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Human limb vibration and neuromuscular control

Colleen Louise McHenry
University of Iowa

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HUMAN LIMB VIBRATION AND NEUROMUSCULAR CONTROL

by

Colleen Louise McHenry

A thesis submitted in partial fulfillment
of the requirements for the Doctor of
Philosophy degree in Physical Rehabilitation Science
in the Graduate College of
The University of Iowa

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Thesis Supervisor: Professor Richard K. Shields

Graduate College
The University of Iowa
Iowa City, Iowa

CERTIFICATE OF APPROVAL

PH.D. THESIS

This is to certify that the Ph.D. thesis of

Colleen Louise McHenry

has been approved by the Examining Committee
for the thesis requirement for the Doctor of Philosophy
degree in Physical Rehabilitation Science
at the May 2015 graduation.

Thesis Committee: ___________________________
Richard Shields, Thesis Supervisor

____
Kelly Cole

____
Thomas Cook

____
Nicole Grosland

____
Laura Frey Law

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ABSTRACT

Mechanical loading can modulate tissue plasticity and has potential applications in rehabilitation science and regenerative medicine. To safely and effectively introduce mechanical loads to human cells, tissues, and the entire body, we need to understand the optimal loading environment to promote growth and health. The purpose of this research was 1) to validate a limb vibration and compression system; 2) to determine the effect of limb vibration on neural excitability measured by sub-threshold TMS-conditioned H-reflexes and supra-threshold TMS; 3) to determine changes in center of pressure, ankle muscle activity, and kinematics during a postural task following limb vibration; and 4) to determine the effect of limb vibration and whole body vibration on movement accuracy of a weight bearing visuomotor task and muscle responses to an unexpected pertubation.

The major findings of this research are 1) the mechanical system presented in the manuscript can deliver limb vibration and compression reliably, accurate, and safely to human tissue. 2) Sub-threshold cortical stimulation reduces the vibration-induced presynaptic inhibition of the H-reflex. This reduction cannot be attributed to an increase in cortical excitability during limb vibration because the MEP remains unchanged with limb vibration. 3) Limb vibration altered the soleus and tibialis EMG activity during a postural control task. The vibration-induced increase in muscle activity was associated with unchanged center of pressure variability but reduced center of pressure complexity. 4) Simulated fallers were able to accommodate extraneous afferent information due to the vibration interventions to maintain similar levels of accuracy but muscle responses to an unexpected pertubation were altered. Taken together, vibration has immediate applications to improve various human tissues.

PUBLIC ABSTRACT

Mechanical loading, particularly vibration, has recently been incorporated into rehabilitation programs to treat individuals with musculoskeletal and neurodegenerative diseases. Prior research has shown that vibration impacts stem cells, bone, muscle, cartilage, and balance. To safely and effectively introduce mechanical loads to human cells, tissues, and the entire body, we need to understand the optimal loading environment to promote growth and health. The research contained in this manuscript presents a novel device which can safely deliver vibration and compression to a human leg and the impact this system has on the nervous system and movement control. Vibration of the leg changes the excitability of the nervous system and therefore has the potential to be integrated into current treatments for those with nervous system injuries. This type of human limb vibration was also shown to change balance strategies and thus could be incorporated into rehabilitation techniques for individuals at risk for a fall. Finally, vibration offers a novel intervention in which all types of human populations can train movement control strategies and muscle responses geared towards injury prevention. Taken together, vibration has immediate applications in physical therapy and medicine to improve human health.

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CHAPTER 1 INTRODUCTION

Human tissues are highly influenced by mechanical loading and functionally adapt to this stimuli. There are many ways to deliver a load to the human body including exercise, electrical stimulation, vibration, compression, and countless methods and combinations of the aforementioned techniques. Many of these interventions are incorporated into rehabilitation strategies with the goal of positively impacting the musculoskeletal and nervous systems. The benefits of exercise as a mechanical stimulus have been well-documented and are widely accepted (1). However, other forms of mechanical loading, such as vibration and compression, are more contemporary and ultimately more controversial.

The pioneering work of Rubin demonstrated that hind limb vibration training in an animal increased bone mineral density (2). In humans, bone loss was attenuated in women with osteoporosis following a low-magnitude vibration training regime (3). Despite these beneficial findings, others have reported no change in bone following vibration training (4). Skeletal muscle also had a variety of effects in response to mechanical loading. Vibration platforms increase muscle activity and strength (5, 6) but tendon vibration decreases muscle activation (7). In addition to the musculoskeletal adaptations, vibration affects the nervous system by modulating segmental excitability (8), cortical excitability (9), postural control (10), and responses to perturbation (11).

There are countless vibration protocols but two classical types of human vibration are tendon vibration and whole body vibration. Tendon vibration is limited to a single muscle and whole body vibration activates multiple muscles and biological systems in conjunction with the head and the vestibular system. The findings from whole body vibration research are difficult to interpret because of the activation of the whole organism and therefore several different systems. In order to provide a mechanical load to multiple muscles without transmission to the head we designed a system to deliver vibration and/or compression to an entire human limb. Following the development and implementation of the device, the effects of limb vibration on biological tissues, particularly the nervous system, can be explored. Therefore, the purpose of this proposal is to present a novel device for mechanical loading of the human limb and to determine how this device modulates neural excitability and task-specific neuromuscular control.

Background

Mechanical Loading and Human Tissues

Human tissues are sensitive to their mechanical environment. Specific types of mechanical loads, such as vibration and compression, impact bone (2), cartilage (12), skeletal muscle (13, 14), and nerve tissue (15). Exposure to optimal mechanical load promotes advantageous adaptations and fosters a healthy environment for growth. However, excessive loading damages tissues (16, 17) while insufficient mechanical stimuli leads to deterioration of existing tissues (18, 19). Following periods of extreme inactivity such as bed rest (20), spaceflight (21), or spinal cord injury (22-25) there is a significant decline in the musculoskeletal system.

A timely dose of mechanical load could offset the catastrophic effects of injury, disease, or paralysis. Frost's mechanostat theory states that bone functionally adapts to the mechanical loading (26, 27). If the mechanical stimuli are above a certain threshold then bone is formed but if below another threshold then bone is resorbed (26, 27). Many other biological tissues operate under the same principle and require specific mechanical loads for optimal health. Dynamic loading regimes have proved to be more effective than prolonged static loads for bone (28, 29) and cartilage (30-32). Low-magnitude vibration has also shown to stimulate bone growth (2, 33, 34) and improve the integrity of articular cartilage (35-37). Skeletal muscle and the musculo-tendinous junction have a similar response to loading and vibration. Following whole body vibration training, individuals have increased quadriceps muscle activity and power output (38, 39). In the absence of mechanical loading, tendons become more compliant and are less effective in force transmission (18). Intermittent compressive loading upregulates essential genes required to maintain structural integrity of the tendon (40). Central nervous system adaptations are also accompanied with exposure to vibration. Functional magnetic resonance imaging (fMRI) during foot tendon vibration showed increased activity in the sensorimotor cortical areas (41-43) which is associated with enhanced balance control (42). Whole body vibration training also improves postural control in elderly (10). Focal vibration can impact neurological diseases and disorders and act has a valuable rehabilitation tool (44). The applications of mechanical loading and vibration on the human body are vast and continued research is essential.

Types of Human Vibration

Tendon Vibration

Early vibration studies were limited to vibration applied to the muscle tendon. Muscles are composed of specialized receptors that relay information about the muscle to the central nervous system. One such receptor is the muscle spindle which provides information about changes in length of the muscle. Primary or Ia afferent endings are contained within muscle spindles and respond the stretching of muscle. Tendon vibration activates the Ia afferents and creates the illusion of muscle lengthening (45). Initial tendon vibration research focused on joint perception and showed that tendon vibration impairs proprioception (45, 46). During vibration of the patellar tendon, individuals underestimated the angle of their knee (46). Similarly, vibration of the tibialis anterior muscle gives the illusion of muscle lengthening and causes the individual to correct by moving their center of pressure anteriorly (47). However, when the agonist and antagonist are vibrated using the same frequency then there is no perception of movement. When the biceps tendon is vibrated at a higher frequency than triceps then the individual perceives elbow flexion in the absence of actual movement (48). Tendon vibration also has important applications in neurorehabilitation. Recently, muscle vibration has been shown to improve gait patterns in Parkinson's patients (49, 50) and reduce spasticity in spinal cord injury patients (51).

Whole Body Vibration

Whole body vibration (WBV) is delivered by having individuals stand on vibration platforms. The more upright an individual stands the greater the transmissibility of the vibration signal (52). Vibration of the entire body and the head will influence the vestibular, visual, and somatosensory systems. WBV offsets the reduction in bone loss following 90 days of bed rest (53), reduces spasticity in those with multiple sclerosis (54), and improves postural stability and mobility in elderly (55). Because WBV activates multiple systems it is difficult to determine which system or combination of systems is responsible for these positive effects. The subsequent section outlines a potential mechanical system that activates multiple muscles but limits the vibration to a single human segment.

Limb Vibration

A limb vibration system contained later in this document outlines a device for delivering vibration to a human leg. The vibration was limited to the leg on the platform and was not transmitted to the contralateral limb or head. In humans, focal vibration has typically been limited to tendon vibration but animal research has begun to implement limb vibration. A murine model showed that low level vibration in the absence of weight-bearing increases bone formation by 66% in the tibia (56). The effects of limb vibration in animals are primarily limited to bone. Some human research has been completed determining the result of limb vibration on segmental excitability (57) but extensive examination of limb vibration on motor cortical excitability and functional tasks remain unexplored. A mechanical system capable of delivering localized limb vibration would allow us to replicate the animal research on bone and determine if the same benefits of whole body vibration remain in the absence of vestibular activation.

Response of Vibration on Neural Excitability

Segmental Excitability

The Hoffmann reflex or H-reflex is a widely used metric for quantifying segmental excitability or the excitability of the α-motoneuron pool. It is the electrical equivalent of the stretch reflex which is mechanically induced via a tendon tap. The H-reflex is a monosynaptic reflex meaning the Ia afferents are electrically activated, synapse on the α-motoneuron, and result in a muscle twitch or H-reflex. Specifically, to elicit a soleus H-reflex the tibial nerve is activated in the popliteal fossa and the Ia afferents propagate action potentials to the spinal cord. Depolarization of the motoneuron occurs when there is adequate activation of the Ia afferents. The soleus H-reflex has been extensively used to measure segmental excitability in individuals with and without neurological disorders.

Muscle vibration modulates the Ia afferents within the muscle spindle (45) and the H-reflex selectively activates these Ia afferents. Therefore, it is not surprising that muscle vibration impacts a measure of segmental excitability, the soleus H-reflex. Tendon vibration of the soleus muscle at 50 Hz reduces the H-reflex by 47% (58). The suppression of the soleus H-reflex during vibration is a robust finding and has been repeated by many others (8, 59-61). Tendon vibration causes presynaptic inhibition of the Ia afferents and thus suppresses the H-reflex.

Whole-body vibration research has more varied results with respect to segmental excitability. In several studies, WBV suppresses the H-reflex similar to tendon vibration (62-66) but others showed no effect on H-reflexes with WBV (67, 68). Upon further review, those that did not show an effect did not collect the H-reflexes during WBV but immediately following vibration. The vibration-induced suppression of the H-reflex is transient and thus the H-reflex could have recovered before the post-vibration collection.

Isolated limb vibration is a relatively new concept and another method to investigate changes in segmental excitability during vibration of multiple muscles. The novelty of limb vibration is that an entire limb can receive vibratory input with minimal vestibular activation. During the initial human limb vibration study, segmental excitability was quantified by eliciting two H-reflexes using a doublet with a 500 ms inter-pulse interval (57). The peak-to-peak amplitude of the first H-reflex provides a valuable metric even in the absence of a subsequent pulse. The first H-reflex was suppressed over 80% of baseline during limb vibration (57). The doublet is used to study post-activation depression, the phenomenon in which the amplitude of second H-reflex is reduced compared to the first H-reflex (69). The magnitude of post-activation depression during limb vibration was close to 0 because of the large reduction in the first H-reflex (57).

Motor Cortical Excitability

Transcranial magnetic stimulation (TMS) is a non-invasive method to quantify motor cortical excitability. Introduced in 1985, a TMS coil is placed on the scalp and over the primary motor cortex to elicit a response from a target muscle (70). The muscle response termed a motor-evoked potential (MEP) is recorded from an electromyography (EMG) electrode placed on the target muscle. Changes in cortical excitability are reflected as changes in MEP amplitude. For instance, voluntary contraction of the target muscle increases the MEP amplitude by 50% indicating enhanced cortical excitability (71).

The same principle can be used to determine the effect of other interventions such as vibration on cortical excitability. In subhuman primates, biceps muscle vibration produces primarily excitatory changes and increases the firing rate of motor cortical cells (72). As previously stated, tendon vibration is a strong, selective stimulus for Ia afferents (73, 74) and the link between Ia afferent modulation and motor cortical activation has been well-established (75, 76). Specifically, vibration of the flexor carpi radialis muscle at 75 Hz and 120 Hz increased the MEP amplitude by 49.1% and 33.8%, respectively (77). Rosenkranz et al 2003 reported a 162% increase in MEP amplitude of the vibrated hand muscle and 72% suppression in two non-vibrated hand muscles (78). When multiple muscles are vibrated simultaneously via vibration of the palmar surface of the hand, there is an increase in MEP amplitude of the first dorsal interosseous and abductor pollicis brevis muscles (79). Much of the previous research focused on the cortical excitability of the upper extremities during tendon vibration but recently Lapole et al 2012 showed no acute changes in the MEP amplitude of the soleus or tibialis anterior muscles following Achilles tendon vibration (58). Unfortunately, research on whole body vibration and cortical excitability is also limited. Only one published work uses single TMS pulses to assess cortical excitability following whole body vibration (80). During whole body vibration, TMS elicited 56% higher MEP amplitude for tibialis anterior muscle compared to the controlled condition (80). To date no work has been published exploring the simultaneous vibration of multiple lower extremities muscles in the absence of head vibration. The device proposed in this manuscript will allow a lower extremity (whole limb) vibration without transmission of the vibratory signal to the head.

<u>TMS-conditioned H-reflexes</u>

The H-reflex determines the α-motoneuron excitability while TMS activates descending pathways to generate a motor-evoked potential in the target muscle. These two neural excitability metrics can be coupled to produce a TMS-conditioned H-reflex wherein a TMS pulse is delivered prior to the peripheral nerve stimulation. When a TMS pulse is delivered 10-20 ms before the peripheral nerve stimulation there is a facilitation of the H-reflex (81). The descending corticospinal inputs from the TMS pulse increases the motoneuronal excitability resulting in an increased H-reflex (82-84). The facilitation in the H-reflex amplitude can be attributed to the TMS arriving at approximately the same time as the nerve stimulation enhancing the H-reflex. Tendon vibration suppresses the H-reflex but this inhibition can be overcome with a conditioning, sub-threshold TMS pulse

(84, 85). Our lab has previously established that the soleus H-reflex virtually disappears during limb vibration (57) but it has yet to be determined if a TMS conditioning stimulus can counteract this post activation depression, one of the aims of this manuscript.

Postural Control

Fundamentals of Postural Control

Effective postural control involves successful integration of afferent information from the visual, vestibular, and somatosensory systems. To maintain upright stance, these systems are used to accurately interpret one's surroundings and to correct deviations accordingly. Altered or lost vision, vestibular information, or proprioception diminishes feedback control and increases postural sway (86, 87). When vision is removed (eyes closed) an individual must rely on the vestibular and somatosensory systems to maintain balance. In healthy individuals, the vestibular and proprioceptive inputs are sufficient to account for the loss of vision and prevent falling. However, in pathological groups such as those with a vestibular disorder or sensory neuropathy this is much more challenging. Without vision, individuals with vestibular insufficiencies cannot maintain balance (88). The vestibular system gives information about acceleration and head orientation. A deficient vestibular system coupled with loss of vision forces the individual to rely solely on the somatosensory system (89). Sensory receptors of the somatosensory system include cutaneous receptors and proprioceptors. In regards to controlling upright stance, the cutaneous receptors provide information about shear forces and pressure under the feet while proprioceptors can relay information about joint angles, muscle length, and muscle tension (90). Those with diabetic peripheral neuropathy have diminished somatosensory input and ultimately reduced postural control (91). Intact visual, vestibular, and somatosensory systems are vital to postural control and removing one or more of these systems disrupts sensorimotor integration and increases reliance on the other systems.

Postural Control Metrics

During stance the center of mass (COM) of the human body is constantly moving but small adjustments will keep the COM within the base of support and prevent a fall. The nervous system controls the COM by modulating the center of pressure (COP). Postural control is commonly quantified as the COP displacement which can be separated into displacements in the anterior/posterior (A/P) direction and the medial/lateral (M/L) direction. Descriptive statistics such as average displacement, standard deviation, coefficient of variation, and velocity in either or both of these directions are common metrics for postural control.

Response of Vibration on Postural Control

Researchers have introduced various types of vibration to the human body to determine how different modalities impact neural excitability and movement control. Tendon vibration evokes a tonic vibration reflex (TVR) which results in postural sway in the direction of the vibrated muscle (92). Muscle vibration activates Ia afferents giving the illusion of muscle lengthening and compelling the individual to shift towards the vibration to correct sensation. Many times this vibration-induced postural shift also triggers antagonist muscle activation (93, 94). These muscle and postural responses to vibration could originate from changes to the initial conditions of the muscle or higher order supra-spinal inputs. The support surface plays a large role in the muscle response to vibration resulting in less muscle response when standing on an unstable (95, 96) or tilted surface (97). Muscles in the lengthened position are more sensitive to vibratory stimuli

(98, 99). However, additional proprioceptive inputs such as standing on an altered support surface weaken the vibratory response. For instance, ankle dorsiflexion due to standing on a tilted platform produces the same COP changes compared to when coupled with Achilles tendon vibration (97). Taken together, relevant afferent information is extracted by the central nervous system to maintain balance in challenging situations.

Recently, whole body vibration platforms have been introduced as a clinical intervention to improve balance particularly in the elderly. Previous research has shown that WBV training enhances response to perturbation (11), improves Tinetti Score of gait and balance (100), and increases stability during stance (101). One potential explanation for improved balance is the increased strength and muscle performance associated with WBV training (6, 38, 39); however, not all research supports this finding. Others have found no change or a temporary reduction in force production following an acute bout of WBV (102-104). Inconsistent vibration parameters between studies are the most likely reason for different findings (38). WBV also modulates the cutaneous afferents on the plantar surface of the foot but this reduction in sensitivity is associated with enhanced postural control (105). On the contrary, when the plantar surface of the foot is vibrated in the absence of other muscle vibration or whole body vibration then there is increased postural sway (106). As Kanakis et al. 2014 states, the presence of several sensory inputs results in the central nervous system selecting the ideal motor plan based on the available afferent information (107). Whole body vibration includes vibration of multiple muscles, body segments, the head, and the vestibular system forcing the central nervous system to weigh multiple inputs and control posture accordingly. Currently, there is only one study that quantifies postural control during vibration of multiple muscles simultaneously

(108). Han et al 2013 showed that agonist and antagonist muscle vibration reduced the COP area and path length during the eyes closed condition (108). The mechanical system proposed in this manuscript can be used to determine if limb vibration, the vibration of multiple muscles through the plantar surface of the foot, alters postural sway.

Neuromuscular Control of Visuomotor Task and Long Latency Responses

Visuomotor Tracking Task

Postural control is an important metric and can be an indicator of successful independent living; however, many other activities of daily life require additional types of weight-bearing tasks. Functional tasks such as ascending or descending stairs, bending down to retrieve an object, and standing from a seated position are all considered important activities of daily living. In rehabilitation, these weight-bearing activities are valuable tools to assess and train neuromuscular control. Specifically, a single leg squat (SLS) is a multisegmental, weight-bearing exercise involving flexion and extension of the knee and hip, much like the aforementioned exercises, and is commonly recommended to improve neuromuscular control.

In 2005, Shields and Madhavan presented a SLS device that allowed an individual to complete a single leg squat in the sagittal plane using visual feedback (109). The system displayed a sinusoid which the user could trace by knee flexion and extension. The knee of the user is strapped into a pad which is attached to a brake that provides resistance in flexion and extension. The system also generates an accuracy score by comparing the computer generated sinusoid to the user signal. When the user becomes proficient and obtains a high degree of accuracy there is reduced co-activation of hamstrings and quadriceps (110). The system is also capable of delivering random perturbations during the task. Throughout the SLS task the resistance of the brake is set to a percentage of the user's body weight. To deliver a perturbation the brake shuts off to 0% of body weight so there is no longer any resistance. The perturbation occurs randomly and at a point in the target signal when the user is moving into knee flexion. The perturbation offers valuable information about user performance, especially triggered long latency responses from the muscle (111).

Neuromuscular Response to Perturbations: Long Latency Responses

The rapid stretch of a muscle due to an unexpected perturbation results in short latency spinal reflexes and long latency muscle responses (LLR) (112). The spinal stretch reflex, M1, has a latency of approximately 30 ms and activates Ia afferents from the muscle spindle causing the monosynaptic reflex (113). Long latency responses have latencies ranging from 50-200 ms after the perturbation and can be subdivided into M2 and M3 components (114). The M2 component with 50-80 ms latency stimulates the slower, secondary or group II afferents (115). The long latency response of the quadriceps including the M3 component with a latency of 85-200 ms is mediated by supraspinal inputs (116). Spinal reflexes and long latency responses provide feedback information in response to a perturbation and contribute to initial corrections prior to volitional activity. Due to the transcortical aspect, LLRs can provide a more sophisticated and amplified response compared to spinal reflexes alone (117, 118).

The magnitude of the long latency responses depend on supraspinal inputs from the visual, somatosensory, vestibular systems at the time of the perturbation. Timmann et al 1994 showed that eliminating vision during a perturbation increases the LLR and delays the latency; however, additional somatosensory information reduces the LLR (119).

Individual with vestibular deficits have reduced muscle responses to a perturbation compared to healthy controls and these deficits often led to falls (120). Long latency responses are also graded based on the magnitude and velocity of the perturbation with increased responses to large or high velocity movements (121, 122).

Any unexpected event such as stepping off an unforeseen curb can elicit LLRs; however, these perturbations are more difficult to deliver in the laboratory. One current method involves a platform perturbation, a sudden shift to the platform while the subject is standing on it. Snyder-Mackler and colleagues have used it extensively to measure changes in LLRs in response to knee injury and gender (123, 124). Unfortunately, after the initial platform perturbation the subject is no longer naïve to the experiment therefore the subject could alter their control strategy during subsequent trials. Alternatively, our SLS system can trigger LLRs by delivering a perturbation during the SLS task. Because the user is engaged in the task with the goal of optimal performance, the perturbation is always unexpected. If the user adopts a strategy of co-contraction in anticipation of the perturbation then their performance will be very poor (125). For this reason, the SLS system is an ideal device to deliver unexpected perturbations because researchers can identify users adopting a co-contraction strategy based on poor performance. Our laboratory has used the SLS system to explore altered neuromuscular control due to age, fatigue, and injury. Elderly had similar accuracy compared to young individuals during the SLS task but required greater muscle activation to perform the task (111). Madhavan et al 2009 also reported elderly had increased LLRs of the quadriceps muscle with the perturbation compared to the younger cohort (111). Quadriceps muscle fatigue resulted in a less controlled movement following a perturbation and required more quadriceps muscles activity (117). Females with anterior cruciate ligament repair also had greater error and increased LLRs in response to a perturbation compared to age-matched controls (126). The SLS system with perturbations is an ideal method to gain insight into neuromuscular responses to an unexpected event and explore different conditions which could alter that response.

Effects of Vibration on Neuromuscular Response to Perturbations

Vibration has the capacity to impact many different systems including vision, vestibular, and somatosensory, all of which are used for neuromuscular control of functional tasks. The acute effects of tendon vibration on platform perturbation responses are mixed. In one study, the proprioceptive information from Achilles tendon vibration results in reduced center of pressure displacement following a platform perturbation (127). Alternatively, Radhakrishnan and colleagues reported an increase in soleus and tibialis anterior activation during Achilles tendon vibration of a tracking task (128). However, a long-term whole body vibration training study showed that upon completion older individuals had less falls during platform perturbations (11). To date, no one has explored the effects of vibration, specifically isolated limb vibration and whole body vibration, on accuracy of a visuomotor tracking task or the perturbation-induced, long latency responses elicited during this task.

Purpose

The purpose of this research was 1) to validate a limb vibration and limb compression system; 2) to determine the effect of limb vibration on neural excitability measured by sub-threshold TMS-conditioned H-reflexes and supra-threshold TMS; 3) to determine changes in center of pressure, ankle muscle activity, and kinematics during a postural task following limb vibration; 4) to determine the effect of limb vibration and whole body vibration on accuracy of weight bearing visuomotor task and muscle response to an unexpected event.

Specific Aims

Specific Aim 1 (Chapter 2): To validate a method of delivering localized mechanical load (vibration and/or compression) to a human limb.

Specific Aim 1a: To confirm output of vibration and quantify the transmissibility of the vibration.

Hypothesis 1a: The vibration from the platform will occur primarily in the vertical direction at the specified vibration parameters and the vibration will be limited to the testing leg with minimal transmissibility to the contralateral limb and the head.

Specific Aim 1b: To determine the accuracy of the compression system.

Hypothesis 1b: The linearity, repeatability, and percent error of the compression system will be less than 5% full scale and intra-class correlation coefficients (ICC) of the between day reliability of delivering a load to a human limb will be greater than 0.80.

Specific Aim 1c: To assess the effectiveness of the safety switch to shut down the mechanical load delivery system.

Hypothesis 1c: The vibration system will stop if any of the vibration parameters are exceeded and the compression system will prevent transmission of excessive load to a human limb within 5% of intended load.

Specific Aim 2 (Chapter 3): To determine the effect of limb vibration on spinal and cortical excitability in humans.

Specific Aim 2a: To determine if vibration-induced suppression of the soleus H-reflex can be overcome with a sub-threshold TMS conditioning stimulus.

Hypothesis 2a: The sub-threshold TMS pulse will facilitate the soleus H-reflex during limb vibration ($p < 0.05$).

Specific Aim 2b: To determine if cortical excitability is modulated with limb vibration.

Hypothesis 2b: Limb vibration will increase the amplitude of the soleus motor-evoked potential compared to the control condition ($p < 0.05$).

Specific Aim 3 (Chapter 4): To determine the effect of limb vibration on neural control strategies during a postural task.

Specific Aim 3a: To determine alterations in center of pressure variability following limb vibration.

Hypothesis 3a: Limb vibration will increase displacement and velocity of the center of pressure in the anterior/posterior (A/P) and medial/lateral (M/L) directions ($p < 0.05$).

Specific Aim 3b: To determine changes in center of pressure complexity following limb vibration.

Hypothesis 3b: Limb vibration will increase complexity of center of pressure velocity quantified using nonlinear fractal analysis ($p < 0.05$).

Specific Aim 3c: To quantify changes in soleus and tibialis anterior EMG activity due to limb vibration.

Hypothesis 3c: After limb vibration there will be an increase in soleus and tibialis anterior muscle activity during a blinded, single leg stance task ($p < 0.05$).

Specific Aim 3d: To quantify changes in ankle, knee, and hip kinematics after limb vibration.

Hypothesis 3d: Limb vibration will increase the ankle, knee, and hip angles during the single leg stance task ($p < 0.05$).

Limb vibration will increase the ankle, knee, and hip angles during a blinded, single leg stance task.

Specific Aim 4 (Chapter 5): To determine the effect of limb vibration and whole body vibration on accuracy and muscle responses of a weight bearing visuomotor task.

Specific Aim 4a: To determine changes in accuracy of a visuomotor tracking task following a bout of limb vibration.

Hypothesis 4a: Limb vibration prior to a visuomotor tracking task will increase the accuracy indicated by reduced peak absolute error and peak velocity error compared to the control condition ($p < 0.05$).

Specific Aim 4b: To determine changes in accuracy of a visuomotor tracking task during whole body vibration.

Hypothesis 4b: Whole body vibration during a visuomotor tracking task will increase the accuracy indicated by redcued peak absolute error and peak velocity error compared to the control condition ($p < 0.05$).

Specific Aim 4c: To determine changes in muscle responses (vastus medialis, lateral hamstrings, soleus, and tibialis anterior) to a perturbation during a visuomotor tracking task following limb vibration.

Hypothesis 4c: Limb vibration prior to a visuomotor tracking task will increase muscle responses of vastus medialis, lateral hamstrings, soleus, and tibialis anterior following a perturbation compared to the control condition ($p < 0.05$).

Specific Aim 4d: To determine changes in muscle responses (vastus medialis, lateral hamstrings, soleus, and tibialis anterior) to a perturbation during whole body vibration while performing visuomotor tracking task.

Hypothesis 4d: Whole body vibration during a visuomotor tracking task will increase muscle responses of vastus medialis, lateral hamstrings, soleus, and tibialis anterior following a perturbation compared to the control condition ($p < 0.05$).

CHAPTER 2 POTENTIAL REGENERATIVE REHABILITATION TECHNOLOGY: IMPLICATIONS OF MECHANICAL STIMULI TO TISSUE HEALTH

Introduction

Vibration and compressive loads are mechanical stimuli that have a powerful influence on biological tissues. Recent studies in animal models demonstrate that certain types of mechanical load regulates bone (2), fat (129, 130), skeletal muscle (14, 131), and nerve tissues (15). In addition, it is also well known that “over exposure” to mechanical stimuli is damaging to tissues (16, 17, 132). With the emergence of regenerative medicine in tissue repair, rehabilitation specialists must understand the correct type and dose of mechanical stress that promotes cell survival and cell proliferation in bone, cartilage, ligaments, and muscle. However, to our knowledge, there is no technology that directs specific types of mechanical stimuli to limbs of humans. A method to study mechanical stimuli in humans is necessary to guide future research to determine optimal rehabilitation prescriptions. The importance is underscored as multi-potent adult stem cells are harvested and implanted after surgery, injury, disease, and paralysis as regenerative medicine advances. Our long term goal is to establish the extent to which various types of mechanical stimuli optimally influence the regenerative capacity of cells in humans. In this technological report, we present an innovative technology that may assist in determining the impact of mechanical stimuli of human tissues and discuss the importance of a partnership between engineers, bioscience researchers, and rehabilitation specialists.

The underlying need to study the value of therapeutic stress in humans is well grounded in the literature. For example, Wolff’s law supports that bone tissue (osteocytes) exposed to high loads triggers osteogenesis (133). Subsequent studies verified that exerting high strain in a dynamic fashion to bone tissue was more effective than delivering a sustained strain (28, 29). For many years, the dynamic delivery of high stress to bone was considered the primary mechanical method to up-regulate osteogenesis (134-136). However, more recently, low amplitude vibration stimuli, in the absence of high mechanical loads, were equally effective at up-regulating bone development in mice (14, 33, 34, 137, 138). Indeed, regular mechanical stress promotes a healthy environment for bone (2), fat (129, 130), skeletal muscle (14, 131), nerve tissue (15), and cartilage (articular, menisci) (12, 139) in animal or reduced preparations in the laboratory. Translating these findings into human studies has been hampered by the lack of a capacity to dynamically deliver high passive loads and/or low vibration either independently or in various combinations with or without muscle activation (electrically or volitionally).

The dose of various mechanical loads has not been carefully examined. For example, most studies evaluating vibration deliver the load to the entire animal (14, 137, 138, 140-142) or human (4, 6, 53, 143-145) which limits the ability to understand adaptive effects of localized vibration directly on tissues (muscle and bone). This point was emphasized when whole body vibration of mice had a systemic increase in bone density (14, 34, 138) and decrease in whole body adipogenesis (130). The direct effect of the vibration stimuli on bone tissue was confounded by vestibular (146) and/or endocrine system (147) mechanical activation.

The purpose of this technological report is to present a novel method to introduce localized compressive loads and/or vibration into the limbs of humans. The accuracy, repeatability, transmissibility and safety of the instrument will be presented in this report. Future studies are recommended using technology that will assist in better understanding the impact of mechanical stimuli on tissue health. The need for collaborative and inter-disciplinary teams of engineers and cellular physiologists will be emphasized.

Methods

Technology Development and Testing Study

Eight individuals with complete paralysis have been tested on two occasions to determine the ability to reliably and accurately deliver the mechanical oscillations and loads to the limb of people with spinal cord injury (SCI). A power analysis revealed that 8 participants were required to have power to assess the reproducibility of the system (> 80%). Informed written consent was obtained from all subjects prior to participation. All experimental protocols were approved by the University of Iowa Institutional Review Board.

General Description of Instrumentation

A servo-controlled vibration system (Figure 2.1) consists of five primary components from the Ling Dynamic Systems (Royston, England): PA1000L power amplifier, FPS10L field power supply, V722 shaker, cooling fan, and Laser USB 6.30 controller. The power amplifier and field power supply are connected in cascade and generate the required power for the vibration system. A magnetic field within the shaker is generated from the field power supply while the power amplifier drives the shaker and supplies power to the cooling fan. The cooling fan dissipates the heat generated. An accelerometer is attached to the shaker and connected to the controller, which is directed to the amplifier creating a feedback loop. The vibration frequency in Hertz (Hz) and acceleration in gravitational force of earth ($g = 9.81\ m/s^2$), respectively, are controlled. The software also allows the user to program multiple loops thereby creating a series of on and off cycles of vibration. The controller is also equipped with an abort button designed to stop the vibration quickly. When providing a mechanical intervention to humans it is important to have built in safety mechanisms in the event of an emergency.

We interfaced a custom designed, pneumatically controlled piston that can safely deliver compressive loads to a limb segment either with our without the vibration (Figure 2.2). The mechanical loading system is driven by a pneumatic compression pump that is controlled by a custom circuit board communicating via the computer interface board. Custom software allows for parameter specification, feedback control, and safety shut down when unwanted loads are inadvertently applied.

The air flow to the limb loading piston begins at the air compressor, a Super Silent DR 500 Air Compressor (Silentaire Technology, Houston, TX). It regulates the air pressure entering the regulator to approximately 552 kPa. The air then passes through a Humphrey 3-way solenoid valve (Skarda Equipment Company, Inc., Omaha, NE). When the solenoid receives 12 Volts from the electrical portion of the system the valve closes and the compressed air remains in the pneumatic system. However, in the absence of power the valve remains open and the air vents to the atmosphere. If the valve is closed then the air continues to the next component, an electrical pressure regulator, T500X Miniature E/P Transducer (Control Air Inc., Amherst, NH). The pressure regulator converts a voltage from a buffer amplifier to a corresponding pneumatic output. The air then moves through a second 3-way solenoid valve and continues to an air manifold. The air manifold divides the air between a pressure switch, 2PSW2SYT5 Pressure Switch (Solon Manufacturing Co., Chardon, OH), a pressure transducer, PT100R13LU2H1131 Pressure Transducer (Turck Inc., Minneapolis, MN) , and an air cylinder, USR-32-1 Pneumatic Cylinder (Clippard Instrument Laboratory, Inc., Cincinnati, OH). The pressure switch is composed of two electrical switches and a diaphragm sensing element. If the pressure is greater than 414 kPa then the circuit is tripped and the loading system shuts down. The pressure switch is one of the safety mechanisms built into the system. The pressure transducer converts the pneumatic input to a voltage that is sent to the electrical portion of the system. The desired air pressure continues into the chamber of the air cylinder causing the piston to move downward. A force transducer, 1210ACK-300lb Load Cell (Interface, Scottsdale, AZ), and pad are attached in series to the piston and allows pressure and force measurements simultaneously.

The limb loading system was designed to introduce a vertical compression load to the tibia via a load applied over the top of the femoral condyles (knee) as a percentage of body weight (%BW). A feedback loop was incorporated into the software design written in LabVIEW 8.6 (National Instruments, Austin, TX) to continuously monitor the force and pressure through the transducers and adjust accordingly. The user can define the time that the load is on and off in seconds, the number of cycles, and the magnitude of the force. In addition, data is collected with real-time display of force, pressure, electromyography (EMG), vibration, and other mechanical factors.

The apparatus that serves to hold the human limb consists of a custom designed frame that was fabricated and attached to the shaker so that vibration and load can be delivered concurrently (Figure 2.3). The novelty of this system is that it enables the load to be applied while the entire limb segment receives vibratory stimuli. Thus, during vibration, a force-time impulse may be delivered to the extremity. The frame is made of an aluminum base plate and foot plate connected with T-slot frames. The uprights and cross bar are also made with aluminum struts. Aluminum housing contains the air cylinder and slides within the frame uprights allowing full adjustability for limb length. In addition, a tilt in space chair was welded to a lift that allows any subject, including individuals with paralysis to be positioned correctly into the device.

Vibration Verification and Transmissibility Testing

We applied an independent external accelerometer, Model 3233A High-Sensitivity triaxial accelerometer (Dytran Instruments, Inc., Chatsworth, CA), to the vibration platform. The Laser vibration software is capable of various vibration parameters. We included settings aligned with those found to be effective in previous studies (0.1g-10g at 20-90 Hz) (4, 6, 53, 143-145). In 2009, Totosy de Zepetnek presented a review of whole body vibration which concluded the optimal vibration parameters for humans have yet to be determined (148). To test the transmissibility of the vibration signal, the software was programmed for 0.6g at 30 Hz for 1 minute. The work of Garman and Ozcivici demonstrated the vibration of 0.6g enhanced the bone of the vibrated limb compared to the contra lateral limb (33, 34). During the vibration, acceleration was collected in all the cardinal directions. The x and y axes were parallel to the platform and the z axis was a perpendicular measure of the acceleration in the vertical direction. A custom MATLAB program (MathWorks, Natick, MA) was written to determine the peak of the acceleration and its frequency content. The peak was defined as the maximum value of the acceleration signal. To determine the frequency of the signal a fast Fourier transform

(FFT) was performed. Based on the sampling frequency of 4,000, 32.7680 seconds or 2^17 data points of acceleration data were used for the FFT. This window of data was chosen so the length of data was a power of 2, the recommended length for a FFT.

An accelerometer was attached to the leg, thigh, and head during the vibration protocol of both the vibrated and contra lateral limbs in a single subject. Anatomical locations were defined as tibia tuberosity, distal thigh, and forehead. We defined transmissibility as the ratio of the root mean square (RMS) of acceleration of the anatomical site to the RMS of the acceleration at the mechanical apparatus, consistent with Rubin et al. (52).

$$Transmissibility = \frac{RMS_{acceleration\_body}}{RMS_{acceleration\_platform}}$$

Repeatability, Linearity, and Accuracy Testing of Limb Load

The custom software controls the instrumentation to deliver air pressure to the desired load to the lower leg. The calibration between the air pressure and the delivered force to the limb was determined using five known input pressures (138, 207, 276, 345, 414 kPa). The five input pressures were chosen to calibrate the system. We targeted loads that were able to secure the limb to the device and loads that we previously published to modulate spinal cord activity (149, 150). Ten cycles were collected at each pressure. The accuracy of the limb loading system was measured by determining the linearity, repeatability, and percent error. Linearity was defined as the maximum deviation of the mean difference between the predicted response and the measured load. Repeatability was the maximum difference between measures under the same testing conditions, while percent error was calculated using the following equation, ((measured value-predicted value)/predicted value)*100. Repeatability and percent error were normalized and expressed at percentage of full scale (%FS). Prior to this air pressure validation, the load cell was calibrated. The maximum acceptable error for these three measurement was less than 5%FS.

We delivered limb loads to individuals with complete paralysis to test the reproducibility of the apparatus. Eight individuals underwent two sessions on different days to determine the between day reliability of load delivery to human limbs. Ninety compressive load cycles of 50% of body weight were delivered to one leg of the individuals with paralysis. These five second loading cycles were separated by five second rest periods so ninety cycles took 15 minutes to complete. The peak load was measured after cycles 1, 30, 60, and 90 for each session. The percent difference between days and the intra-class correlation coefficients (ICC) at each time point were calculated (IBM SPSS Statistics Version 19). An ICC > 0.8 indicates that the system has high reproducibility in delivering mechanical load on a day to day basis (151). Included in this error assessment is the ability to connect the human subject to the mechanical interface system. Any error less than 10% was considered low for the between day reliability assessment.

Load Safety Assessment

Since this device is designed to interface with a human tibia, safety is of utmost importance. Although, the vibration parameters (0.6g, 30 Hz) for this intervention are safe for humans, the system is capable of generating much larger vibration signals (66.3g, 400 Hz) The shaker parameters were altered so that the maximum acceleration is 6g and the shaker itself has an over travel protection that limits the peak-to-peak excursion to 11 mm. Finally, the vibration controller is equipped with an abort button that will immediately shut down the system.

The compressive system also has several safety features including an emergency stop switch that removes the load by venting the air to the environment. In addition to a mechanical stop, before starting the compression system, the user must input the cycle time, air pressure, and maximum load. The maximum load is the safety parameter which can be set to ensure that an excessive load for human tibia cannot be inadvertently applied.

To assess the safety of the compression an air pressure of 263 kPa or 445 N was programmed into the system while varying the maximum load. Seven maximum load settings, 423N, 437 N, 441 N, 445 N, 449 N, 454 N, and 467 N were tested. The force was recorded using custom LabVIEW software written to control the compression system. The effectiveness of the maximum load safety setting was determined by examining the force signal and measuring the peak force delivered.

Results

Transmissibility and Quality of Vibration Signal

At a setting for a 0.6 vertical (z) acceleration and 30 Hz frequency the actual peaks were 0.0406g, 0.0732g, and 0.6289g, for the x, y, and z directions, respectively. There was minimal acceleration in the planes parallel to the vertical platform direction. Through a Fast Fourier Transform we verified that over 98% of the signal power was in the intended 30 Hz frequency domain (Figure 2.4). Transmissibility, defined as the ratio of vibration amplitude at the anatomical site to the vibration amplitude measured at the shaker, should be equal to 1.0 if there is perfect transmissibility of the vibration to the limb segment. The transmissibility at the tibia and femur were 0.71 and 1.17, respectively. The transmissibility of vibration at the human head and the contra lateral tibia and femur was less than 0.02 (Figure 2.5). Therefore, the entire system directs the most of the mechanical events specifically to the targeted limb segment.

Limb Load Testing Results

The linearity, repeatability, and error were calculated at each air pressure was 4%, 1%, and 1%, respectively (Table 2.1). The between session reproducibility assessment using human subjects was excellent with an intra-class correlation of 0.90 (Table 2.2). The percent change in limb load never exceeded 7% during between day tests. These data support that total error associated with "setting up" a human subject was low.

Vibration and Limb Load Safety Results

The vibration system consistently shutdown when the acceleration exceeded a 6.1g, if the platform exceeded 11 mm of displacement, or the user manually pushed the shutdown switch built into the controller. In addition, activating the emergency stop switch consistently aborted the limb loading system by exhausting the compressed air into the environment. To formally test the safety mechanisms under software control, we input a load of 445 N (263 kPa) to the simulated extremity. We then intentionally exceeded the maximum load by programming in loads in excess of the 445N threshold. The system consistently exhausted the air by the 3-way valve when the 445N threshold was exceeded. We next set the threshold at 423 N, 437 N, and 441 N and delivered a load of 445N. Because of a one second delay in the release of pressure, the limb segment received 435 N, 445 N, and 448 N rather than the 423 N, 437 N, and 441 N that were intended. Thus, the safety shut off was effective to within 3% of the intended load.

We had no subjective complaints from any subjects during this testing. There were no tissue areas of reddening or indentations that support that mechanical load of vibration and compression can be delivered concurrently to human tissue.

Discussion

Currently, there are no existing devices that can provide isolated mechanical loading to a human limb by delivering controlled vibration and/or compression. There are devices which can vibrate (34) or compress (152) the limb of a rodent but neither can deliver vibration and compression simultaneously. Many of the existing devices for humans are commercial vibration platforms that are inherently noisy (153) and typically used for whole body vibration and not localized vibration. The vibration system presented in this paper is servo-controlled and therefore provides a constant vibration using the feedback from the accelerometer to modulate the vibration. Vibration platforms have been widely used in human research; however, prior to the mechanical system presented in this article, there was not a device capable of delivering limb vibration with or without limb compression to an isolated segment.

Bridging the Gap: Engineering and Bioscience

The primary purpose of this technological report was to present the development of an accurate, controlled, repeatable, and safe mechanical system that would be able to induce localized biological stress to tissues within a limb of humans. Based on our presentation of the findings, we are confident that this system can reliably deliver the stresses within the loads tested based on animal studies and preliminary human reports. Our secondary purpose was to use this report to appeal to the scientific community about the importance of inter-disciplinary teams partnering as cellular therapies are developed in the bioscience laboratories. Our ability to test and learn about the optimal methods to stress tissues is paramount for many new cellular therapies developing today. A brief review of the impact of mechanical stimuli on various tissues will be presented in the subsequent sections.

Mechanical Stimuli and Bone Tissue Adaptation

The relationship between mechanical loads and tissue adaptation is long standing. Wolff (133) and Frost (26, 27) demonstrated many years ago that bone tissue is highly mutable and adapts to mechanical stress. In recent years it is well documented that the musculoskeletal system deteriorates in people with SCI (22-25, 154), people on bed rest (20), or people exposed to spaceflight (21, 155). In just two years after paralysis, people with spinal cord injury have 23%, 25%, and 19% less articular cartilage in the patella, medial tibia, and lateral tibia, respectively (156). Timely mechanical stress reduced the loss of bone by 32% in people with SCI (26, 157), which may ultimately be lifesaving (19). Even secondary systemic complications like renal failure and metabolic syndrome are linked to deteriorating skeletal muscle and bone tissues (158-165).

Low-magnitude whole body mechanical oscillation (0.2-0.3g, 30 Hz), which would be well tolerated in people who already have osteoporosis, has been shown to attenuate bone loss in women with low bone mineral density (3, 143). Whole body vibration (0.3g, 45 Hz), at doses similar to that tested in this study, led to 75% increase in trabeculae of the proximal metaphyses of rats (14, 138). Vibration (0.3g, 30 Hz) of the sheep hind limb showed 34.2% increase in femur bone density (2). However, only one animal study delivered direct limb segment vibration in-vivo, but showed the tibia had a 88% higher rate of bone formation using the same 0.6g force demonstrated in the technology presented in this report (56). Because the vestibular system was likely activated during the weight bearing studies, it is possible that reflexes caused muscle activations that contributed to the tissue changes observed. These studies suggest that understanding the effects of mechanical stress on tissue is complicated and the field may benefit from technologies that isolate these mechanical stresses.

Mechanical Stimuli and Cartilage Adaptations

Mechanical loading can alter articular cartilage, intervertebral discs, and menisci (32, 166-169). Knee menisci are particularly susceptible to injury (170) and are often resistant to healing (171). Cyclic loading and intermittent tensile strain up-regulates VEGF(vascular endothelial growth factor), a gene directly involved with blood vessel formation (172). Importantly, regular mechanical load reduces inflammation initiated by interleukin-1 following menisci injury (139, 173). A torn porcine meniscus exposed to various mechanical compressive loading conditions (1, 10, or 26% strain, and 4h/day for 14 days) showed a reduced inflammatory response and repaired mechanical tissue shear strength (139). The value of cyclic repetitive loads on meniscus health is well documented (174, 175). Importantly, in the absence of natural mechanisms of meniscus tissue repair, regenerative rehabilitation engineers have developed a new scaffold consisting of viable undifferentiated cells that require a healthy environment (optimal stress) to proliferate and differentiate cells (176, 177). Injured meniscus cartilage was merely removed from the knee as little as 25 years ago. Today, the emphasis is in preserving and healing the tissue; however, the effect of controlled dynamic loads with vibration has never been explored in humans with menisci injury or repair. Hence there is a need for technologies to better study the interface between mechanical stimuli and tissue repair in humans.

Mechanical Stimuli and Muscle/CNS adaptations

Localized limb vibration modulates several central nervous system and muscle signaling pathways in people with and without spinal cord injury (57, 149, 150, 178). During single limb segment vibration, the activity of the soleus muscle was suppressed (178). Vibration caused an 83% reduction in the Hoffmann reflex (H-reflex), but limb load facilitated segmental excitability (decreased H-reflex post activation depression) (57, 149). Likewise, direct vibration over a muscle tendon increased pre-synaptic inhibition of the H-reflex (8, 59-61, 179) and loading (standing) reduces H-reflex post activation depression (180-182). Recent research has shown that deficiencies in postural control were associated with brain activity during localized vibration of the foot (42).

Vibration platforms for balance control have been reported to cause increased skeletal muscle activity, strength, and power (5, 6, 183, 184). These whole body vibration protocols used 2.3g-30g at 15-50 Hz, parameters within the range tested in the technology reported in this paper. However, these findings are not supported with direct tendon or muscle vibration; subsequent studies with tendon vibration support a decrease in quadriceps muscle activity and force (7, 185). Some intriguing findings suggest that localized vibration mitigates muscle atrophy during reduced activity (186, 187) and regulates certain genes associated with atrophy and synaptic plasticity (57, 131). It may be that the same dose that is optimal for bone is also optimal for cartilage, muscle, and nervous system tissue.

Mechanical Stimuli and Stem Cell Stimulation

An in depth coverage of stem cells is beyond the scope of this technical report. However, a brief summary is warranted. We now know that stem cells require an environment with appropriate stresses to foster survival, proliferation, and ultimately specialization. We also know that vibration input at a 5 g force and 30 Hz frequency caused adult stem cells to differentiate into bone cells (188), and cartilage precursor cells differentiated into cartilage after cyclic mechanical loading (1 Hz, 10% strain rate) (189), similar to the stimuli that we tested in this technical report.. Furthermore, recently, chondrocytes were shown to survive longer if they had been exposed to vibratory input and intermittent compressive loading (32, 36). Quiescent satellite cells in skeletal muscle showed enhanced gene regulation for protein synthesis following vibratory input at 30 Hz frequency (131). Clearly, the degree to which a satellite cell will evolve from the undifferentiated state to the specialized state is under the direction of the mechanical environment. Thus, the need for technology to translate these mechanical stresses is fundamental to establishing the efficacy for preserving health of tissues in the future.

In summary, the instrumentation presented in this technological report is novel, reliable, accurate, and safe for human tissues. To fully translate technology from the laboratory to human studies will require that experts from engineering, rehabilitation, and biosciences, work collaboratively to advance the field of human regenerative rehabilitation.

Conclusions

This report presents a novel example of how to deliver compressive and vibratory loads to the lower limb in humans via a new technology. Mechanical loads such as vibration and direct limb load have not been systematically studied in various combinations in humans. Importantly, the vibration stimuli developed in this report is directed to a single limb, rather than to the whole body, allowing a method to compare the direct effects of load to specific tissue. By delivering isolated therapeutic doses of mechanical stress to human tissues, we anticipate that the optimal methods of mechanically and physiologically stressing tissues may be ascertained in future studies.

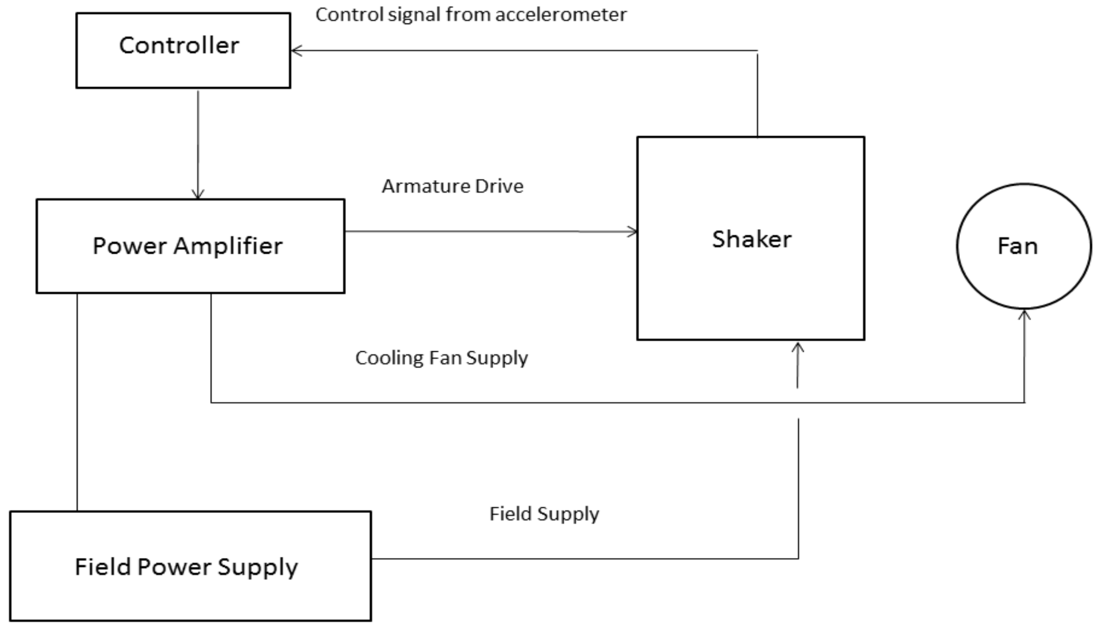

Figure 2.1 Schematic of the Vibration System. The power amplifier and field power supply generate power for the system and supply the shaker and the cooling fan. An accelerometer is attached to the shaker and controller creating a feedback loop to control the frequency and magnitude of vibration.

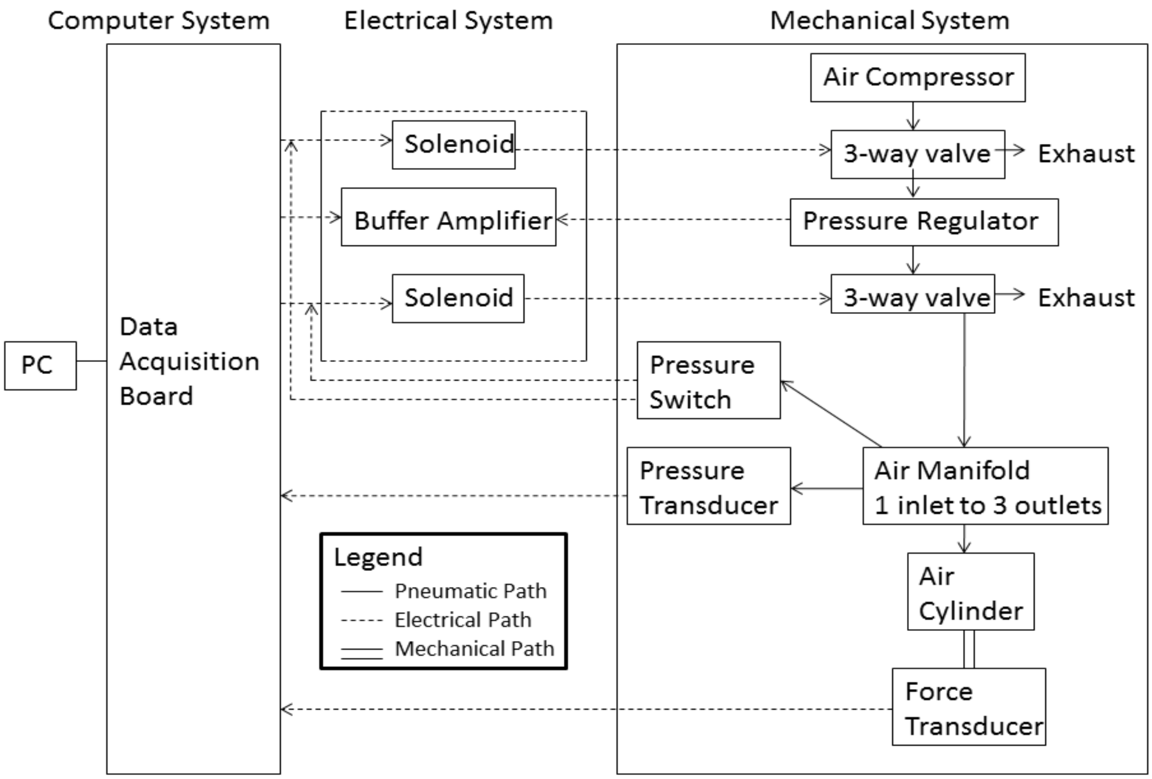

Figure 2.2 Schematic of the Compression System. The mechanical portion consists of a series of hardware components which regulate the amount of air pressure delivered to the air cylinder and subsequently the load applied to the human tibia. The electrical system provides power to many of the mechanical components and links them to the data acquisition (DAQ) board. The personal computer (PC) and the DAQ board control the compression system and allow the user to program the compressive system.

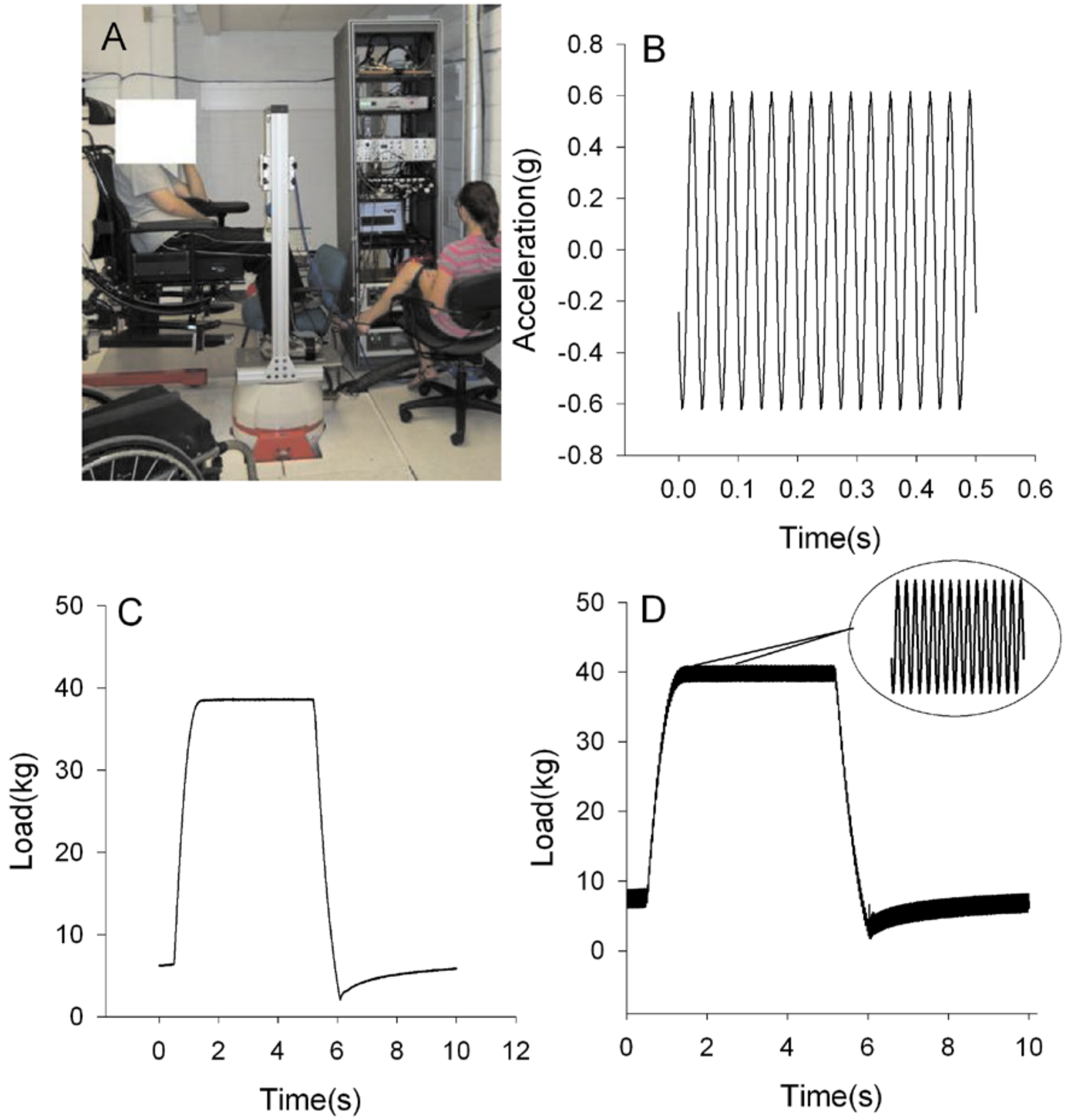

Figure 2.3 Vibration and Compression Systems. A) A participant seated in the adjustable wheelchair with the lower limb secured to custom designed compression frame which is fixed to the vibration shaker. The cabinet rack houses the compression hardware, DAQ board, computer, vibration controller, field power supply, and power amplifier. B-D) The output of the B) vibration, C) compression, and D) the two systems together was measured for 10 seconds or 1 cycle.

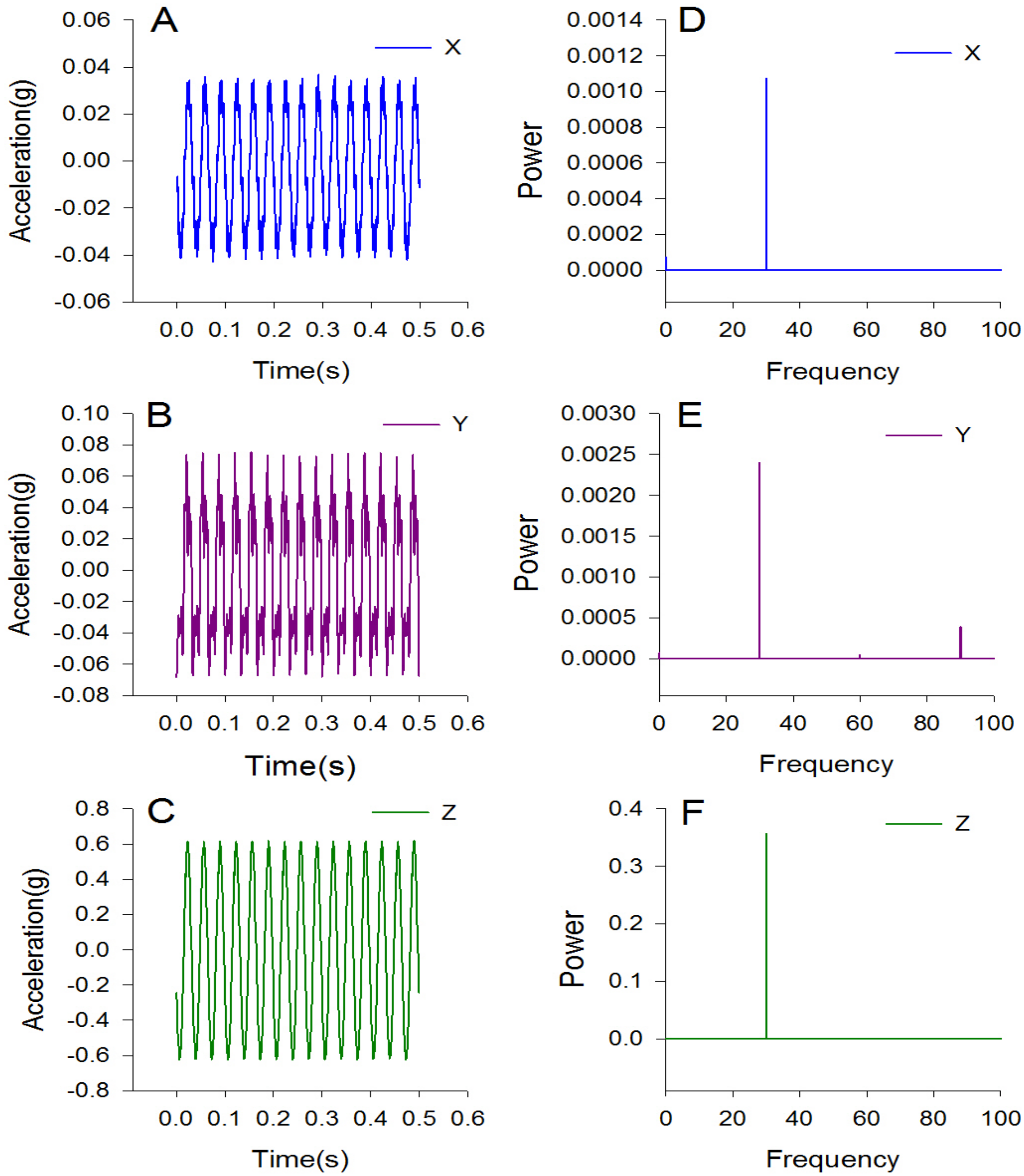

Figure 2.4 Acceleration of the Vibration Platform. A-C) Magnitude of acceleration in the x, y, and z directions are shown. As designed, virtually all of the vibration occurs in the vertical or z direction with minimal acceleration in the axes parallel to the platform. D-E) Fast Fourier transform of the vibration signal confirms that the frequency content of the vibration is desired frequency of 30 Hz. It also demonstrated that the z-direction contained most of the frequency content.

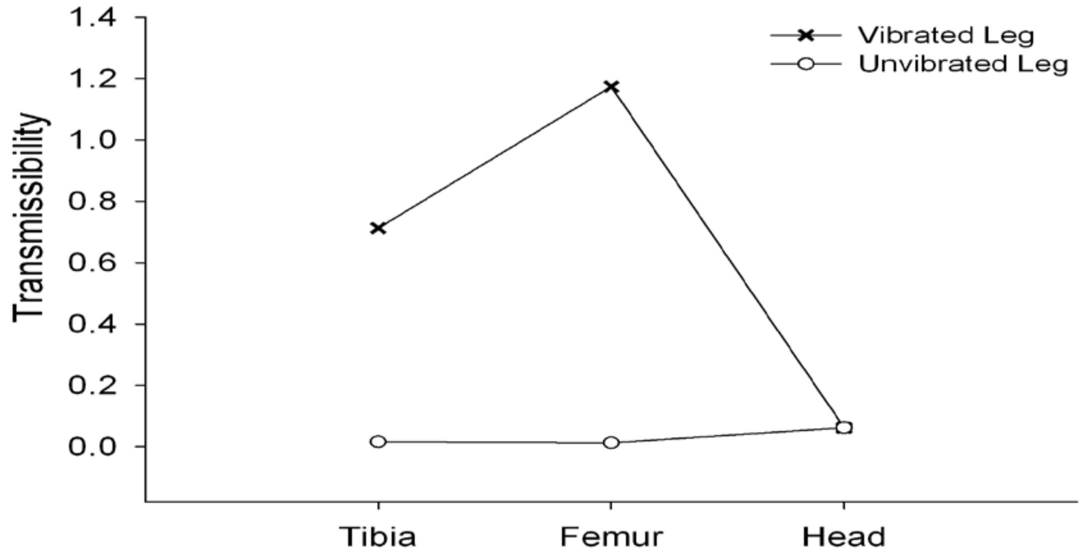

Figure 2.5 Transmissibility of the Vibration. The transmissibility of the vibration signal was calculated as a ratio of the anatomical landmark RMS to the RMS of the platform. An accelerometer was place on the tibia and femur of the vibrated and unvibrated leg as well as the head. A transmissibility of 1.0 indicates that the acceleration of the anatomical site is equal to the vibration platform.

Table 2.1 Accuracy of the Compression System. The compression system performed with a high level of accuracy which is indicated by the low linearity, repeatability, and percent error. These metrics were calculated using the 10 cycles at each air pressure (%FS = percent full scale).

Pressure(kPa)	Linearity(%)	Repeatability(%FS)	Error(%FS)
138	3.79	0.54	0.51
207	1.75	0.57	0.42
276	1.26	0.61	0.44
345	0.83	0.69	0.38
414	0.58	0.54	0.32

Table 2.2 Reliability of Compression System. The data of eight spinal cord injury subjects were used to determine the inter-session reliability of the compression system. The difference in force between session at the same time points (after cycles 1, 30, 60 and 90) showed minimal changes and a high intra-class correlation.

Cycle	Change (%) ± SD	ICC
1	5.07 ± 2.74	0.917
30	3.43 ± 1.43	0.965
60	6.53 ± 3.98	0.899
90	3.06 ± 2.75	0.965

CHAPTER 3 LOWER EXTREMITY VIBRATION MODULATES CORTICAL AND SEGMENTAL EXCITABILITY IN HUMANS

Introduction

Vibration training has recently been incorporated into rehabilitation programs to treat various musculoskeletal and neurodegenerative diseases despite inconclusive evidence of its benefits (190). Several researchers have shown the positive effect of vibration on bone (2), muscle (5), and neuromuscular control (10). Because this peripheral stimulation influences many systems simultaneously it is difficult to determine the mechanism responsible for the impact, specifically with respect to the nervous system. For instance, tendon vibration increases presynaptic inhibition of spinal reflexes (peripheral) (8, 59-61, 179), whereas tendon vibration over the metatarsal heads enhances sensory signaling in the brain (central) (42). However, the peripheral and central nervous systems do no act in isolation and perhaps the inhibition of the spinal reflexes is due to the enhanced signaling in the brain.

Spinal reflexes, particularly soleus H-reflexes, are a longstanding metric used to quantify segmental excitability. Many early vibration studies showed direct tendon vibration inhibits soleus H-reflexes due to an increase in presynaptic inhibition (8, 59-61). More recently whole body vibration has been introduced to accelerate and enhance tissue training leading to increased muscle strength (191), power output (183), and bone density (192). Unlike tendon vibration, whole body vibration oscillates the entire body, including the head and vestibular system. The effects of whole body vibration on segmental excitability are also more controversial. Whole body vibration has been frequently cited as an intervention that reduces the excitability of the segmental system (H-reflex) (62-66) but this finding is not consistent among all whole body vibration studies (67, 68).

In addition to changes in segmental reflexes, vibration has been shown to modulate sensory as well as motor areas of the brain. Using functional magnetic resonance imaging (fMRI), vibratory input to the sole of the foot increases neural activity to several cortical structures including the motor cortex and parietal areas (41, 193, 194). Transcranial magnetic stimulation (TMS), another method to quantify cortical excitability, demonstrates that tendon vibration increases the motor evoked potential (MEP) of the vibrated muscle and its antagonist (9). Vibration of the entire hand (multiple muscles) increased the MEP amplitude of the first dorsal interosseous and abductor pollicis brevis (79). Whole body vibration also increases cortical excitability of the tibialis anterior muscle indicated by a 56% increase compared to a controlled condition (80).

Vibration seemingly reduces segmental excitability (H-reflexes) but increases cortical excitability (TMS evoked MEP); however, the effect of descending inputs on H-reflexes during vibration remain more ambiguous. Recently, Goulart and colleagues examined the muscle response of TMS-conditioned H-reflexes in the absence of vibration where a TMS pulse is delivered before an H-reflex (81). They found that a short inter-stimulus interval (ISI) of 10-20 ms between the sub-threshold TMS pulse and the peripheral nerve stimulation resulted in a facilitation of the H-reflex (81). However, when vibration was applied to the tendon the H-reflex was suppressed but showed recovery after TMS conditioning (84). This reduction in the vibration-induced H-reflex inhibition may be attributed to reduced post activation depression. (82-84). Three different mechanisms could be responsible for the reduction in H-reflex post activation depression during vibration: 1) reduced presynaptic inhibition due to the sub-threshold TMS, 2) enhanced postsynaptic potentials (EPSPs) from the sub-threshold TMS pulse itself, or 3) increased cortical excitability during vibration. Vibration has been shown to inhibit the soleus H-reflex and the sub-threshold TMS could partially preclude the presynaptic inhibition (84). In the absence of vibration, a sub-threshold TMS conditioning stimulus has been shown to increase the motor evoked potential of the subsequent supra-threshold TMS by 120-300% (195). Simply introducing a sub-threshold TMS conditioning stimulus could provide enough EPSPs to reduce the vibration-induced H-reflex inhibition. Alternatively, cortical excitability has also been shown to increase with tendon vibration (9, 196) and whole body vibration (80).

Tendon or whole body vibration does not address the extent to which the stimulus is transmitted to the head inducing vestibular modulation. We recently developed a method to introduce a controlled platform vibration to an entire limb including multiple muscles and joints while minimizing the mechanical transmission to the head or vestibular system. We have reported that this platform vibration induces significant inhibition of the soleus H-reflex (57), which is partly eliminated with an applied load (149, 150). We do not know the effect of this form of limb platform vibration on the TMS-conditioned H-reflex or cortical excitability. If limb vibration increases cortical excitability then those with neurological deficiencies could potentially benefit from peripheral vibration without having to balance on a vibration platform. Previous studies have shown that prolonged vibration can enhance cortical excitability of the primary motor cortex (197, 198). Individuals who can effectively incorporate and integrate afferent information have enhanced motor cortex excitability and motor learning (199). Accordingly, the purpose of this project is to determine if the vibration-induced H-reflex inhibition can be attenuated by conditioning the motor cortex and if cortical excitability is modulated by mechanical oscillations. We hypothesize that a sub-threshold TMS conditioning stimulus will reduce vibration-induced H-reflex inhibition and limb vibration will increase cortical excitability.

Methods

Subjects

A total of 23 healthy adults participated in this study. In the first experiment, 15 subjects (3 males, mean age of 23.5 ± 0.6 years) were recruited to examine the modulation of the TMS conditioned H-reflex during limb vibration. In the second experiment, 8 subjects (2 males, mean age of 25.8 ± 3.1 years) were tested to determine the effect of limb vibration on cortical excitability. Exclusion criteria included 1) history of neurological, muscular, or cardiovascular disorders, 2) history of seizures, 3) implanted cardiac devices, and 4) non-dental metal in the head. All subjects passed a TMS safety screening and provided informed consent approved by the University of Iowa Institutional Review Board.

Instrumentation and Data Collection

Muscle activity of the left soleus was recorded using bipolar Ag-AgCl electrodes (8 mm diameter with a 20 mm inter-electrode distance). The skin over the left soleus muscle was abraded and cleaned before the recording EMG electrode was placed over the soleus muscle, 2 cm distal to the gastrocnemius and 2 cm lateral of the midline. The reference electrode was attached to the anterior aspect of the left tibia. The EMG signal was collected at a sampling rate of 3000 Hz.

Soleus H-reflexes were elicited by electrically activating the tibial nerve at the popliteal fossa. The cathode, a dispersive electrode, was placed on the anterior aspect of the thigh, above the knee. After determining the optimal position for the stimulating electrode, a maximal H-reflex was elicited. The stimulus intensity was then adjusted to provide 50% of the maximal H-reflex to ensure all subsequent H-reflexes were on the ascending portion of the recruitment curve. Electrical pulses were delivered as square waves of pulse width 1000 μs using a constant-current electrical stimulator DS7A (Digitimer Ltd., Welwyn Garden City, Herts, UK). A maximum M-wave was collected at the end of the experiment in order to normalize the EMG data.

A single-pulse TMS was delivered using a Magstim 200^2 stimulator (Magstim Company Ltd., Whitland, Dyfed, UK) equipped with a double-cone coil. The coil was positioned over the right motor cortex and fine adjustments were made until the largest motor evoked potential (MEP) of the soleus was elicited. To ensure the coil remained in the same position throughout the collection, a TMS Navigator System (Northern Digital, Inc., Waterloo, Ontario, Canada) was used. The TMS coil was fitted with passive markers and the subjects wore a head reference also containing these markers. The Polaris Vicra System (Northern Digital, Inc., Waterloo, Ontario, Canada) emitted infrared light which is reflected back to the system by the passive markers. Due to the ability to constantly monitor the coil position with respect to the head, the coil remained in the same position throughout the collection.

The servo-controlled vibration system (Ling Dynamic Systems Ltd., Royston, Herts, UK) generated a sinusoid with an acceleration of 0.6g and frequency of 30 Hz. To briefly describe the vibration system, the PA100L power amplifier and FPS10L field power supply were connecting in cascade to supply power to the V722 shaker. An accelerometer connected the shaker and LaserUSB 6.30 controller to create feedback loop, allowing precision control of the vibration. We have quantified the transmissibility of limb vibration to the vibrated limb, contralateral limb, and the head. With perfect transmissibility of the vibration as 1.0, we found the vibrated limb had 0.71 whereas the contralateral limb and head was less than 0.02 (Figure 3.1). The minimum vibration threshold for vestibular system is 0.036g (200) which is approximately twice the acceleration (0.017g) measured at the head during limb vibration. Therefore, our vibration system is capable of limb segment vibration in the absence of vestibular activation.

Experimental Procedure

For both experiments, subjects were seated comfortably in a tilt-space chair, slightly reclined, and head fully supported. Due to the slightly reclined position the hip and knee were flexed to 80° and 110°, respectively. The left leg was placed on the vibration platform with the ankle in the neural position. The leg was secured to the device at the knee with a height-adjustable pad over the femoral condyles and at the forefoot with a Velcro strap. To minimize the impact of supra spinal inputs on cortical excitability, the subjects wore ear plugs and were told to remain relaxed throughout the collection.

<u>Experiment 1</u>

The experiment consisted of six conditions (Figure 3.2). Soleus EMG was recorded during the H-reflexes, TMS pulses, and TMS-conditioned H-reflexes. Baseline conditions were collected first without limb vibration. There were five pulses for each of the three conditions (H-reflex, TMS, TMS-conditioned H-reflex) and 20 seconds between each pulse. The stimulating intensity was set to elicit an H-reflex which was 50% H-max and the TMS intensity was set at sub-threshold intensity. To determine the TMS stimulating threshold, the intensity was increased until a MEP was produced during a sub-maximal soleus contraction, approximately 5% of maximum torque. If the MEP disappeared in the absence of muscle contraction then this intensity was selected. During the TMS-conditioned H-reflex, a single TMS pulse was delivered 10 ms before the H-reflex. These three conditions (H-reflex, TMS, and TMS-conditioned H-reflex) were repeated during limb vibration.

Experiment 2

The findings of Experiment 1, a sub-threshold TMS pulse reducing the H-reflex suppression during limb vibration, led to a second experiment. We proposed increased cortical excitability as a potential explanation for this reduction in H-reflex suppression. Therefore, we collected an additional cohort of different subjects to test this hypothesis. For Experiment 2, the resting motor threshold (RMT) was determined as lowest TMS stimulator intensity producing MEP amplitude of 50 μV in at least 4 of 8 trials. The stimulator was then set to 120% of RMT for duration of the experiment. A total of 10 TMS pulses were delivered every 20 seconds, 5 without limb vibration and 5 during limb vibration. Following TMS, 3 maximum voluntary contractions were collected to normalize the soleus EMG data. The subjects remained seated in the device and were instructed to plantar flex to their maximum contraction and then hold for 5 seconds. Verbal encouragement was given to promote a maximal effort.

Data Analysis

For experiment 1, a custom DIAdem 2012 (National Instruments, Ireland) script was created to completed offline data analyses. The program was written to find the minimum and maximum EMG signal both of which were manually verified by the user. The peak-to-peak amplitude was then calculated as the difference between the maximum and minimum and normalized to the maximum M-wave.

For experiment 2, the maximum and minimum of the MEP were manually determined using DIAdem 2012. The peak-to-peak MEP amplitude was defined as the difference between the maximum and minimum values. To determine the MVC, first the root means squared of the soleus signal was calculated. Then the maximum RMS value was determined and the values 200ms before the maximum and 200ms after the maximum were extracted. The average of this 400ms window around the maximum RMS value was calculated and used to normalize the data.

Statistical Analysis

For the first experiment, a priori statistical test (paired t-test) was performed comparing four conditions. The following comparisons were made: 1) H-reflex and H-reflex during vibration, 2) H-reflex during vibration and TMS conditioned H-reflex during vibration, 3) H-reflex and TMS conditioned H-reflex and 4) TMS and TMS during vibration. To account for the multiple comparisons, Bonferroni correction was applied to the p-value. To be significant at the 0.05 level, the p-value of any paired t-tests must be smaller than the adjusted p-value, $p_{adj} = 0.0125$ ($p_{adj} = 0.05/c$, where c is the number of comparisons).

For the second experiment, a paired t-test was also performed comparing the soleus MEP amplitude with and without limb vibration. A p-value less than 0.05 was considered significant.

Results

Experiment 1

Soleus H-reflexes with and without limb vibration is depicted in Figure 3.3A. Limb vibration suppressed H-reflex amplitude by 96% ($p = 0.005$). However, this suppression can be mitigated with a sub threshold TMS conditioning stimulus as shown in Figure 3.3B.

During limb vibration, a sub threshold TMS conditioning stimulus facilitates the H-reflex and results in a fourfold increase in amplitude ($p = 0.001$). In the absence of limb vibration, the TMS conditioning pulse did not change the H-reflex (Figure 3.4, $p = 0.133$).

Sub-threshold TMS delivered during limb vibration revealed no change in motor evoked potentials (Figure 3.5, $p=0.934$). Also, baseline EMG during this experiment was approximately 1.0% M-max (Figure 3.5).

Some subjects showed a greater increase in the TMS conditioned H-reflexes during vibration (greater recovery of the H-reflex) compared to others (Figure 3.6B). One outlier was removed from this dataset but the statistical analysis did not change with the removal. A subject-by-subject analysis revealed that the 4 subjects who showed the greatest recovery of the H-reflex also had evidence of an increase in cortical excitability

(Figure 3.6D, Pearson correlation, r =0.65). While the group means data did not show a significant increase in cortical excitability during vibration, individual data suggests that select subjects experienced an increase in cortical excitability with vibration. This increase could have impacted the magnitude of the TMS conditioned H-reflex during vibration.

Experiment 2

To determine the effect of vibration on cortical excitability, a cohort was collected using supra-threshold TMS during limb vibration. The motor evoked potentials from supra-threshold TMS are shown in Figure 3.7. Limb vibration did not change the cortical excitability (p=0.796).

Discussion

A sub-threshold TMS conditioned stimulus can reduce the post activation depression of the soleus H-reflex due to limb vibration. During limb vibration, the TMS conditioned H-reflex was 400% greater than the H-reflex alone. In agreement with previous research (57), H-reflexes were inhibited during limb vibration by 96%. This confirms that a conditioning TMS pulse is necessary to counteract the vibration-induced H-reflex inhibition. We also showed in the absence of limb vibration that a TMS conditioning stimulus did not facilitate the H-reflex amplitude. We further demonstrated that limb vibration did not alter cortical excitability (Figure 3.7). Taken together, it appears to be the unique combination of TMS and H-reflex during vibration that results in a larger response compared to H-reflex and vibration.

There are several possible mechanisms that could explain why the TMS-conditioned H-reflex during limb vibration is significantly greater than the H-reflex during limb vibration (Figure 3.8). First, the sub-threshold TMS stimulus could inhibit the inhibitory interneuron which suppresses the H-reflex during vibration. This presynaptic mechanism is indicated in Figure 3.8 in blue. Second, the H-reflex could be enhanced due to postsynaptic facilitation from the TMS pulse itself, shown in red. Lastly, limb vibration might increase cortical excitability, also indicated in red. Experiment 2 tested this alternative postsynaptic mechanism by quantifying changes in MEPs of supra-threshold TMS during limb vibration.

A reduction of the H-reflex amplitude during vibration has been well established for various types of vibration including tendon vibration (8, 84), whole body vibration (66), and limb vibration (57). Prior research has shown that a TMS conditioning stimulus 20 ms prior to peripheral nerve stimulation facilitates an H-reflex during tendon vibration (84, 85). These researchers suggest that a presynaptic mechanism was responsible for the TMS pulse reducing the H-reflex suppression during vibration (84, 85). According to these studies, a TMS pulse blocks the post activation depression of the H-reflex during vibration. However, the magnitude of facilitation of the H-reflex due to a TMS conditioning stimulus was the same with and without tendon vibration (84). Because the magnitude of facilitation from the TMS stimulus is independent of vibration then the mechanism could be postsynaptic in nature. Secondly, our results showed that a sub-threshold TMS conditioning stimulus did not significantly facilitate the H-reflex. Our findings are unlike previous research which showed that a sub-threshold TMS pulse 10-20 ms before peripheral nerve stimulation increased H-reflex amplitude (81, 84, 85).

During these previous studies the leg and foot remained unloaded. In order to apply limb vibration, the foot is placed on the vibration platform and the leg is secured. The sensory input coupled with the load required to secure the limb during vibration could inhibit the H-reflex. Others have shown that the H-reflex is depressed during stance (201) and walking (202) due to increased peripheral afferent information. If the H-reflex is slightly inhibited then the addition of a sub-threshold TMS conditioning stimulus might not provide adequate excitatory input to facilitate the H-reflex. Because the H-reflex is not different compared to the TMS conditioned H-reflex then we can eliminate the postsynaptic mechanism of enhanced EPSPs from the TMS pulse itself as the explanation for the reduced H-reflex suppression.

A third explanation could be that vibration increases cortical excitability and consequently the TMS-conditioned H-reflex during vibration is greater than the H-reflex during vibration. In the first experiment, we found no change in soleus EMG response to sub-threshold TMS during limb vibration. Other researchers have explored changes in cortical excitability following various types of vibration such as WBV and tendon vibration. One such study showed a TMS pulse facilitated the tibialis anterior MEP following whole body vibration (80). However, vibration of the Achilles tendon showed no change in MEP amplitude for the soleus or tibialis anterior muscles immediately after the vibration (58). It is difficult to accurately compare the results of WBV or tendon vibration to the findings of limb vibration because all these modes of vibration are very different. Whole body vibration involves the activation of the vestibular system, somatosensory system, and multiple tissues throughout the body. Alternatively, tendon vibration limits the vibration to only one muscle without transmission to the head or any other parts of the body. Limb vibration contains components of each, comparable to WBV multiple muscles are vibrated but like tendon vibration the vibration is confined to the target muscles. Similar to tendon vibration findings, limb vibration shows no change in EMG during sub-threshold TMS. Inspection of individual data revealed that several subjects showed an increase in EMG during sub-threshold TMS and limb vibration (Figure 3.6D) and these individuals also had the most prominent response to TMS conditioned H-reflex during vibration (Figure 3.6B). To date, Christova provides the only supporting evidence for increased cortical excitability immediately following peripheral vibration without vibration of the head (79). They introduced mechanical vibration to the entire hand which increased the cortical excitability of the hand muscles (79). Our vibration apparatus most closely mimics the hand vibration as they both deliver a vibratory input to multiple muscles.

Because the TMS was delivered at sub-threshold intensity we cannot conclude limb vibration modulated cortical excitability. Based on the findings of Experiment 1, the reduction in the vibration induced H-reflex inhibition could be due to presynaptic inhibition of the inhibitory interneuron or increased cortical excitability during limb vibration. An additional collection was necessary to determine the mechanism responsible for the reduction in vibration-induced H-reflex suppression when conditioned with a TMS stimulus. Experiment 2 used supra-threshold TMS to determine if limb vibration increased cortical excitability.

We found that limb vibration does not induce an increase in motor cortical excitability. Although we are the first to introduce a vibratory input to the entire limb segment, others have delivered localized vibration to single muscles. Vibration of a single muscle increases motor-evoked potentials following a single TMS pulse (9, 77, 203) unlike our findings which showed no change during limb vibration. High-frequency vibration, 70-80 Hz, is ideal for modulation of cortical excitability (9, 77) and activation of the somatosensory cortex and the motor cortex (41, 204, 205); however our vibration was delivered at a lower frequency, 30 Hz. The discrepancy in our findings compared to previous work could be linked to the different vibration frequencies. It is conceivable that if we increased the frequency of limb vibration we could modulate cortical excitability and brain activity. Recently, Murillo and colleagues reviewed the effects of focal vibration on various neurological disorders revealing many benefits of localized vibration (44). Focal vibration reduces spasticity in individuals with stroke (206, 207), spinal cord injury (51), and multiple sclerosis (208) and improves gait following a stroke (209, 210) or Parkinson's disease (50). Single muscle vibration can also promote cortical reorganization and facilitate motor learning of novel tasks (44). Our limb vibration system offers a unique opportunity to examine the effects of entire limb segment vibration and multiple muscles without transmission to the head. Using this system, we can conclude that a descending conditioning stimulus temporarily removes the vibration-induced segmental inhibition at a presynaptic level. Future work is needed to determine if this neurophysiological response to limb vibration will translate to altered proficiency of a functional task.

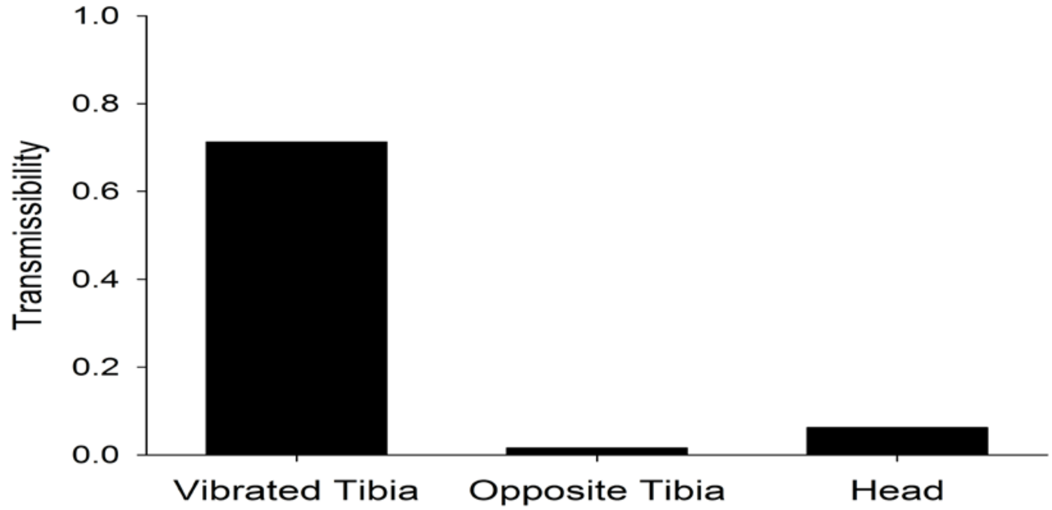

Figure 3.1 Transmissibility of Platform Vibration. Transmissibility of the vibration from the platform to the vibrated tibia, opposite tibia, and the head. Transmissibility of 1.0 indicates that the acceleration of the anatomical site is equal to the vibration platform.

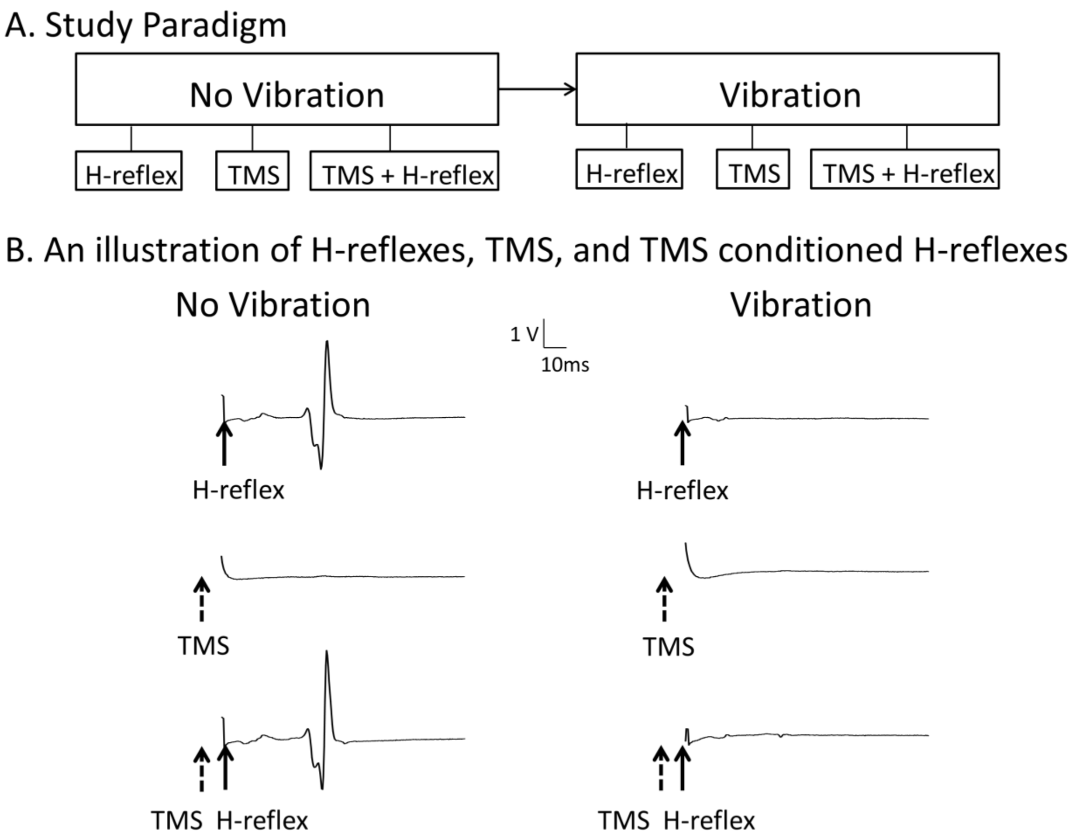

Figure 3.2 Study Paradigm. The study paradigm consisting of three distinct conditions: the peripheral stimulation of the tibial nerve (H-reflex), sub-threshold TMS over the motor cortex, and TMS-conditioned H-reflexes. Each of these conditions will occur with and without vibration.

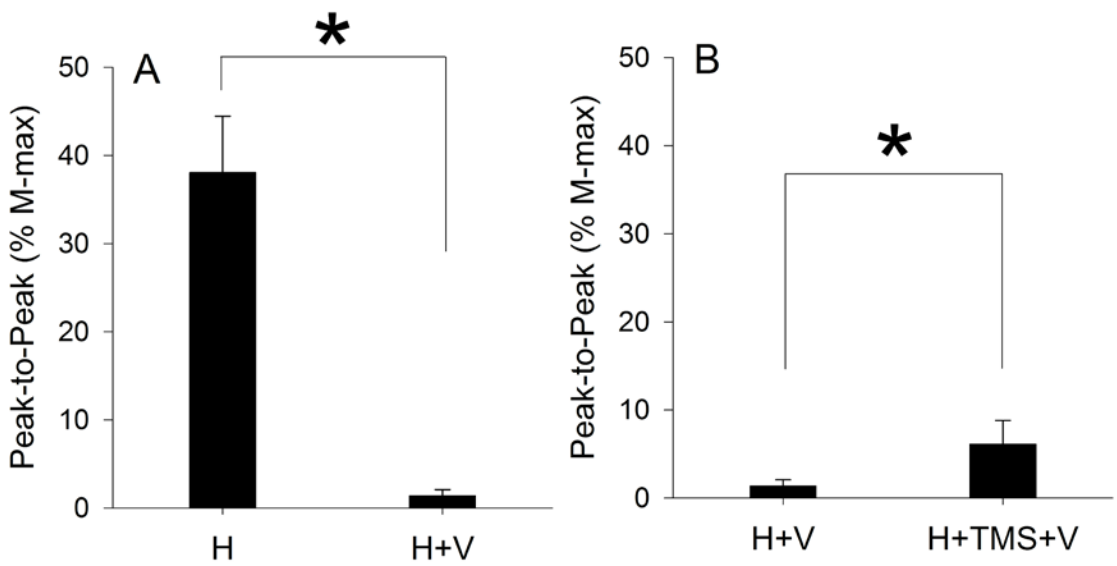

Figure 3.3 Response to Limb Vibration. A) Peak-to-peak amplitude of the H-reflexes with and without vibration. B) Peak-to-peak amplitude of the H-reflexes with vibration and TMS-conditioned H-reflexes with vibration. All values were normalized to % M-max. * Indicated significance of $p < 0.05$.

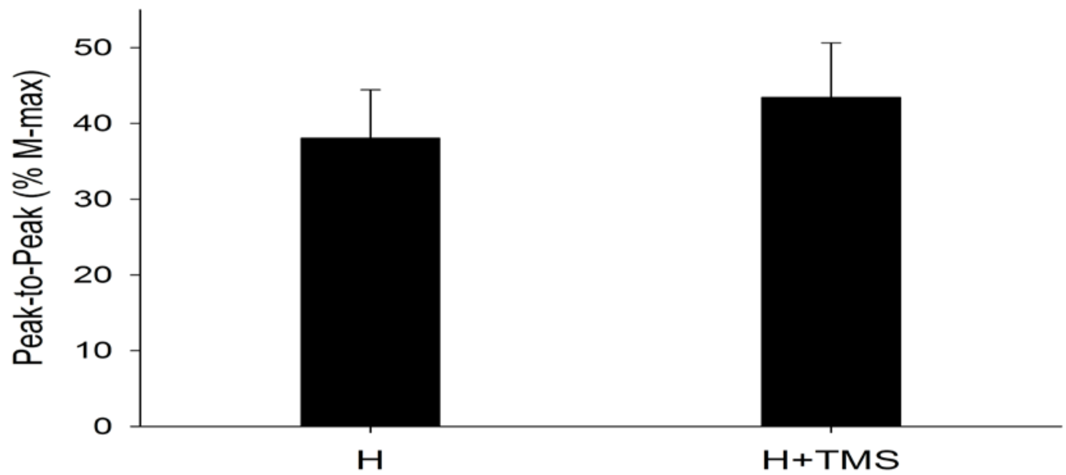

Figure 3.4 Effect of Sub-threshold TMS on Soleus H-reflex. Peak-to-peak amplitude of the H-reflexes compared to the TMS-conditioned H-reflexes. All values were normalized to % M-max.

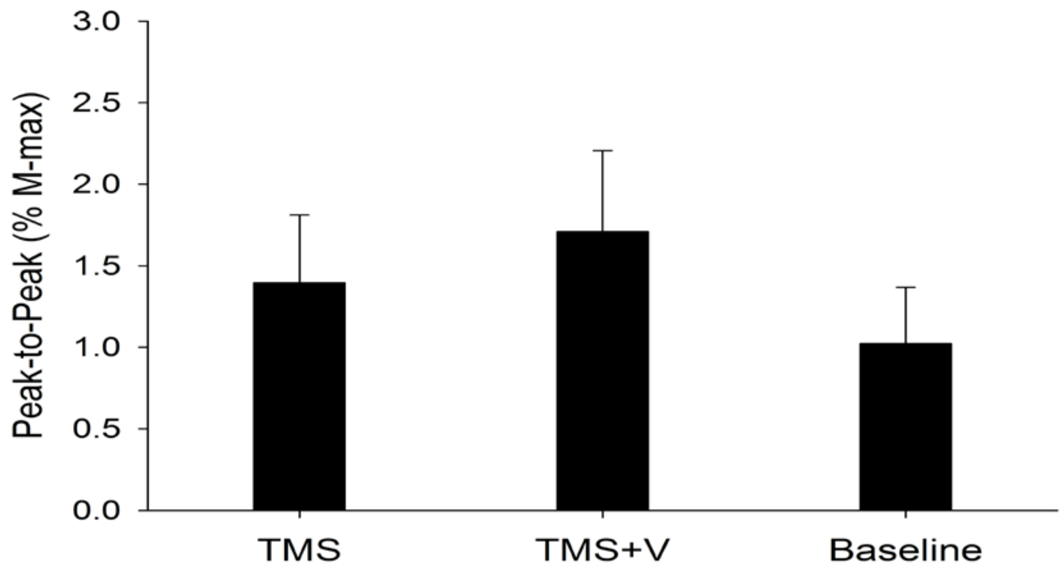

Figure 3.5 Soleus EMG during subthreshold TMS. EMG activity during subthreshold TMS with or without vibration did not show any difference. There is also no difference between baseline EMG and EMG during sub-threshold TMS. All values were normalized to % M-max.

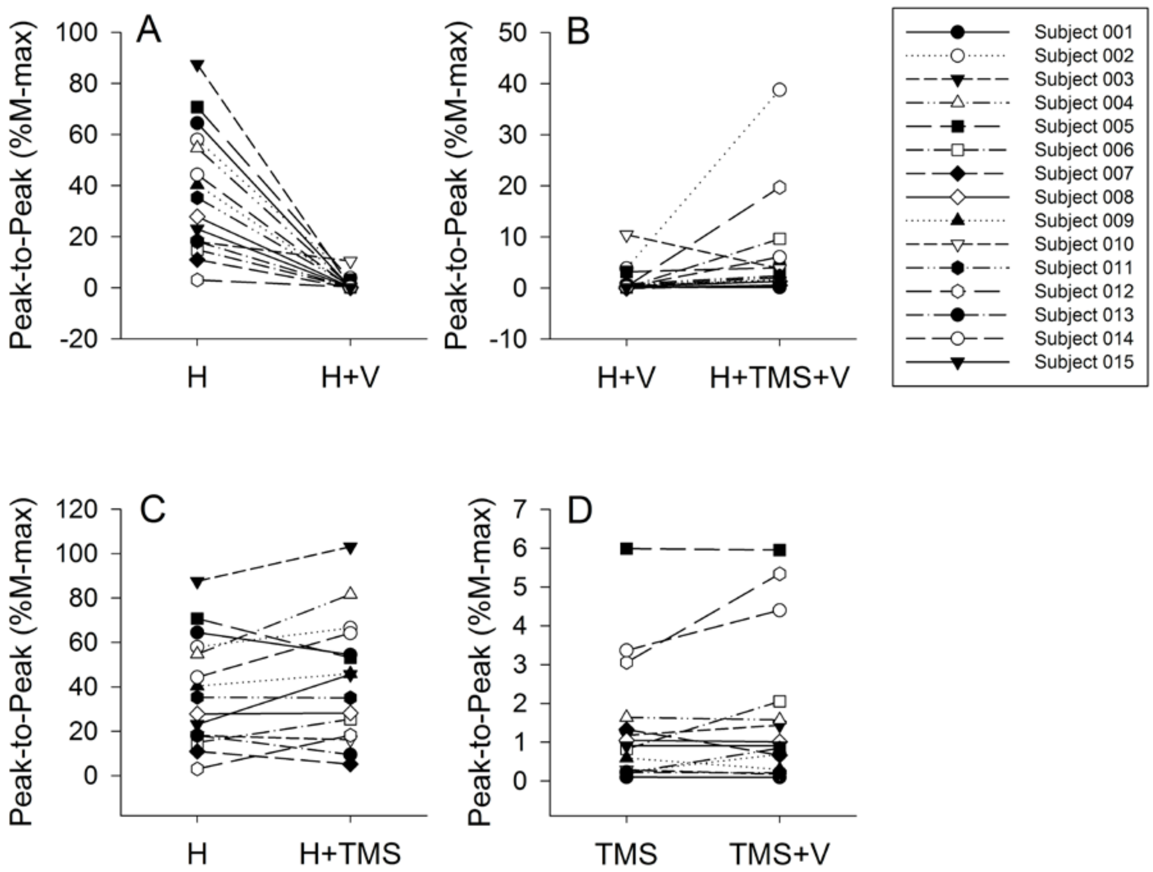

Figure 3.6 Individual data of four comparisons. A) Peak-to-peak amplitude of the H-reflexes and H-reflexes with vibration. B) Peak-to-peak amplitude of the H-reflexes with vibration and TMS-conditioned H-reflexes with vibration. C) Peak-to-peak amplitude of the H-reflexes compared to the TMS-conditioned H-reflexes. D) EMG activity during TMS with and without vibration. All values were normalized to % H-reflex.

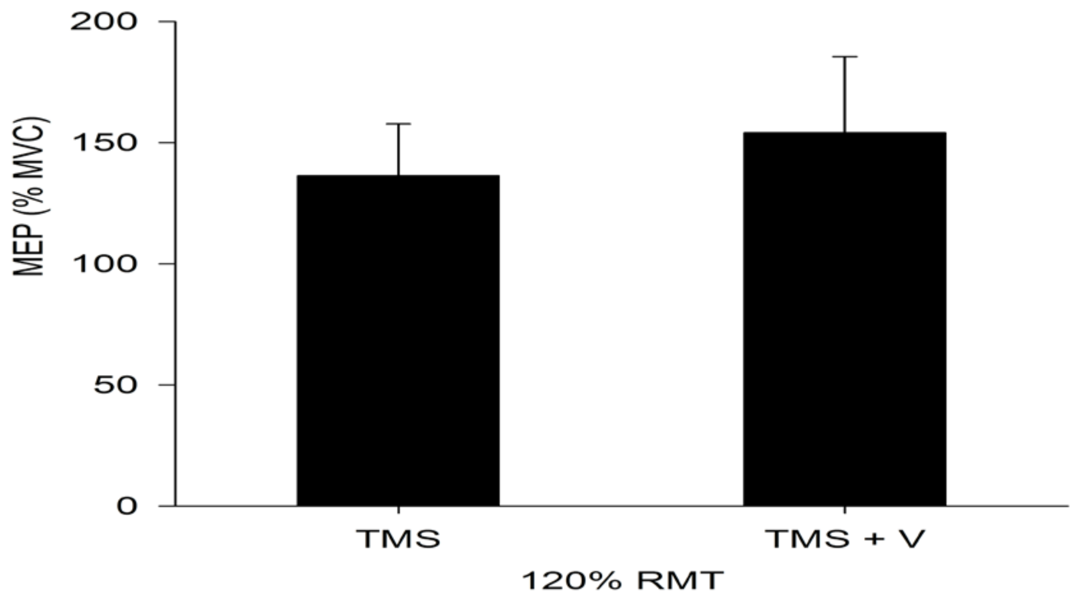

Figure 3.7 Limb Vibration and Supra-threshold TMS. Limb vibration did not induce a change in supra-threshold TMS motor evoked potentials. All values were normalized to % MVC.

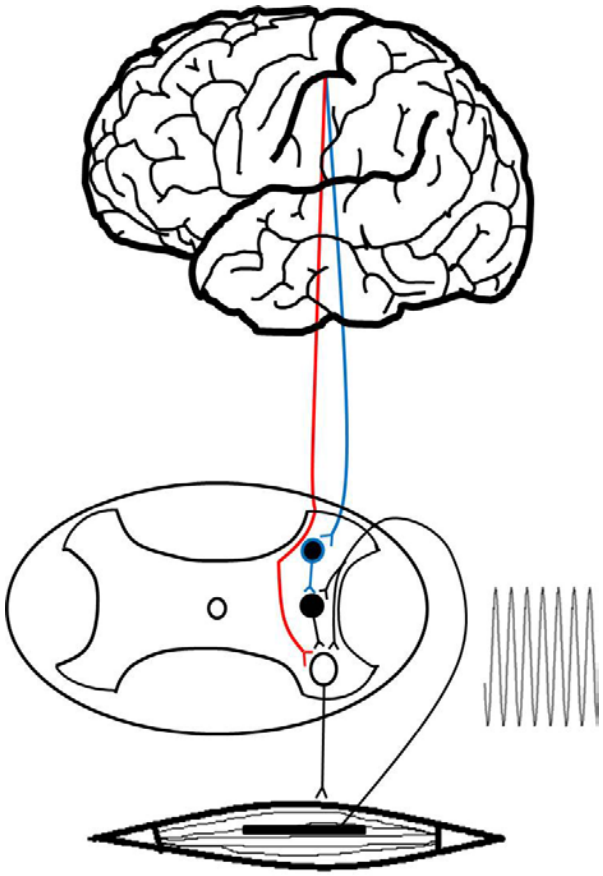

Figure 3.8 Potential mechanisms responsible for reducing the vibration-induced H-reflex suppression. Limb vibration, the black pathway, inhibits the soleus H-reflex by activating the inhibitory neuron. A TMS conditioning pulse inhibits the H-reflex suppression during limb vibration. The blue pathway indicates a potential presynaptic mechanism and the red pathway shows the potential postsynaptic mechanisms. The presynaptic mechanism inhibits the inhibitory neuron. The postsynaptic mechanisms synapse directly on the alpha motorneuron and delivers excitatory postsynaptic potentials.

CHAPTER 4 LIMB VIBRATION MODULATES NEURAL CONTROL STRATEGIES DURING A POSTURAL TASK

Introduction

Postural stability depends on accurate processing and integration of the somatosensory, visual, and vestibular systems. Various environmental perturbations can alter one's ability to accurately interpret this information and maintain upright stance. A perturbation due to platform translation or rotation (211) as well as local anesthesia of the foot (212) can disrupt the somatosensory system. Visual inputs can be altered by obstruction of vision or exposure to a moving visional scene (213). Similarly, galvanic stimulation of the mastoid process disturbs the postural control of the vestibular system (87). Manipulation of one or more of these systems allows researchers to determine how each contributes to the neuromuscular control of posture.

Vibration is one specific perturbation that can induce postural control disruptions by altering the somatosensory, visual and vestibular inputs. Early studies showed that tendon vibration of a single muscle impairs proprioception and leads to the illusion of movement (92, 214). Direct tendon vibration activates Ia afferents (215) and gives the sensation of muscle lengthening. In order to correct this misperception the individual will lean toward the direction of the muscle that is being vibrated. Specifically, vibration of Achilles tendon increases sway in the posterior direction (92). The effect of tendon vibration on postural control depends on how it is applied and certain tendon vibration paradigms have been shown to improve postural control. Han and colleagues showed that simultaneous vibration of the agonist (tibialis anterior) and antagonist (gastrocnemius) improved balance during double stance with eyes closed (108). If the vibration is limited to the tactile aspect of the somatosensory system by vibrating only the plantar surface of the forefoot then there is an increase in posterior sway (106). The findings of whole body vibration on postural control are more contentious. Several have stated that whole-body vibration enhances postural control (39, 105, 216) while others have reported no change (217, 218). Unlike tendon vibration or vibration of the plantar surface of the foot which primarily affects the somatosensory system, whole body vibration also influences vision and the vestibular system. The increased complexity of sensory feedback and inconsistent vibration parameters are likely contributors to the varying results of previous work.

In order to reduce the influence of vibration on the vestibular system, we developed a method to deliver a servo-controlled vibration to an entire limb with minimal transmission to the head, and, the vestibular system (219). Using this system, we verified that limb vibration induces a lasting effect (several minutes) on spinal cord excitability (57) but minimally regulates cortical excitability (Chapter 3). However, the effects of limb vibration on various postural control metrics have yet to be determined.

Healthy postural control contains a natural amount of variability, quantified using linear metrics, and an optimum complexity, measured by nonlinear variables. Traditional metrics (displacement, path length, standard deviation, velocity) have been used to show postural control changes during tendon vibration and whole-body vibration (105, 108, 220) but others have only found changes using nonlinear quantifications of postural control (221). Newell contended that the averaging characteristic of conventional metrics might fail to capture the nonlinear aspects of postural control (222). Unlike traditional measures which assume a stationary time series (223, 224), nonlinear metrics employ fractal analysis to describe the self-similar structure of center of pressure and infer information about the neuromuscular control of posture (225, 226).

In 2006, Stergiou and colleagues presented the concept of optimal movement variability stating that a successful neuromuscular control system operates within a specific bandwidth of variability (227). The conventional perspective suggests increased variability indicates a noisy, unstable movement strategy whereas decreased variability indicates stable postural control. However, the movement pattern needs to have adequate variability otherwise the system is too rigid to adapt to changing environments. Additionally, reduced complexity even with sufficient variability can reveal developing movement control pathologies (228). Detrended fluctuation analysis as used by Ihlen, is a form of fractal analysis that appears well suited to quantify the complexity or nonlinearity of the center of pressure (229). Nonlinear, fractal metrics have been used to assess postural changes due to age (230), pathology (228), and fall risk (231) and may effectively discriminate movement control adaptations attributed to limb vibration.

The purpose of this study is to determine if limb vibration alters postural control as quantified by the center of pressure, ankle muscle activity, and kinematics. We hypothesize that isolated peripheral limb vibration will disrupt the ability to sustain a normal postural control strategy. Specifically, prior isolated limb vibration will increase center of pressure variability/complexity, increase agonist/antagonist muscle activity, and alter limb kinematics during single limb stance.

Methods

Participants

Twenty healthy adults, 11 males, 9 females (age 25 ± 3.7 yr, weight 69.3 ± 10.4kg, height 176 ± 9.83 cm) participated in the study. They had no history of musculoskeletal, neurological, vestibular, or balance disorders. Prior to participation all subjects gave informed written consent and all protocols were approved by the University of Iowa Human Subjects Institutional Review Board.

Procedure

Single limb stance was performed on a custom force plate with a transducer on each corner to determine the center of pressure. Participants were instructed to stand on their non-dominant leg with their eyes closed for 10 seconds. The trial was then repeated with their eyes open. Foot position was marked to ensure consistent foot placement throughout all trials. Joint kinematics of the ankle, knee, and hip were collected using sixteen motion capture markers and a ten camera system (Vicon Motion Systems, Inc., Centennial, CO).

Muscle activity of the soleus (SOL) and tibialis anterior (TA) of the non-dominant (vibrated limb) were measured using surface electrodes with 8mm active bipolar Ag-AgCl discs 20 mm apart. The skin was abraded with sandpaper and then cleaned with alcohol prior to electrode attachment. To determine the correct placement of the soleus electromyography (EMG) electrode the participants were instructed to stand on their forefoot. The electrode was then placed distal to the gastrocnemius, lateral of the midline, along the line of the soleus muscle fibers. To locate the TA the participants performed dorsiflexion with their heel on the floor. The TA electrode was then placed on the upper 1/3 of the muscle, lateral to the tibia, and in line with the muscle fibers. The reference electrode was placed on the tibia, distal to the recording electrodes. The EMG signal was collected using a Vicon analog to digital interface unit (Vicon Motion Systems, Inc., Centennial, CO) at a sampling rate of 1000 Hz.

In order to normalize the muscle activity during the task, three maximum voluntary contractions (MVCs) for each muscle were collected. All participants performed MVCs in a standing position so that the muscle length remained similar to single leg stance. For the soleus MVCs the participants were instructed to stand on the forefoot of the non-dominant leg and wait for the cue to begin maximal effort. To provide resistance the participants were allowed to steady themselves against bars placed slightly above shoulder level but instructed not to push against them. Once in position the subjects were told to ramp up to MVC and hold for five seconds. Participants were allowed to rest for 1 minute between trials. To obtain the TA MVCs the forefoot of the non-dominant leg was secured while the participants stood. A railing was provided for balance but not mechanical support. Three MVCs were collected for the TA separated by 1 minute of rest. Verbal encouragement was given throughout all MVC trials to promote a maximal effort.

Following the single leg stance trials, participants were seated in an adjustable chair with the non-dominant leg placed to the vibration device. The vibration system consists of a PA1000L power amplifier, FPS10L field power supply unit, LaserUSB 6.30 controller, and V722 shaker (Ling Dynamic Systems, Royston, England) (219). The non-dominant leg was secured with the hip and knee slightly flexed to 80° and 110°, respectively, and ankle in the neutral position while the opposite limb rested comfortably next to the shaker. Mechanical oscillation was delivered to the single segment at 0.6g and 30 Hz for 15 minutes. Following limb vibration, the single leg stance protocol was repeated.

Data Analysis

Variability of center of pressure was quantified in the anterior/posterior and medial/lateral planes by calculating root means squared (RMS) displacement and the velocity using a custom DIAdem 2012 script (National Instruments, Ireland). RMS displacement was chosen because it quantifies the magnitude of variation and is suited for situations that fluctuate between positive and negative. Velocity has been suggested to be the most sensitive linear metric to detect changes in postural control especially as a result of age or neurological deficits (224, 232, 233).

Complexity of postural control was also determined by using fractal analysis specifically detrended fluctuation analysis which is a specific type of nonlinear mathematical technique aimed at quantifying the dynamic, temporal structure of postural control. The MATLAB code from Ihlen et al 2012 was modified to perform the fractal analysis of our center of pressure dataset and calculate an alpha value (α) (234). This alpha value measures the long-range correlation of the center of pressure and typically occurs between 0 and 1.5. Low alpha values (0-0.5) indicate anti-correlated structure but the higher the alpha value, the more complex and smoother the movement pattern (Figure 4.1). Monofractal is one type of structure, independent of time and space, contained in biological signals and is defined by a single scaling exponent, α. However, most biological signals are more complex including structures that vary across time and space and require multifractal analysis. We also performed mulitifractal analysis which calculates several alpha values, sensitive to small and large fluctuations of the signal.

Electromyography activity of the soleus and tibialis anterior muscles of the non-dominant leg was collected during all the standing trials. The root means square (RMS) of each EMG signal were performed using 10 ms time bins, normalized to the MVC of the participant, and averaged over the 10 second task.

The kinematic data were first analyzed using Nexus software (Vicon Motion Systems, Inc., Centennial, CO) and further processed with a custom DIAdem 2012 script (National Instruments, Ireland). Joint kinematics of the ankle, knee, and hip were calculated to determine if the intervention altered the functional range of motion. The motion capture markers were positioned on each participant in such a way that the three dimensional kinematic data at the ankle, knee, and hip could be automatically quantified using the commercial Nexus software.

Statistical Analysis

A two-way repeated measures analysis of variance (ANOVA) used to determine the effects of vision (eyes open; closed) and limb vibration (before; after) on postural control metrics, muscle activity, and kinematics (degrees of freedom = 19). All post hoc analysis was completed using the Tukey procedure. An alpha level of 0.05 was considered significant for all statistical tests.

<u>Results</u>

Center of Pressure Measurements

The center of pressure (RMS) in the A/P direction was unchanged from the pre to post limb vibration conditions (12.9 mm to 13.3 mm, respectively; $p = 0.541$, Figure 4.2A). There was also no change from pre to post limb vibration of the center of pressure in the

M/L direction (11.4 mm and 11.1 mm, respectively; $p = 0.578$, Figure 4.2A). When unblinded, the RMS displacement was reduced by 36% in the A/P and 47% M/L directions compared to the blinded conditions ($p < 0.001$).

In the blinded condition , the center of pressure velocity was unchanged from pre to post limb vibration 187 mm/s and 174 mm/s, respectively ($p = 0.638$, Figure 4.2B) for the A/P direction; and 242 mm/s and 262 mm/s, respectively, for the M/L direction ($p = 0.702$, Figure 4.2B). Center of pressure velocity did not change when the participants were unblinded in either the A/P or M/L directions compared to the blinded conditions ($p = 0.843$, $p = 0.617$).

The blinded pre to post center of pressure A/P velocity, evaluated using the nonlinear fractal analysis, changed from 1.011 to 1.057 ($p = 0.140$), 0.816 to 0.880 ($p = 0.008$), 0.614 to 0.686 ($p = 0.064$), respectively for small, neutral, and large fluctuations (Figure 4.3A). When the fractal analysis was repeated for the blinded center of pressure M/L velocity, limb vibration changed the small, neutral, and large fluctuations from1.072 to 1.088 ($p = 0.729$), 0.833 to 0.876 ($p = 0.120$), and 0.608 to 0.686 ($p = 0.003$), respectively (Figure 4.3B). In summary, size-independent fluctuations of anterior/posterior velocity and large fluctuations of medial/lateral velocity became less complex following limb vibration.

Agonist and Antagonist Strategies

After limb vibration, the EMG activity of the soleus and tibialis anterior muscles increased by 13.4% and 20.5% respectively, during the blinded condition ($p = 0.022$, $p = 0.009$, Figure 4.4). There was no change in soleus or tibialis anterior EMG when the subjects were unblinded ($p = 0.945$, $p = 0.319$, respectively). When unblinded, the EMG activity was reduced by 30% for the soleus and 55% the tibialis anterior compared to the blinded conditions ($p < 0.001$).

Joint Kinematics

Joint kinematics were relatively stable after the vibration intervention during the blinded condition. Ankle inversion, dorsiflexion, and internal rotation varied from 11.5˚ to 12.3˚, 1.84˚ to 1.90˚, and -8.36˚ to -8.54˚, respectively ($p = 0.097$, $p = 0.754$, $p = 0.838$), from pre to post limb vibration (Figure 4.5A). Knee adduction, flexion, and internal rotation varied from 10.9˚ to 12.1˚, 3.38˚ to 3.16˚, and -3.94˚ to -2.96˚, respectively ($p = 0.239$, $p = 0.446$, $p = 0.076$), from pre to post limb vibration (Figure 4.5B). Limb vibration did not change hip adduction, flexion, and internal rotation, from 11.5 to 10.7 ($p = 0.452$), from 1.56 to 2.43 ($p = 0.808$), and from 6.05 to 6.65 ($p = 0.522$), respectively (Figure 4.5C).

Discussion

In this study, we used whole segment vibration to investigate the after effects of limb vibration on postural control. We determined altered agonist and antagonist activation strategies, as illustrated by the increased muscle activity of the soleus and tibialis anterior following peripheral limb vibration. Limb vibration also changed the postural control strategy by reducing the complexity of the center of pressure velocity. However, despite differences in muscle activation and center of pressure complexity, limb vibration did not change center of pressure variability or lower extremity kinematics.

The vibration-induced increase in ankle muscle activity during the postural control task could be due to an increase in neural excitability at the muscle, the spinal cord, or the motor cortex. At the muscular level, tendon vibration typically results in the gradual increase in muscle activity known as the tonic vibration reflex (235, 236). The tonic vibration reflex is frequently cited as the neural mechanism explaining the vibration-induced changes in postural control (92). H-reflexes are extensively used to quantify α-motoneuron excitability within the spinal cord. H-reflexes occur by electrically activating the Ia afferents in the muscle spindle and Ia afferents synapse on the alpha-motoneuron within the spinal cord resulting in a muscle twitch or H-reflex. Tendon vibration first activates the Ia afferents followed by activation of the inhibitory interneuron which suppresses the H-reflex through a presynaptic pathway (215). The soleus H-reflexes specifically are inhibited during Achilles tendon vibration due to an increase in presynaptic inhibition (8, 59-61). Activation of multiple muscles through whole body vibration likewise reduces spinal excitability indicated by decreased H-reflex amplitudes (62-66). We have also shown that low amplitude, limb vibration reduces the soleus H-reflex amplitude (57). In addition to H-reflexes changes, alterations of muscle afferent input can also change corticospinal pathway excitability (237) and cortical motor excitability (238). Information sent from the muscle afferents to the cerebral cortex is also a key component in motor control (239). Specifically, whole body vibration facilitates the transcortical magnetic stimulation elicited motor evoked potential of the tibialis anterior muscle (80). Tendon vibration also increases cortical excitability demonstrated by an increase in the motor evoked potential of the vibrated muscle and its antagonist, 30-60 minutes after vibration (9, 58). Therefore, these changes in muscle activity, segmental spinal excitability, and cortical excitability associated with vibration likely play a role in postural control.

The increase in muscle activity during the blinded condition after limb vibration was not associated with any change in center of pressure variability but fractal analysis showed a reduction in the complexity of the center of pressure. Nonlinear, fractal analysis showed that the large fluctuations of medial/lateral velocity and size-independent fluctuations of anterior/posterior velocity became more organized and occurred less often following limb vibration. Lower complexity is equated with greater control when there is an adequate baseline of variability and indicates a healthy, robust movement control system. Norris et al. 2005 showed young, healthy individuals have an organized COP ($\alpha = 1.25$) accompanied with sufficient variation (displacement of 10.7 mm) in order to maintain postural control. However, elderly individuals with a high complexity ($\alpha = 1.06$) and high magnitude of variation (displacement = 29 mm) have a high risk of fall (230). Our results showed 15 mm of displacement in the blinded condition which was slightly higher than the young group but was two-fold lower than the unstable elderly individuals. The center of pressure during blinded, single leg stance showed sufficient baseline variation but simulated an unstable system based on the high, nonlinear complexity measurement ($\alpha = 0.82$). Therefore, we were able to demonstrate that limb vibration lowered the complexity of center of pressure which indicates a shift towards more stable movement control.

Fractal analysis provided a sophisticated analysis to quantify the dynamic aspect of postural control and was required to measure the change in center of pressure due to an "a priori" limb vibration. Many have shown that postural control diminishes with age (240, 241) but only recently have more sensitive analyses been implemented to differentiate between elderly "fallers" and "non-fallers" (230, 231). In the present study, the linear measurements of variability remained unchanged following limb vibration but the fractal analysis showed reduced complexity of postural control. Our results showcase another instance where more advanced analyses are essential to detect movement control modifications.

Finally, there was no change in the joint angles of the ankle, knee, or hip following limb vibration. Other previous studies demonstrating altered kinematics during stance are usually preceded by increased variability of postural sway. Our findings did not shown a change in the variability of postural control supporting no change in joint kinematics. Horstmann et al 2015 showed that ankle joint kinematics remained unchanged even in the presence of altered muscle activation due to standing on various support surfaces (242). The lack of change in kinematics is consistent with the plasticity of the nervous system and its ability to adapt to different environmental conditions.

There were several methodological considerations that should be addressed with respect to this study. We were testing individuals with normal CNS systems, however, used single limb stance under blinded conditions. This condition is generally a challenging task, quite comparable to an elderly individual during bilateral stance with vision. Hence, we created a challenging environment to test if delivering vibration to a limb triggers adaptations that may be assistive to performing the task. With the exception of EMG and two nonlinear metrics, the changes in postural control were inconsistent with the predicted outcomes. A power calculation for the fractal, nonlinear metrics suggested that only the measurements which showed significance had an adequate sample size to detect a change. Also, a time series analysis of the data was not performed but rather the metrics were averaged over the entire sample.

In conclusion, a short duration of peripherally applied vibration has a significant impact on the neural control strategies of a simulated faller. Isolated limb vibration increased soleus and tibialis anterior EMG activity and reduced complexity of center of pressure during blinded, single leg stance. These findings suggest that localized limb vibration may provide method to influence neuromuscular control strategies of upright stance. Future work is necessary to determine if these results of simulated instability can be extrapolated to individuals with balance dysfunction.

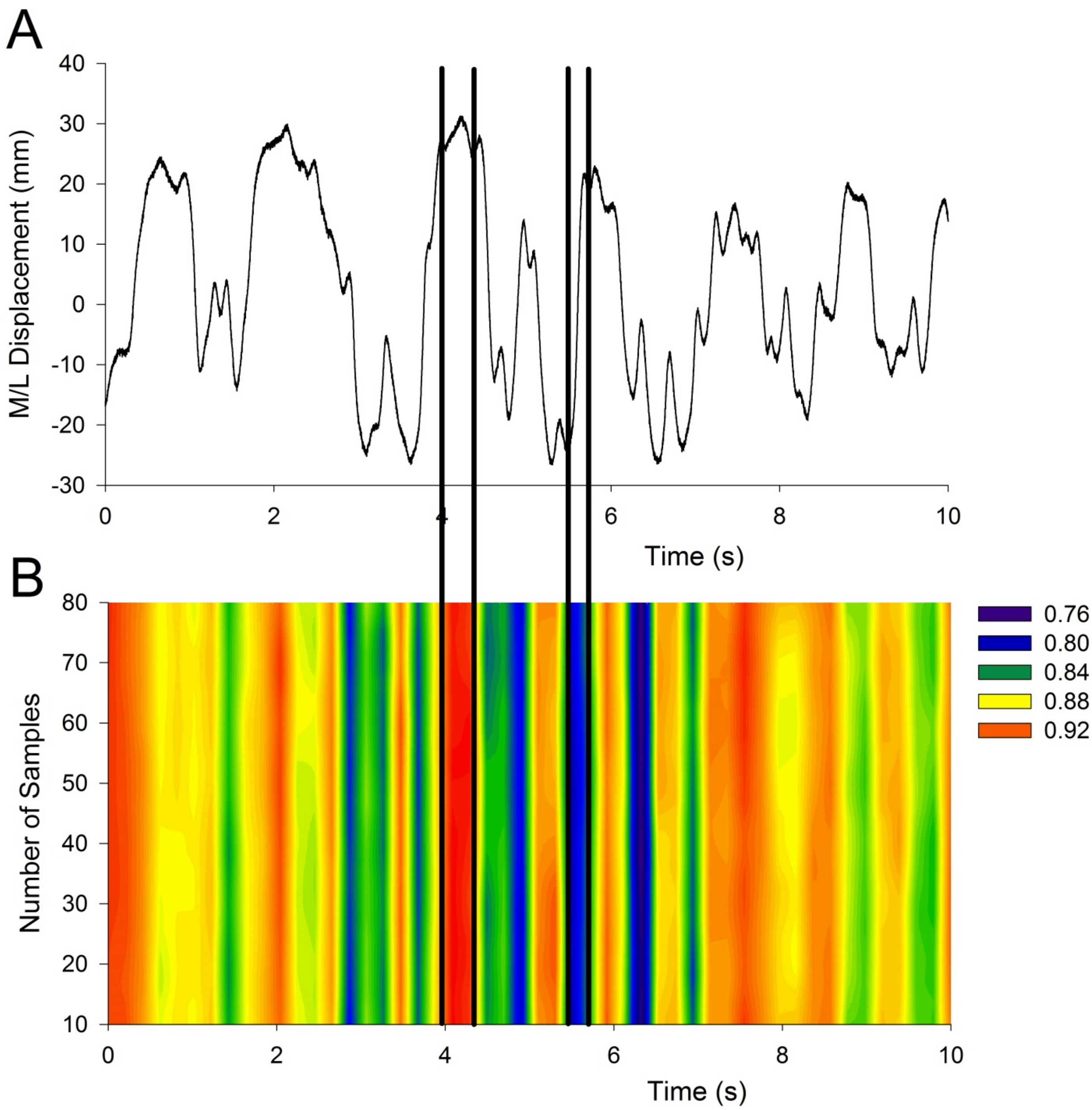

Figure 4.1 Representation of Fractal Analysis. A) Trace of center of pressure in the medial/lateral direction and B) Contour plot displaying the temporal variations of the center of pressure where red depicts periods of regular structure and blue reflect periods of irregular structure.

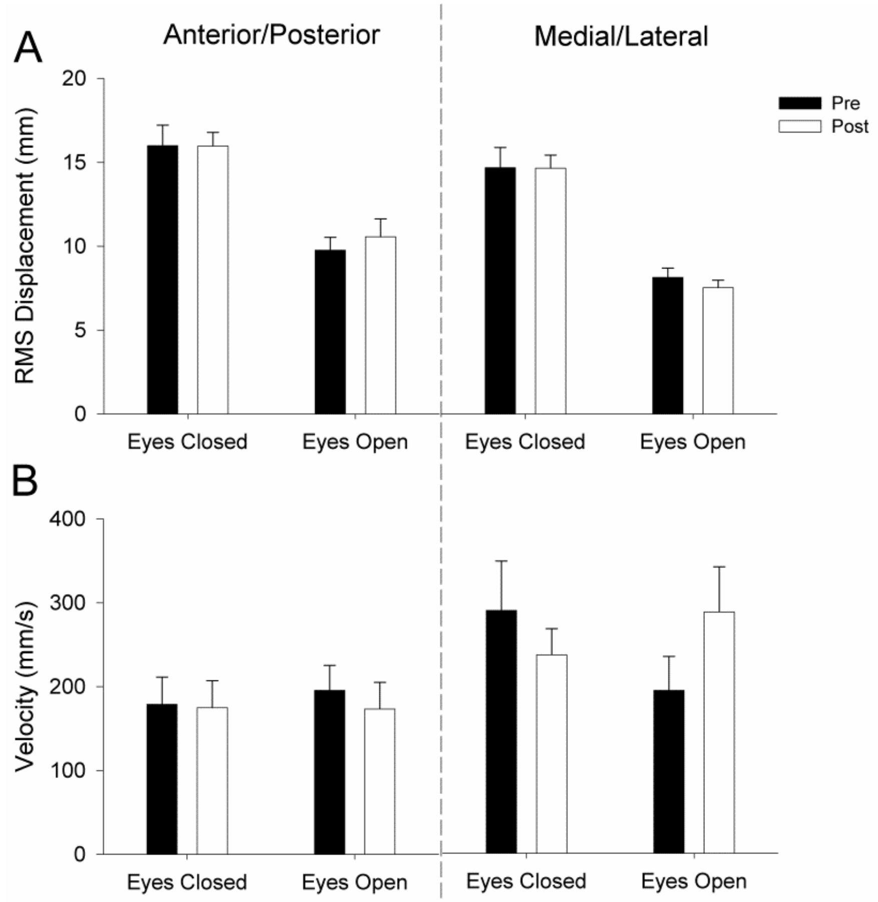

Figure 4.2 Center of Pressure Metrics. A) RMS displacement and B) velocity, did not significantly change as a result of limb vibration.

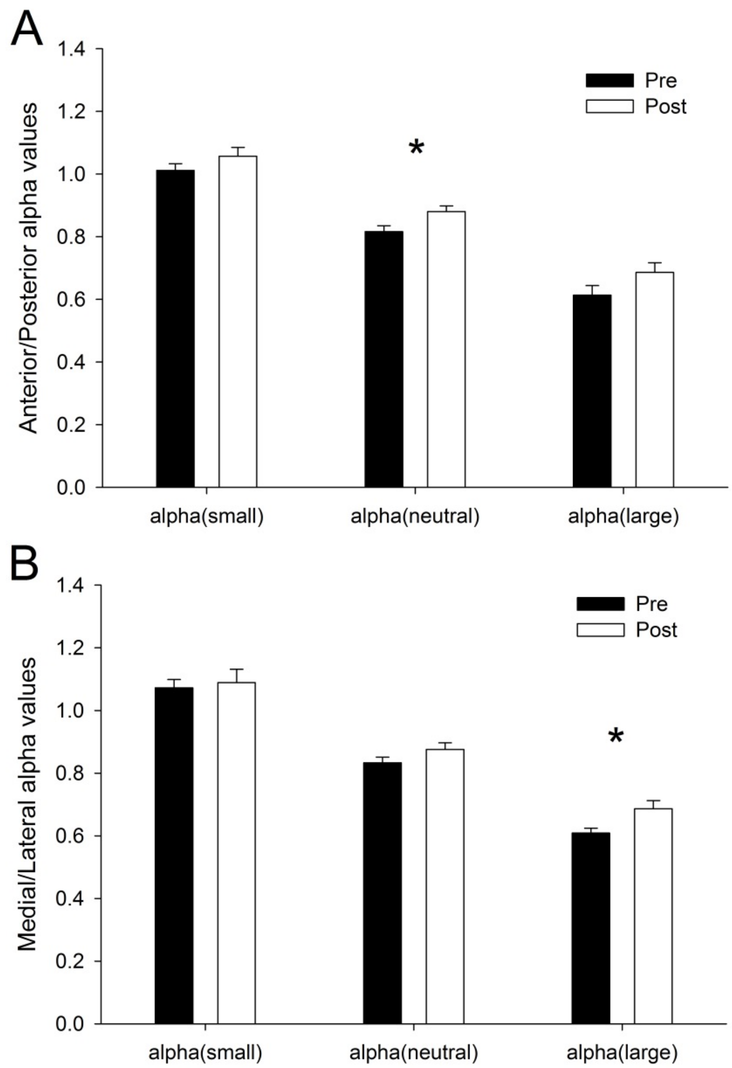

Figure 4.3 Fractal Analysis. Fractal analysis of center of pressure velocity in A) anterior/posterior and B) medial/ lateral directions.

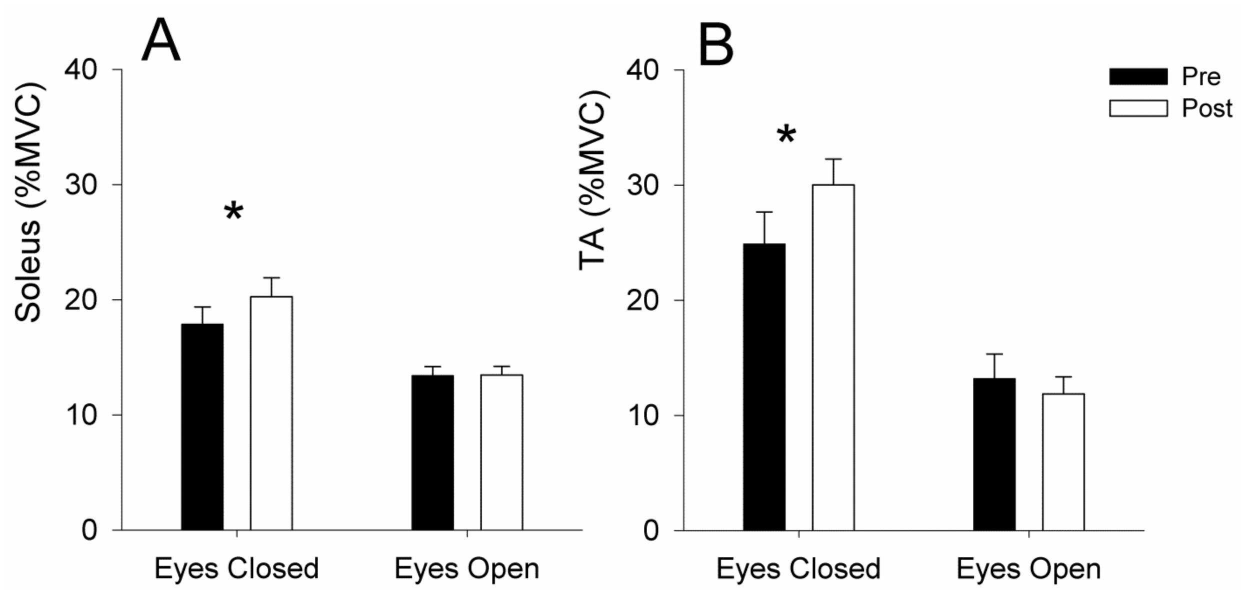

Figure 4.4 EMG Activity after Limb Vibration. Soleus and tibialis anterior muscles increased by 13.4% MVC and 20.5% MVC, respectively, following limb vibration in the eyes closed condition.

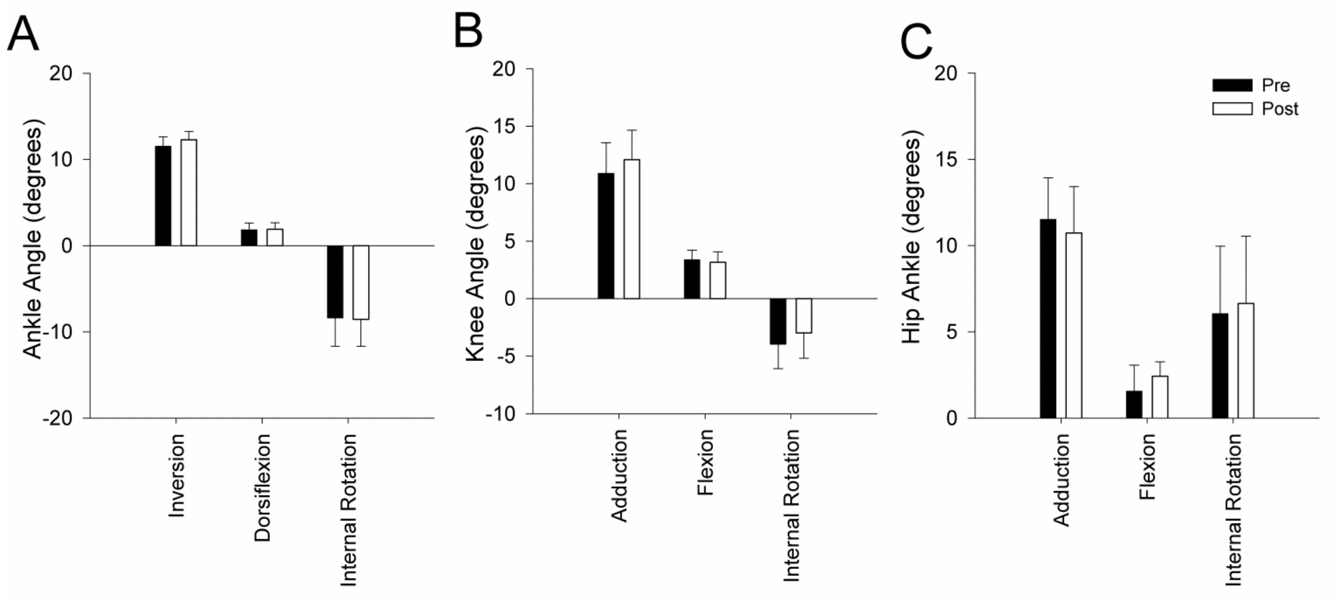

Figure 4.5 Kinematic data. A) Ankle, B) knee, and C) hip angles during a single leg stance. There was no change lower extremity joint kinematics following limb vibration.

CHAPTER 5 VIBRATION AND NEUROMUSCULAR CONTROL BEFORE AND DURING A WEIGHT BEARING VISUOMOTOR TASK

Introduction

Deficient movement control strategies are associated with falls and fractures which cost society 19 million dollars annually (243). Mechanical oscillation training can reduce the movement control disruptions resulting from age (10) and extended bed rest (244). Accordingly, understanding the vibration-induced changes to the neuromuscular control system may help develop novel rehabilitation techniques aimed at improving movement control, reducing falls, and preventing injury.

Depending on the method, vibration can influence movement control by impacting vision, vestibular, or somatosensory information. Early vibration research disrupted proprioception through tendon vibration and showed large reductions in postural control (92). More recently, whole body vibration has been touted as a method to improve balance by influencing visual, vestibular, and somatosensory feedback (39, 105, 216). In 2011, our laboratory developed a vibration system capable of vibrating the lower limb segment with minimal transmission of the vibratory signal to the visual or vestibular systems (219). In subsequent studies we found that limb vibration increased soleus and tibialis anterior muscle activity but minimally affected postural sway during the single limb stance (Chapter 4).

Although postural stability is one way to assess independent living, it does not evaluate other weight-bearing tasks, such as, the ability to respond to an unexpected event or the feed forward control used during a task where unexpected events occur. Such tasks like standing from a seated position, bending down to pick up an object, or descending stairs may respond differently to vibratory input when compared to upright postural control. Radhakrishnan and colleagues reported Achilles tendon vibration during a weight-bearing tracking task increased soleus and tibialis anterior muscle activity (128). Following a whole body vibration training study, the elderly participants showed no change in postural control metrics but did have less falls during platform perturbations (11). To our knowledge, no previous study has addressed the influence of vibration on the ability to respond to an unexpected event during a weight-bearing tracking task. In this context, we were interested in whether vibration modulates movement accuracy and muscle responses to unexpected perturbation.

Unexpected perturbations trigger short latency responses and long latency responses (LLR) of the muscle providing valuable insights into the spinal excitability and transcortical response to a specific intervention (112). The unexpected events activate the muscle spindle to trigger a well-known monosynaptic spinal reflex with a 30-50 ms latency (113). The perturbation also elicits long latency responses, 50-200 ms after the perturbation, which are triggered from redundant sources including vision, vestibular, or somatosensory input (114). Importantly, the "central set" or excitability of the CNS is thought to prime the long latency reflexes. A knowledge gap in rehabilitation research is whether vibration primes the CNS to have a greater influence on long latency reflexes and consequently assist to train and individual to respond to an unexpected event.

The purposes of this study are to establish the effect of limb vibration and whole body vibration on neuromuscular control strategies before and during a weight-bearing visuomotor task. Specifically, we will determine if limb vibration or whole body vibration impacts one's ability to accurately track a target. We will also determine if these vibration interventions alter muscle responses to an unexpected perturbation. Because vibration can modulate various levels of the CNS, we hypothesize that vibration before or during a weight bearing tracking task will regulate the muscle activity after an unexpected perturbation. This is the first study to determine if mechanical vibratory input plays a role in modulating responses used during unexpected events. If effective, combining mechanical vibration with weight bearing training may be a worthy intervention to prevent injury from unexpected events.

Methods

Participants

Fifteen individuals (7 male; Age 27.8 ± 6.7) participated in this study by giving their written informed consent. All procedures and protocols were approved by the University of Iowa Human Subjects Institutional Review Board. Those with history of musculoskeletal or neurological disorders, previous hip or knee surgery, or were excluded.

Experimental Procedure and Instrumentation

A single leg squat (SLS) device was developed in our laboratory as a way to introduce an unexpected perturbation during a weight-bearing control task. Visual feedback during the task focuses the attention of the participant on performance rather than anticipation of a perturbation. The custom designed device has been described previously (109, 110) but briefly, the anterior surface of the knee was attached to the device while the individual performed a controlled SLS exercise. The device was composed of a rack and pinion gear system which translated knee angle to linear motion that was quantified by a potentiometer. The visual feedback was a sinusoidal target which the subjects attempted to match using knee flexion and extension. The peak-to-peak amplitude of the sinusoid required a 15 cm horizontal displacement of the shaft of the SLS device. The knee flexion angle was highly correlated to the linear displacement ($r = 0.98$). To match the peak-to-peak amplitude of the sinusoid, the knee flexion range of motion was 0-40°. Throughout the SLS task, the brake provided a resistance based on percent body weight (%BW). The brake was also used to deliver a perturbation by suddenly dropping to 0%BW at a specific point of knee flexion. Each trial contained 5 cycles of knee flexion and extension and the perturbation occurred randomly during one of those cycles.

Muscle activity of the vastus medialis, lateral hamstrings, soleus, and tibialis anterior muscles were recorded throughout the single leg squat task. The skin was abraded and cleaned with alcohol before placing the EMG electrodes over the muscles. An EMG electrode was placed over the vastus medialis at 80% of the distance a line from the anterior superior iliac spine (ASIS) to the medial knee joint (245). The lateral hamstring EMG was placed 50% between the ischial tuberosity and the lateral knee joint (245). Placement for the soleus EMG was determined by having the participant stand on their forefoot to palpate the gasctrocnemius muscle; the electrode was then placed distal to the gastrocnemius and lateral to the midline. Participants performed dorsiflexion with their heel on the floor to determine the ideal location for the tibialis anterior muscle. The tibialis anterior electrode was placed on the upper 1/3 of the muscle and lateral to the tibia. The reference electrode was placed on the tibia, distal to the recording electrodes. The EMG electrodes were bipolar silver-silver chloride with a 8mm diameter and 20 mm inter-electrode distance were used. The data was collected at a sampling rate of 2000 Hz.

Prior to the SLS task, maximum voluntary contractions were collected in order to normalize muscle activation. For the vastus medialis and lateral hamstrings muscles, the participants were seated with the knee in 90° of flexion. They performed three maximum knee extensions followed by three maximum knee flexion contractions to obtain a maximum contraction from the vastus medialis and lateral hamstrings, respectively. To collect the maximum voluntary contractions of the soleus and tibialis anterior muscles, the participants were seated with leg extended and the ankle at about 90°. All participants were given verbal encouragement during the five second maximum voluntary contraction with 1 minute of rest between each contraction.

The limb vibration was administered while the subjects were seated with their non-dominant leg resting on the vibration device. The vibration systems consisted of a PA1000L power amplifier, FPS10L field power supply unit, LaserUSB 6.30 controller, and V722 shaker (Ling Dynamic Systems, Royston, England) (219). The leg was secured to the device the over the anterior aspect of the knee, with the hip flexed to 80° and the knee flexed to 110°. The opposite leg was supported outside of the vibration device. Limb vibration was delivered at a frequency of 30 Hz and an acceleration of 0.6g for 15 minutes. To deliver the whole body vibration, the participants stood on a vibration plate (Juvent Inc, Somerset, NJ) with vibration at 30 Hz and 0.6g.

Data Collection

When the subjects arrived on Day 1 they were fitted with EMG electrodes and performed maximum voluntary contractions. The subjects were oriented to the SLS system and first underwent five sets of training trials. Each set of the training trials consisted of 3 trials at different velocities (0.2Hz, 0.4 Hz, 0.6 Hz) and an intermediate resistance (10% BW)

(Figure 5.1A). Preliminary data from a previous study showed that this short training session allowed individuals to become proficient at the single leg squat tracking task. The participants were then seated in the vibration system and received limb vibration or sat quietly (control). Following this period, a testing session of the 9 SLS conditions of varying resistances (5% BW, 10% BW, 15% BW) and velocities based on varying target frequencies (0.2 Hz, 0.4 Hz, 0.6 Hz) were completed (Figure 5.1B). Participants were allowed to place 2 fingers on the frame but were instructed to use light touch and not use the frame as a biomechanical support. Forty-eight hours after the Day 1 collection, the participants returned to complete the same 9 SLS conditions but were exposed opposite form of vibration as Day 1 (no limb vibration or limb vibration). The final test for all participants was to repeat the 9 testing conditions while standing on a vibration plate (whole body vibration) (Figure 5.1C). The target sinusoid, linear potentiometer, and EMG of vastus medialis, lateral hamstrings, soleus and tibialis anterior muscles were collected using custom Labview software (version 8.6; National Instruments Co., Austin, TX).

Data Analysis

A custom DIAdem 2012 script (National Instruments Co., Austin, TX) was used to calculate the outcome measures. Two variables were calculated to quantify the accuracy of the tracking task: 1) peak absolute error and 2) peak velocity error. Peak absolute error was the maximum difference between the target sinusoid and the user signal during the flexion portion of the task. The peak absolute error measurements were expressed as changes in knee flexion angle. Knee flexion angles were determined based on the horizontal displacement of the shaft of the testing device. The linear displacement of the shaft was highly correlated to knee flexion angle (r = 0.98). For the training trials, the peak absolute error was determined during the cycle containing the perturbation as well as the non-perturbed cycles. To determine the peak absolute error of the non-perturbed cycles, the first cycle was excluded and the remaining three cycles were averaged. The peak velocity errors of the perturbation cycle and the non-perturbation cycle were also determined. For the training trials, peak velocity error was defined as the maximum velocity of the user signal within the time bin 50-200 ms after the perturbation, normalized to the velocity of the target signal in the same time window. The peak velocity error ratio was determined during a perturbation cycle and for a non-perturbation cycle based on a time point where a perturbation would have occurred in a non-perturbed cycle.

For the nine testing trials, peak absolute error and peak velocity error were calculated within several time bins after the perturbation. Time bin 1 was defined as 0-50 ms after the perturbation, time bin 2 occurred 50-200 ms after the perturbation and time 3 was 200-550 ms after the perturbation. The perturbation cycle only was examined for the nine testing trials.

The root means square (RMS) of each EMG signal from the vastus medialis, lateral hamstrings, soleus, and tibialis anterior muscles was calculated using 10 ms time bins and then normalized to the maximum voluntary contraction. The muscle responses to the perturbation were quantified as the peak EMG response within each of the three time bins. When describing muscle responses to a perturbation, the three time bins have specific nomenclature. Short latency responses occurred within the 50ms after the perturbation. The long latency response time bin was defined as 50 to 200 ms after the perturbation. The reaction time bin or volitional control occurred 200ms to 550ms after the perturbation.

Statistical Analysis

A statistical analysis was completed to determine the effect of limb vibration and whole body vibration on the accuracy of the tracking task and the muscle activation during an unexpected perturbation. First, the effect of training was determined using two-way repeated measures ANOVA with two factors, set of training trials and the presence of a perturbation. All post hoc analyses were completed using the Tukey procedure. An alpha level less than 0.05 will be considered significant for all statistical tests.

Statistical comparisons of peak absolute error, peak velocity error, and muscle response to a perturbation were then made using paired t-tests. Separate paired t-tests were completed within each time bin, for each variable (peak absolute error, peak velocity error, vastus medialis, lateral hamstring, soleus, and tibialis anterior) to compare control to limb vibration as well as control to whole body vibration.

<u>Results</u>

Motor Learning Effects from Practice Sessions

<u>Absolute Error</u>

The peak absolute error measurements for the first set of training trials were 12.5° and 11.6° for the perturbed and non-perturbed cycles (Figure 5.2A). After five sets of training trials, peak absolute error was reduced by 35.2% for the perturbation cycle and 38.8% for the non-perturbation cycle ($p<0.001$). The perturbation resulted in peak absolute error of 10.1 degrees of knee flexion while the non-perturbed cycles had peak absolute error of

8.77 degrees of knee flexion ($p<0.001$). These data support that the training protocol was successful in producing a stable baseline score (Figure 5.2A) before delivering the intervention (vibration).

Velocity Error

For the first set of training trials, the peak velocity error ratio, defined as the maximum velocity normalized to target velocity during the 50-200 ms time window was 2.21. The average velocity was 70°/s ± 12°/s. For the first set of training trials, the non-perturbed cycles had a velocity error ratio of 1.23 with a mean velocity of 41°/s ± 12°/s (Figure 5.2B). The peak velocity error ratio remained consistent after the five sets of training trials (Figure 5.2B; $p = 0.079$). The perturbation cycles had 44.3% higher peak velocity compared to the non-perturbation cycles (Figure 5.2B; $p<0.001$).

Effect of Isolated Limb Vibration on Weight Bearing Task

Absolute Error during an Unexpected Event

The peak absolute error 50 ms after the perturbation was 3.84° and 4.01° for the control and limb vibration intervention conditions, respectively (Figure 5.3A). The peak absolute error was 5.25° to 5.53° for control and limb vibration, respectively, for the 50-200 ms time period (Figure 5.3A). The peak absolute error after the perturbation was 5.77° without vibration and 6.06° with limb vibration for the 200-550 ms time bin (Figure 5.3A). Overall, there were no changes in error related to time bin 1 (50 ms after the perturbation), time bin 2 (50-200 ms after the perturbation), or time bin 3 (200-550 ms after the perturbation) as a result of the vibration intervention delivered prior to testing the weight bearing task (Figure 5.3A; $p = 0.609$, $p = 0.492$, $p = 0.548$).

Velocity Error during an Unexpected Event

The peak velocity error ratio for the 0-50 ms time bin was 1.65 and 1.56 for the control and limb vibration, respectively, which corresponds to a mean velocity of 44°/s ± 8°/s and 42°/s ± 4°/s, respectively (Figure 5.3B). The velocity error ratio was 2.11 (63°/s ± 7°/s) and 2.14 (64°/s ± 8°/s) for control and limb vibration, respectively, 50-200 ms after the perturbation (Figure 5.3B). The control velocity error ratio was 1.27 or 37°/s ± 5°/s and the limb vibration velocity error ratio was 1.36 or 40°/s ± 7°/s, 200-550 ms after the perturbation. In general, the velocity error ratio remained unchanged across all three time bins after the isolated limb vibration protocol (Figure 5.3B; $p = 0.235$, $p = 0.671$, $p = 0.150$).

EMG Responses during Unexpected Events

The short latency EMG response(< 50 ms) for the vastus medialis was 14.3% lower following isolated limb vibration (Figure 5.4A; $p = 0.017$). The vastus medialis EMG was 31.1%MVC and 27.3%MVC for control and limb vibration, respectively, in the 50 to 200 ms time bin (Figure 5.4A; $p = 0.068$). The vastus medialis EMG was 28.9%MVC during the control condition and 26.8%MVC after limb vibration which was a reduction of 7.27%, in the 200-550 time bin (Figure 5.4A; $p = 0.031$).

The lateral hamstring EMG was 23.7%MVC and 21.3%MVC for control and limb vibration, respectively, in the 0 to 50 time bin (Figure 5.4B; $p = 0.421$). The control and limb vibration conditions were unchanged ($p = 0.188$; $p = 0.454$) for the 50-200 and 200-550 time bins (Figure 5.4B).

The soleus EMG was 16.4%MVC for the control condition and 17.3%MVC for the limb vibration condition in the 0 to 50 ms time bin (Figure 5.5A; $p = 0.756$). The long latency soleus EMG was 31.6%MVC and 33.4%MVC for the control and limb vibration conditions, respectively (Figure 5.5A; $p = 0.709$). The soleus EMG was 34.3%MVC and 35.5%MVC for the control and limb vibration conditions, respectively, for the 200-550 ms time bin (Figure 5.5A; $p = 0.791$).

The average tibialis anterior EMG for the 0-50 time bin was 19.0%MVC and 19.1%MVC, respectively (Figure 5.5B; $p = 0.454$). The tibialis anterior EMG was 22.3%MVC and 19.1%MVC for control and limb vibration, respectively, in the 50 to 200 ms time bin (Figure 5.5B; $p = 0.346$). The tibialis anterior EMG activity was 17.1%MVC and 16.3%MVC for the control and limb vibration conditions, respectively, for the 200-550 ms time bin (Figure 5.5B, $p = 0.639$). In summary isolated limb vibration yielded lower vastus medialis EMG activity in the short latency and reaction time bins.

Effect of Whole Body Vibration during Task

<u>Absolute Error during an Unexpected Event</u>

The average peak absolute error for the 50 ms time bin was 3.84° and 3.57° for the control and whole body vibration interventions, respectively (Figure 5.3A; $p = 0.241$). The peak absolute error was 5.25° to 5.28° for control and whole body vibration, respectively, for the time 50-200 ms time period (Figure 5.3A; $p = 0.916$). The peak absolute error was 5.77° without vibration and 5.69° with whole body vibration, for 200-550 ms after the perturbation (Figure 5.3A; $p = 0.266$). There were no changes in absolute error during whole body vibration.

Velocity Error during Unexpected Event

The peak velocity error ratio was 1.65 and 1.56 for the control and whole body vibration conditions, respectively, within the time bin 0-50 ms after the perturbation. These velocity error ratios corresponded to a rate of knee angle change of 44°/s ± 8°/s and 42°/s ± 5°/s (Figure 5.3B; $p = 0.262$). The velocity error ratio was 2.11 (63°/s ± 7°/s) and 2.02 (60°/s ± 8°/s) for control and whole body vibration, respectively, 50-200 ms after the perturbation (Figure 5.3B; $p = 0.272$). The velocity error ratio was 1.27 or 37°/s ± 5°/s and 1.22 or 36°/s ± 7°/s for control and whole body vibration, respectively, 200-550 ms after the perturbation (Figure 5.3B; $p = 0.357$). The velocity error ratio remained unchanged across all three time bins during whole body vibration.

EMG Responses during Unexpected Events

The vastus medialis EMG response was 20.3%MVC and 18.3%MVC for the control and whole body vibration, respectively (Figure 5.4A; $p = 0.257$). The vastus medialis EMG was 31.1%MVC during the control condition and 32.1%MVC during the whole body vibration condition in the 50-200 ms time bin (Figure 5.4A; $p = 0.642$). The vastus medialis EMG response was 28.9%MVC and 28.8%MVC for the control and whole body vibration conditions, respectively, in the 200-550 ms time bin (Figure 5.4A; $p = 0.939$).

The lateral hamstring EMG was 23.7%MVC and 22.1%MVC for control and whole body vibration, respectively, in the 0-50 time bin (Figure 5.4B; $p = 0.384$). The long latency hamstring EMG was 16.4%MVC and 23.8%MVC for the control and whole body vibration conditions, respectively (Figure 5.4B; $p = 0.242$). The lateral hamstring EMG was 24.0%MVC and 22.6%MVC for the control and whole body vibration conditions, respectively, in the 200-550 ms time bin (Figure 5.4B; p = 0.573).

The soleus EMG was 16.4%MVC and 17.8%MVC for the control and whole body vibration conditions, respectively, in the 0 to 50 ms time bin (Figure 5.5A; p = 0.463). The long latency soleus EMG was 31.6%MVC and 34.4%MVC during the control and whole body vibration conditions, respectively (Figure 5.5A; p = 0.546). The soleus EMG was 34.3%MVC and 32.9% for the control and whole body vibration conditions, respectively, in the 200-550 ms time bin (Figure 5.5A; p = 0.734).

The tibialis anterior EMG was 19.0%MVC and 18.7%MVC during the control and whole body vibration conditions, respectively, in the 0-50 ms time bin (Figure 5.5B; p = 0.121). The tibialis anterior EMG was 22.3%MVC during the control condition and 17.7%MVC during whole body vibration which was a reduction of 20.6%, in the 50-200 ms time bin (Figure 5.5B, p = 0.028). The tibialis anterior EMG was 17.7%MVC for the control condition and14.7% MVC during the whole body vibration condition (Figure 5.5B, p = 0.252). In summary, whole body vibration triggered lower tibialis anterior EMG activity in the long latency time bin, 50-200 ms after the perturbation.

Discussion

In this study, we determined the effect of vibration before and during a weight-bearing tracking task. We showed no change in any error measurement as a result of vibration before or during the weight bearing task. We did discover that there was a greater inhibition of the vastus medialis muscle during an unexpected event which occurred only after isolated limb vibration. We also found that there was greater inhibition of the tibialis anterior muscle, but only if the vibration was delivered during the weight bearing task. Taken together, these findings support that vibration does not influence motor performance of a tracking task but it does modulate muscle responses to an unexpected event.

Our findings suggest that healthy individuals can complete a visuomotor tracking task with minimal change in error regardless of an “a priori” or “online” mechanical event. These findings are consistent with several previous findings regarding the effects of vibration on movement accuracy. Conrad et al. 2011 showed wrist vibration did not change absolute error or velocity of a tracking task in healthy individuals (246). Similarly, low magnitude whole body vibration did not change tracking error or reaction time (247). It was hypothesized that there would be an increase in the accuracy of a tracking task with vibration.

The predicted outcome was based on supporting evidence that vibration inhibited spinal H-reflexes (8, 57, 59, 62, 66), enhanced cortical excitability (79, 80), and could act as a potential method to prepare the CNS to respond to an unexpected event. Priming of the motor cortex through some peripheral stimuli has been investigated as a potential precursor to improve motor performance (248). Vibration could be that mechanical stimuli which primes the nervous system. Vibration of the foot increased cortical excitability (42, 43, 193, 194) as well as improved neuromuscular control of posture (42). In our laboratory, enhanced cortical excitability was associated with greater proficiency of an upper extremity tracking task (in review). We have also demonstrated limb vibration inhibited the soleus H-reflex through presynaptic inhibition (57). Due to the sensitivity of presynaptic inhibition to sensory and descending inputs (249, 250), presynaptic inhibition, plays a crucial role in regulating motor output.

Vastus medialis EMG was reduced in the 0-50 ms and 200-550 ms time bins after isolated limb vibration. Short latency muscle responses (< 50 ms) have been shown to decrease during vibration (251) in response to an unexpected stretch. The group Ia afferents within the muscle spindle mediate the short latency responses which have the same latency as the monosynaptic reflex. Vibration first activated the Ia afferents and then the inhibitory interneuron was activated which suppressed the monosynaptic reflex (215). Volitional vastus medialis EMG was also decreased after limb vibration. Similarly, Rice and colleagues showed reduced vastus medialis activity but unchanged hamstring activity following quadriceps tendon vibration (185). Individuals poststroke also have reduced muscle activity after tendon vibration during an upper extremity tracking task (246). Short bouts of “a priori” vibration altered muscle activity for up to 3 hours after cessation of the vibratory input (252, 253). Given the potentially long lasting effects, this vibratory intervention could be a novel way to modulate muscle activity and possibly neural control.

Another important finding was whole body vibration increased the inhibition of the tibialis anterior muscle 50 to 200 ms after the perturbation. Long latency EMG responses occur 50-200 ms after an unexpected event. This is prior to volitional reaction time and therefore targeted neuromuscular training of these responses could reduce the risk of injury (116). The increased inhibition of the tibialis anterior may be attributed to a change in the somatosensory, visual, or vestibular systems. Increased activation of the vestibular system has been shown to inhibit the antagonist following an unexpected event (87). The threshold required to stimulate the vestibular system was 0.036g (200). The vibratory signal to the head and thus the vestibular system was approximately 0.08g during whole body vibration. Therefore, whole body vibration activated the vestibular system and could explain the inhibition of the long latency response of the tibialis anterior.

Interestingly, the magnitude of tibialis anterior EMG of the long latency responses were inversely related to dose of head vibration. The control, limb vibration, and whole body vibration conditions resulted in 22%MVC, 19%MVC, and 17%MVC, respectively, of the tibialis anterior muscle. Alternatively, as the dose of head vibration increased so did the long latency soleus excitation. The control, limb vibration, and whole body vibration conditions resulted in 32%MVC, 33%MVC, and 34%MVC, respectively, of the soleus muscle. The unexpected stretch the soleus muscle resulted in a trend of increased long latency response although this did not reach significance. When a muscle is stretched unexpectedly(soleus) there is an activation accompanied by an inhibition of the antagonist(tibialis anterior) (117).

In summary, the short latency and volitional control responses were inhibited in the vastus medialis after limb vibration. We also showed the long latency response was inhibited in the tibialis muscle during whole body vibration. The neuromuscular control system is constantly bombarded with sensory information about the environment; however, successfully completing a motor task relies on differentiating relevant, meaningful information from environmental noise. Our cohort of healthy individuals was able to accommodate any extraneous afferent information due to the vibration interventions and maintain the same level of accuracy compared to the control condition.

Taken together, these findings support vibration before and during movement control do not influence accuracy but differentially regulate the CNS response to unexpected events.

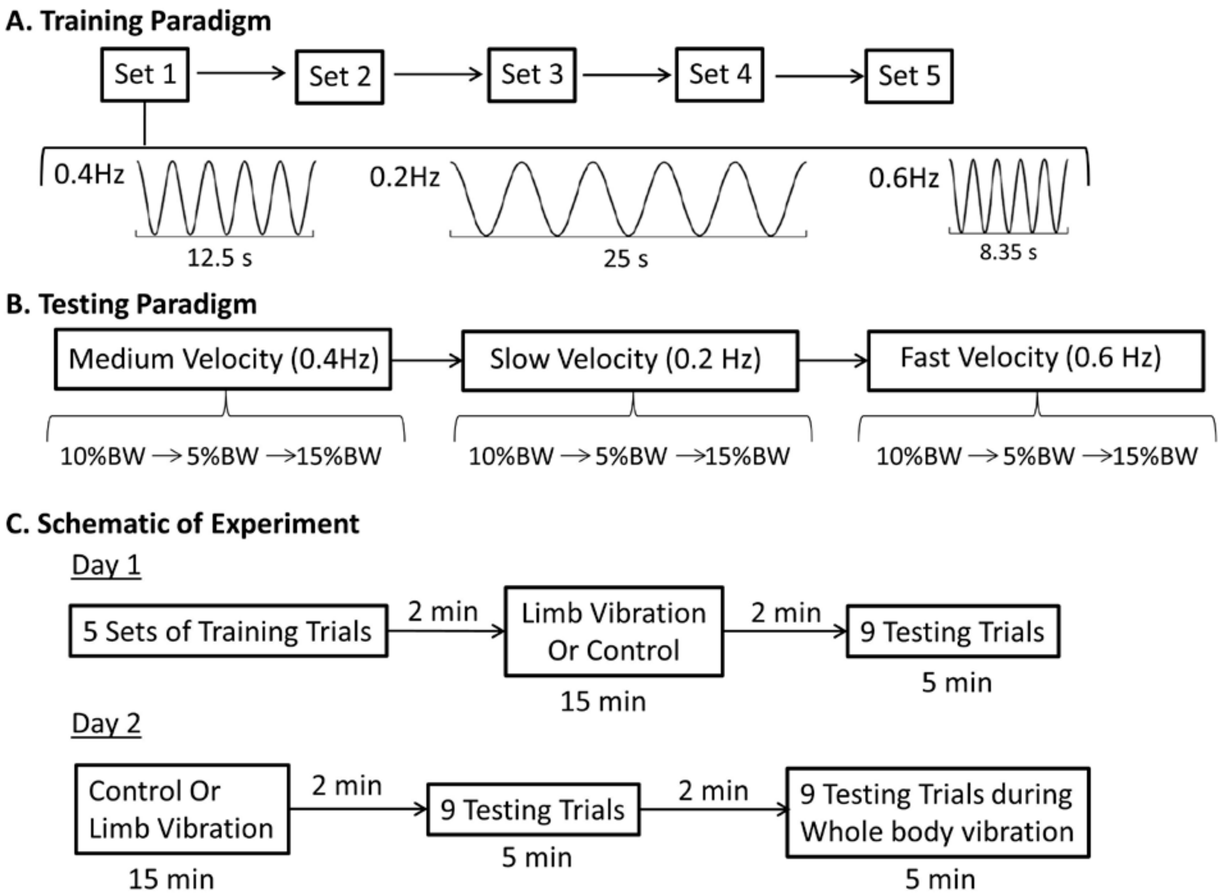

Figure 5.1 Experimental Protocol. A) Five sets of training trials were administered to participants with the resistance set to 10% of body weight(%BW). Each set contained three trials at different velocities (0.2 Hz, 0.4 Hz, and 0.6 Hz). The velocity of the trial was randomly selected within each set. B) The testing paradigm was administered after the intervention and consisted of nine conditions at varying velocities and resistances (5%BW, 10%BW, 15%BW). The order of the nine conditions remained consistent throughout. C) Schematic of the experiment showing the order of the training trials and vibration interventions.

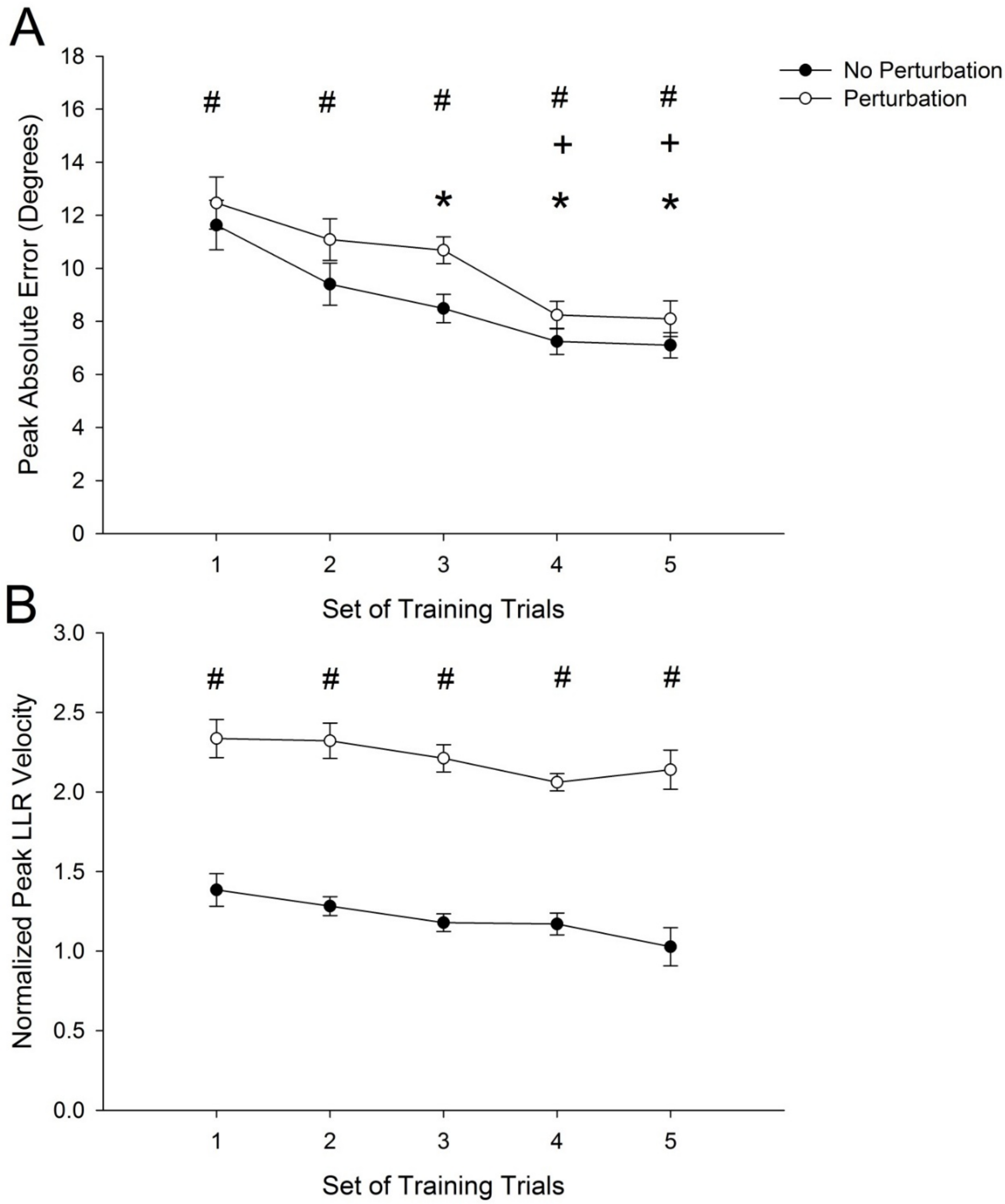

Figure 5.2 Training Effects on Absolute Error and Velocity Error. A) Peak absolute error and B) peak velocity error during the 50-200 ms after the perturbation across the five sets of training trials for perturbed (open symbols) and non-perturbed (closed symbols) cycles. * Represents significant difference to cycle 1 ($p < 0.05$). + Represents significant difference compared to cycle 2 ($p < 0.05$). # Represents a significant difference between perturbed and non-perturbed cycles ($p < 0.05$).

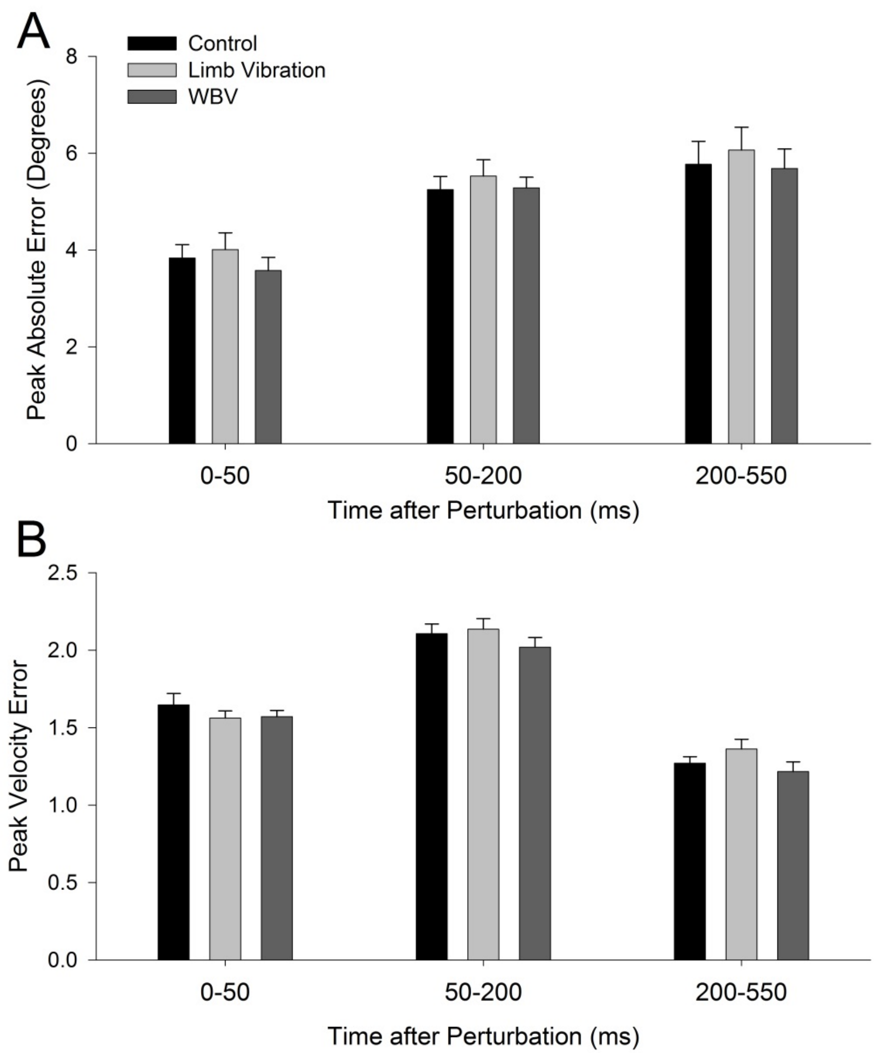

Figure 5.3 Effect of Vibration on Absolute Error and Velocity Error.) Peak absolute error and B) peak velocity error for control (black), limb vibration (light grey), and whole-body vibration (dark grey) during perturbation cycle. Data are represented in time bins after the perturbation (time =0), short latency response is the 50 ms after the perturbation, long latency is the 50 to 200 ms after the perturbation, and reaction time is the 200-550 ms after the perturbation.

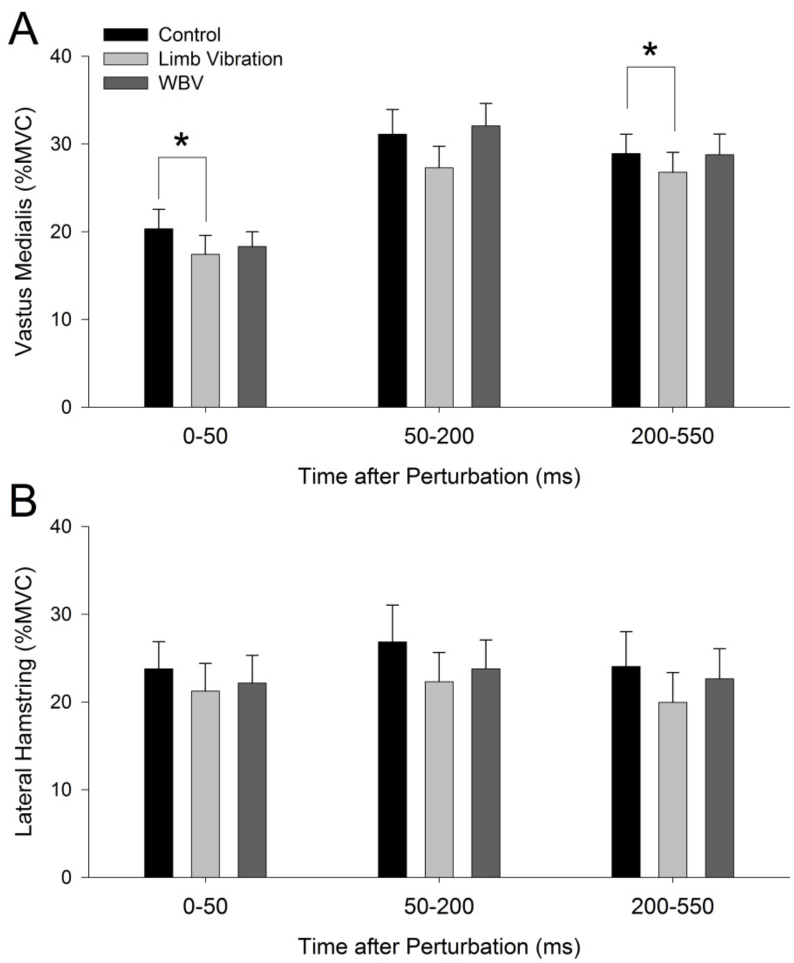

Figure 5.4 Effect of Vibration on Vastus Medialis and Lateral Hamstring Activity. Peak EMG activity of the A) vastus medialis and B) lateral hamstrings for control (black), limb vibration (light grey), and whole-body vibration (dark grey) during perturbation cycle. Data are represented in time bins after the perturbation (time =0), short latency response is the 50 ms after the perturbation, long latency is the 50 to 200 ms after the perturbation, and reaction time is the 200-550 ms after the perturbation. * Represents a significant difference between control and limb vibration ($p<0.05$).

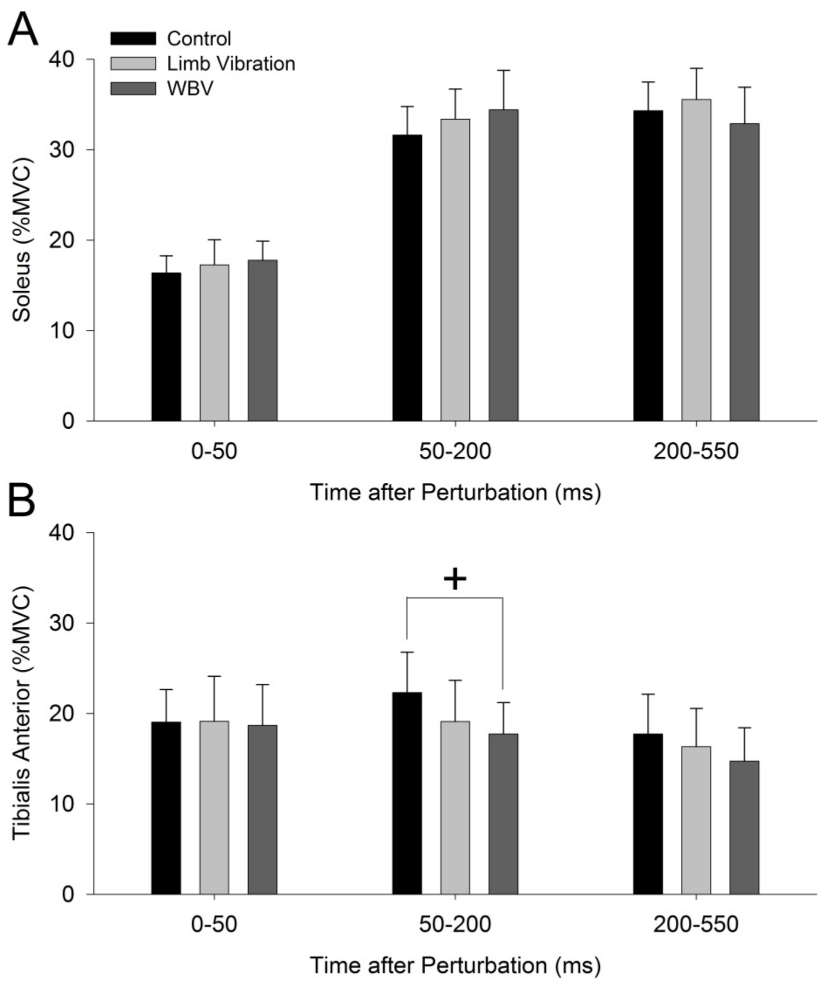

Figure 5.5 Effect of Vibration on Soleus and Tibialis Anterior Activity. Peak EMG activity of the A) soleus and B) tibialis anterior for control (black), limb vibration (light grey), and whole-body vibration (dark grey) during perturbation cycle. Data are represented in time bins after the perturbation (time =0), short latency response is the 50 ms after the perturbation, long latency is the 50 to 200 ms after the perturbation, and reaction time is the 200-550 ms after the perturbation. + Represents a significant difference between control and whole body vibration ($p<0.05$).

CHAPTER 6 CONCLUSIONS

Mechanical loading is thought to modulate tissue plasticity and has potential applications in regenerative medicine. To safely and effectively introduce mechanical loads to human cells, tissues, and the entire body, we need to understand the optimal loading environment to promote growth and health. The purpose of this research was 1) to validate a limb vibration and compression system; 2) to determine the effect of limb vibration on neural excitability measured by sub-threshold TMS-conditioned H-reflexes and supra-threshold TMS; 3) to determine changes in center of pressure, muscle activity, and kinematics during a postural task following limb vibration; 4) to determine the effect of limb vibration and whole body vibration on accuracy of a weight bearing visuomotor task and muscle responses to an unexpected pertubation.

Specific Aim 1

Hypothesis 1a

The vibration from the platform will occur primarily in the vertical direction at the specified vibration parameters and the vibration will be limited to the testing leg with minimal transmissibility to the contralateral limb and the head.

Supported: The transmissibility to the testing leg was 0.71 with the transmissibility to the contralateral limb and head remaining below 0.02.

Hypothesis 1b

The linearity, repeatability, and percent error of the compression system will be less than 5% full scale and intra-class correlation coefficients (ICC) of the between day reliability of delivering a load to a human limb will be greater than 0.80.

Supported: The linearity, repeatability, and error remained below 5% full scale, at 4%, 1%, and 1%, respectively. The between day reliability was excellent (ICC = 0.90).

Hypothesis 1c

The vibration system will stop if any of the vibration parameters are exceeded and the compression system will prevent transmission of excessive load to a human limb within 5% of intended load.

Supported: The vibration system ceased when the acceleration exceeded 6.1g, the vibration platform exceeded 11mm of displacement, or the manual shutdown from the controller was initiated. The safety shut off for the compression system was effective within 3% of the intended load. We also had no participant complaints during the testing or tissue reddening supporting that mechanical vibration and compression can be delivered concurrently to human tissue.

Specific Aim 2

Hypothesis 2a

The sub-threshold TMS pulse will facilitate the soleus H-reflex during limb vibration.

Supported: There was a fourfold increase in the H-reflex amplitude during limb vibration, when conditioned by a sub-threshold TMS pulse. Sub-threshold cortical stimulation reduces the vibration-induced presynaptic inhibition of the H-reflex.

Hypothesis 2b

Limb vibration will increase the amplitude of the soleus motor-evoked potential compared to the control condition.

Not supported: There was no change in the supra-threshold TMS motor evoked-potential during limb vibration. Therefore, the reduction in the vibration-induced presynaptic inhibition of the H-reflex cannot be attributed to an increase in cortical excitability during limb vibration.

Specific Aim 3

Hypothesis 3a

Limb vibration will increase displacement and velocity of the center of pressure in the anterior/posterior (A/P) and medial/lateral (M/L) directions.

Not supported: Limb vibration did not alter the blinded, center of pressure variability quantified by RMS displacement and velocity in the A/P and M/L directions.

Hypothesis 3b

Limb vibration will increase complexity of center of pressure velocity quantified using nonlinear fractal analysis ($p < 0.05$).

Partially Supported: Following limb vibration, the complexity of size-independent fluctuations for the center of pressure A/P velocity and large fluctuations for the center of pressure M/L velocity increased. However, the fractal analysis revealed no change pre to post limb vibration in the complexity of the small or large fluctuations for the center of pressure A/P velocity the small or size-independent fluctuations for the center of pressure M/L velocity.

Hypothesis 3c

After limb vibration there will be an increase in soleus and tibialis anterior muscle activity during the blinded single leg stance task.

Supported: After limb vibration, the EMG activity of the soleus and tibialis anterior muscles increased by 13.4% and 20.5% respectively, during the blinded condition.

Hypothesis 3d

Limb vibration will increase the ankle, knee, and hip angles during a blinded, single leg stance task.

Not supported: During a blinded, postural control task, joint angles of the ankle, knee, and hip did not change the following limb vibration.

Specific Aim 4

Hypothesis 4a

Limb vibration prior to a visuomotor tracking task will increase the accuracy indicated by reduced peak absolute error and peak velocity error compared to the control condition.

Not supported: Limb vibration did not change the peak absolute error or the peak velocity error during the visuomotor tracking task.

Hypothesis 4b

Whole body vibration during a visuomotor tracking task will increase the accuracy indicated by reduced peak absolute error and peak velocity error compared to the control condition.

Not supported: Whole body vibration during the visuomotor tracking task did not change the peak absolute error or the peak velocity error.

Hypothesis 4c

Limb vibration prior to a visuomotor tracking task will increase muscle responses following a perturbation compared to the control condition.

Not supported: Limb vibration yielded lower vastus medialis EMG in the short latency and reaction time bins. There was no change in the lateral hamstrings, soleus, or tibialis anterior muscle responses following a bout of isolated limb vibration.

Hypothesis 4d

Whole body vibration during a visuomotor tracking task will increase muscle responses following a perturbation compared to the control condition.

Not supported: Whole body vibration triggered lower tibialis anterior EMG in the long latency time bin. There was no change in the vastus medialis, lateral hamstrings, or soleus activity during whole body vibration.

Summary

In summary, the instrumentation presented in the manuscript can reliably, accurately, and safely deliver limb vibration and compression to human tissue. The initial technological report was essential to the subsequent projects and provided a device capable of introducing a novel mechanical load. Using this mechanical device, the effects of limb vibration on neural excitability, postural control, visuomotor tracking accuracy, and muscle responses to an unexpected perturbation were investigated. Limb vibration has been shown to suppress segmental excitability (H-reflex) (57). Findings from this research showed sub-threshold cortical stimulation reduced the vibration-induced presynaptic inhibition of the H-reflex. This reduction cannot be attributed to an increase in cortical excitability during limb vibration because the MEP remained unchanged with limb vibration. Based on the neurophysiological changes associated with vibration, the next progression was to determine if vibration also influenced movement control. During a blinded, postural control task, limb vibration increased the soleus and tibialis muscle activity. This vibration-induced increase in muscle activity was associated with an unchanged center of pressure variability but a reduced center of pressure complexity. A weight-bearing, visuomotor tracking task showed that participants had similar accuracy following limb vibration as well as during whole-body vibration. An isolated vibratory intervention before a weight bearing task causes a reduction in vastus medialis activity to an unexpected perturbation. Whole body vibration also reduces long latency responses of tibialis anterior following an unexpected perturbation. Future studies are needed to determine if limb vibration can aid in the rehabilitation of individuals with neurological deficits including those with balance dysfunction and movement control strategy impairments. The technology presented here has the capacity to impact rehabilitation techniques and regenerative medicine for many different human populations.

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