Pre 2	0	3	1+	4	1+	1+	2	3	1+
Pre 3	0	3	1+	4	2	1+	1+	3	0
Post	1	0 *	0 *	4	2	0	0 *	3	0

Asterisk indicates post-test score lower than all pre-test scores

Table 5. Modified Ashworth Scale Scores: Dorsiflexion with Knee Flexed

	P1	P2	P3	P4	P5	P6	P7	P8	P9
Pre 1	0	2	0	4	1+	1+	3	3	0
Pre 2	1	2	1	4	1+	2	3	3	1
Pre 3	0	3	1	4	1	1+	0	3	0
Post	0	0 *	0	4	2	0 *	0	3	0

Asterisk indicates post-test score lower than all pre-test scores

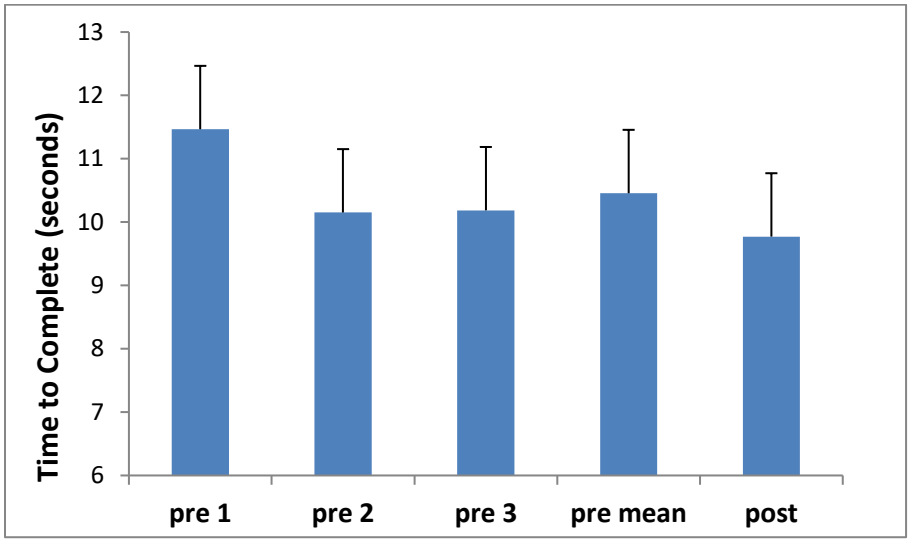

Figure 7. Average time to complete 10 m Walk Test (participants with spasticity).

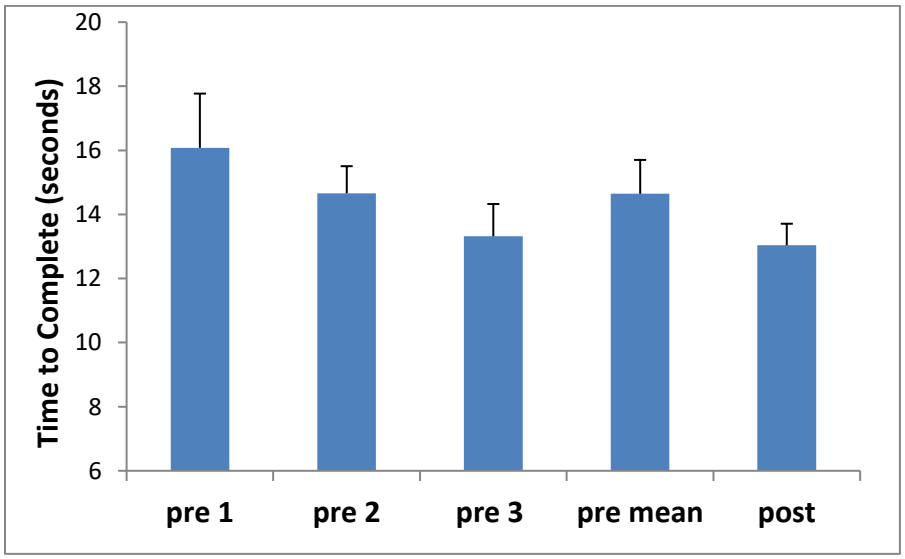

Figure 8. Average time to complete Timed Up and Go Test (participants with spasticity).

Modified Ashworth Scale scores are reported for the movements where a post-test score lower than all pre-test scores occurred for at least 1 participant. For the movements *dorsiflexion with the knee extended* and *dorsiflexion with knee flexed* there were 3 and 2 participants who met this criterion, respectively.

2.6.4 Strength

There was no statistically significant change in plantarflexion or dorsiflexion force production during maximal voluntary isometric contractions (MVIC) on either the MA or LA side. No significant differences were found for pretest baseline data. Following training, plantarflexion force on the MA side was (90.0 ± 218.8% change $p = 0.52$, and $d = 0.27$) and on the LA side (11.5 ± 81.9% change $p = 0.87$, and $d = 0.08$). Dorsiflexion force on the MA side was (0.36 ± 51.6% change $p = 0.97$, and $d = 0.01$) and on the LA side (4.1 ± 74.5% change $p = 0.78$, and $d = 0.10$).

2.6.5 Treadmill Walking

There were no statistically significant changes in walking parameters including average stride duration and stride frequency for the MA or LA side following training. No significant differences were found for pretest baseline data. Stride duration during treadmill walking decreased on the MA side (1.8 ± 7.1% change $p = 0.32$, and $d = 0.07$) while stride frequency increased (2.1 ± 7.4% change $p = 0.76$, and $d = 0.02$). On the LA side stride duration increased (0.34 ± 6.4% change $p = 0.83$, and $d = 0.01$) with a decrease in frequency (0.1 ± 6.3% change $p = 0.80$, and $d = 0.02$).

2.6.6 H-Reflex Excitability –Acute CPM

The group percent change in recruitment curve variables across the ascending limb for the MA and LA sides following acute CPM of the MA side only are shown in Figure 9. In 2-way repeated

measures ANOVA with pooled data from the MA and LA sides, it was determined pre-training acute CPM significantly increased H@Thres and H@50. However, there was no significant effect of CPM on these variable post-training. As shown in Figure 9, there was a similar increase in reflex excitability following acute CPM to both limbs. It is also evident that CPM increased H@Thres significantly more than H@50 and H@100. The high variability in the acute effect of CPM on H@Thres is a similar result to the effect of acute CPM on neurologically intact individuals, where a bi-modal distribution with 'facilitation' and 'suppression' groups occurred. As shown in Figure 10, some participants had increased excitability at the foot of the ascending limb while others had decreased excitability.

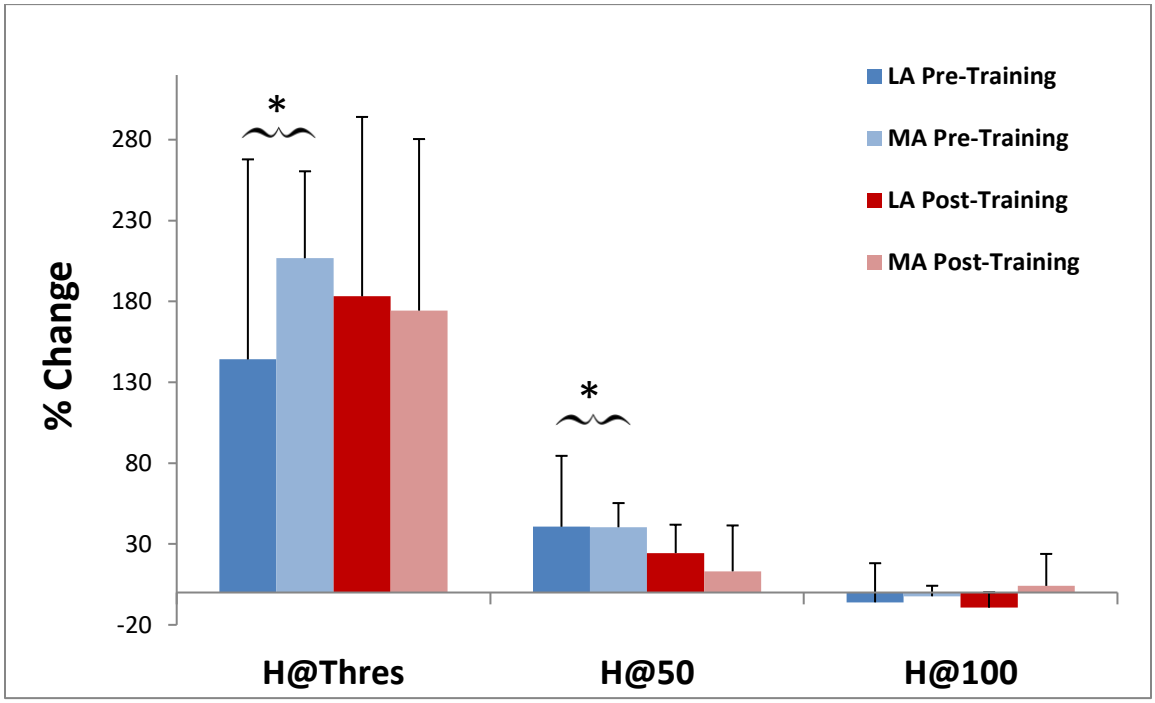

Figure 9. The acute effect of unilateral CPM on change in amplitude of H-reflex at various points of the recruitment curve ascending limb (participants with spasticity). *Asterisk indicates significant difference ($p<0.05$).*

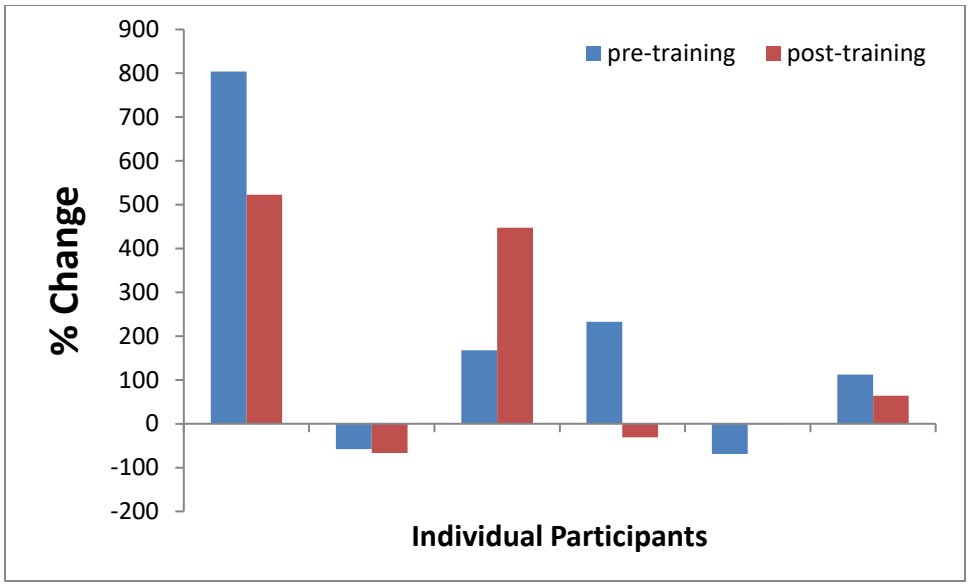

Figure 10. The acute effect of unilateral CPM on H@Thres of the MA side among 6 participants (with spasticity) before and after 6 weeks of bilateral CPM training.

The acute effect of 30 min of CPM to the MA side H_{max}/M_{max} was a decrease of 2.6 ± 19.4% during the pre-tests and an increase of 5.0 ± 35.3% in the post test. For the LA side that did not receive CPM, there was a 3.3 ± 34.0% decrease pre-training and 13.3 ± 23.3% decrease post-training. There were no statistically significant differences between pre- and post-training ratios for either side. No significant differences were found for pretest baseline data.

2.6.7 H-Reflex Excitability – Effect of CPM Training

The H-reflex recruitment curve analysis shows a significant decrease in baseline H-reflex excitability following 6 weeks of CPM training. The H-reflexes and M-waves from the recruitment curve for one participant is shown in Figure 11. The MA side has hyperexcitable reflexes relative to the LA side. An example of one participant's baseline soleus H-reflex recruitment curve from the 3 combined pre-tests and the post-test is shown in Figure 12 and Figure 13 for the right and left sides, respectively (for this individual both sides are spastic due

to progressive MS). It is clear in both figures that the curve from the post-test is shifted to the right, indicating greater relative stimulus intensity was required to obtain the same H-reflex amplitude throughout the ascending limb.

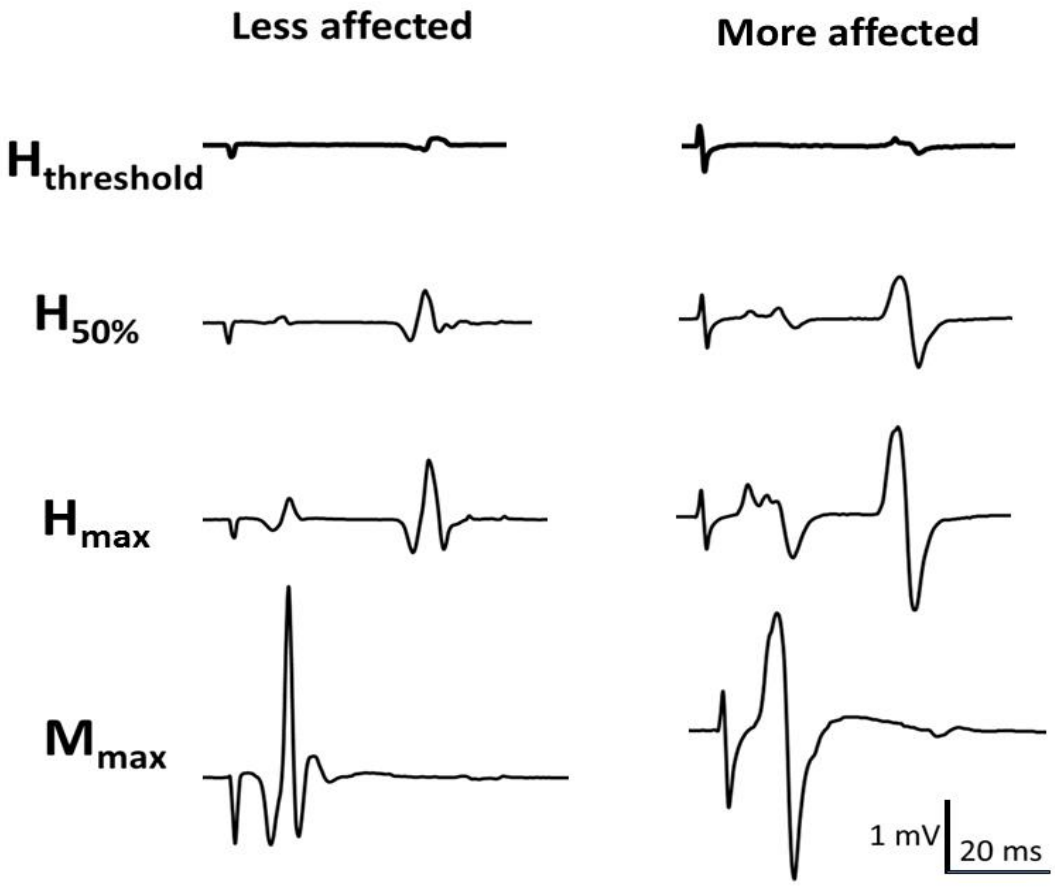

Figure 11. One participant's pre-CPM M-wave and H-reflexes on the MA and LA side.

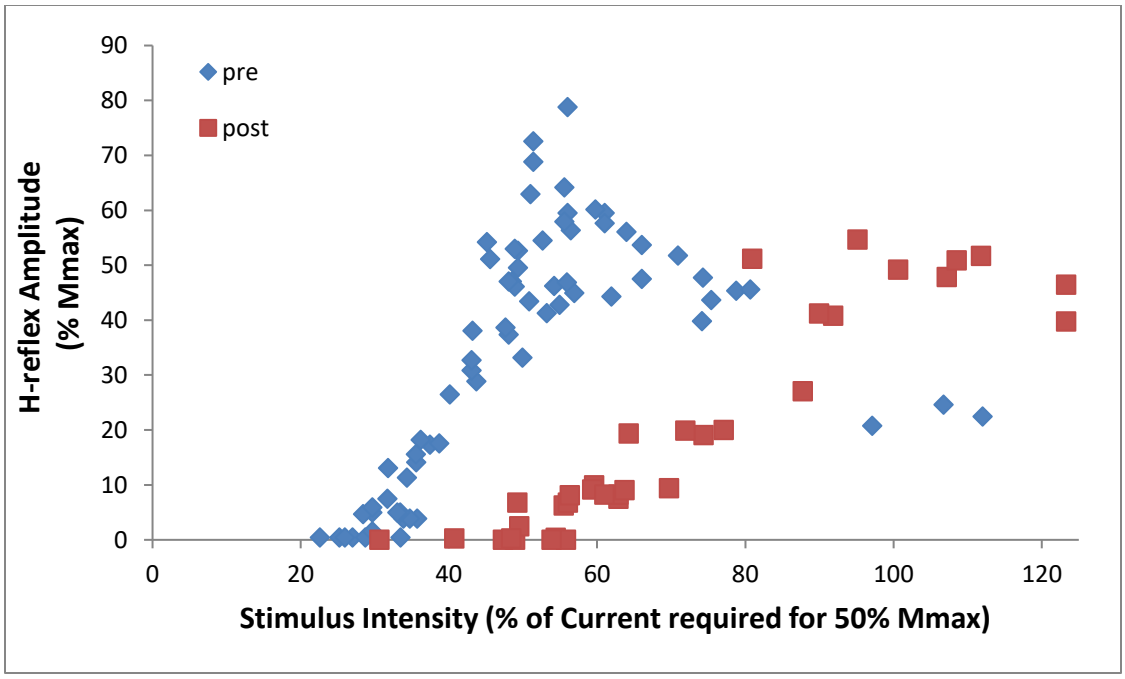

Figure 12. H-reflex recruitment curve of right soleus pre- and post-training (in spasticity).

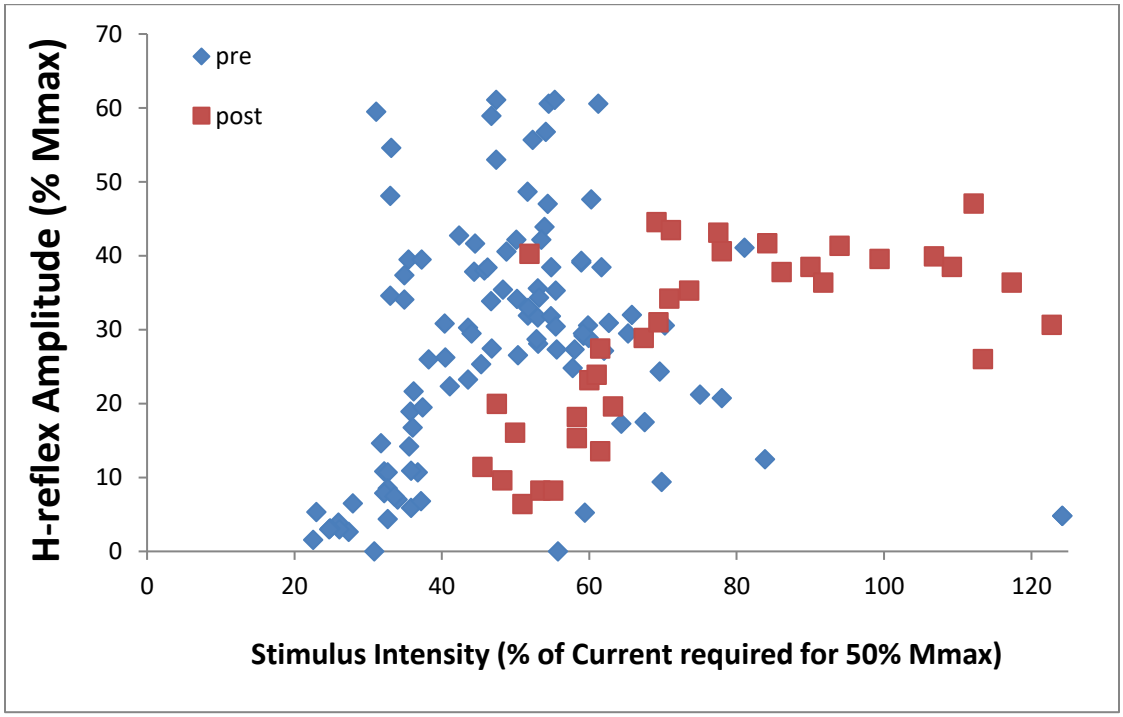

Figure 13. H-reflex recruitment curve of left soleus pre- and post-training (in spasticity).

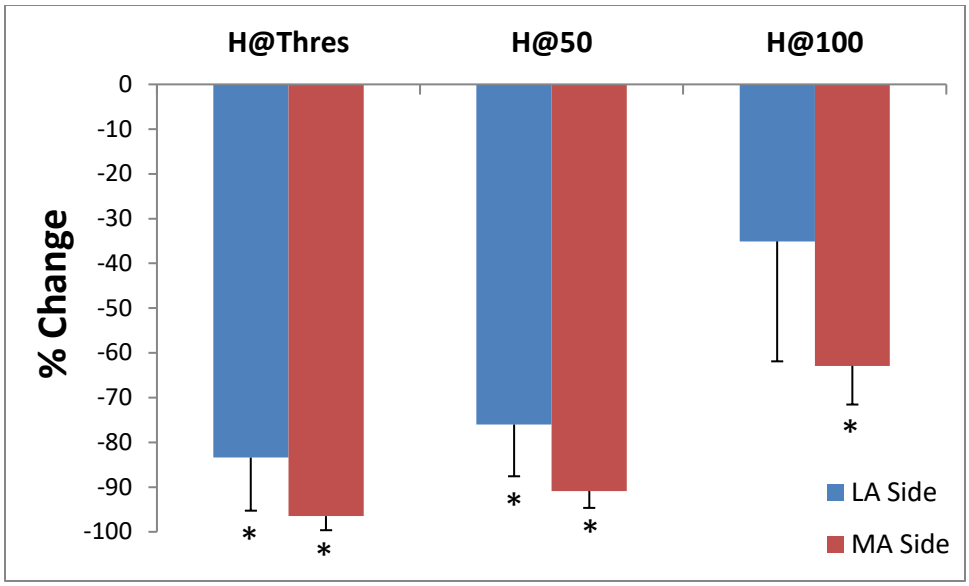

Figure 14. Mean change in amplitude of H-reflex at various points of the recruitment curve ascending limb following CPM training in spasticity. *Asterisk indicates significant difference (p<0.05)*

The group percent change in recruitment curve variables across the ascending limb for the MA and LA sides are shown in Figure 14. On the MA side H@Thres, H@50 and H@100 all significantly decreased following CPM training by 96.5 ± 7.7%, 90.9 ± 9.2%, and 62.9 ± 21.1%, respectively. On the LA side there was a significant decrease in H@Thres and H@50 by 83.4 ± 29.0% and 76.0 ± 28.3%.

The H_{max}/M_{max} ratios from the MA side (n = 8), taken from pre-CPM recruitment curves, did not significantly change following CPM training (51.2 ± 19.3% pre- and 52.3 ± 24.1% post-training, *d* = 0.05). On the LA side there was a decrease in the ratio with a small effect size (48.1 ± 21.2% pre- and 39.8 ± 20.0% post-training, *d* = 0.40). No significant differences were found for pretest baseline data.

2.7 Discussion

2.7.1 Changes to H-Reflex Excitability

The main observation from this study is that CPM of the ankle can significantly alter spinal cord excitability. H-reflex amplitudes were altered in both neurologically intact individuals and participants with lower limb spasticity. Within both of these cohorts there were bidirectional responses: some participants had increased while others had decreased reflex excitability. In Experiment Two there were significantly increased H-reflex amplitudes in the acute response to CPM. After the 6 weeks of CPM training there was no significant effect. Training resulted in a significant overall decrease in pre-CPM H-reflex amplitude on both the MA and LA sides.

The result of a bi-modal effect for neurologically intact individuals and significantly increased reflex excitability following acute passive movement in participants with spasticity is inconsistent with previous research which display a decrease in reflex excitability as a result of acute passive movement [8,10,16,47,48]. This may be related to the unique slow single joint CPM of the current study. Additionally, earlier studies did not typically conduct single subject data analysis and some similar results may be embedded in earlier data. The finding of a prolonged depression of H-reflex excitability following CPM training is of interest because previous work investigating the H-reflex after 4 weeks of passive leg cycling reported no change to H_{max}/M_{max} ratios [7].

2.7.2 IaPSI as the Site of Modulation

A probable candidate for the modulation of the H-reflex is IaPSI induced by CPM [47,49]. Experiment One suggests this mechanism because resting soleus EMG activity was not different following CPM, indicating no change in alpha motoneuron excitability due to a post-synaptic

mechanism. Further, the effect of inhibiting IaPSI by conditioning the H-reflex with sural stimulation was altered following CPM. This is evidence that CPM of the ankle and sural nerve conditioning share a common presynaptic pathway.

The IaPSI following CPM also likely extends to the contralateral side. This is supported by the fact that in the current study, acute CPM occurred only at the MA ankle, yet H-reflex modulation occurred similarly to both the MA and LA sides. It has previously been shown during single leg passive cycling, Ia afferent feedback from activation of muscle spindle receptors in the quadriceps modulates the ipsilateral and contralateral soleus H-reflex [48] and because this also occurs in those with quadriplegia and complete lesions [50] a spinal pathway is suggested.

The source of the afferent feedback to drive modulation of IaPSI is less clear. There are numerous convergent inputs onto Ia presynaptic interneurons, and the current experiments were not designed to elucidate the source of this input. However, based on the nature of the movement and previous research, some sources are more likely involved than others.

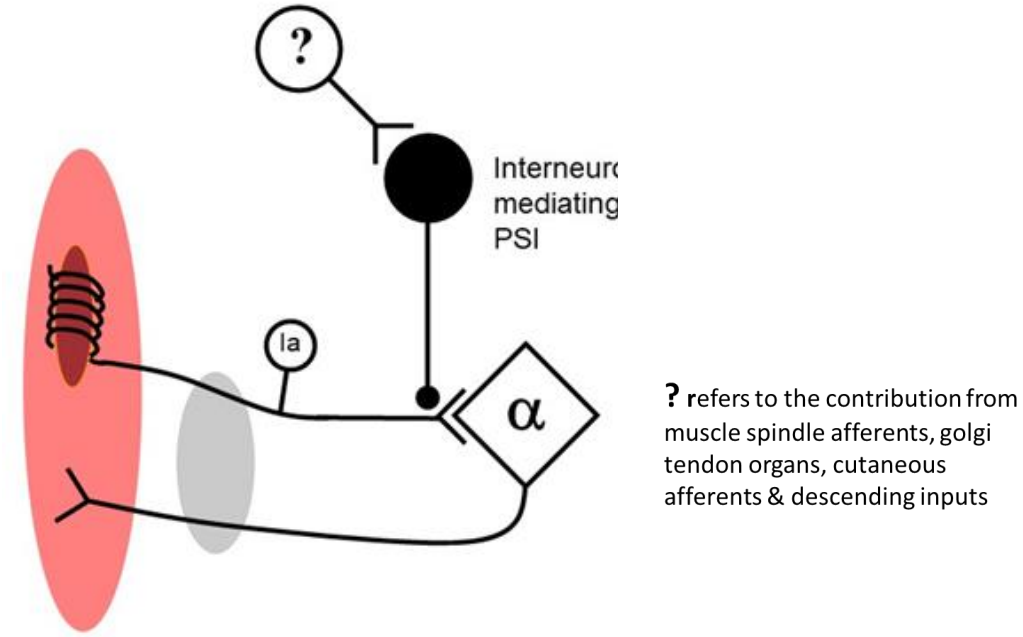

Figure 15. The mechanism of Ia presynaptic inhibition from an unknown source of afferent input. (Figure adapted from Zehr, 2002) [27]

2.7.3 Muscle Spindles as the Source of Input

The primary sensory endings of large diameter Ia afferent fibres relay highly sensitive changes in length of muscle fibres, and are a primary candidate as the source of input to modulate IaPSI. The CPM produced in the current study provided very slow continuous ankle oscillation, presumably inducing gradual length change to the triceps surae muscle fibres. This would likely cause ongoing activation of the Ia afferents. Work in reduced cat preparations show changes to the length of the lateral gastrocnemius muscle alone can produce IaPSI in the soleus and medial gastrocnemius [51,52].

Group II muscle afferents are also involved in modulation of afferent transmission and subsequent reflex modulation [53]. These afferents primarily indicate changes in static muscle

length [54], therefore likely had increased activity from muscle spindle discharge when the CPM device reached and held the stretch of the plantar flexors.

The influence of Ib afferents of Golgi Tendon Organs are not likely the cause of reflex modulation because although they are sensitive to small changes in muscle tension, they predominantly discharge during active muscle contractions, and EMG data suggests muscle activity did not change following CPM [54].

2.7.4 Cutaneous Mechanoreceptors

The CPM delivered in this study likely increased afferent feedback from cutaneous mechanoreceptors due to both the pressure produced below the foot and also the stretch of soft tissues, including the skin, produced by passive stretching [54–56]. Due to the slow stretch provided by CPM in the current study, cutaneous receptors are not likely the predominant source of input.

2.7.5 Muscle Activity Following CPM

Descending input during antagonist contraction causes excitation of inhibitory interneurons via collateral axons structurally organized to allow higher centers to send a single command for a voluntary movement (reciprocal inhibition) [57]. Therefore, increased TA activity could inhibit the H-reflex via reciprocal inhibition to the soleus motoneuron pool through the Ia inhibitory interneuron [25,58,59] or increased IaPSI [58,60]. In Experiment One EMG was used to monitor activity of TA and SOL and to calculate the ratio of activity between these muscles during the reflex recordings. The TA/SOL EMG activity ratio did not change pre- to post-CPM, suggesting changes in TA activity was not leading to alterations in spinal cord pathways. CPM did not alter the ratio between SOL and VL, indicating that afferent feedback from proximal heterogeneous muscles

was likely not driving the modulation of H-reflex amplitudes. In summary, changes in muscle activity from any muscle group and reciprocal inhibition from antagonists likely did not contribute afferent feedback responsible for soleus IaPSI.

2.7.6 Other Sources of Modulation

Some studies suggest post-activation depression (a form of neural fatigue where following repetitive afferent firing there is depletion of the neurotransmitters available at the Ia axon presynaptic terminal), can explain a reduction in H-reflex magnitude following a protocol that increases transmission in this pathway [61,62]. Although it is presumed CPM did cause repetitive activation of Ia afferents, this is unlikely the mechanism behind the acute depression of the H-reflex for subjects in the current study because reflexes were recorded approximately 40 seconds post-CPM while post-activation depression is suggested to persist for at most 10 seconds [62].

The afferent feedback generated by CPM is not contained in the spinal cord; proprioceptive input from limb movements can activate various cortical areas [47,54]. With IaPSI known to be a modulatory site for descending influence on the stretch reflex pathway [54], - it is possible ascending afferent feedback from CPM altered descending influence on IaPSI. This source of input cannot be ruled out.

2.7.7 The Bi-Modal Response to Acute CPM

The resting level of IaPSI in humans is unknown. It is likely there is significant variability within the population in the level of tonic resting IaPSI based on physiological differences such as training status, muscle characteristics, or neurological condition. Consequently, some individuals may be at the higher end of this human IaPSI operating range, while others may be

at the lower end. For those at the high end of this range, the level of inhibition may be reduced by CPM while individuals at the low end of this range may have increased IaPSI induced by the movement. The H-reflexes conditioned by cutaneous stimulation (which decreases IaPSI) offer support for this interpretation. Half of those with an initial high level of IaPSI had a significantly decreased conditioning effect post-CPM (perhaps because IaPSI was already near a floor level). Half of the other group had a significantly larger conditioning effect post-CPM, consistent with the proposal that the movement increased IaPSI and the conditioning was then able to partially return the inhibition towards resting levels. A high variability in reflex modulation following passive movement of the triceps surae has been previously reported [63].

2.7.8 Acute Facilitation and Chronic Depression of H-Reflex Amplitudes

Acute CPM likely increased afferent feedback which may have led to a decrease in IaPSI through an interneuron responsible for transforming the excitatory input of the afferent into an inhibitory input to the Ia presynaptic inhibitory interneuron, similar to the sural nerve pathway [64]. The immobility often occurring in those with spasticity could likely leave the neural circuitry of this pathway highly inactive, which may produce a state primed for plasticity. Repeated activation of this pathway with CPM training may have led to spinal plasticity responsible for the depression in excitability observed before CPM in the post-training test. The neurons in this pathway repeatedly exposed to a new stimulus may have adapted to prevent the disruption of homeostasis evoked by the stimulus. An analogy for this speculation is the phenomenon where acutely after physical exercise there is an elevation of heart-rate, though chronic exercise can lead to a decrease in resting heart-rate due to the physiological adaptations which occur following training [65].

2.7.9 Clinical Measures and Strength

Following CPM training there was a significant decrease in time taken to complete the 10 m Walk and TUG tests for 5/8 and 4/8 participants, respectively. The group results showed a significant improvement in TUG but not for the 10 m Walk. Modified Ashworth Scale scores of dorsiflexion were significantly reduced in 4/9 participants. These improvements in clinical outcomes following CPM training are consistent with the results of previous studies involving similar passive movement of the ankle in spasticity [16,17,66]. In a recent study spasticity was found to be decreased for 45 min following CPM of the quadriceps muscles [67]. These findings may suggest a transfer of reduced reflex excitability to functional tasks.

Some participants had changes in stride duration and frequency, although there was no trend to the direction of change and no significant effect for the group. This finding contrasts the results of an arm and leg cycling training intervention in those with spasticity which resulted in a significant decrease in stride duration and increase in stride frequency on the MA and LA sides [9]. It is difficult to draw any conclusions from these data.

Similarly, there were no significant changes in the group to dorsiflexion or plantarflexion strength on the MA or LA side, although some individual participants had significant changes. A lack of significant change in force production is not surprising, in a review of the literature on muscle stretching in spasticity it is evident that muscle strength is not typically included as an outcome measure following stretching interventions for spasticity [14].

2.7.10 Conclusion and Future Directions

In summary, unilateral CPM of the ankle was found to modulate H-reflex excitability in a bi-modal manner, to both the ipsilateral and contralateral limb. In 18 sessions of bilateral CPM

training in participants with lower limb spasticity, a significant decrease in reflex excitability was observed. Further, 7 out of 9 participants who completed the training had a significant improvement in at least 1 of the clinical assessments.

The findings of this thesis lead to a variety of future directions worth pursuing to gain a deeper understanding of the benefit of CPM as a therapy for lower limb spasticity. The following questions are of specific interest to build on the present work:

What is the source of the modulation of the H-reflex following CPM and why is there bi-modal modulation following acute CPM among participants? Is the mechanism responsible for the increase in H-reflex excitability after acute CPM related to the presumed neural adaptations occurring to produce decreased H-reflex excitability after chronic CPM?

Why did the CPM training improve clinical outcomes in some participants but not in others? Are there some neurological conditions for which this intervention is more beneficial? Would an increased dosage of CPM training lead to improved outcomes compared to those of the current study? How long does the depression of excitability last following training?

Finally, the culmination of this thesis was implementation of the proof of principle that CPM of the ankle can alter spinal cord excitability with both an acute and chronic effect in individuals with lower limb spasticity, which can be associated with improvements in clinical outcomes.

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Appendix A: Reflex Collection Protocol

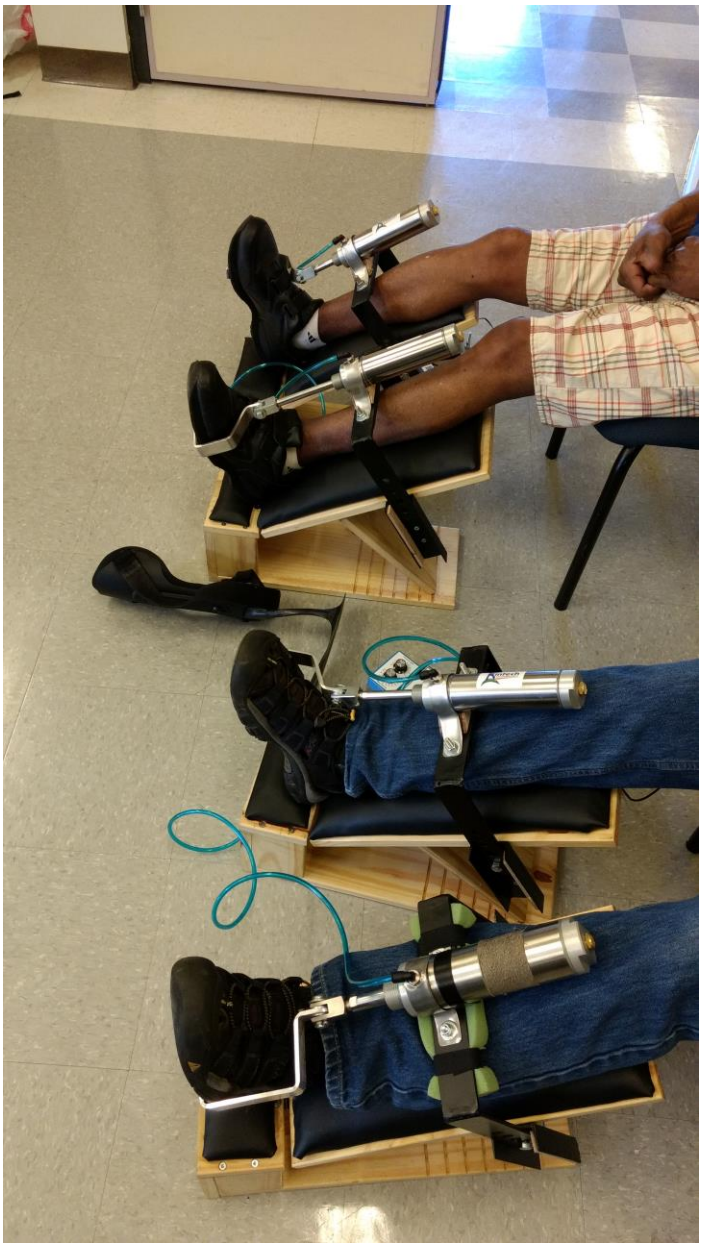
Overview of CPM Protocol and Reflex Data Collection – Experiment One

- Subject prepared and fitted to the device, cutaneous stimulation intensities determined
- H-reflex recruitment curve (40 sweeps)
- H-reflex recruitment curve with cutaneous stimulation (40 sweeps)
- 10 steady-state H-reflexes
- 10 steady-state H-reflexes with cutaneous stimulation
- 30min CPM begins
- 10 Steady state H-reflexes (no cutaneous stimulation) recorded in the rest period after a stretching cycle during the middle of the stretching protocol
- 30min CPM culminates
- 10 steady-state H-reflexes with cutaneous stimulation
- 10 steady-state H-reflexes
- H-reflex recruitment curve with cutaneous stimulation (40 sweeps)
- H-reflex recruitment curve (40 sweeps)

Overview of Reflex Data Collection – Experiment Two

- Subject prepared and fitted to the device
- H-reflex recruitment curve (40 sweeps)
- 30min CPM
- H-reflex recruitment curve (40 sweeps)

Appendix B: CPM Training Set-Up at QA Spasticity Clinic



Appendix C: Consent Form

Efficacy of Novel Movement Treatment Regimes in Decreasing Spasticity

You are invited to participate in a study entitled *Efficacy of Novel Movement Treatment Regimes in Decreasing Spasticity* that is being conducted by Steven Noble, Dr. Caroline Quartly and Dr. Paul Zehr.

Steven Noble is a Graduate student enrolled in a Master's of Science (Neuroscience) in the department of Exercise Physical and Health Education at the University of Victoria, and is the primary contact for any questions regarding this study. You may contact him if you have further questions by email or phone at rnl@uvic.ca or 250-472-5487. As a graduate student he is required to conduct research as part of the degree requirements. This research is being conducted under the supervision of Dr. E. Paul Zehr.

This research is being partially funded by a collaborative research grant from the Vancouver Island Health Authority.

Purpose and Objectives
The purpose and goal of this research project is to test if exercising one limb on a special machine (single limb oscillation) can improve range of motion and mobility. This "oscillation training" will involve sitting in a chair and putting the foot into a cuff attached to a piston, which will shorten to flex your leg muscles (like pointing your toes upwards). This motion stretches the lower leg muscles in a cycle which lasts approximetly 1 minute, and is repeated for 30 minutes. The stretch is pain-free.

Certain neurological conditions cause problems during walking and changes in arm and leg coordination. Because of this, there can be flexed postures of one arm and one foot that often scuffs the floor when walking. These are combined with too much muscle activity that causes shaking at the ankle, knee, elbow or wrist. This "spasticity" worsens the pattern of movements of the arms and legs. Interventions that could reduce excessive muscle activity and increase activity in muscles that are abnormally weak would be very helpful to recovery of walking after stroke. Interventions that are beneficial involve rhythmic arm and leg training on an exercise machine (i.e. on a SCI Fit arm or leg cycling machine which is a form of standard care for spasticity). Unfortunatly, sometimes the spasticity makes it impossible to have enough movement to actually train on any exercise equipment. Consequently, the single limb oscillation training is currently being used to attempt to regain enough movement to allow for rhythmic exercise.

Importance of this Research
The main goals of this project are to add knowledge in the following areas: 1) to guide future spasticity therapies that physiatrists, nurses, physiotherapists, and other healthcare personel can use to advance the standard of care for this clinical population, and 2) to increase the scientific knowledge base surrounding the mechanisms responsible for spasticity to guide future research.

Participants Selection
Participation in this study is voluntary. You are being invited to participate in this study because you currently experience spasticity. There is no control group for this study, all participants are in the same group and will serve as their own control. The use of the passive stretching device throughout this study will be included as part of the standard of care to manage spasticity. 20 participants will be recruited for this study.

What is involved?
If you consent to voluntarily participate in this research, your participation will include 4 sessions at the Rehabiliation Neuroscience Laboratory each taking approximately 2 hours. These sessions will include assessment of limb flexibility, strength, balance, walking ability, and spinal cord excitability. Before each session a readiness questionnaire will be completed including assessing your heart rate and blood pressure.

Inconvenience
Participation in this study may cause some inconvenience to you because there is a significant time commitment required. To mitigate this inconvienience, we will book all data collection appointments at times that are convenient for you.

Risks

- Participants may experience physical and mental fatigue following the cognitive, balance or exercise tests.
- Participants may sustain a physical injury (e.g. muscle strain or similar) during the balance and exercise tests.
- Frequent breaks will be provided within the appointments to minimize help the risk of fatigue. Also, if you are unable to complete the exercises, you can withdraw at any time from the study.

Benefits
There may be no direct benefit to participants from participation in this study. However, information gathered will benefit society as a whole by contributing to the knowledge base and scientific community surrounding spasticity treatment therapies.

Voluntary Participation
Your participation in this research must be completely voluntary and you will not receive any compensation for participation. If you do decide to participate, you may withdraw at any time without any consequences or any explanation. If you choose to withdraw from the study your data will be used only if you agree to its use.

Researcher's Relationship with Participants
Dr. Caroline Quartly may be involved in providing standard care (e.g. passive stretching, Botox injections) spasticity management therapies to participants of this study. However, Dr. Quartly is not involved in the recruitment process to prevent power-over effects. Dr. Quartly will not be involved in the data collection sessions of the study. Dr. Quartly will be involved in this study by helping to interpret the results of the study after data collection is complete, and by ensuring the regular standard of care provided at the QA spasticity clinic is maintained.

Anonymity
In terms of protecting your anonymity, you will be assigned a unique participant number (i.e. your identity is de-identified using a code to link your name to a participant number). When presenting our findings, only participant number will identify case studies.

Confidentiality & Data Disposal
There are no significant limits to confidentiality in this study. Only members of the research team will be present in the lab for data collection sessions. When data collection is completed, data will be completely de-identified using a code. Coded paper and electronic data will be kept for 5 years (and then destroyed) in the locked and password protected Rehabilitation Neuroscience Laboratory at the University of Victoria. Only researchers of this lab will have access to the data during this period of time. During this time the data may be used for future publications by reporting the group mean results of the study. This research study includes data storage within Canada only.

Dissemination of Results
It is anticipated that the results of this study will be shared with the scientific community and general public in the following ways: thesis, dissertations, class presentations, presentations at scholarly meetings, published article, chapter or book, internet, online library collections, media, directly to participants and/or groups involved. When presenting our findings, only the participant number will identify case studies. You will not be identified in the presentations.

Future Research
This study may be the first of multiple studies to be conducted by researchers of the Rehabilitation Neuroscience Laboratory on passive stretching and spasticity. For this reason, it is possible the data collected in this study is included and published in future research studies which also investigate this emerging therapeutic technique. Similar to the current study, any future use of the data will be de-identified. These potential future studies will undergo ethical and scientific review. Dr. E. Paul Zehr will be the steward of the data during the 5 years it will be kept.

Your signature below indicates that you understand the above conditions of participation in this study, that you have had the opportunity to have your questions answered by the researchers, and that you consent to participate in this research project.

Initial in **ONLY ONE** of the options below:

I **DO** consent to the use of my data in future research by UVic	

*** OR ***

I **DO NOT** consent to the use of my data for future research by UVic	

Name of Participant	*Signature*	*Date*

Appendix D: Physical Activity Readiness Questionnaire

Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO	
☐	☐	**1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	**2. Do you feel pain in your chest when you do physical activity?**
☐	☐	**3. In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	**4. Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	**5. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	**6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	**7. Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

CSEP | SCPE

Appendix F: Recruitment Poster

The Rehabilitation Neuroscience Laboratory at the

University of Victoria is looking for participants with spasticity

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- Spasticity and movement function assessment will be offered to participants with spasticity in the arms or legs in order to understand the mechanisms of spasticity.

- Assessments will be provided before and after your regular rehabilitation training. There will be multiple visits to the lab before and after the training.

- Assessments include level of spasticity, neurophysiology, joint range of motion, functional movement tests, gait analysis on body-weight support system, walking and balance tests.

Who can help?	Anyone who has upper or lower limb spasticity (from any neurological condition)
How much time?	About 4 visits to Rehabilitation Neuroscience lab: approximately 2 hours per visit.
Where?	Rehabilitation Neuroscience Laboratory, MacLaurin building, D-wing Room 015. University of Victoria
Contact:	Steve Noble (MSc student) Phone: 250-472-5487 Email: rnl@uvic.ca