THE EFFECT OF VIBRATORY STIMULI ON MEASURES OF NEUROMUSCULAR FUNCTION

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ABSTRACT

Derek N. Pamukoff: The Effect Of Vibratory Stimuli On Cortical And Spinal Neuron Excitability
(Under the direction of J. Troy Blackburn)

Context: Muscle vibration enhances neuromuscular function, but the mechanism of improvement is unclear. Heightened motor neuron excitability within the spinal cord could be responsible for improved muscle function following vibration. However, the response of supraspinal structures – such as the motor cortex – to vibration is unclear. Vibratory treatments could benefit individuals with quadriceps dysfunction, such as patients with knee pathologies. Whole body (WBV) and local muscle vibration (LMV) improve quadriceps function but the efficacy of treatment may vary. **Objective:** To compare the effects of whole body and local muscle vibration on measures of quadriceps function. **Participants:** Sixty recreationally active young adults, and twenty individuals with anterior cruciate ligament reconstruction. **Interventions:** Healthy subjects were randomized to one of three groups (WBV, LMV and control) and completed three testing sessions. Subjects completed testing of quadriceps spinal neuron excitability, corticomotor excitability, or a maximal voluntary isometric contraction and then completed an intervention based on group assignment. Subjects repeated the assessment immediately, ten minutes, and twenty minutes following the intervention. Subjects completed the remaining two assessments in separate sessions. Injured subjects completed testing of quadriceps spinal neuron excitability, corticomotor excitability, and maximal voluntary isometric contraction, and then complete one of three treatment conditions (WBV, LMV, control). Subjects

completed follow up testing following the intervention. Subjects completed the remaining two treatment conditions in separate visits. **Main Outcome Measures:** Quadriceps peak torque (PT), rate of torque development (RTD), electromyography (EMG), central activation ratio (CAR), active motor threshold (AMT), motor evoked potential (MEP) amplitude, and Hoffman Reflex. **Results:** Healthy subjects in the WBV group improved in quadriceps PT, EMG, CAR, AMT and MEP amplitude. Healthy subjects in the LMV group improved in quadriceps EMG and AMT. Injured subjects improved in quadriceps PT, EMG, CAR, and AMT in the WBV and LMV conditions. **Conclusions:** WBV and LMV improve quadriceps function and could be a useful tool to improve the efficacy of strengthening protocols in patients with knee pathologies. Improvements in quadriceps function resulting from WBV and LMV can be attributed to greater corticomotor excitability. WBV may be more suitable to improve quadriceps function in healthy individuals compared to LMV.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ACLR	Anterior Cruciate Ligament Reconstruction
OA	Osteoarthritis
AMI	Arthrogenic Muscle Inhibition
VT	Vibration Therapy
WBV	Whole Body Vibration
LMV	Local Muscle Vibration
CAR	Central Activation Ratio
EMG	Electromyography
TMS	Transcranial Magnetic Stimulation
AMT	Active Motor Threshold
MEP	Motor Evoked Potential

CHAPTER 1: INTRODUCTION

As many as 250,000 anterior cruciate ligament (ACL) injuries occur each year in the United States.[3] ACL reconstruction is costly, amounting to nearly $50,000 per procedure in direct medical costs.[4,5] However, patients with ACL injury and reconstruction are at much greater risk for developing osteoarthritis (OA),[6-10] which drastically elevates the cost associated with ACL injury.[4] OA is a gradual reduction of articular cartilage within a joint, and patients with ACL injury are 3-5 times more likely to develop tibiofemoral OA compared to those without injury.[6-11] Despite surgical reconstruction, patients with ACL injury show evidence of tibiofemoral OA between 5 and 15 years following initial injury.[7,12-14] Radiographic evidence of OA is seen in up to 13% of all knees with no concomitant meniscal injury, and up to 48% of knees with a concomitant meniscal injury at 10 years or less of follow-up.[8] Importantly, ACL injuries are most common among youth populations.[15] Therefore, these patients develop degenerative joint changes at much younger ages, which elevates the lifetime cost of an ACL injury attributable to OA. The annual lifetime cost of ACL injuries borne on the United States health care system, which includes the cost of long-term complications such as OA, is $7.6 billion when treated with reconstruction and $17.7 billion when treated with rehabilitation.[4] Furthermore, OA affects nearly one third of older adults and is a leading cause of physical disability.[16] In the long term, OA contributes to sedentary behavior and comorbidities such as cardiovascular disease.[17,18] Overall, the direct costs attributable to knee OA in the United States is $51 billion and affects 9 million Americans.[19]

The pathway from ACL injury to tibiofemoral OA is multifactorial and can in part be explained by alterations in neuromuscular function following injury.[20-24] Quadriceps weakness is common following ACL reconstruction due to arthogenic muscle inhibition (AMI).[21-24] Alterations in afferent input to the central nervous system decrease the excitability of the quadriceps, ultimately leading to a compromised ability to activate the quadriceps voluntarily.[20] This altered afferent input stems from joint effusion, excessive joint laxity, pain, or deafferentation of the native ACL from reconstruction or deficiency, or a combination thereof.[25,26] Lesser quadriceps activation leads to reductions in knee extensor strength, which may contribute to the development of OA. Several studies suggest that baseline quadriceps function is a predictor of OA progression.[23,24,27-30] Furthermore, OA is considered to be a mechanically driven disease, meaning that alterations in joint loading influence OA development.[2,31-33] The quadriceps act as a shock absorber during the early stance phase of gait, and failure to effectively absorb energy caused by impact with the ground may alter the loading characteristics of articular cartilage. Individuals with ACL injury have lesser internal knee extensor moments and knee flexion angles during gait resulting from quadriceps weakness and hamstring co-contraction. These alterations reduce the time interval over which ground reaction force is absorbed, thereby increasing the impulsive load.[2,34-36] Articular cartilage is viscoelastic and is, therefore, sensitive to loading rate. Cartilage loaded at a faster rate will stiffen and is more likely to breakdown, potentially leading to OA.[37] Additionally, kinematic alterations following ACL injury and reconstruction may change nutrient-waste exchange in the articular cartilage. Altered gait kinematics shift the tibiofemoral contact areas and expose areas of articular cartilage that are not conditioned to habitual stress. As these biomechanical alterations linked to the development of OA are, at least in part, attributable to quadriceps dysfunction,

improving neuromuscular function by addressing lingering quadriceps weakness is an important strategy to prevent or delay the development of OA in patients with ACL injury.

Rehabilitation strategies aimed to improve quadriceps strength are largely ineffective because they do not address underlying deficits in neuromuscular function (i.e. AMI).[38,39] Patients with inhibition respond poorly to traditional rehabilitation protocols and display minimal improvements in knee extensor strength.[39] Therefore, novel strategies are needed to enhance the efficacy of current rehabilitation programs. Vibration therapy (VT) is an increasingly popular mode of exercise due to reports of improved muscle strength, power, EMG amplitude, and physical function.[40-49] When a muscle is vibrated, a reflexive contraction known as the tonic vibratory reflex (TVR) is evoked.[50-52] Essentially, there is a discharge of the primary endings of the muscle spindle (Ia afferent) via repeated rapid lengthening of the muscle from vibration.[53] This excites the alpha motor neurons, resulting in muscle contraction. However, the TVR only accounts for increases in muscle activity during VT, and does not account for improvements that are observed following cessation of VT.[54,55] Therefore, it is likely that there are other mechanisms that explain why improvements in muscle function persist following VT. The intent of VT is to increase the number and frequency of excitatory stimuli sent to α-motorneurons in an attempt to override the inhibitory afferents coming from the damaged joint. Therefore, VT may be an effective method for improving quadriceps function following knee joint injury to prevent or delay the onset of OA.

Despite reports of enhanced muscle strength and power following VT,[40,41,56] there is paucity in the literature regarding the mechanisms by which VT alters neuromuscular function. Early studies suggest that enhanced motor neuron excitability within the spinal cord is responsible for these improvements.[51] However, reports are mixed because VT has both

excitatory and inhibitory influences on spinal reflex activity. For example, some studies suggest a suppression of spinal neuron excitability following VT in healthy individuals[57-59] and in patients with spinal cord injury,[58] potentially due to presynaptic inhibition.[60] These findings suggest that any improvement in muscle function following VT cannot be attributed to gains in spinal neuron excitability. What remains unclear is the role of supraspinal structures, such as the motor cortex following VT. Cortical areas also receive and process afferent signals and produce cortical potentials in response to VT.[61] Furthermore, muscle afferent input to the cerebral cortex is a major contributor in motor control.[62] Limited evidence using transcranial magnetic stimulation (TMS) suggests that brief exposure to VT enhances corticospinal excitability.[63-65] This is particularly relevant, as studies show that patients with knee pathology have lesser corticospinal excitability.[66,67] As such, if VT elicits improvements in cortical and spinal excitability, it could be a potent adjunct treatment to improve quadriceps function. However, studies evaluating the effect of VT on corticospinal excitability have used small samples, and no study, to my knowledge, has concurrently evaluated spinal and cortical neuron excitability following VT.

The majority of studies have reported enhanced muscle function following whole body vibration (WBV).[40,47,48,56,68-73] However, WBV platforms are cost prohibitive (up to $10,000) and provide limited portability. Local muscle vibration (LMV) also improves muscle function,[41,46,74] and may be a cost effective and portable alternative to WBV. WBV and LMV provide similar stimuli, but the efficacy of the stimulus may differ. During WBV, energy from vibration is dampened by the ankle joint, knee joint, and calf muscles, which may influence the magnitude of the vibration stimulus delivered to the quadriceps. The reduction in energy from the vibration signal may be less if the stimulus is delivered directly to the muscle via LMV rather

than indirectly via WBV. We recently demonstrate that LMV improves quadriceps activity for a sustained period of time post-application in healthy individuals[55] and that WBV and LMV produce similar increases in voluntary quadriceps activation following experimental knee joint effusion.[75] However, no studies have compared the effects of WBV and LMV on cortical and spinal neuron excitability.

Patients with ACL injury have deficits in corticospinal excitability that contribute to AMI and reduce quadriceps function.[66,76,77] Reduced quadriceps function may contribute to the development of OA, and current rehabilitation strategies are largely ineffective in individuals with AMI. Novel strategies are needed to address AMI, and VT may provide an adjunct treatment to improve quadriceps function. However, it is unclear how VT alters neuromuscular function. Therefore, the purpose of this study is to evaluate the effects of VT on measures of neuromuscular function. The specific aims are as follows:

1) To determine the effects of WBV and LMV on corticospinal excitability, spinal neuron excitability, electromyography (EMG) amplitude, and voluntary muscle activation during a maximal isometric contraction in healthy adults. *I hypothesize that WBV and LMV will increase EMG amplitude and corticospinal excitability, but will suppress spinal neuron excitability, and that these changes will be greater than those observed in a control group receiving no treatment.*

2) To compare the effects of WBV and LMV on corticospinal excitability, spinal neuron excitability, EMG amplitude, and voluntary muscle activation during a maximal isometric contraction in healthy adults. *I hypothesize that LMV and WBV will enhance*

corticospinal excitability and EMG amplitude, but attenuate spinal neuron excitability, relative to the control group receiving no treatment, but the magnitude of these improvements will not differ between WBV and LMV.

3) To determine the duration of the effect of WBV and LMV on corticospinal excitability, spinal neuron excitability, EMG amplitude, and voluntary muscle activation during a maximal isometric contraction in healthy adults. *I hypothesize that the effect of LMV and WBV on corticospinal, spinal neuron excitability, and EMG amplitude will persist for at least 10 minutes following cessation of treatment.*

4) To compare the effects of WBV and LMV on EMG, corticospinal excitability, spinal neuron excitability, voluntary muscle activation, and EMG during a maximal isometric contraction in a subset of patients with ACL injury. *I hypothesize that LMV and WBV will enhance corticospinal excitability and EMG amplitude, but attenuate spinal neuron excitability, relative to the control condition receiving no treatment, but the magnitude of these improvements will not differ between WBV and LMV.*

If VT enhances corticospinal excitability and quadriceps function, it would be a particularly potent treatment for individuals with knee pathologies who experience AMI. Furthermore, LMV represents a portable and less expensive alternative to WBV, and demonstrating equivalent effects would greatly enhance the viability of VT as a treatment. A description of possible outcomes and interpretations is detailed in table 1.

Table 1: Possible Outcomes

EMG	H-Reflex	AMT	MEP	Interpretation
↑	↓	↓	↑	↑ in muscle function due to enhanced cortical neuron excitability
↑	↑	↓	↑	↑ in muscle function due to enhanced spinal neuron & cortical neuron excitability
↑	↑	–	–	↑ in muscle function due to enhanced spinal neuron excitability
↑	–	–	–	↑ in muscle function due to post-activation potentiation and warm-up

CHAPTER 2: REVIEW OF LITERATURE

INTRODUCTION

The purpose of this literature review was to review pertinent studies and deficiencies in understanding. Specifically, this review focuses on short-term and long-term neuromuscular alterations following anterior cruciate ligament injury, such as impaired quadriceps muscle function, and altered gait kinematics and kinetics. This review addresses how deficiencies in quadriceps function alter knee joint loading during gait, and contribute to joint degeneration and tibiofemoral osteoarthritis development. Second, this review identifies areas of deficiency in rehabilitation for ACL injuries, and why novel strategies to improve quadriceps function are needed. Thirdly, this review provides evidence for the use of vibration therapy to improve muscle function, and how it may specifically apply to patients with ACL injury. Additionally, this literature review illustrates how and why LMV may provide a cost-effective and portable alternative to WBV. Lastly, results of this review are summarized and proposed aims are suggested.

ANTERIOR CRUCIATE LIGAMENT INJURY

Epidemiology

As many as 250,000 anterior cruciate ligament (ACL) injuries occur each year in the United States with nearly 200,000 ACL reconstruction procedures. [3] ACL reconstruction costs approximately $50,000 per procedure in direct medical costs, and ACL injury carries a cost of

$7.6 billion annually in the United States when treated with reconstruction, and $17 billion annually when treated with rehabilitation.[4,5] Following ACL injury, alterations in muscle function and gait biomechanics elevate the risk of developing tibiofemoral osteoarthritis (OA). [6-10] Patients with ACL injury are between three and five times more likely to develop OA compared to individuals with no injury. [6-11] Interestingly, patients with ACL injury are at greater risk for OA development regardless of reconstruction procedures. Patients with ACL injury that undergo reconstruction are 3-5 times more likely to develop OA compared to healthy individuals, and patients with ACL injury that do not undergo reconstruction are equally likely to develop OA compared to those with reconstruction.[10] Overall, OA is seen in up to 13% of all knees with no concomitant meniscal injury, and up to 48% of knees with a concomitant meniscal injury at ten years or less of follow-up.[8] Therefore, while ACL reconstruction may be effective for restoring near normal knee joint function, long-term consequences on joint health following injury are unchanged, and rehabilitation programs are ineffective.[38,39] Importantly, the majority of ACL injuries occur in youth populations,[15] which greatly elevates the lifetime cost of an ACL injury when considering the increased risk of OA development.

Anterior Cruciate Ligament Anatomy

The ACL is a 2-4 centimeter long dense band of connective tissue between the femur and tibia. It is an important structure in the knee joint and serves primarily to resist and limit anterior tibial translation and rotational loads.[78-82] The ACL is divided into two bundles largely comprised of type I collegen fibers: the anteromedial bundle, and the posterolateral bundle.[83] The anteromedial bundle originates at the most anterior and proximal aspect of the attachment to the femur and inserts along the anteromedial attachment of the tibia.[78] The fibers of the

posterolateral bundle originate along the postero-distal aspect of the femoral attachment and insert along the posterolateral aspect of the tibial attachment.[78] These bundles are not isometric, and the anteromedial bundle tightens as the knee moves into flexion, while the posterolateral sbundle becomes slack. [81]

The ACL receives innervation from the posterior articular branches of the tibial nerve, and also has several mechanoreceptors (Ruffini, Pacini, free nerve endings, and golgi-like receptors). [84-86] These mechanoreceptors have a role in proprioception and provide afferent information regarding knee position. For instance, Ruffini receptors are sensitive to changes in length. Deformation of the ACL influences output of the spindles in muscles surrounding the joint. [87,88] Furthermore, free nerve endings act as nociceptors for pain. If the ACL is damaged or ruptured, loss of afferent information from these receptors contributes to diminished quadriceps function.[88,89] Additionally, the ACL provides information regarding joint position sense. Therefore, patients with ACL injury would have diminished proprioceptive function. Reconstructive procedures are aimed to restore structural stability to the knee joint, and make no attempt at restoring function of the mechanoreceptors, which partially explains why quadriceps weakness may persist in patients with ACL injury. Lastly, the ACL is also vascularized with blood supply from the middle gennicular artery.[81] However, the distal area of the ACL that is subject to compressive loads has poor vascularity, which may explain why the ACL does not heal on its own.

Injury Risk Factors

The majority of ACL injuries (~70%) are the result of non-contact mechanisms. Despite a vast body of literature regarding ACL injury, no single causative mechanism has been identified. However, risk factors for non-contact ACL injury are anatomical, biomechanical, and

physiological. Firstly, sex hormone concentration may influence collagen synthesis of the ACL thus contributing to its integrity and function.[90,91] Furthermore, ACL function may vary depending on the phase of the menstrual cycle. For instance, greater joint laxity is observed in the periovulatory and luteal phases of the menstrual cycle.[92,93] Fluctuations in sex hormone concentration during the menstrual cycle may contribute to the high prevalence of ACL injuries among females compared to males. Secondly, anatomical risk factors for ACL injury include smaller ACL size, greater quadriceps angle, and smaller intracondylar notch size. Interestingly, females have smaller ACLs, greater quadriceps angles, and smaller intracodylar notches compared to males, and this likely increases their risk for ACL injury. Thirdly, there are biomechanical factors that influence risk for ACL injury. For example, landing with greater vertical impact force increases the risk for ACL injury.[94,95] Furthermore, kinematic and kinetic differences during athletic tasks may influence ACL loading such as anterior tibial shear force, knee valgus position, internal knee extension moment, and knee flexion angle. Females have greater anterior tibial shear force, greater knee valgus, greater knee extension moments, and lesser knee flexion during landing tasks compared to males.[94,96,97] Importantly, while anatomical and hormonal risk factors are not modifiable characteristics, biomechanical factors may be modified through supplementary training.

Lastly, current rehabilitation programs often leave individuals at risk for re-injury. Patients with ACL injury are 12% more likely to tear their ACL compared to healthy individuals. Therefore, it is likely that rehabilitation programs are not effective in restoring neuromuscular [38,39] and biomechanical function. Patients with ACL reconstruction have abnormal landing biomechanics such as lesser knee flexion [36] and greater internal rotation [2] compared to healthy individuals that may increase their risk for re-injury. Additionally, patients with ACL

reconstruction have alterations in gait that influence risk for knee OA.[2,36,98,99] These alterations are detailed later in this summary.

KNEE OSTEOARTHRITIS EPIDEMIOLOGY

Osteoarthritis (OA) is a gradual reduction of articular cartilage within a joint. Clinical diagnosis of OA is typically guided by symptoms and physical examination. However, radiographic evidence is used to assess OA severity and progression, and is defined by joint space narrowing and presence of osteophytes. The Kelgren-Lawrence scale is a common metric of OA progression (grade 1 – doubtful narrowing of joint space and possible osteophytic lipping, grade 2 – definite osteophytes and definite narrowing of joint space, grade 3 – moderate multiple osteophytes and definite narrowing of joint space, grade 4 – large osteophytes and marked narrowing of joint space). OA affects approximately one third of adults older than 65, and is a leading cause of physical disability.[16] Knee OA is the most common kind of OA, affecting 9 million Americans at an annual cost of $51 billion.[100] Specifically, patients with ACL injury are three to five times more likely to develop knee OA compared to those without injury, regardless of whether they undergo reconstruction.[6-11]

Knee OA can be classified as post-traumatic (e.g. following ACL injury) or idiopathic (as a result of other non-specific causes). Patients with ACL injury who develop knee OA account for nearly 10% of all knee OA cases.[4] The direct cost of ACL when considering knee OA development is estimated at approximately $7.6 billion annually when patients undergo ACL reconstruction.[4] The cost of knee OA also increases with severity. Mild knee OA incurs a direct annual cost of $9,801 per patient, moderate knee OA has a direct annual cost of $14,761 per patient, and severe knee OA has a cost of $22,111 per patient.[4] Therefore, slowing the progression of knee OA is an important strategy to reduce the financial burden associated with

knee OA. Lastly, knee OA contributes to lower extremity disability, sedentary behavior, and comorbidities such as cardiovascular disease.[17] Additional risk factors that may predispose one to post traumatic knee OA include concomitant meniscal injury,[15] obesity,[101] joint alignment,[102,103] age, gender, sedentary lifestyle, and muscle weakness.[104]

Articular Cartilage Anatomy

Articular cartilage is a connective tissue that provides a smooth and lubricated surface for articulation, and attenuates joint loading.[105] Articular cartilage is made of hyaline cartilage and is between two and four millimeters thick.[106] Interestingly, articular cartilage does not receive blood supply or innervation. Therefore, it has limited intrinsic healing capabilities. Despite a lack of innervation and blood supply to articular cartilage, patients with OA still experience pain from nociceptors in other areas of the knee joint, bone marrow lesions, joint effusion, and inflammation. Articular cartilage is composed of a dense extracellular matrix and distribution of specialized cells called chondrocytes. Chondrocytes are the dominant cell type in articular cartilage. They are highly specialized metabolically active cells that play an important role in maintenance and repair of the extracellular matrix. [106] Chondrocytes respond to many stimuli such as growth factors, mechanical loads, and hydrostatic pressures.[107] However, chondrocytes cannot replicate, and therefore have limited healing ability in response to injury. The extracellular matrix is made primarily of water, collagen, proteoglycans, and glycoproteins. [106] The contents of the extracellular matrix assist in retaining water, which is essential to proper function.

The articular cartilage is divided into zones (superficial, middle, deep, and calcified).[108] The superficial zone is thin and comprises up to twenty percent of articular cartilage thickness. It is made of mainly type II collagen, and fibers are aligned parallel to the articular surface. This

layer contains a high number of chondrocytes, and protects deeper layers from sheer stress. The superficial zone is in contact with synovial fluid, and is responsible for providing resistance to sheer, tensile, and compressive forces from joint articulation. The middle zone provides a transition between the superficial and deep zones and represents up to sixty percent of total cartilage volume. It is comprised of proteoglycans and thicker collagen fibers. These fibers are arranged obliquely, and the middle layer contains a low number of chondrocytes. The middle layer functions to resist compressive force. The deep zone represents nearly thirty percent of articular cartilage volume, and has the largest concentration of proteoglycans, but lowest water concentration compared to the other zones. Collagen fibers are arranged perpendicular to the articular surface and provide the greatest resistance to tensile forces compared to the other zones. Lastly, the calcified zone secures the cartilage to the bone by anchoring the collagen fibers of the deep zone to the subchondral bone.

In addition to zones, the extracellular matrix consist of distinct regions based on proximity to the chondrocytes, composition, and collagen fiber diameter. The extracellular matrix can be divided into pericellular, territorial, and interterritorial regions. Firstly, the pericellular matrix is a thin layer adjacent to the cell membrane and completely surrounds the chondrocytes. It is composed of proteoglycans and glycoproteins, and serves to initiate signal transduction within cartilage during load bearing.[109] Secondly, the territorial matrix surrounds the pericellular matrix and is composed of fine collagen forming a network around the cells. This region is much thicker and protects cartilage against mechanical stresses. [110] Lastly, the interterritorial region is the largest of the regions, and largely contributes to the biomechanical properties of articular cartilage.[111]

Articular cartilage has unique viscoelastic properties that facilitate the transmission of loads to the underlying subchondral bone. Articular cartilage is able to undergo high cyclic loading while demonstrating little or no evidence of damage under normal circumstances.[112,113] Application of joint loading causes an increase in interstitial fluid pressure. The increase in pressure causes fluid to flow out of the extracellular matrix, and create frictional drag on the matrix.[114] When the load is removed, the interstitial fluid flows back into the tissue. As stated above, articular cartilage is viscoelastic and displays a time-dependent behavior when subject to constant loading due to flow-dependent, and flow-independent mechanisms. Firstly, the permeability of articular cartilage is very low, and thus there is frictional drag on the matrix as fluid slowly flows in and out of the tissue from changes in pressure. Additionally, the amount of frictional drag on the matrix increases with higher loading rates, thus increasing the load placed on the articular cartilage. Secondly, the structure of the collagen-proteoglycan matrix provides intrinsic viscoelastic characteristics. Overall, these mechanisms provide support and reduce the stress that acts on the solid matrix. The viscoelastic nature of cartilage has implications for cartilage loading and development of knee OA, and is detailed later in this summary.

Articular cartilage also exhibits creep and stress-relaxation responses to loading. When a constant compressive stress is applied to cartilage, the cartilage will deform or creep until equilibrium between stress and deformation is reached. Likewise, when a constant strain is applied, stress will increase until a peak when a stress-relaxation occurs. Furthermore, articular cartilage stiffens when subject to greater strain, and is very sensitive to changes in strain rate. Animal models have shown that high loading rates (5 milliseconds to peak) provide more damage to articular cartilage compared to low loading rates (50 milliseconds to peak) at the

same magnitude of impact load.[37] Deficits in quadriceps function may contribute to greater loading rates during gait, and thus contribute to articular cartilage breakdown.

NEUROMUSCULAR ALTERATIONS FOLLOWING INJURY

Quadriceps weakness is common following ACL injury,[20,115] despite surgical reconstruction and subsequent rehabilitation.[22,38,39] Muscle weakness is likely attributable to disuse atrophy. However, atrophy does not occur instantaneously, and thus does not acutely influence force production. Alternatively, arthrogenic muscle inhibition (AMI) occurs immediately following injury causing an immediate reduction in force production.[20] AMI also contributes to ongoing quadriceps weakness associated with ACL injury.[38] AMI is a form of reflexive neural inhibition that results in diminished motor drive to muscles associated with the injured joint.[20] Although AMI functions as a protective mechanism to prevent pain and excessive motion, the ultimate result is further weakness and wasting of the surrounding musculature. AMI is commonly measured using the central activation ratio (CAR), which estimates the percentage of motor units (recruitment and rate coding) that can be activated voluntarily. In patients with ACL injury, deficits in quadriceps activation are commonly reported, but vary between 8 and 45%.[104] Unfortunately, deficits in activation persist for several years following reconstruction and rehabilitation, and may contribute to joint degeneration and osteoarthritis. For instance, Urbach and colleagues [22] found that the quadriceps were still inhibited by 15% nearly 2 years following reconstruction in a sample of 12 patients with an isolated ACL injury. In addition, similar findings exist in patients with knee OA. A recent meta-analysis suggests that the quadriceps in patients with tibiofemoral OA are inhibited by

approximately 20%.[116] Interestingly, deficits in quadriceps activation are also observed in the uninjured limb in patients with ACL injury.[77,117,118] Previous studies have found inhibition in the uninjured limb ranging from 7 to 24%, and some have reported nearly equal inhibition to that of the injured limb.[39,118] Inhibition in the quadriceps of the contralateral limb suggest that AMI is caused by both local mechanisms surrounding the joint, and central mechanisms that control movement and muscle function throughout the body (Figure 1).

In addition to providing stability to the knee joint, the ACL also has mechanoreceptors that provide sensory information to spinal and supraspinal regions regarding joint movement, position, and loading.[81]

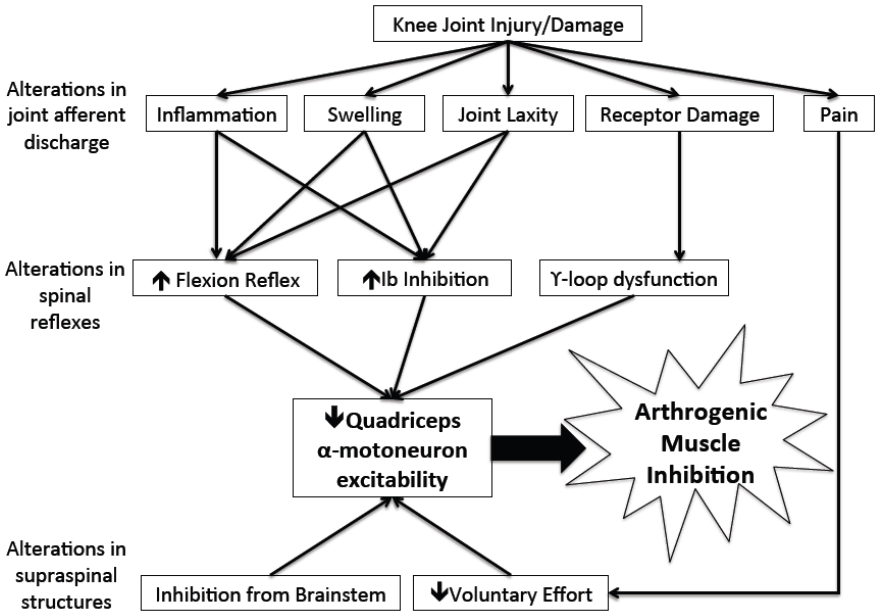

Figure 1: Mechanisms of Arthrogenic Muscle Inhibition (adapted from Rice and McNair1)

Following injury, altered afferent information is transmitted to the central nervous system, resulting in a decrease in the excitability of the quadriceps alpha motoneuron pool.[81] Abnormal afferent discharge can come from stimulation or damage to mechanoreceptors, joint effusion, joint laxity, or nociceptors in response to pain. The ACL also has projections to the muscle spindles in adjacent muscles, which are sensitive to changes in length, thus providing additional proprioceptive information. Lastly, alterations in spinal reflex and corticospinal function can contribute to AMI and are detailed below.

Changes in Afferent Discharge

Swelling is common following knee injury and surgery and contributes to AMI. Moreover, swelling persists for up to 3 months following initial ACL injury, and for up to 12 months following reconstruction.[119] Swelling can also contribute to AMI independently of other factors such as inflammation, pain, and structural damage.[1] For instance, injecting saline into a knee joint to increase intra-articular pressure (IAP) in uninjured joints can artificially cause AMI.[25,75] Swelling raises the IAP within the knee joint, thus increasing the firing frequency and recruitment of group 2 afferent fibers, which are sensitive to changes in stretch and pressure.[120,121] Therefore, greater discharge of group 2 afferents likely has a large inhibitory effect on quadriceps function. For instance, prior studies have also shown that swelling reduces quadriceps activation measured via electromyography,[122-124] H-reflex amplitude,[125,126] and force output.[75,127,128]

Inflammation also occurs following injury and surgery. Inflammation alters the sensitivity of articular nerve endings supplied by group 3 and 4 afferents via a process called peripheral sensitization.[129] The activation threshold of these receptors is lowered following injury, thus increasing afferent output to the central nervous system.[129-131] Importantly, these types of fibers constitute the majority of afferent fibers within the knee joint. Group 3 and 4 afferents are nociceptive, and inflammation increases pain in association with afferent discharge, and pain may contribute to the magnitude of AMI.[132] Also, the inflammatory process may increase the activity of otherwise silent free nerve endings.[130,131] In response to inflammation, the firing threshold of these receptors is lowered, thus increasing afferent output contributing to AMI.

Structural damage or joint degeneration results in greater translation of the knee joint surfaces (femur and tibia) during movement that increase activation of mechanoreceptors and nociceptors that signal the end ranges of joint motion.[133] For example, animals with transected ACLs have greater afferent activity in the major nerves supplying the knee joint.[134] Although ACL reconstruction reduces joint laxity and afferent discharge, alterations in afferent activity persist following reconstruction.[135] These results suggest that ACLR is not entirely effective in restoring normal function, which may partially explain why AMI persists following reconstructive procedures.

Lastly, acute injury may also damage the sensory endings located within the ACL, thus reducing afferent output.[133,136] Although factors such as swelling, inflammation, and joint laxity increase joint afferent discharge, different types of joint afferents may have contrasting effects (inhibitory vs. excitatory) on motor neuron excitability. Acute damage to articular receptors within the ACL or joint capsule may reduce excitatory afferent input to the alpha motoneuron pool, thus contributing to lower quadriceps activation.[136] Overall, swelling, inflammation, pain, joint laxity, and damage to articular receptors contribute to alterations in afferent discharge to the central nervous system, which causes AMI.

Spinal Reflex Pathways

Abnormal afferent discharge from a damaged knee joint alters the excitability of reflexive pathways within the spinal cord.[133,136,137] As a result, excitability of the quadriceps alpha motoneuron pool is reduced, which prevents full activation of the corresponding muscle.[133,136,137] Essentially, there are four main spinal pathways that may contribute to AMI: Ib inhibitory pathway, the flexion reflex, gamma loop inhibition, and pre-synaptic inhibition of the Ia afferent.

Firstly, Ib inhibitory interneurons located within the spinal cord receive input from Ib afferent fibers and other joint afferents.[138] Alterations in afferent discharge described above facilitate the Ib inhibitory pathway, thus contributing to AMI by inhibiting the agonist muscle.[137] For example, artificial knee joint effusion has been shown to increase Ib inhibition of the quadriceps H-reflex during voluntary muscle contractions.[137]

The flexion reflex is a polysynaptic pathway that produces a pattern of flexor facilitation and extensor inhibition.[139,140] Therefore, any facilitation of the flexion reflex would contribute to knee extensor (quadriceps) AMI. The flexion reflex is mediated by a variety of different interneurons that receive input from many peripheral afferents, such as the articular receptors.[141] In response to joint inflammation, the activation threshold of afferent neurons associated with the flexion reflex is lowered and these neurons become hyperexcitable.[142] In addition, lower flexion reflex thresholds are found in patients with knee pathology – such as those with knee osteoarthritis and ACL injury – compared to healthy controls.[143-145] Furthermore, activation of the flexion reflex also produces inhibition of the quadriceps during maximal isometric contractions of the knee extensors. In summary, any activation or facilitation of the flexion reflex likely contributes to AMI of the quadriceps.

The gamma loop may also mediate quadriceps activation. Gamma motoneurons innervate muscle spindles that in turn transmit excitatory input to the alpha motoneuron pool of the homonymous muscle.[1] Therefore, it is necessary that the gamma loop functions normally to achieve full activation of a muscle, and any interruption in the gamma loop may contribute to AMI.[136] Patients with ACL injury have deficits in the transmission of Ia sensory input, partially explained by gamma loop inhibition.[146-148] These patients have a disruption of excitatory output to the gamma motoneuron pool thus decreasing gamma motoneuron discharge.[136] Ultimately,

this leads to a reduction in Ia afferent facilitation of the quadriceps alpha motoneuron pool, thus reducing overall quadriceps activation. Pre-synaptic inhibition may also influence excitability of the alpha motoneuron pool and thus contribute to AMI.[26] Pre-synaptic inhibition excites inhibitory interneurons that project to the synaptic terminal of the Ia afferent fibers. Excitation of an inhibitory interneuron causes a reduction in the quantity of neurotransmitter released following an afferent volley. In addition, this form of inhibition contributes to further gamma loop inhibition, which leads to AMI.

Supraspinal Centers

Joint afferents have projections to both spinal and supraspinal areas.[149,150] Supraspinal centers are influenced by joint afferent activity and contribute to AMI. Transcranial magnetic stimulation (TMS) of the motor cortex provides a method to quantify changes in corticospinal excitability associated with knee pathology.[66,151] Interestingly, some studies have found that corticospinal excitability measured via TMS (amplitude of motor evoked potential) is greater in individuals with knee pathology compared to healthy control subjects.[151] This seems counterintuitive since patients with knee pathologies would be expected to have lesser corticospinal excitability, and there is only limited evidence available suggesting lesser corticospinal excitability among patients with knee pathologies. However, authors suggest that greater corticospinal excitability following injury may be indicative of a compensatory response in an attempt to overcome inhibition of the quadriceps alpha motoneuron pool. Heroux et al. [66] found lesser resting motor thresholds in patients with unilateral ACL injury compared to healthy controls, suggesting enhanced excitability of musculature surrounding the injured joint. Secondly, the brainstem has inhibitory control over spinal neurons involved in pain perception

and the flexion reflex. Injury to the knee joint enhances descending input from the brainstem, which increases excitability of the flexion reflex and increase AMI. Last, studies show that changes in quadriceps activation rely on motivation. Any reduction in quadriceps strength or activation may be due to an adjustment in voluntary effort in response to fear of pain or eliciting further damage to an injured joint.

POST TRAUMATIC OSTEOARTHRITIS FOLLOWING ACL INJURY

Quadriceps weakness resulting from AMI is common following ACL injury despite reconstruction and rehabilitation, and AMI is found in up to 78% of patients with ACL reconstruction and up to 100% in patients who are ACL deficient.[104] The quadriceps are essential to normal ambulation. In healthy individuals, the quadriceps act to attenuate shock during gait, and assist in evenly distributing load across the knee joint. However, deficits in quadriceps function from injury result in loads being transmitted in greater magnitude and at a faster rate to the lower limb.[20] Specifically, patients with ACL injury have alterations in lower extremity kinematics and kinetics that may elevate the risk of developing OA, and quadriceps dysfunction is thought to play a major role in the genesis of these biomechanical alterations (Figure 2).[2]

Osteoarthritis is a gradual breakdown of articular cartilage from repetitive joint loading. Moreover, articular cartilage is viscoelastic and is, therefore, sensitive to the rate at which it is

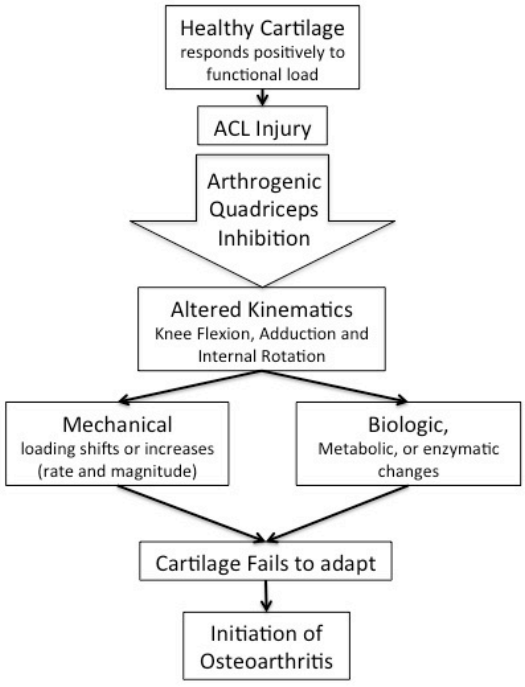

Figure 2: How gait mechanics can initiate osteoarthritis (adapted from Andriacchi and Mundermann[2])

loaded.[152] When articular cartilage is loaded at faster rates it stiffens, thus elevating its risk for failure and breakdown. Previous studies in animal models demonstrate that repetitive impulsive loading of the limbs results in rapid degeneration of articular cartilage, regardless of the magnitude of the load.[152] Impulsive loading refers to the relationship of a force applied over time and can be mathematically expressed as the product of force and velocity (displacement over time). Therefore, reducing the time interval over which ground reaction force is absorbed would elevate the impulse experienced in the lower extremity.

Articular cartilage adapts to habitual loading that occurs during walking.[153-155] Immobilization of the knee joint causes cartilage thinning, suggesting that functional loading is necessary to maintain cartilage health. Following acute loading of the limb, cartilage adjusts its metabolism, resulting in greater proteoglycan production and proliferation of chondrocytes – the functional unit of cartilage.[99] Ultimately, these alterations result in thicker cartilage and improved joint health. However, alterations in gait kinematics may shift the contact areas between bony surfaces that form joints to areas that are not typically loaded.[156] Therefore, areas of thickest cartilage that are conditioned to frequent load bearing are no longer in contact with each other. Areas of pressure are shifted, resulting in lesser joint space and the initiation of osteoarthritis.

Patients with ACL injury and knee osteoarthritis have lesser quadriceps strength resulting from AMI as discussed above. Deficits in quadriceps function influence gait biomechanics in the sagittal plane.[34,36,98,157] During weight acceptance, the limb must accept full support of the body, and attenuate shock by flexing the knees, which is largely controlled by eccentric action of the quadriceps. Patients who are ACL-deficient or ACL-reconstructed with weaker quadriceps display lesser knee flexion and smaller knee extensor moments during gait,[36,98] a condition that

has been labeled “quadriceps avoidance gait”. Lesser knee flexion excursion reduces the time interval over which ground reaction forces are absorbed, and therefore increase impulse at the knee joint. In brief, lesser quadriceps activation influences shock absorption during gait via lesser knee flexion, which elevates the impulsive load at the knee and likely increases the risk of osteoarthritis development.

While the quadriceps largely act to control loading at the knee joint in the sagittal plane, alterations in quadriceps function also influence frontal plane loading. The quadriceps have a small moment arm capable of contributing to adduction/abduction at the knee.[31] Quadriceps and hamstrings co-contraction provides most of the support for the knee adduction moment during gait.[31] The knee adduction moment is an indicator of osteoarthritis risk.[158] Tibiofemoral osteoarthritis most commonly affects the medial compartment of the knee joint. Excessive knee adduction places a greater load on the medial compartment, and increases the risk of joint degeneration.[102,158] Furthermore, greater knee adduction moment is associated with greater disease incidence, progression, and severity.[158-160] Importantly, patients with ACL injury have greater knee adduction moments compared to healthy individuals.[161] However, the relationship between quadriceps strength and adduction moment in patients with ACL injury is not clear. Nevertheless, improvement of quadriceps strength may contribute to lesser adduction moments and reduce the risk of further joint degeneration following knee injury.

Lastly, patients who are ACL deficient or ACL reconstructed commonly display an offset towards excessive internal tibial rotation.[156,162] The thickest areas of cartilage are loaded when the knee is at full extension at heel strike. Any shift in rotational alignment shifts the normal load bearing contact areas to regions that are not conditioned to high loads.[2] Therefore,

excessive internal rotation potentially loads thin areas of cartilage that are more likely to break down.

VIBRATION TRAINING

Rehabilitation programs in patients with knee pathologies are largely ineffective in restoring quadriceps function due to AMI.[38,39,163] Vibration therapy is a growing alternative modality for exercise due to reports of enhanced muscle strength, power, and electromyography.[164] Vibration also has positive effects on flexibility, bone and joint health, and many common measures of physical function.[53] However, despite several studies that report improvements in markers of physical health, there are studies that report detrimental or equivocal results following vibration.[46,70] Nonetheless, vibration may provide a novel treatment that could be used in conjunction with traditional rehabilitation programs to reduce AMI.

Vibration employs sinusoidal mechanical oscillations with periodic alterations of force and acceleration over time. Vibration provides a forced oscillation, and energy is transmitted from an actuator (the source of vibration, i.e. – vibrating platform) to a resonator (i.e. the human body or muscle) to produce a neuromuscular response. Essentially, the human body is accelerated by vibration, which causes a reactive force within.[53] This force is proportional to acceleration, assuming a constant mass ($F = m \bullet a$). Muscles and tendons are capable of storing and releasing mechanical energy, and energy storage occurs when the frequency of the actuator matches the frequency of the resonator. In turn, the vibration amplitude of the resonator begins to exceed that of the actuator (amplitude amplification).[53] The resonator will experience a greater internal force, and is at risk for damage. Importantly, the human body attempts to dampen the vibratory signal to avoid injury by altering stiffness or introducing a frictional element. For

example, posture can adjust the axial stiffness of the body to reduce the transmission of the vibratory stimulus as it travels from its source throughout the body. For example, standing in an erect posture compared to a squatting evokes a stronger transmission of vibration to the head during WBV. Likewise, shifting body weight to the forefoot rather than the mid or rear foot reduces vibration transmission. Attenuation of the signal increases as ankle, knee, and hip joint angle increases. Modulation of muscle activity is also relevant, and assuming a squat position will increase tension within the lower extremity musculature and increase signal transmission to these muscles.

There is also an internal response from muscle when vibration is applied to the body. Muscles go through a rapid series of eccentric (lengthening) and concentric (shortening) actions. Changes in muscle length trigger a neural reflex – the tonic vibratory reflex – due to stimulation of the muscle spindles.[51,52,165] The muscle spindles are a specialized group of muscle fibers arranged in parallel with the contractile fibers of skeletal muscle.[166] The functional unit of the muscle spindle is the intrafusal fiber, which is further categorized into three types: the nuclear chain fiber, the dynamic nuclear bag fiber, and the static nuclear bag fiber.[167] Intrafusal fibers lie within connective tissue that forms the shape of a spindle. Each muscle spindle is composed of up to 10 intrafusal fibers that lie between extrafusal fibers responsible for muscle contraction.[167] These intrafusal fibers are affixed by the extrafusal fibers by the perimysium.[166] Therefore, any increase in muscle length also causes a change in length of the muscle spindles. The muscle spindle receives innervation from two sensory neurons: the type Ia afferent, and the type II afferent. Both the type Ia afferent and type II afferent are activated when the muscle spindle changes length. However, the type Ia afferent is sensitive to the rate of change in length, whereas the type II afferent is sensitive to the static length of a muscle.[166] Excitation of the

muscle spindles following rapid increases in length from vibration will increase excitatory input to the alpha motoneuron pool. This causes a reflexive contraction in the homonymous muscle, which may facilitate increases in muscle function (strength, power, EMG etc.).

However, the tonic vibratory reflex only accounts for heightened muscle function during vibration, and there are studies that report enhancements of muscle function following vibration that persist for several minutes.[54,55] Some authors suggest adaptations such as elevated muscle temperature and blood flow akin to traditional warm-up activities, increased gravitation force placed on a muscle producing a training effect, and enhanced corticospinal excitability and intracortical processes.[69,168,169] Overall, it is unclear why muscle function improves following vibration, and additional research is necessary to evaluate other mechanisms that may be responsible for improvements in muscle function following vibration, such as changes in corticospinal excitability and intracortical processes.

As described above, vibration largely activates the Ia afferents of the muscle spindle system to produce a reflexive contraction. However, the spinal circuitry is the first stage within the motor feedback loop for generating fast efferent reactions to proprioceptive input. Moreover, supraspinal areas also receive and process proprioceptive information and generate evoked cortical potentials following vibration.[61] Afferent input from muscles is a requirement for proper neuromuscular control, and muscle afferent facilitation accounts for a large proportion of central motor drive. Prior studies have shown that altered Ia afferent input influences the excitability of corticospinal pathways and activation of cortical motor areas.[62] Vibration applied directly to a muscle or tendon facilitates Ia afferent firing rate. Therefore, changes in spinal reflexes and corticospinal processes following vibration seem reasonable as explanations for improvements in neuromuscular function.

Effects on Spinal and Supraspinal pathways

To my knowledge, there are only three studies that have evaluated the effects of vibration on the excitability of corticospinal pathways using TMS. Mileva et al. ,[64] Kossev et al.,[170] and Siggelkow et al. [65] found that vibration heightens the activity of the brain in healthy individuals during vibration, suggesting enhanced corticospinal excitability. Specifically, motor evoked potential (MEP) amplitude [64,65,170] and latency [65] measured using single-pulse suprathreshold transcranial magnetic stimulation were augmented and shortened, respectively. Additionally, increases in corticospinal excitability were found during LMV [65,170] and WBV.[64] For example, Mileva et al.[64] found that tibialis anterior MEP amplitude was augmented during WBV at 30Hz and amplitude of 1.5mm, and Siggelkow et al.[65] found that MEP amplitudes were increased in the extensor carpi radialis during 80Hz and 120Hz, 0.5mm peak-to-peak amplitude LMV. These findings suggest that adaptations following vibration are not restricted to the periphery, but also involve corticospinal processes. Moreover, these results suggest that vibration may improve corticospinal excitability. However, these studies used very small samples (n=7, n=10) thus warranting more comprehensive evaluations. Furthermore these studies largely evaluated MEP amplitude during the vibratory stimulus. Siggelkow et al.[65] measured MEP 1 second after the offset of LMV, and Mileva et al.[64] measured MEP characteristics for up to 110 seconds post WBV. Therefore, what also remains unclear is if the effect of vibration on corticospinal excitability persists following cessation of the stimulus. A fourth study by Pollock et al.[171] also found indirect evidence of enhanced corticospinal excitability during 1 minute bouts of 30Hz, 3mm peak to peak amplitude WBV by measuring the recruitment threshold of single motor units in the vastus lateralis. Specifically, the recruitment threshold of high threshold motor units was reduced following WBV, suggesting a lower active motor threshold. However, this study only

used 7 healthy subjects and testing was completed and no testing was completed to determine if the change in recruitment threshold persisted following WBV.

Alpha motoneuron excitability within the spinal cord can also influence muscle function. However, there is inconsistent evidence regarding the effect of vibration on spinal reflexes. Some studies have found a suppression of the Hoffman (H) reflex following prolonged LMV and WBV, [57,58,172,173] whereas others have observed facilitated reflexes after WBV.[169,174] The duration of the vibratory stimulus can greatly influence the outcome. Following prolonged vibration (15-30 minutes), it is possible that the muscle becomes fatigued due to neurotransmitter depletion from rapid muscle contractions. Furthermore, prolonged vibration (several minutes to one hour) can temporarily dampen the transmission in Ia afferent fibers by increasing presynaptic inhibition, raising the activation threshold of Ia fibers.[115,175,176] Therefore, the duration of the stimulus is a crucial moderator of the relationship between vibration and muscle function. Ritwegger [53] suggests that WBV differentially influences reflex responses (H-reflex vs. spinal stretch reflex). This is an important consideration because the H-reflex does not naturally occur in human movement despite being an electrically evoked analog of the stretch reflex. Additionally, Arcangel et al.[177] proposed that the time interval between WBV exposure and reflex measurement may influence the outcome. Lastly, muscle spindles are less responsive after vibration termination,[177] lending further support that any enhancement following vibration may be due to elevated cortical activity. Importantly, all studies evaluating the efficacy of vibration on neuromuscular function have used heterogeneous stimulus parameters, which diminish our ability to draw meaningful conclusions regarding the influence of vibration on neuromuscular function.

Effects on Muscle Function

Surface electromyography (EMG) provides an easy method to measure activation of a muscle, and can be altered during and following vibration. Authors suggest that vibration causes a change in motor unit discharge, which is observable via EMG. However, there is discrepancy in the literature regarding the efficacy of vibration on EMG. For example, some studies report elevated EMG amplitude following vibration [55,68,178-181] However, others report reductions or equivocal findings in EMG following vibration.[46,70] Ambiguous findings in the current literature could be the result of heterogeneous stimulation parameters. Muscle activity and function in the lower extremity may be modified as a response to changes in the frequency of stimulation. Greater damping of the vibration stimulus occurs when the stimulus frequency is close to the natural frequency of soft tissue. Therefore, a muscle's electrical and mechanical responses to vibration could be related to the frequency of stimulation. For instance, Cardinale and Lim observed greater EMG amplitudes in the quadriceps during 30Hz WBV compared to 40Hz and 50Hz.[178] Likewise, we previously demonstrated that LMV also acutely increases EMG of the quadriceps by 5-10% in healthy control subjects, and is most effective at 30Hz compared to 60Hz.[55] Importantly, these effects were evident for several minutes following vibration treatment, which greatly enhances the utility of vibration as a treatment modality. These same stimulating parameters and protocol will be utilized in this study.

There are studies that report improvements in muscle strength and power following vibration, suggesting that vibration may be useful as a rehabilitative and performance enhancing tool. For example, Bosco et al.[42] reported increased leg power of 6-8% in volleyball players following vibration, and increased elbow flexion power in boxers following vibration. Other studies report similar findings [182,183] and suggest that enhanced neuromuscular facilitation is

responsible for muscle power improvements. Similarly, there are studies that report increases in functional tasks such as vertical jump height [54,184] and one repetition maximum.[56,185] However, some studies report equivocal findings on one repetition maximum [55,73,186] and rate of torque development,[55] and detrimental effects on muscle strength.[70,187,188] For example, De Ruiter et al.[70] found that knee extensor strength was reduced by 7% following an acute bout of 5 by 1 minute exposures to WBV. However, this study used a vibration frequency of 30Hz and 8mm peak-to-peak amplitude, whereas Tihanyi et al.[56] used the same frequency but smaller amplitude (2mm peak-to-peak), and found acute increases in peak knee extensor strength following WBV. Decreases in muscle strength may be a result of overstimulation of a muscle, which depletes the availability of excitatory neurotransmitters necessary for maximal muscle contraction. Cochrane et al. [168] suggests that the improvement in muscle power is from a warm-up effect and elevated muscle temperature following vibration. This study compared the effects of warm-up modality (stationary cycling for 10 minutes at 70W, hot water bath emersion, WBV – 26Hz, 6mm peak-to-peak amplitude for 6 minutes) on muscle power and counter movement jump performance and found similar gains across warm-up modalities. There is also evidence that vibration stimuli cause post-synaptic potentiation,[68] which may be responsible for observed improvements in muscle strength and power. However, no study has examined concurrent changes in muscle function and corticospinal excitability following vibration, and altered spinal and supraspinal function may be responsible for the ascribed gains or losses in muscle strength.

Whole Body Vibration vs. Local Muscle Vibration

Much of the current literature has evaluated the effects of WBV on muscle function. However, commercially available WBV platforms are cost prohibitive (~$12,000) and provide limited portability. LMV also improves muscle function [43,55,75,189] and may provide a cost

effective (~$200) and portable alternative to WBV platforms. For example, Iodice et al.[190] showed that leg extension muscle strength and counter movement jump performance were increased following acute and chronic exposure to focused local vibration. Additionally, Pamukoff et al.[55] found that EMG of the quadriceps was elevated following acute exposure to 30Hz local vibration. There are studies that show equivocal results following LMV.[45,46] However, it is difficult to gain an overall interpretation of results due to differential stimulating parameters. For instance, Moran et al.[46] and Luo et al.[45] used a frequency of 65Hz with an amplitude of 1.2mm, whereas Pamukoff et al.[55] used a frequency of 30Hz and acceleration of 2 *g,* and Iodice et al.[190] used a frequency of 300Hz and amplitude of 2mm. Additionally, Moran et al.[46] studied the biceps brachii and found no significant results. Therefore, optimal treatment parameters (frequency, amplitude, duration) are unclear, and may vary by delivery method and muscle of interest. While WBV and LMV provide similar stimuli, the efficacy of adaptation may be different due to differential damping characteristics.

During WBV, the vibratory stimulus is damped by the musculature surrounding the ankle and knee joints, which reduces the magnitude of the vibration stimulus delivered to the quadriceps and, therefore, its neuromuscular response.[68] This reduction in energy from the vibration signal may be minimized if the stimulus is delivered directly to the muscle via LMV rather than WBV. However, only one study [75] has compared the effects of WBV and LMV on muscle function. Albeit limited evidence, this study suggests that WBV and LMV have equivalent effects on voluntary quadriceps activation and peak torque in a group of healthy control subjects with artificial knee effusion. However, no study has compared the effects of WBV and LMV on EMG, spinal reflexes, and cortical excitability.

MEASUREMENT TOOLS AND METHODOLOGICAL CONSIDERATIONS

Electromyography

A motor unit is comprised of an alpha motoneuron and all of the muscle fibers that it innervates. To produce force, muscle fibers must receive an impulse from their alpha motoneuron. Once a motoneuron is activated by spinal or supraspinal inputs, an electrical impulse propagates down to the motoneuron to each motor endplate. At this point, a muscle fiber's membrane permeability to sodium increases and sodium begins to rapidly enter the cell. Eventually, action potential will be generated at the point where threshold is exceeded due to a shift in membrane polarity from sodium ion transport. EMG refers to the experimental technique concerned with the development, recording, and analysis of myoelectric signals that are formed by the physiologic variations in the state of muscle fiber membranes.[191] Furthermore, surface EMG provides an easy way to estimate overall motor unit activation.

The nervous system can modulate muscle force via two mechanisms: motor unit recruitment and frequency of motor unit action potentials/rate coding. In other words, an individual can create more force by recruiting more motor units, or recruiting motor units at a higher frequency. At any point in time, the EMG signal is a composite electrical sum of all of the active motor units. The EMG signal is observed by placing an electrode directly over a superficial muscle, and a second electrode over an electrically neutral site. A differential amplifier detects the difference between the two recording electrodes, and attenuates any signal common to both sites. Surface EMG must be interpreted with caution, and it can be influenced by several confounding factors. Firstly, it is very important that the site of recording is carefully prepared to reduce signal impedance by removing dead skin cells and skin oils. Affixing electrodes and their wires firmly to the skin can minimize motion artifact. Careful electrode

placement is extremely important. Electrodes must be placed in areas from which action potentials from the underlying muscle fibers can be recorded. Therefore, they should be placed away from highly tendinous areas and motor end points, and the orientation of the electrode must be parallel to muscle fibers. The EMG signal can also be influenced by blood flow, muscle length, muscle depth, and crosstalk from adjacent synergist or antagonist muscles.

I have previously demonstrated that exposure to LMV applied to the patellar tendon causes acute increases in EMG amplitude of the quadriceps during maximal voluntary isometric contractions.[55] However, no study has compared the effects of WBV, and LMV on quadriceps EMG. Furthermore, it is unclear how long the effect lasts. My previous data showed significant increases in EMG amplitude five minutes following treatment ($p<0.01$), and that seven additional subjects were needed to observe a significant increase up to thirty minutes following treatment.

Hoffman's Reflex

The Hoffman (H) Reflex is analogous to the spinal stretch reflex, but evoked electrically rather than mechanically.[192] The spinal stretch reflex is initiated by an action potential generated by the muscle spindle in response to acute muscle stretch, whereas the H-reflex is initiated through external electrical stimulation of a nerve supplying the agonist muscle.[193] With regard to the quadriceps, electrical stimulation is given to the femoral nerve in the femoral triangle. The stimulus provided will bypass the muscle spindle and directly excite the Ia afferent neuron, causing an action potential in the homonymous alpha motoneurons that triggers a muscle contraction.[193] Therefore, the H-reflex measures the efficacy of synaptic transmission as the electrical stimulus travels in afferent fibers to the motoneuron pool of the corresponding muscle and to the efferent fibers.[194] Essentially, the H-reflex provides an estimate of the excitatory state

of the alpha motoneurons located in the spinal cord when presynaptic inhibition and intrinsic excitability are held constant.[194,195]

The H-reflex in the quadriceps can be measured using surface EMG on the vastus medialis. The electrical stimulus of the femoral nerve results in clear deflections of the EMG signal. The first deflection represents the stimulus itself (i.e. the stimulus artifact). The second fluctuation is the M-wave, which occurs ~5 milliseconds following the electrical stimulus. The M-wave results from direct stimulation of motoneuron axons in the nerve being stimulated and a subsequent action potential. Lastly, the H-reflex in the quadriceps appears approximately 15 milliseconds following electrical stimulation. The order of the M and H waves are determined by the order of neural fiber recruitment and distribution of alpha motoneurons. For example, fibers with larger diameters have less resistance to stimulation compared to smaller fibers, and can thus be stimulated at lower intensities.[196] Additionally, Ia afferent fibers have larger cross sectional areas than efferent alpha motoneurons, and respond to lower stimulating intensities. At very large stimulating intensities, both the afferent and efferent fibers are excited, which results in the M-wave because the alpha motoneurons have been directly stimulated.[192] However, the H-reflex is controlled by monosynaptic pathways, and thus the M-wave will always occur before the H-reflex even when efferents and afferents are stimulated together. When the stimulating intensity is small, initial recruitment only involves the largest alpha motoneurons and a small M-wave is produced. As the stimulus increases, smaller fibers are progressively recruited due to their higher activation thresholds, and an increase is seen in M-wave amplitude.[192]

Conversely, the H-reflex can be observed at fairly low intensities in the absence of an M-wave.[193] Low intensity stimuli depolarize Ia afferent fibers, resulting in an action potential in the alpha motoneurons and muscle contraction. Essentially, small alpha motoneurons are excited by

synapses with Ia afferents and are not directly stimulated. The recruitment curves of the M-wave and H-reflex differ which make them distinguishable. The M-wave is S-shaped, and the H-reflex is U-shaped. The stimulus intensity threshold needed to stimulate the Ia afferent, the maximal H-reflex amplitude, and its decline with increasing intensity determine the shape of the H-reflex. The decline observed in the H-reflex corresponds with an increase in the amplitude of the M-wave. When the M-wave is maximal, the H-reflex is depressed and not observable. The H-reflex will increase as stimulus intensity gradually increases until a maximal amplitude at which the M-wave is initially produced. The reduction in H-reflex amplitude can be explained by antidromic collision.[197] At this stimulus intensity, both the Ia afferent and the alpha motoneurons are stimulated. However, the Ia afferent projects its afferent signal onto the alpha motoneuron, and the efferent signal is sent to the muscle by the alpha motoneurons. The efferent signal is met by the stimulus from the alpha motoneurons resulting in a depression of the H-reflex, and propagation of the M-wave. Essentially, antidromic activity refers to a volley of electrical activity traveling in the incorrect direction in motor axons. The antidromic volley travels backward up the motor axon toward the spinal cord and it will collide with the reflexive volley, which is traveling in the correct direction from the sensory axon. If both volleys are of similar size, then collision results in neither continuing along their respective pathways. However, if one is larger than the other, then it will be diminished but continue along its path. For example, if the antidromic volley is smaller than the afferent volley, then the afferent volley will be decreased but continue to the muscle. Therefore, the H-reflex tracing in the recruitment curve begins to decrease after it reaches plateau and stimulus intensity is increased. When the antidromic volley exceeds the afferent volley, no signal reaches the muscle and the H-reflex disappears from the tracing, and all that is observed is the M-wave.

There are several factors that may confound or influence the H-reflex. Firstly, the testing position while eliciting the H-reflex will influence the amplitude. Specifically, any change in joint position that influences muscle length will affect the amplitude of the H-reflex. For instance, the H-reflex amplitude is larger when muscles are tested in shorter positions. At longer lengths, greater background EMG activity is observed due to autogenic inhibition of the agonist.[198] Secondly, background EMG activity in a muscle will influence H-reflex amplitude. The H-reflex increases if the background EMG of the agonist increases. Therefore, muscle contraction, which increases EMG, would increase H-reflex amplitude.[199-201] Likewise, similar H-reflex amplitudes can be elicited using smaller stimulus intensities if there is greater agonist background EMG. However, the opposite is observed if there is excessive antagonist background EMG.[200,202] Overall, baseline activity of a muscle should be kept minimal, and subject position should remain consistent to allow a clear interpretation of spinal reflex excitability.

There are limitations and assumptions of the H-reflex that must be considered when interpreting findings. Firstly, the H-reflex does not occur naturally in human movement since it's an electrically induced response. Although it is considered the analog of the mechanically-evoked spinal stretch reflex, it ignores the contribution of the muscle spindle system, which modulates reflex output during human movements.[203] Secondly, the H-reflex precludes the influence of presynaptic inhibition. Presynaptic inhibition influences neurotransmitter release at the synapse of the Ia afferent and the alpha motoneuron. Therefore, the H-reflex can be modified independently of changes in motoneuron membrane potential. Importantly, alterations in presynaptic inhibition occur following joint effusion,[26] thus the H-reflex may not adequately describe neuromuscular function following ACL injury. Interestingly, there is some limited

evidence to suggest that direct tendon vibration suppresses the H-reflex. This could be due to disfacilitation and autogenic inhibition causing withdrawal of Ia afferent activation, and increased selectivity of Ib afferent fiber stimulation [204].

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) provides a non-invasive and safe way to assess human motor control. TMS was developed nearly 30 years ago by Barker et al.[205] who showed that the corticospinal tract could be activated by a short lasting magnetic stimulus applied over the scalp of a human subject. Corticospinal activation is demonstrated as a contraction of muscles on the contralateral side of the body by measuring the latency and amplitude of the evoked potential using surface electromyography (EMG).[206] This EMG response is referred to as a motor-evoked potential (MEP). Characteristics of MEPs can be used to quantify corticospinal excitability and intracortical inhibition and facilitation.[206]

Within the motor cortex, the TMS stimulus produces epidural waves, which are the summative effect of excitatory and inhibitory neurons in each layer. If the stimulus is great enough and the net effect is excitatory, the signal will be sent down the corticospinal tract and an MEP will be generated.[206] Essentially, passing an electric current through a wire coil generates a magnetic field, which is placed over the scalp. The magnetic pulse created will induce a current in an electrically conductive region, like the motor cortex. This current will flow perpendicular to the magnetic field at an intensity proportional to the magnetic field (measured in a percentage of Tesla). The skull provides low impedance to magnetic fields, thus currents are produced in the brain and these currents can stimulate neural tissue. When magnetic stimulation is provided to the motor cortex, the stimulus travels down the corticospinal pathway to stimulate the alpha motoneurons within the spinal cord, and electromyographic responses can be recorded (MEPs) in

contralateral muscles. TMS stimulates motoneurons indirectly and directly.[207] Firstly, a direct (D) wave can also be created through direct stimulation of the axonal segment of the corticospinal neuron.[208] The D-wave represents direct activation of the upper motoneurons.[208] The D-wave is observed first and its short latency suggests that it originates from direct activation of corticospinal axons just below the gray matter of the brain.[208] Secondly, TMS produces descending volleys of the pyramidal neurons via presynaptic neurons that initially create an indirect (I) wave that stimulates the most superficial layers of the motor cortex, which propagates to the deep layers and eventually down to the spinal cord.[207] Each I-wave is generated from the depolarization of an axon synapsing directly onto a corticospinal neuron.[207] I-waves on their own are very small, but continue to grow in size and number with increasing stimulus intensity. Therefore, the propagation of I-waves can be considered dose-dependent.

Operationally, corticospinal excitability is commonly measured in two ways using single pulse TMS: the motor threshold (MT) and MEP amplitude.[206] Firstly, MT reflects the minimum amount of magnetic energy needed to excite neural tissue and cause a measurable MEP. This measure represents the excitability of motor neurons in the motor cortex, spinal cord, neuromuscular junction, and muscle. Therefore, additional measures such as H-reflex must be measured concurrently to assist in distinguishing the location of corticospinal deficits. In addition, the motor threshold represents activity of neural input to the pyramidal cells that influence membrane excitability. A higher MT reflects a greater need for magnetic energy to elicit a response, and lower corticospinal excitability. Conversely, lower MT means that less magnetic energy is required to excite neural tissue reflecting higher corticospinal excitability. Secondly, the peak-to-peak amplitude and latency of the MEP using suprathreshold TMS can also be used as a measure of corticospinal excitability. MEP amplitude represents the

excitability and integrity of the corticospinal tract. TMS excites both inhibitory and excitatory pathways, and the MEP reflects the balance between these pathways. An MEP of larger amplitude reflects greater excitability and vice versa. MEP latency represents the time interval between the TMS stimulus and observable MEP. A shorter latency reflects greater excitability and vice versa. Interestingly, MEP amplitude [64,65,170] and latency [65] measured using single-pulse suprathreshold TMS can be augmented and shortened in the extensor carpi radialis following brief LMV [65,170] and WBV.[64] These findings suggest that the effects of vibration are not restricted to the periphery, but also involve corticospinal processes.

MT and MEP amplitude are commonly assessed using single pulse TMS. However, paired pulse TMS can also be used to assess intracortical inhibitory and facilitatory processes. During paired-pulse testing, the two pulses termed the conditioning stimulus (CS) and testing stimulus (TS) are delivered separated by a specified stimulus interval. The conditioning stimulus is subthreshold when measuring intracortical inhibitory processes, and suprathreshold when measuring intracortical facilitatory processes. The testing stimulus occurs several milliseconds following the CS. The length of the interstimulus interval (ISI) between the CS and TS determines whether the effect of TMS is excitatory or inhibitory.

Cortical inhibition refers to the attenuation of cortical output from gamma-Aminobutyric acidreceptor (GABA) interneurons.[209] GABA is an inhibitory neurotransmitter and influences interneurons that can be divided into two types: $GABA_A$ and $GABA_B$. The $GABA_A$ interneurons contain ligand-gated channel receptors and are responsible for fast acting inhibition (short interval intracortical inhibition – SICI),[209] whereas the $GABA_B$ interneurons contain G-protein coupled receptors and are responsible for slow acting inhibition (long interval intracortical inhibition – LICI).[210] ISIs that are very short (1-5ms), or very long (50-200ms) correspond with

inhibitory post-synaptic potentials mediated by $GABA_A$ and $GABA_{B,}$ respectively. As stated above, the CS to measure SICI and LICI is subthreshold (60-80% of MT). The immediate effect of the CS is synchronous activation of a small number of cortical pre-synaptic fibers. The mild depolarization causes excitation of inhibitory neurons. However, because the CS is below MT, yet still suppresses the MEP following the TS, it is thought that inhibitory interactions occurred at the cortical level and the CS suppressed further recruitment of descending volleys by the testing stimulus. The TS is always suprathreshold. A suprathreshold stimulus determines corticospinal output leading to an MEP, but a subthreshold stimulus will only excite local cortical neruons. Therefore, a subthreshold CS and suprathreshold TS combined can assess the effects of interneurons on cortical output. The overall result is a reduced MEP amplitude.

Intracortical facilitation (ICF) occurs following a CS that is suprathreshold (110-120% MT) and an ISI lasting 7-20ms.[208] These ISI's correspond with intervals between the first indirect wave and the following I wave.[208] Since the peaks of the I-waves are in phase, the input from the TS comes during epochs, which increases the firing probability (facilitation). Essentially, the peak of the second I-wave from the CS is in phase with the peak of the I-wave from the TS. The effect of a facilitatory CS is synchronous activation of a large number of cortical fibers. The CS may raise the excitability of spinal neurons that are more readily discharged, resulting in an increased MEP amplitude.

There are several limitations that must be addressed with regard to using MEPs as a measure of cortical excitability. First, the amplitude of the MEP is influenced by the excitability of the corticospinal cells stimulated by TMS, but also by the spinal motoneurons to which they project.[206] Therefore, it is important to distinguish the contribution of spinal motoneurons by evaluating voluntary EMG activity and the H-reflex. The H-reflex is evoked using electrical

stimulation of a peripheral group of Ia afferents and recorded in the EMG from the muscle innervated by the stimulated nerve. H-reflex is largely monosynaptic and is considered to represent the excitability of the spinal motoneurons and transmission over the group Ia synapses on the motoneurons. However, comparison of MEPs to the H-reflex should be performed with caution, as the H-reflex is not exclusively monosynaptic and may be influenced by changes in spinal interneuronal pathway excitability. Furthermore, changes in neurotransmitter release at the terminals of the Ia afferents (i.e. presynaptic inhibition) influence the H-reflex. The size of the MEP is influenced by changes in the transmitter release from the synapses of the corticospinal cells on the spinal motoneurons.

SUMMARY

Quadriceps dysfunction is ubiquitous following ACL injury. Despite reconstruction procedures and rehabilitation programs, quadriceps dysfunction persists for many years following injury and treatment due to arthrogenic muscle inhibition (AMI). AMI is a result of altered afferent input, and deficits in corticospinal excitability. These deficits likely contribute to the development of posttraumatic knee osteoarthritis via alterations in joint loading during gait. Novel treatments are needed to address AMI, and vibration therapy could be an adjunct treatment tool to reduce AMI and improve quadriceps function. However, it is unclear how vibration improves muscle function. There is limited evidence available to determine if vibration enhances corticospinal excitability. Lastly, most research has shown that WBV improves muscle function, but there is also some evidence suggesting that LMV enhances muscle function, which may be a cost-effective substitute. Therefore, the purpose of this study is to evaluate and compare the effects of WBV and LMV on measures of neuromuscular function (electromyography, H-reflex, corticospinal excitability).

CHAPTER III: EXPERIMENTAL DESIGN AND METHODS

Subjects

Aims 1-3

Sixty healthy individuals (30 males and 30 females) between the ages of 18 and 30 years will be recruited without history of musculoskeletal injury within 6 months prior to testing, lower extremity surgery, neurological disorder, cardiovascular disease, hypertension, diabetes mellitus, concussion or head injury, stroke, epilepsy, peripheral neuropathy, migraine headaches, cranial neural surgery, cancer in the brain or thigh musculature, cardiac pacemaker, implanted foreign metal object, or diagnosed psychiatric disorder. Subjects will also be recreationally active, defined as participation in physical activity for 30 minutes at least 3 times per week. Subjects will be recruited from the student and employee populations at the University of North Carolina at Chapel Hill and from the surrounding area. Each subject will be required to read and sign an informed consent form prior to data collection. Descriptive characteristics are listed in table xx.

Aim 4

Twenty subjects with a history of ACL injury will be recruited from patient referrals and the student population at the University of North Carolina at Chapel Hill. In addition to the above criteria, subjects will have a history of unilateral ACL injury and reconstruction via patellar tendon or hamstring autograft, no history of ACL graft rupture or revision, and no history or symptoms of osteoarthritis, and will be required to be at least 6 months post ACL

reconstruction and cleared by a physician to resume physical activity. Subjects will be excluded for history of musculoskeletal injury within 6 months prior to testing, lower extremity surgery, neurological disorder, cardiovascular disease, hypertension, diabetes mellitus, concussion or head injury, stroke, epilepsy, peripheral neuropathy, migraine headaches, cranial neural surgery, cancer in the brain or thigh musculature, cardiac pacemaker, implanted foreign metal object, or diagnosed psychiatric disorder. Each subject will be required to read and sign an informed consent form prior to data collection. Descriptive characteristics are listed in table xx.

Experimental Design

Aims 1-3

The investigation for aims 1-3 will utilize a randomized controlled trial design. Subjects will be randomized to 1 of 3 groups following pre-test assessments to receive either WBV, LMV or control treatment (n = 20 per group). All subjects will complete 3 testing visits to the Neuromuscular Research Laboratory at the University of North Carolina at Chapel Hill (1 visit for each of corticospinal excitability, H-reflex, and EMG during maximal contraction) in a block randomized order separated by 1-week washout periods, each lasting approximately 1 hour. In each respective session, subjects will complete a baseline test, receive an intervention, and complete follow-up testing immediately, 10 minutes, and 20 minutes following the intervention.

The primary hypotheses are that corticospinal excitability (Active Motor Threshold (AMT) and Motor Evoked Potential (MEP) amplitude) will increase (reduction in AMT, and increase in MEP amplitude) following whole body vibration (WBV) and local muscle vibration (LMV), but not increase following the control intervention. Furthermore, I hypothesize that the magnitude of increase will be similar between WBV and LMV treatment groups and that the effects of WBV and LMV will persist for up to 10 minutes following treatment. I also

hypothesize that spinal neuron excitability (H-reflex amplitude) will be depressed following WBV and LMV compared to the control group, and that this effect will persist for up to 10 minutes. Lastly, I hypothesize that EMG amplitude of the quadriceps muscles during maximal voluntary knee extension will increase similarly following WBV and LMV compared to a control group, and that these effects will persist for up to 10 minutes following treatment.

Aim 4

The investigation for Aim 4 will utilize a crossover design. Subjects will complete 3 testing sessions in which they will receive one of three treatments (WBV, LMV or control) in each session in a block-randomized order to reduce the change of an order effect. Subjects will complete baseline tests of corticospinal excitability, spinal neuron excitability, and EMG amplitude during a maximal contraction followed by an intervention (WBV, LMV, or control), and corresponding follow up tests immediately following each intervention. I hypothesize that corticospinal excitability will increase (i.e. reduction in AMT, and increase in MEP amplitude), that spinal neuron excitability will decrease (i.e. reduced H-reflex amplitude), and that EMG amplitude during a maximal contraction will increase following the WBV and LMV treatments, but not the control treatment. I also hypothesize that there will not be a difference in improvement between the WBV and LMV treatments.

Assessments

EMG and Maximal Activation

Subjects will first undergo a brief 5-minute aerobic warm-up on a stationary cycle ergometer followed by baseline tests of isometric knee extensor strength using a dynamometer (Humac Norm, Stoughton MA). This test will be performed on the dominant limb in healthy subjects, defined as the limb that would be used to kick a ball, and in the ACLR limb in ACLR

subjects. The thighs, hips and upper body will be firmly stabilized with straps (Figure 3, Right). The lever arm will be adjusted so that the ankle strap is placed 2 finger widths above the medial malleolus. The knee will be positioned so that the lateral femoral epicondyle is aligned with the rotational axis of the dynamometer. The knee will be flexed at 60° and 2 repetitions of 5 seconds will be completed. The mean RMS of the EMG signal over the 5-second MVIC of the trial resulting in the highest recorded torque will be used for data analysis. Sixty seconds rest will be given between torque measurements. Subjects will be instructed to "kick as hard and as fast as they can" and will receive verbal encouragement for each trial.

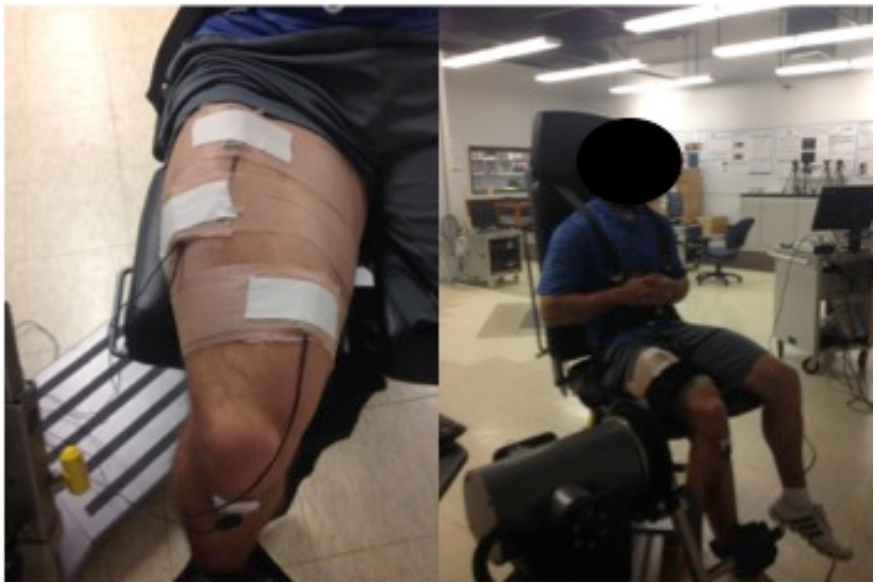

Figure 3: Left - Electrode placement, Right - Testing Position

Sites for EMG electrodes will be shaved if necessary and the skin will be lightly abraded and cleaned with alcohol to improve signal quality. Preamplified electrodes (Biopac systems) will be placed on the vastus lateralis (VL), vastus medialis (VM) and rectus femoris (RF) according to the SENIAM guidelines (VL – one third the distance along a line from the superior lateral side of the patella to the anterior superior iliac spine, RF – half the distance from the ASIS to the center of the patella, VM – 80% on the line between the ASIS and the joint space in front of the anterior border of the medial ligament) to record EMG activity during each contraction (Figure 3 Left). A reference electrode will be placed on the flat surface of the proximal anteromedial tibia. All electrodes

will be secured with prewrap and athletic tape. All data will be sampled at 2 KHz using the Biopac data acquisition system (MP150WSW, Biopac Systems Inc., Santa Barbara, CA).

Voluntary activation will be assessed using CAR during the MVICs. A brief non-painful electrical stimulus (2-pulse train, 600μs duration, 100Hz, 150V) will be manually delivered via two adhesive electrodes placed on the proximal and distal quadriceps once an individual reaches MVIC using an isolated stimulator (Grass Telefactor model SK84). Hamstrings EMG will also be recorded from the biceps femoris and medial hamstrings to verify our interpretation of quadriceps CAR. Subjects in the healthy cohort will complete this test prior to the intervention, immediately, 10 minutes, and 20 minutes following the intervention, whereas subjects in the injured cohort will only complete testing pre and immediately post intervention.

Hoffman Reflex

Hoffmann (H) reflex and M-wave measurements of the vastus medialis will be collected with surface electromyography (EMG). Reflexes will be elicited with the BIOPAC stimulator module (STIM100A, BIOPAC Systems, Inc.), a 200 V maximum stimulus isolation adaptor (STIMSOC BIOPAC Systems, Inc), a 2 mm shield disk electrode, (EL254S BIOPAC Systems, Inc.) and a 7 cm carbon impregnated dispersive pad. Subjects will lie supine on a padded table with their arms placed comfortably at their sides, their heads resting on a pillow, and their knees slightly flexed (~10-15º) with a bolster. A stimulating bar electrode (EL351, BIOPAC Systems Inc) will be positioned over the femoral nerve. A 1ms square wave stimulus will be delivered to the femoral nerve with a STMISOLA Constant Current and Constant Voltage Isolated Linear Stimulator (STMISOLA, BIOPAC Systems, Inc). The electrical stimulus will be delivered to the femoral nerve and increased in 0.2 volt increments until a maximum H- reflex is elicited, and then 3 maximal H-reflexes will be collected at that voltage. The stimulus will then be increased

until a maximal M-wave is elicited. All data will be sampled at 2 KHz. Subjects will complete this test prior to the intervention, and immediately, 10 minutes, and 20 minutes following the intervention. H-max and M-max will be re-established for the post-intervention assessments to account for potential local effects of the vibratory stimuli on EMG characteristics (e.g. a "warmup" effect). The ratio of maximal H-wave to maximal M-wave will be used for analysis.[57]

Corticospinal Excitability

Corticospinal excitability will be assessed via AMT and amplitudes of MEPs using transcranial magnetic stimulation (TMS). This method involves introducing a brief, non-painful magnetic stimulus that excites neurons in the motor cortex associated with a specific muscle, and subsequent nervous system pathways are activated causing a contraction of the targeted muscle. These small contractions, MEPs, are measured to determine function of the brain cells and corresponding neural pathways that dictate muscle activation. MEPs will be measured in the vastus medialis via EMG electrodes. Subjects will be seated in the dynamometer with their knee in 60° of knee flexion. Subjects will be asked to produce 5% of their maximal voluntary isometric contraction (MVIC) during active motor threshold/MEP testing to standardize the level of effort. A computer screen depicting real-time feedback of subject's torque output will be used to ensure this criterion is met. First, the area of the motor cortex will be mapped to identify that elicits the greatest MEP response on the VM. A lycra swim cap will be placed over the subject's head, and the TMS coil will be moved until a maximal response is found. The lycra swim cap features a grid that can be used to systematically and reliably stimulate portions of the motor cortex in 1cm intervals (Figure 4). The coil will be

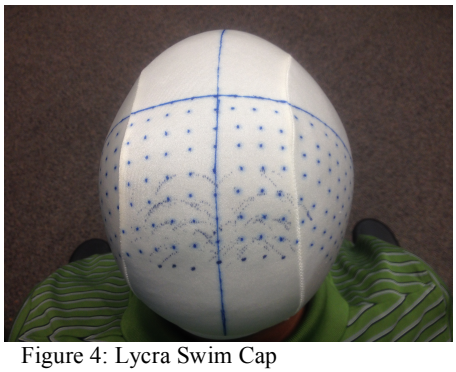

Figure 4: Lycra Swim Cap

moved about each grid point until a maximal response is found. The point that elicits the greatest MEP amplitude during stimulation will be marked for use during the remainder of the testing session. AMT refers to the lowest TMS intensity necessary to evoke a MEP in the contralateral target muscle in response to a single stimulus applied over the motor cortex. AMT will be determined as the lowest stimulator intensity required to elicit a measureable MEP (>100μV) in at least 5 out of 10 trials. MEP responses will be elicited at 120% of AMT. Five MEPs will be recorded and averaged for analysis. Subjects will complete tests of AMT and MEP amplitude prior to the intervention, immediately, 10 minutes, and 20 minutes following the intervention.

Intervention Procedures

Following baseline testing, subjects will be randomized to LMV, WBV, or control groups. The LMV group will receive 6 bouts of 60 seconds vibration with 2 minutes rest between each bout while standing with the knees flexed approximately 60°. A custom-made LMV device will be placed on the quadriceps tendon (Figure 5, right). Subjects randomized to the WBV group will stand on a vibrating platform that provides a similar stimulus (Figure 5, left). The LMV and WBV stimuli will be held constant at 2g of acceleration at a frequency of 30Hz. The control group will perform the same procedures but will not receive VT. These parameters are the same as in prior studies in our laboratory demonstrating similar effects between LMV and WBV on voluntary muscle activation. Immediately following the intervention, subjects will repeat the

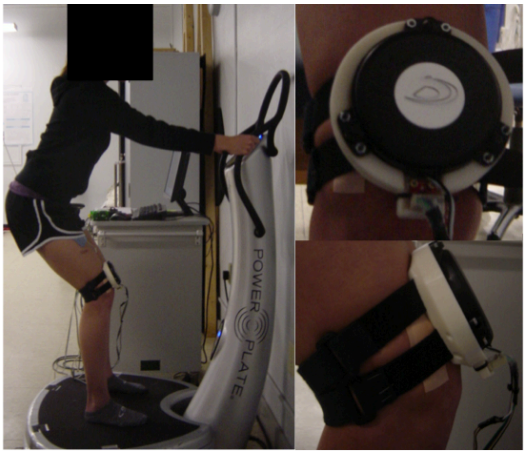

Figure 5: Left - WBV platform, Right - LMV device

aforementioned assessments of corticospinal excitability, spinal neuron excitability, and EMG amplitude during a maximal isometric contraction.

Data Reduction

The raw EMG signal during maximal contractions will be corrected for DC bias, bandpass filtered using a 4th order zero-phase lag Butterworth filter (20-350Hz) and notch filtered (59.5-60.5Hz). The filtered data will be smoothed using a 20ms root-mean-square (RMS) sliding window function. EMG amplitude will be calculated as the mean amplitude during the MVIC (RMS_{avg}). All data will be normalized to an M-wave recorded at the start of each session. The baseline amplitude values from each respective session will be used as a standardization criterion, and the percent of baseline amplitude will be calculated [($Followup_{amp}$/$Baseline_{amp}$) x 100] for each muscle (VL, VM, and RF) and averaged across the VL, VM, and RF to create a composite measure of quadriceps activity for analysis. CAR will be calculated as the ratio of maximal voluntary torque production divided by any additional torque produced by the superimposed electrical stimulus. This value represents the amount of force that can be generated from a muscle voluntarily.

H-reflex amplitude will be calculated as the peak-to-peak voltage following the stimulus and will be expressed as a percentage of maximal M-wave to allow for comparison between subjects. M-wave amplitude will be calculated as the peak-to-peak voltage difference following maximal stimulus. M-wave will also be treated as an outcome as vibration may induce post activation potentiation. Corticospinal excitability will be assessed using AMT and MEP. AMT will refer to the lowest stimulating intensity needed to generate a measurable MEP (>10mV) in the VM. Secondly, peak-to-peak amplitude will be measured to determine the size of elicited

MEPs at 120% of AMT. All MEPs will be normalized to an M-wave recorded at the beginning of each session.

Data Analysis

An *a priori* power analysis based on our previous data suggests that 16 subjects (f_2=0.43) per group would be necessary to achieve 80% power for $\alpha \leq 0.05$. However, this power analysis was on quadriceps EMG data only, thus effect size may vary for other neuromuscular measures. Mileva et al.[64] reported an effect size of 0.9 (n=7 healthy young males) when measuring MEP amplitude of the tibialis anterior during WBV exposure compared to control (no WBV), and Ritzmann et al.[57] reported an effect size of 0.6 (n=22 healthy young adults) when measuring the ratio of H-max/M-max in the soleus pre and post WBV. However, we will have more degrees of freedom due to the fact that we will utilize 3 groups, and 4 time points. Conservatively, 20 subjects per group should ensure adequate power to test hypotheses. The effects of the interventions (Aims 1-3) will be evaluated via 3 (Group: WBV, LMV, Control) x4 (Time: Baseline, Immediately Post, 10 min post, 20 min post) repeated measures analyses of variance will be used to evaluate the difference between groups from pre to post intervention for all dependent variables (AMT, MEP, H-Reflex, M-wave, EMG amplitude, CAR). Bonferroni *post hoc* procedures will be used to evaluate pairwise comparisons. Aim 4 is considered exploratory and little data are available with regard to the effect of VT on patients with ACL injury. However, assuming similar effects as in healthy individuals, 14 subjects would be required to achieve 80% power for $\alpha \leq 0.05$ using a within-subjects design. 3x2 (condition x time) repeated measures analysis of variance will be used for all dependent variables (AMT, MEP, H-reflex, EMG amplitude, M-wave, CAR) and Bonferonni *post hoc* procedures will be used to evaluate pairwise comparisons.

Reliability

Reliability data are presented in Tables 2 – 6. EMG amplitude intersession reliability was calculated between the average of two trials collected on two separate testing days one week apart by a single rater. EMG amplitude intrasession reliability was calculated between 2 trials of a single rater. EMG reliability data were collected in a prior study.[55] Intrarater, intrasession, and intersession reliability for AMT, MEP amplitude and H_{max}/M_{max} were conducted using 5 subjects. Intrarater refers to the reliability of a single rater in a single session, intrasession refers to the reliability of a single rater in one session pre-test to post-test (removal from testing position and repositioned), and intersession refers to the reliability of a single rater on two days.

Table 2: EMG - Intersession Reliability (n=20)

Muscle	ICC (2,k)
Vastus Medialis	0.843
Vastus Lateralis	0.739
Rectus Femoris	0.871

Calculated between the average of 2 measures

Table 3: EMG - Intrasession Reliability (n=20)

Muscle	ICC (3,1)
Vastus Medialis	0.941
Vastus Lateralis	0.948
Rectus Femoris	0.919

Calculated between 2 measurements

Table 4: H_{max}/M_{max} Reliability (n=5)

	ICC
Intrarater ($ICC_{3,1}$)[a]	0.957
Intrasession ($ICC_{2,k}$)[b]	0.901
Intersession ($ICC_{2,k}$)[b]	0.864

[a] *calculated between 5 measurements*
[b] *calculated between the average of 5 measurements*

Table 5: AMT Reliability (n=5)

	ICC
Intrarater ($ICC_{3,1}$)[a]	0.909
Intrasession ($ICC_{3,1}$)[a]	0.901
Intersession ($ICC_{3,1}$)[a]	0.851

[a] calculated between 2 measurements

Table 6: MEP Reliability (n=5)

	ICC
Intrarater ($ICC_{3,1}$)[a]	0.942
Intrasession ($ICC_{2,k}$)[b]	0.951
Intersession ($ICC_{2,k}$)[b]	0.809

[a] calculated between 8 measurements
[b] calculated between the average of 8 measurements

CHAPTER 4: RESULTS AND DISCUSSION SUMMARY

Results – Healthy Cohort

The group by time interaction effect was significant for peak torque and *post hoc* analyses revealed a significant increase from pre-test to post-test in peak torque in the WBV group only. The group by time interaction effect was significant for EMG amplitude, and *post hoc* analyses revealed a significant increase in EMG amplitude in the WBV group and LMV group. Furthermore, EMG amplitude was greater in the WBV group and LMV group compared to control immediately post-test. Next, there was no effect of WBV or LMV on RTD. There was no difference between the WBV and LMV group immediately post-test, and no differences were observed at 10 or 20 minutes post-test among any variable.

The group by time interaction was significant for AMT, and *post hoc* analyses revealed a significant reduction in AMT immediately post treatment, 10 minutes post treatment, and 20 minutes post treatment in the WBV group and LMV group. The group by time interaction was significant for MEP amplitude, and *post hoc* analyses revealed a significant increase in MEP amplitude immediately post treatment, 10 minutes post treatment, and 20 minutes post treatment in the WBV group only. The group by time interaction was significant for quadriceps CAR, and *post hoc* analyses revealed a significant increase in CAR immediately post treatment in the WBV group. Relative to the control group, the WBV group had a greater CAR compared to the control group immediately post- treatment. There was no difference in CAR between the WBV group and LMV group immediately post-treatment. No differences were observed in CAR in any group at 10 or 20 minutes post-treatment. Lastly, there was no effect of WBV or LMV on H-reflex.

In evaluating the mechanisms that contributed to a change in quadriceps function, multiple regression indicated that the linear combination of AMT, MEP amplitude, H-reflex, and M-wave amplitude explained 17% of the variance in CAR, 25% in EMG amplitude, and 16% of the variance in PT.

Results – ACLR Cohort

The condition by time interaction was significant for peak torque and quadriceps EMG amplitude, but not for RTD. *Post hoc* analyses indicated that peak torque in the WBV and LMV conditions was greater than in the control condition at post-test. However, the increase in peak torque was not significant in the WBV or LMV due to the conservative nature of the *post hoc* test procedure. However, inspection of the 95% confidence intervals and effect sizes of the change from pre-test to post-test suggest a trend towards an increase in peak torque in the WBV and LMV conditions. We also observed a decrease in peak torque in the control condition from pre-test to post-test. There was no difference in peak torque between the WBV and LMV conditions at post-test. *Post hoc* analyses also indicated that quadriceps EMG amplitude increased in the WBV condition from pre-test to post-test. Furthermore, quadriceps EMG amplitude was greater in the WBV condition compared to the control condition at post-test. Similar to the trend in peak torque data, an evaluation of the 95% confidence intervals and effect sizes of the change from pre-test to post-test suggest a trend towards an increase in EMG amplitude in the LMV condition. There was no difference between the WBV and LMV conditions at posttest in quadriceps EMG.

The condition by time interaction was significant for AMT and CAR, but not for MEP amplitude or H-reflex amplitude. *Post hoc* analyses indicated a significant reduction in AMT in the WBV and LMV conditions from pre-test to post-test, and a significant increase in CAR in the

WBV and LMV conditions. Furthermore, CAR in the WBV condition was greater than the control at post-test, and AMT was less than in the control condition at post-test in the WBV and LMV conditions. CAR in the LMV condition was not greater than in the control condition due to the conservative nature of the *post hoc* testing procedure. Finally, WBV did not differ from LMV at post-test for AMT or CAR.

Discussion – Healthy Cohort

The main findings of this study were that both WBV and LMV improved quadriceps function. Specifically, the WBV group had enhanced knee extension peak torque, quadriceps EMG, voluntary activation (CAR), and corticomotor excitability immediately post-treatment. The LMV group improved quadriceps EMG and corticomotor excitability immediately post treatment. Furthermore, improvements were sustained for up to 20 minutes in corticomotor excitability. No improvements were observed in RTD or H-reflex in either group. However, these individuals were healthy with no underlying deficits in quadriceps function. Therefore, we could have observed a ceiling effect among some measures of neuromuscular function (i.e. RTD). Next, given that we did not observe a change in H-reflex, it is likely that the overall improvement in quadriceps function is attributable to greater corticomotor excitability (Reduced AMT and increased MEP amplitude). However, given that only up to 25% of the variance in quadriceps function could be explained by the mechanisms evaluated in this study, future research is needed to account for the remaining unexplained variability in quadriceps CAR, PT and EMG amplitude. Finally, these findings indicate that muscle vibration – particularly WBV – could be a useful tool to acutely increase quadriceps function. Future research should consider evaluating the effects of repeated treatments and the efficacy of adding vibratory stimuli to traditional strengthening protocols.

Discussion – ACLR Cohort

The main findings of this study were that WBV and LMV improve knee extensor peak torque production, quadriceps EMG amplitude, corticomotor excitability (AMT) and voluntary activation (CAR) in individuals with ACLR. We also found no difference in the magnitudes of the improvements caused by WBV and LMV, suggesting that these treatments produce equivalent effects. Finally, we found no effect of WBV or LMV on spinal neuron excitability (H-reflex) or knee extensor RTD. Given that we observed no change in H-reflex in either LMV or WBV, the improvements in quadriceps function are likely attributable to greater corticomotor excitability following treatment. This is an important finding, as patients with ACLR have deficits in voluntary quadriceps activation, which may contribute to the development of knee OA. Furthermore, traditional rehabilitation methods are often ineffective, and novel approaches such as WBV and LMV are needed to improve the efficacy of strengthening protocols. Therefore, WBV and LMV may provide a suitable adjunct treatment to other forms of muscle strengthening since they acutely increase quadriceps voluntary activation. Future studies are needed to examine the duration of the effect in patients with ACLR, and the effects of adding WBV and LMV to strengthening exercises.

CHAPTER 5: MANUSCRIPT 1

The Effects of Whole Body and Local Muscle Vibration on Peak Torque, Rate Of Torque Development, and Electromyography in Healthy Young Adults

Overview

Context: Whole body vibration and local muscle vibration acutely improve muscle function, and may be suitable tools in performance enhancement and injury rehabilitation. However, the efficacy of these treatments has not been compared. **Objective:** To compare the effects of whole body and local muscle vibration on quadriceps function in healthy young adults. **Design:** Single blind randomized controlled trial. **Setting:** Laboratory **Patients or Other Participants:** Sixty healthy and recreationally active young adults. **Interventions:** Subjects were randomized to one of three groups (WBV, LMV and control) and data were collected in a single session. Subjects completed testing of maximal voluntary isometric strength, and then completed an intervention based on group assignment. Subjects repeated the assessment immediately, ten minutes, and twenty minutes following the intervention. **Main Outcome Measures:** Peak torque was defined as the maximal voluntary torque produced during the assessment. Rate of torque development was defined as the peak of the first derivative of the torque-time curve. Maximal EMG amplitude was defined as the greatest one second average during the strength assessment, and average across the quadriceps as a percentage of baseline for analyses. **Results:** Data were analyzed using 3(goup) by 4(time) ANOVA. The group by time interaction was significant for peak torque, and EMG amplitude. Subjects in the WBV group improved in quadriceps PT, and EMG amplitude. Subjects in the LMV group improved in quadriceps EMG amplitude. No effect was

observed on rate of torque development. **Conclusions:** These findings suggest that whole body and local muscle vibration improve quadriceps EMG amplitude. However, whole body vibration may be more effective as it caused a simultaneous increase in knee extensor torque.

Introduction

Vibratory stimuli have practical uses in rehabilitation and performance enhancement. Vibratory treatments potentially enhance muscle function through stimulation of the muscle spindle system,[50-52] increased corticospinal excitability,[64,65,171] and increased muscle temperature.[211] Vibration is commonly applied using whole body vibration (WBV) platforms, and these devices acutely increase muscle strength,[40,45,47] muscle power,[41] and EMG[178] during and following the cessation of treatment. Furthermore, WBV improves functional tasks such as vertical and countermovement jumps.[54] However, WBV platforms are cost prohibitive and are not portable or specific to a muscle group. Local muscle vibration (LMV) applied directly to a muscle-tendon unit also improves muscle function,[212-214] and may provide a cost-effective alternative to WBV.

While WBV and LMV provide similar stimuli, their efficacy may differ. During WBV, energy from vibration is dampened by the ankle joint, knee joint, and calf musculature, which may influence the magnitude of the vibration stimulus applied to more proximal structures (i.e. the quadriceps).[40] The reduction in energy from the vibration signal could be less if it were applied directly to the muscle of interest via LMV rather than WBV. In contrast, WBV could have a larger effect since it stimulates additional sensory receptors throughout the lower extremity that could influence excitability of the targeted musculature.[215] However, there are few studies comparing the effects of WBV to LMV on muscle function. For example, similar

improvements in voluntary quadriceps activation and peak torque production have been found following WBV compared to LMV. [212] However, this study utilized a sample with artificially induced quadriceps inhibition, and it is unclear if the same effects are present in a healthy population. If muscle function improves following vibratory stimuli in healthy individuals, then it may be a suitable method to acutely increase the capacity for resistance training and improve the efficacy of traditional strengthening protocols. Therefore, the primary purpose of this study was to compare the effects of WBV and LMV on quadriceps EMG amplitude, peak torque, and rate of torque development during maximal voluntary isometric contraction (MVIC) in a group of healthy individuals. We hypothesized that there would be similar improvements in WBV and LMV following treatment.

Additionally, it is unclear how long the effects of WBV and LMV last following the cessation of treatment. A previous study[214] found that LMV acutely increased quadriceps EMG amplitude, and that these effects persisted for at least 5 minutes following treatment. However, this study only evaluated muscle function at 5, 15, and 30 minutes following treatment, and it is unclear if these benefits persist beyond 5 minutes following treatment. The utility of vibratory stimuli would be greatly enhanced if the effects persist for the duration of an exercise bout (i.e. a set of resistance training exercises), and understanding the time course of the effect is essential to program design. Therefore, a secondary purpose of this study was to determine the duration of the effect during a 20 minute followup period of WBV and LMV on quadriceps EMG amplitude, peak torque, and rate of torque development during MVIC in a group of healthy individuals following the cessation of treatment. We hypothesized that the effects of WBV and LMV would persist for up to 10 minutes following treatment.

Methods

Experimental Design

A single blind randomized controlled trial design was used in this study in which subjects were randomized to 1 of 3 groups to receive either WBV, LMV, or control interventions (n = 20 per group) following pre-test assessments of quadriceps function. All subjects completed 3 testing visits to the laboratory as a part of larger study in a block randomized order separated by 1-week washout periods. The data reported here were obtained from one session. Subjects completed a baseline test, received an intervention, and completed follow-up testing immediately, 10 minutes, and 20 minutes following the intervention. Prior to testing, subjects completed a familiarization session of all testing and intervention procedures to reduce the chance of a learning effect. The tester completing all analyses was blinded to group assignment.

Subjects

An *a priori* power analysis based on previous data[214] suggested that 16 subjects per group ($f_2 = 0.43$, $\alpha = 0.05$, power = 0.8) would be necessary to detect a significant difference in quadriceps function between groups. Therefore, 60 healthy individuals were recruited (Table 7) to provide adequate statistical power. To be eligible for participation, subjects were required to be recreationally active, defined as participation in physical activity for 30 minutes at least 3 times per week. Subjects were excluded for a history of musculoskeletal injury within 6 months prior to testing, lower extremity surgery, neurological disorder, cardiovascular disease, hypertension, diabetes mellitus, concussion or head injury, stroke, epilepsy, peripheral neuropathy, migraine headaches, cranial neural surgery, cancer in the brain or thigh musculature, cardiac pacemaker, implanted foreign metal object, or diagnosed psychiatric disorder. The study

was approved by the university's institutional review board, and all subjects provided written informed consent prior to participation.

Electromyography

Sites for EMG electrodes were shaved if necessary and the skin was lightly abraded and cleaned with alcohol to improve signal quality. Preamplified electrodes (EL503, Ag/AgCl contact 11mm diameter, Biopac systems) were placed over the vastus lateralis (VL), vastus medialis (VM), and rectus femoris (RF) according to the SENIAM guidelines (VL – one third the distance along a line from the superior lateral side of the patella to the anterior superior iliac spine, RF – half the distance from the ASIS to the center of the patella, VM – 80% of the distance between the ASIS and the joint space in front of the anterior border of the medial collateral ligament) to record EMG activity during each contraction.[216] A reference electrode was placed on the medial malleolus. All electrodes were secured with prewrap and athletic tape. All data were sampled at 2 KHz using the Biopac data acquisition system (MP150WSW, Input Impedance: 1.0 MΩ, Biopac Systems Inc., Santa Barbara, CA) and EMG100C Amplifiers (CMRR: 110 dB min, actual gain used: 10000, Biopac Systems Inc., Santa Barbara, CA).

Maximal Voluntary Isometric Contraction (MVIC) procedures

Subjects completed a 5-minute warm-up on a cycle ergometer at a self-selected pace, followed by a series of submaximal quadriceps contractions (25%, 50%, and 75% of their perceived maximal effort) to reduce the chance of injury. An isokinetic dynamometer (Humac Norm, Stoughton MA) was used to assess quadriceps function during maximal isometric knee extension. This test was performed on the dominant limb, defined as the limb that would be used to kick a ball. The thighs, hips, and upper body were stabilized with straps (Figure 3), and the lever arm was adjusted so that the ankle strap was placed 2 finger widths above the medial

malleolus and the knee was flexed to 60°. Subjects were instructed to "kick out as hard and fast as possible" and received verbal encouragement for all trials to ensure a maximal effort during 2 repetitions of 5 seconds with 1 minute of rest between.

Interventions

Following baseline testing, subjects were randomized to LMV, WBV, or control groups. The LMV group received 6 bouts of 60 seconds vibration with 2 minutes rest between each bout while standing with the knees flexed approximately 60°. A custom-made LMV device was placed on the quadriceps tendon (Figure 5, right). Subjects randomized to the WBV group stood with the knees flexed approximately 60°on a vibrating platform (PowerPlate Pro 5, Perfrormance Health Systems, Northbrook IL) that provided a similar stimulus (Figure 5, left). The LMV and WBV stimuli were held constant at 2*g* of acceleration at a frequency of 30Hz. The control group performed the same procedures but did not receive vibration. These parameters were the same as in prior studies in our laboratory demonstrating similar effects between LMV and WBV on voluntary muscle activation. Immediately following the intervention, subjects repeated the aforementioned MVIC procedures.

Data Reduction

The raw EMG signal was corrected for DC bias, bandpass (20-350Hz) and notch (59.5-60.5Hz) filtered (4^{th} order zero-phase lag Butterworth). The filtered data were smoothed using a 20ms root-mean-square (RMS) sliding window function. Peak EMG amplitude was calculated as the largest 1-second moving average of the RMS. All data were normalized to a maximal M-wave recorded at the start of each session. The M-wave was recorded by placing a stimulating bar electrode (EL351, BIOPAC Systems Inc.) over the femoral nerve while subjects were supine with their knees slightly flexed (10-15°). The electrical stimulus was increased in 0.2 Volt

increments until a maximal M-wave as elicited. The baseline maximal EMG amplitude values were used as a standardization criterion, and the percent of baseline amplitude was calculated as [($Followup_{amp}$/$Baseline_{amp}$) x 100] for each muscle (VL, VM, and RF) and averaged across the VL, VM, and RF to create a composite measure of quadriceps activity for analysis.

Torque data were lowpass filtered at 50 Hz (4^{th} order Butterworth), and peak torque and rate of torque development (RTD) were calculated from the torque vs. time curve. Peak torque was defined as the maximal voluntary torque value and was normalized to body mass for analysis (Nm/kg). Maximal RTD was defined as the peak of the first derivative of the torque-time curve. The peak derivative was identified and normalized to body mass for statistical analyses ($Nm/s \cdot kg^{-1}$).

Statistical Analyses

All data were confirmed as being normally distributed using the Shapiro-Wilk test and evaluation of the skewness and kurtosis (ratio of statistic to standard error). All dependent variables (peak torque, rate of torque development, EMG amplitude) were compared between groups at baseline using one-way analysis of variance (ANOVA). The effects of each intervention on peak torque, rate of torque development, and EMG amplitude were evaluated via 3x4 (group x time) ANOVAs. The level of significance was set to $\alpha = 0.05$ and *Bonferroni* adjustments (0.05/18 = 0.003) were used for *post hoc* analysis of significant ANOVA models.

Results

Descriptive statistics for each group are presented in Table 7. Data were screened for outliers and checked for normality prior to further analyses. Four outliers were identified using boxplots in the peak torque dataset, and were removed for subsequent analyses (LMV=1, WBV=1, Control=2). Upon removal of the outliers, data were found to be normal via evaluation

of skewness and kurtosis. However, peak torque data violated the assumption of sphericity, thus the Greenhouse-Geisser test was used to assess the group x time interaction for this variable. No group differences were identified at baseline for any of the dependent variables (Table 8).

Table 7: Healthy Cohort Descriptive Statistics

	Control	WBV	LMV
Age (years)	20.5 (1.2)	20.2 (0.9)	19.5 (1.4)
Sex (males)	8	10	9
Mass (kg)	69.4 (12.9)	66.4 (10.5)	65.5 (10.7)
Height (cm)	172.0 (10.7)	167.3 (8.9)	171.1 (8.8)

Table 8: Healthy Cohort Baseline Comparison (mean (SD))

	Control	WBV	LMV	p
Peak Torque	2.61 (0.61)	2.56 (0.56)	2.58 (0.58)	0.68
RTD	54.31 (20.83)	53.77 (30.83)	47.31 (19.85)	0.63
Vastus Medialis EMG	0.27 (0.13)	0.32 (0.31)	0.32 (0.19)	0.78
Vastus Lateralis EMG	0.28 (0.13)	0.32 (0.25)	0.33 (0.18)	0.71
Rectus Femoris EMG	0.27 (0.13)	0.30 (0.25)	0.35 (0.23)	0.58

The group by time interaction effect was significant for peak torque (Table 9, $F_{2,53}$=4.26, p=0.002) and EMG amplitude (Table 10, $F_{2,53}$ =5.13, p<0.001), but not for RTD (Table 11, $F_{2,53}$ =0.81, p=0.563). There was a significant increase from pre-test to post-test in peak torque in the WBV group only (+0.30 Nm/kg, p=<0.001), and a significant increase in EMG amplitude in the WBV group (+18.4%, p<0.001) and LMV group (+12.6%, p=0.002). Furthermore, EMG amplitude was greater in the WBV group (+19.7%, p<0.001) and LMV group (+13.7%, p=0.001) compared to control immediately post-test. There was no difference between the WBV and LMV group immediately post-test, and no differences were observed at 10 or 20 minutes post-test for any variables.

Table 9: Healthy Cohort Peak Torque Results (mean (SD))

Peak Torque (Nm/kg)	Pre	Post	10 min Post	20 min Post	*P* (group x time)
Control (n=18)	2.61 (0.61)	2.62 (0.66)	2.59 (0.54)	2.56 (0.51)	
WBV (n=19)	2.56 (0.56)	2.85 (0.47)*	2.68 (0.51)	2.63 (0.53)	0.002
LMV (n=19)	2.58 (0.58)	2.47 (0.60)	2.45 (0.57)	2.43 (0.52)	

*indicates significantly greater than pretest ($p<0.003$)

Table 10: Healthy Cohort Rate of Torque Development Results (mean (SD))

RTD (Nm/sec/kg)	Pre	Post	10 min Post	20 min Post	*P* (group x time)
Control (n=18)	54.31 (20.83)	53.44 (25.15)	50.92 (23.89)	56.20 (29.48)	
WBV (n=19)	53.77 (30.83)	59.60 (25.36)	53.68 (25.13)	56.44 (23.31)	0.563
LMV (n=19)	47.31 (19.85)	46.01 (19.71)	45.28 (19.47)	44.62 (20.93)	

Table 11: Healthy Cohort Quadriceps EMG Results (mean (SD))

EMG (% Baseline)	Pre	Post	10 min Post	20 min Post	*P* (group x time)
Control (n=18)	100	98.29 (15.98)	108.32 (22.99)	107.81 (30.06)	
WBV (n=19)	100	118.06 (18.43)* Ŧ	104.59 (17.95)	103.78 (20.36)	<0.001
LMV (n=19)	100	112.55 (26.22)* Ŧ	103.54 (29.03)	103.40 (28.76)	

*indicates significantly greater than pretest ($p<0.003$)
Ŧ indicates significantly greater than control ($p<0.003$)

Discussion

The main findings of this study were that both WBV and LMV increased quadriceps EMG amplitude in healthy individuals immediately following the intervention, but the increase in quadriceps activity was accompanied by an increase in peak torque only in the WBV group. However, these improvements were not sustained 10 and 20 minutes following treatment. We did not observe any effect of vibratory stimuli on RTD, which was contrary to our hypotheses.

These findings are partially in agreement with our hypotheses and are consistent with previous literature with regards to quadriceps EMG amplitude following WBV[178,180,181] and LMV.[190,213,214] Greater EMG activity following vibration suggests greater motor unit activation or firing frequency. However, the physiological mechanisms underlying vibratory stimuli are unclear. Previous research [50,51] indicates that an increase in EMG amplitude and peak torque is

due to greater excitation of the alpha motoneurons via the muscle spindle system during vibration. However, this mechanism would seemingly only be relevant while the vibration stimulus is applied, and does not account for improvements observed when the stimulus is removed as in this study. Therefore, other mechanisms such as enhanced corticospinal excitability and intracortical processes may be responsible for the improvement in quadriceps function.[64,65] For example, Mileva et al.[64] found that motor evoked potentials from the tibialis anterior were augmented during and following WBV, and Siggelkow et al.[65] found similar results in the extensor carpi radialis following LMV. Other mechanisms that may explain the improvement in quadriceps function include a warm-up effect, as vibration has been known to acutely increase muscle temperature.[211] However, while not an aim of the study, we also measured the maximal M-response to electrical stimulation to determine if the interventions produced local changes at the level of the muscle. However, we did not observe significant changes with the interventions (group x time interaction $F_{2,54}$= 1.95, p=0.12), suggesting that the observed effects on quadriceps EMG amplitude and peak torque were not attributable to a warm-up effect.

Interestingly we only observed an increase in peak torque in the WBV group, and did not observe a similar improvement in the LMV group. This was in contrast to our hypotheses, and contrary to a previous study comparing the effects of WBV and LMV on peak torque.[212] However, this study[212] utilized a sample with experimental arthrogenic muscle inhibition caused by injecting saline into the knee joint, and improvement in that study in the LMV group could also be a result of saline diffusion from the knee joint following experimental joint effusion. Furthermore, the discrepancy in findings between WBV and LMV may be explained by differences in the application of the stimulus. WBV stimulates multiple receptors throughout the

lower extremity that may influence excitability of a muscle,[215,217] whereas LMV mainly stimulates the primary endings of muscle spindles and cutaneous receptors in the area of application. However, WBV also influences cutaneous receptors in the plantar aspect of the foot, and mechanoreceptors throughout the ankle and knee joints.[215,217] Therefore, the additional afferent sensory information provided to the central nervous system from WBV compared to LMV may be responsible for the increase in peak torque. This may suggest that LMV, at least using the parameters from the current investigation, does not provide a stimulus that is sufficient to enhance torque production in healthy individuals with normal quadriceps function who are likely subject to a ceiling effect. Lastly, while not an aim of the study, we did consider that hamstrings activity could influence peak torque of the knee extensors, and thus recorded biceps femoris and medial hamstrings EMG simultaneously as an explanatory variable. However, no differences were observed between groups in the biceps femoris ($F_{2,54} = 0.72$, $p=0.634$) or medial hamstrings ($F_{2,54} = 0.88$, $p=0.508$) activation during the knee extension MVIC. Future studies should examine the mechanisms underlying the changes in muscle function following LMV compared to WBV.

We also did not observe any significant improvements 10 and 20 minutes following the interventions. Previous studies indicate that the effects of LMV and WBV on quadriceps EMG,[214] vertical jump,[54] and muscle force production[218] persist for at least 5 minutes. Our immediate post-intervention measurements occurred an average of 2 minutes and 29 seconds following the intervention, and it is unclear if effects were still evident between 2:29 and 10 minutes following the intervention. Future studies should continue to evaluate the duration of the effect and take into consideration the time between intervention and activity, as these findings are relevant to exercise programming.

Lastly, the group by time interaction for RTD was not significant despite an increase in EMG amplitude. RTD is governed by mechanical and neural contributors, and increases in neural drive contribute to greater RTD through enhanced motor unit activation and more importantly, firing frequency.[219] As such, we hypothesized that RTD would increase following both WBV and LMV due to greater motor neuron excitability. Given that motor neuron excitability was not directly assessed, it is difficult to speculate why a concurrent change in RTD was not observed. However, because the cohort in this study was healthy and recreationally active and did not possess deficits in quadriceps function, it is likely that motor unit firing frequency was effectively maximized during MVIC, and a ceiling effect was observed. Therefore, WBV and LMV may have increased EMG amplitude via heightened motor unit recruitment, but had a negligible effect on firing frequency, thus not translating to a gain in RTD. Although this result was contrary to our hypotheses, it was in agreement with previous findings.[218,220]

There are limitations to address in this study. Firstly, it is unlikely that a single bout of vibration is sufficient to elicit chronic effects on muscle function, and the effects of repeated exposure are on unclear. Repeated bouts of vibratory stimuli may be required to elicit improvements. Next, the observed effects were relatively short lived given that they did not persist beyond the immediate posttest. However, this study utilized a healthy cohort, and the effects could persist and be larger in individuals with deficits in quadriceps function, such as patients with knee pathologies. Finally, this study only used surface EMG to measure neural adaptations occurring following vibration. Future studies should consider measures that contribute to muscle function such as corticospinal excitability, intracortical processes, and peripheral vascular perfusion.

Conclusion

Our findings suggest that LMV and WBV acutely increase EMG activity of the quadriceps muscles, and WBV also improves peak torque in healthy individuals. LMV and WBV had no effect on RTD. These findings suggest that muscle vibration – particularly WBV – could be a useful tool to increase quadriceps function. Future research should consider evaluating the effects of repeated treatments and the efficacy of adding vibratory stimuli to traditional strengthening protocols.

CHAPTER 6: MANUSCRIPT 2

The Effects of Whole Body and Local Muscle Vibration on Peak Torque, Rate Of Torque Development, and Electromyography in Patients with Anterior Cruciate Ligament Reconstruction

Overview

Context: Individuals with anterior cruciate ligament reconstruction (ACLR) have deficits in quadriceps function that may contribute to the development of knee osteoarthritis. Whole body vibration and local muscle vibration acutely improve muscle function, and may be suitable tools in injury rehabilitation. **Objective:** To compare the effects of whole body and local muscle vibration on quadriceps function in individuals with ACLR. **Design:** Single blind, single group, crossover **Setting:** Laboratory **Patients or Other Participants:** Twenty individuals with ACLR. **Interventions:** Subjects completed an assessment of peak knee extensor torque, rate of torque development, and quadriceps electromyography (EMG) amplitude and then received a treatment of whole body vibration, local muscle vibration, or control. Subjects repeated the assessment immediately following the intervention. Subjects completed the remaining treatment conditions in separate sessions. **Main Outcome Measures:** Peak torque was defined as the maximal voluntary torque produced during the assessment. Rate of torque development was defined as the peak of the first derivative of the torque-time curve. Maximal EMG amplitude was defined as the greatest one second average during the strength assessment, and average across the quadriceps as a percentage of baseline for analyses. **Results:** Data were analyzed using 3(condition) by 2(time) ANOVA. The group by time interaction was significant for peak torque, and EMG

amplitude. Post hoc analyses indicated a significant improvement in peak torque and quadriceps EMG amplitude following in the WBV and LMV conditions relative to the control condition. **Conclusions:** These findings suggest that whole body and local muscle vibration improve quadriceps EMG amplitude in individuals with ACLR. These treatments may alleviate quadriceps dysfunction and improve the efficacy of rehabilitation protocols to reduce the risk of knee osteoarthritis following ACLR.

Introduction

Individuals who undergo anterior cruciate ligament (ACL) reconstruction are 3-5 times more likely to develop tibiofemoral osteoarthritis (OA) compared to healthy controls.[6,9] OA results from a gradual reduction of articular cartilage within a joint, and patients with ACL reconstruction show evidence of OA as early as one year following reconstruction.[221] Knee osteoarthritis (OA) affects 29 million Americans at an annual cost of $165 billion.[19,222] In the long term, OA contributes to sedentary behavior and comorbidities such as cardiovascular disease.[17,18] Overall, the lifetime burden associated with ACL injury amounts to $7.6 billion annually in the United States when treated with reconstruction, and $17 billion when treated with rehabilitation.[4,5]

Quadriceps weakness is common following ACL injury and reconstruction due, in part, to arthrogenic muscle inhibition (AMI).[24,118] Alterations in afferent input to the central nervous system caused by joint effusion, joint laxity, pain, and/or deafferentation decrease the excitability of the quadriceps,[25,26] ultimately leading to an impaired ability to activate the quadriceps.[20] Reduced quadriceps activation diminishes knee extensor force production, and impaired quadriceps function prospectively predicts OA progression.[24,27,28] The quadriceps act eccentrically to attenuate impact loading during the early stance phase of gait. Reduced

quadriceps activity in patients with ACL injury manifests as lesser internal knee extension moments and knee flexion angles during gait.[36] Therefore, impaired quadriceps function may influence how the articular cartilage is loaded, and may contribute to OA development and progression. As such, improving quadriceps function in patients with ACL reconstruction (ACLR) may preserve articular cartilage health.

Current rehabilitation strategies are often ineffective in restoring quadriceps function.[39,223] Vibratory stimuli may enhance muscle function via stimulation of the muscle spindle system,[50] increased corticospinal excitability,[64,65] and/or increased muscle temperature.[211] Vibration is commonly applied using whole body vibration (WBV) platforms. WBV acutely increases muscle strength,[183] muscle power,[41] rate of force production,[218] and EMG amplitude.[178] Therefore, these stimuli may be an appropriate adjunct treatment to traditional ACLR rehabilitation protocols. Some studies have indicated that incorporating WBV in traditional rehabilitation is superior to conventional rehabilitation alone in patients with ACL reconstruction in improving postural stability, strength, and coordination.[224,225] However, WBV platforms are cost prohibitive and have limited portability. Local muscle vibration (LMV) also improves muscle function[212-214] and may provide a cost-effective alternative to WBV.

While WBV and LMV provide similar stimuli, the efficacy of the treatment may differ. During WBV, energy from vibration is dampened by the ankle joint, knee joint, and calf musculature, which may influence the magnitude of the vibration stimulus applied to more proximal structures (i.e. the quadriceps).[226] The reduction in energy from the vibration signal could be less if it were applied directly to the muscle of interest via LMV rather than WBV. Blackburn et al.[212] found similar improvements in voluntary quadriceps activation and peak torque production following WBV compared to LMV. However, this study utilized a sample

with artificially induced quadriceps inhibition, and it is unclear if the same effects are present in individuals with ACLR who possess chronic quadriceps dysfunction. Therefore, the primary purpose of this study was to compare the effects of WBV and LMV on quadriceps EMG amplitude, peak torque, and rate of torque development in a group of individuals with ACLR. We hypothesized that there would be similar improvements in WBV and LMV following treatment.

Methods

Experimental Design

A single-group, repeated measures, single-blind crossover design was used in this study. Data collection occurred during 3 testing visits (WBV, LMV, control) separated by 1-week washout periods as part of a larger investigation evaluating the effects of vibratory stimuli on quadriceps function, and corticomotor and spinal neuron excitability. Subjects completed a baseline test, received an intervention, and immediately completed follow-up testing. Prior to testing, subjects completed a familiarization session of all testing and intervention procedures to reduce the chance of a learning effect. The order of the testing sessions was counterbalanced via a Latin square to reduce the chance of a learning or order effect. The investigator conducting all analyses was blinded to group assignment, and all interventions were delivered by unblended investigators.

Subjects

An *a priori* power analysis based on previous data[214] suggested that 14 subjects (f_2 = 0.43, $\alpha = 0.05$, power = 0.8) would be necessary to detect a significant difference in quadriceps function in a crossover design. Therefore, 20 individuals with unilateral ACLR were recruited

(mass = 77.2 ± 17.1 kg, height = 170.7 ± 11.1 cm, males = 6, age = 21.1 ± 1.2 years, time since ACLR = 50.7 ± 21.3 month, patellar tendon autograft = 16, hamstring autograft = 3, allograft = 1) to provide adequate statistical power. To be eligible for participation, subjects were required to have unilateral ACLR, be cleared by a physician for participation in physical activity, and be recreationally active, defined as participation in physical activity for 30 minutes at least 3 times per week. Subjects were excluded for any re-injury or revision surgery for the injured limb, a history of musculoskeletal injury within 6 months prior to testing, lower extremity surgery (other than unilateral ACLR), neurological disorder, cardiovascular disease, hypertension, diabetes mellitus, concussion or head injury, stroke, epilepsy, peripheral neuropathy, migraine headaches, cranial neural surgery, cancer in the brain or thigh musculature, cardiac pacemaker, implanted foreign metal object, or diagnosed psychiatric disorder.

Electromyography

Sites for EMG electrodes were shaved if necessary and the skin was lightly abraded and cleaned with alcohol to improve signal quality. Preamplified electrodes (EL503, Ag/AgCl contact 11mm diameter, Biopac systems) were placed on the vastus lateralis (VL), vastus medialis (VM), and rectus femoris (RF) according to the SENIAM guidelines (VL – one third of the distance along a line from the superior lateral side of the patella to the anterior superior iliac spine, RF – half the distance from the ASIS to the center of the patella, VM – 80% of the distance between the ASIS and the joint space in front of the anterior border of the medial collateral ligament.[216] A reference electrode was placed on the medial malleolus. All electrodes were secured with prewrap and athletic tape. All data were sampled at 2 KHz using the Biopac data acquisition system (MP150WSW, Input Impedance: 1.0 MΩ Biopac Systems Inc., Santa

Barbara, CA), and EMG100C Amplifiers (CMRR: 110 dB min, actual gain used: 10000, Biopac Systems Inc., Santa Barbara, CA).

MVIC procedures

Subjects completed a 5-minute warm-up on a cycle ergometer at a self-selected pace, followed by a series of submaximal quadriceps contractions to reduce the chance of injury. An isokinetic dynamometer (Humac Norm, Stoughton MA) was used to test isometric knee extensor function in the ACLR limb. The thighs, hips, and upper body were firmly stabilized with straps (Figure 6). The lever arm was adjusted so that the ankle strap was placed 2 finger widths above the medial malleolus. The knee was positioned so that the lateral femoral epicondyle was aligned with the rotational axis of the dynamometer. The knee was flexed 60° and 3 repetitions of 5 seconds (average used for analyses) were completed with 1 minute of rest between. Subjects were instructed to "kick out as hard and fast as possible" and received verbal encouragement for all trials to ensure a maximal effort.

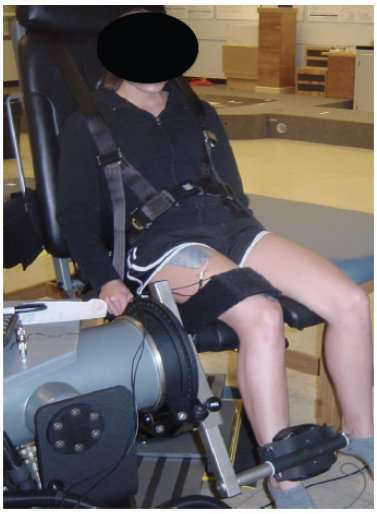

Figure 6: Subject Position for Dynamometer

Intervention

Following baseline testing, subjects received LMV, WBV, or control interventions. The LMV condition consisted of 6 bouts of 60 seconds vibration with 2 minutes rest between each bout while subjects were standing with the knees flexed approximately 60°. A custom-made LMV device was placed on the quadriceps tendon (Figure 5, right). During the WBV condition, subjects stood in an identical position as in the LMV intervention on a vibrating platform (PowerPlate Pro 5, Perfrormance Health Systems, Northbrook IL) that provided a similar

stimulus (Figure 5, left). The LMV and WBV stimuli were held constant at 2*g* of acceleration at a frequency of 30Hz. During the control condition subjects performed the same procedures but did not receive vibration. These parameters were the same as in prior studies in our laboratory demonstrating similar effects between LMV and WBV on voluntary muscle activation. Immediately following the intervention, subjects repeated the aforementioned MVIC assessment

Data Reduction

The raw EMG signal was corrected for DC bias, bandpass (20-350Hz) and notch (59.5-60.5Hz) filtered (4^{th} order zero-phase lag Butterworth filter). The filtered data were smoothed using a 20ms root-mean-square (RMS) sliding window function. Maximal EMG amplitude was calculated as the largest 1-second moving average of the processed signal. All data were normalized to a maximal M-wave recorded at the start of each session. The M-wave was elicited by placing a stimulating bar electrode (EL351, BIOPAC Systems Inc.) over the femoral nerve while subjects were supine with their knees slightly flexed (10-15°). The electrical stimulus was increased in 0.2 Volt increments until a maximal M-wave was obtained. The baseline amplitude values from each respective session were used as a standardization criterion, and the percent of baseline amplitude was calculated [($Followup_{amp}$/$Baseline_{amp}$) x 100] for each muscle (VL, VM, and RF) and averaged across the VL, VM, and RF to create a composite measure of quadriceps activity for analysis.

Torque data were lowpass filtered at 50 Hz (fourth order Butterworth), and peak torque and rate of torque development were calculated from the torque vs. time curve. Peak torque was defined as the maximal voluntary torque value and was normalized to body mass for analysis (Nm/kg). Rate of torque development was calculated as the first derivative of the torque/time

curve, and the peak value was identified and normalized to body mass for statistical analyses ($Nm/s \bullet kg^{-1}$).

Statistical Analyses

All data were confirmed as being normally distributed using the Shapiro-Wilk test and inspection of skewness and kurtosis statistics. All dependent variables (peak torque, rate of torque development, EMG amplitude) were compared between conditions at baseline using one-way ANOVA. The effects of the interventions on the dependent variables were evaluated via separate 3x2 (condition x time) repeated measures ANOVA. The level of significance was established *a priori* as $\alpha = 0.05$ and Bonferroni *post hoc* adjustments ($\alpha = 0.05/6 = 0.0083$) were used to evaluate significant ANOVA models.

Results

All data were found to be normal via the Shaprio-wilk test and evaluation of skewness and kurtosis. No outliers were identified and all cases were included for analysis. Baseline values for the dependent variables did not differ between conditions (Table 12). The condition by time interaction was significant for peak torque (Figure 7, $F_{2,17} = 8.46$, $p=0.001$) and quadriceps EMG amplitude (Figure 8, $F_{2,17} = 2.90$, $p=0.05$), but not for RTD (Figure 9, $F_{2,17} = 0.12$, $p=0.89$).

Table 12: ACLR Cohort Baseline Characteristics (mean (SD))

Variable	Control	WBV	LMV	*p*
Peak Torque ($Nm \bullet kg^{-1}$)	1.84 (0.79)	1.79 (0.80)	1.83 (0.93)	0.82
RTD ($Nm \bullet kg \bullet sec^{-1}$)	39.97 (19.03)	39.74 (20.98)	41.14 (22.68)	0.94
Vastus Medialis EMG	0.32 (0.25)	0.36 (0.33)	0.26 (0.15)	0.47
Vastus Lateralis EMG	0.33 (0.23)	0.31 (0.17)	0.26 (0.13)	0.45
Rectus Femoris EMG	0.31 (0.22)	0.33 (0.25)	0.26 (0.14)	0.57

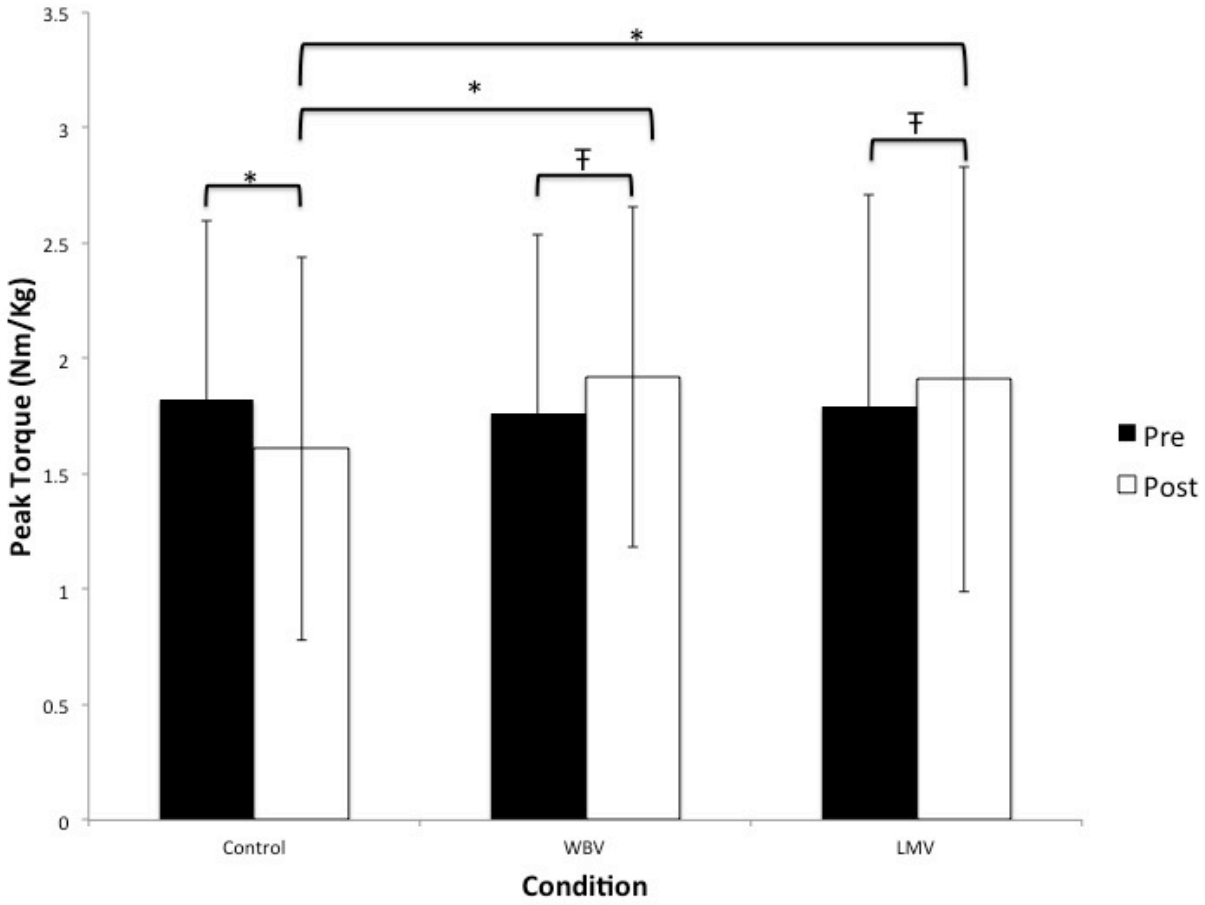

Figure 7: ACLR cohort peak torque condition by time interaction, $p<0.001$; * indicates $p<0.0087$, Ŧ indicates trend towards significance

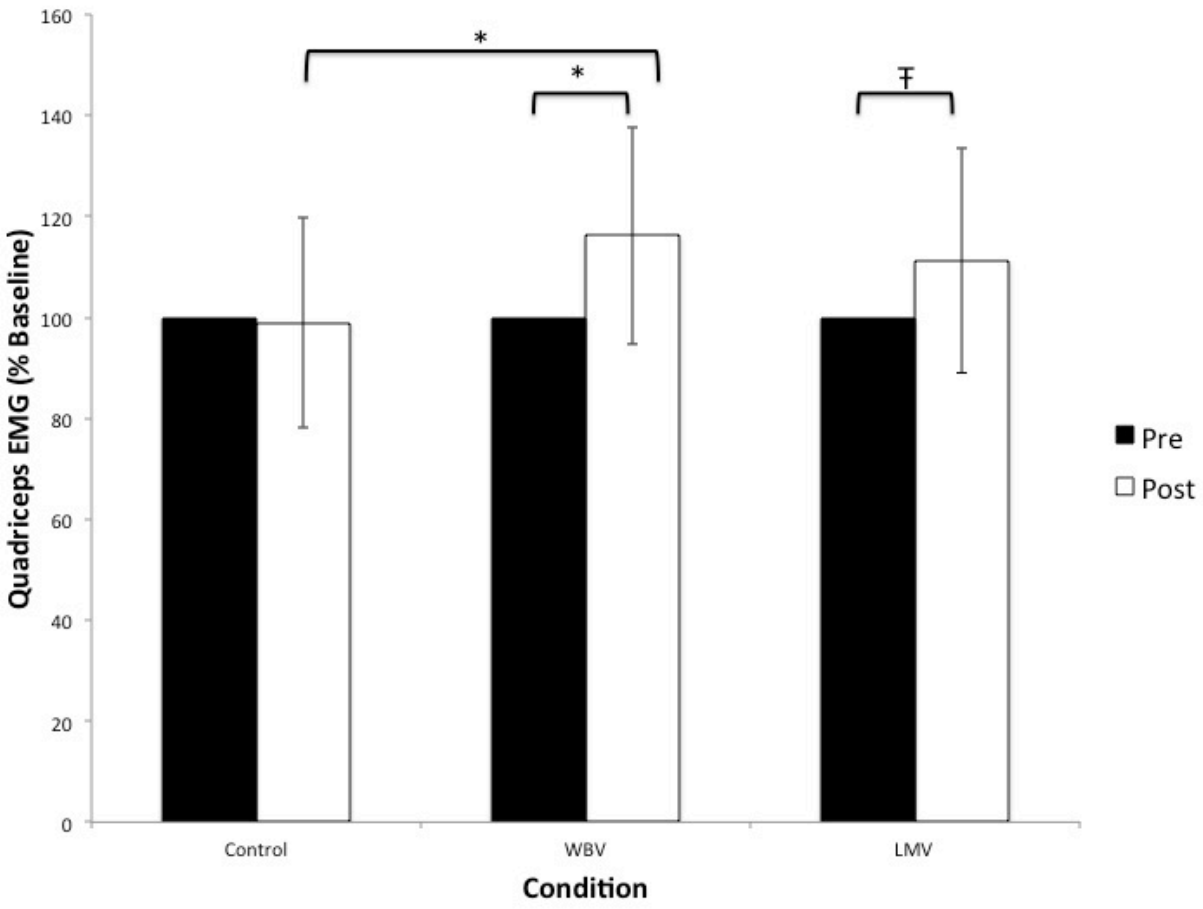

Figure 8: ACLR cohort quadriceps EMG amplitude condition by time interaction, $p<0.001$; * indicates $p<0.0087$, Ŧ indicates trend towards significance

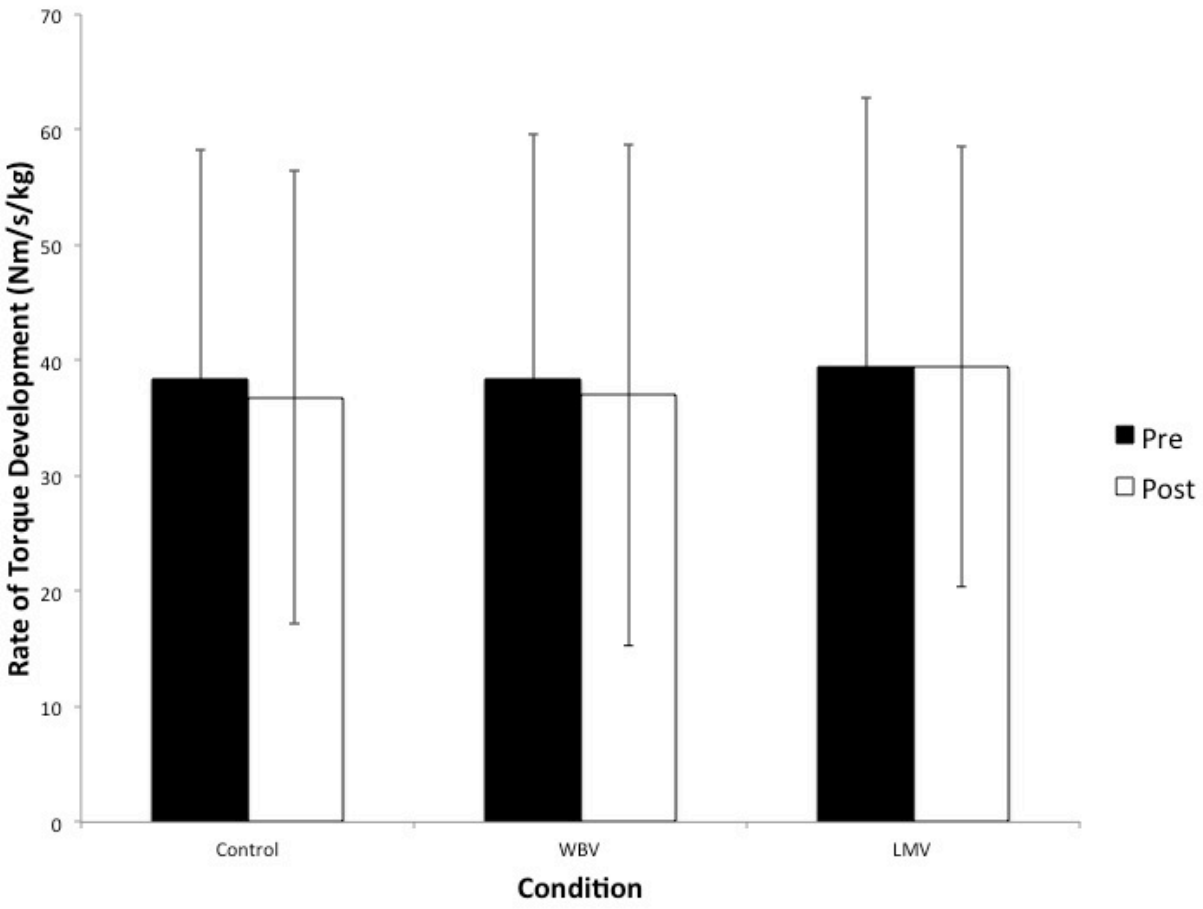

Figure 9: ACLR cohort rate of torque development condition by time interaction, p=0.89

Post hoc analyses indicated that peak torque in the WBV (p=0.004) and LMV (p=0.002) conditions was greater than in the control condition at post-test. However, the increase in peak torque was not significant in the WBV (+0.15 Nm/kg, p = 0.01) or LMV (+0.12 Nm/kg, p = 0.03) conditions (Figure 7) due to the conservative nature of the *post hoc* test procedure. This statistical limitation was evidenced by the fact that the 95% confidence intervals for the pre-post change scores did not cross 0 for the change in peak torque in the WBV (95%CI: 0.04 - 0.27, effect size = 0.73) and LMV (95%CI: 0.02 – 0.22, effect size = 0.65) conditions. We also observed a significant decrease in peak torque in the control condition from pre-test to post-test

(-0.21Nm/kg, p=0.002). There was no difference in peak torque between the WBV and LMV conditions at post-test (p = 0.96).

Post hoc analyses also indicated that quadriceps EMG amplitude increased in the WBV condition (+16.17%, p=0.002). Furthermore, quadriceps EMG amplitude was greater in the WBV condition compared to the control condition at post-test (p = 0.002). Similar to the trend in peak torque data, the change in quadriceps EMG amplitude in the LMV condition (+11.18%, p = 0.018) was not significant (Figure 8) due to the conservative nature of the *post hoc* procedure, but the 95% confidence interval and effect size (95%CI: 2.37-19.99, effect size = 0.71) suggest that a moderate to large effect. EMG amplitude was not different in the LMV condition compared to the control condition at post-test (p = 0.07). There was no difference between the WBV and LMV conditions at posttest in quadriceps EMG (p = 0.44).

Discussion

The main findings of this study were that both WBV and LMV increased peak knee extension torque and quadriceps EMG amplitude in individuals with ACLR. Furthermore, though slightly larger following WBV, the magnitudes of improvement in these indices of quadriceps function did not differ statistically between the vibratory stimuli. However, we observed no change in quadriceps RTD following either WBV or LMV. Overall, these results suggest that vibratory stimuli may be an appropriate method to enhance quadriceps function following ACLR.

Our findings are consistent with previous research regarding the increase in peak torque and EMG amplitude following WBV and LMV in healthy individuals,[45,47,178,212,214] The increases in quadriceps peak torque and EMG activity are likely due to a number of factors. Past studies indicate that improvements in muscle function following vibration result from repeated

stimulation of the muscle spindle and Ia afferent pathway causing a reflexive contribution to muscle force production.[50] However, this mechanism would seemingly only account for enhancements that occur while the stimulus is being applied. We observed an increase following the cessation of treatment, and other contributing mechanisms could include an increase in corticospinal excitability[64,65] or a warm-up effect.[168,211] However, while not an aim of this study, we also examined the quadriceps M-wave amplitude and found no effect of WBV or LMV ($F_{2,17}$= 0.397, p = 0.68). This suggests that improvements in quadriceps function are not due to a local warmup effect, potentially supporting effects of WBV and LMV on corticospinal excitability. We also considered that a change in knee extensor torque could result from a reduction in hamstrings co-contraction, and therefore measured hamstrings EMG simultaneously. However, we observed no effect of WBV or LMV on biceps femoris ($F_{2,17}$ = 0.93, p=0.41) or medial hamstrings ($F_{2,17}$=0.28, p=0.75) EMG, thus isolating the effects of the vibratory stimuli to direct enhancements of quadriceps function.

Though not stististicaly different, WBV resulted in slightly larger improvements in peak torque (+0.15 Nm/kg vs. +0.12 Nm/kg) and EMG amplitude (+16.16% vs. +11.18%) than LMV. WBV stimulates a variety of sensory receptors throughout the lower extremity such as cutaneous receptors in the foot,[215] whereas the effects of LMV are likely restricted to musculotendinous and cutaneous receptors immediately surrounding the area to which it is applied. Only one study[212] to our knowledge has compared these modalities, and reported equivocal improvements in peak torque and voluntary muscle activation similar to our results. However, this study utilized a sample that had artificial AMI from experimental knee effusion, and the results could have been partially attributable to saline effusion during testing. Our findings confirm that WBV and LMV produce similar increases in knee extensor torque and

quadriceps EMG amplitude in a individuals with ACLR. These findings are relevant as individuals with ACLR typically exhibit deficits in quadriceps function[104] that may contribute to the development of knee OA.[20] Importantly, baseline quadriceps function predicts knee OA progression,[24] thus it is an important target for rehabilitation. Unfortunately rehabilitation efforts are often ineffective due to quadriceps AMI.[38,163] Our findings indicate that vibratory stimuli may be an appropriate method to enhance the efficacy of strengthening exercises for patients with knee pathologies.

We did not observe a change in RTD in either the WBV or LMV condition despite a improvements in peak torque and EMG amplitude. While these findings were contrary to our hypotheses, they are in agreement with previous studies in healthy individuals.[214,218,220] Neural and mechanical factors contribute to RTD, and increases in neural drive contribute to RTD via rate coding and motor unit activation.[219] Therefore, we hypothesized that RTD would increase following WBV and LMV from greater motor neuron excitability. It could be that a single session of vibration is not sufficient to elicit a detectable change in RTD. For instance, Lamont et al.[227] reported an increase in RTD with the addition of WBV to squat training, but only after a 7 week period. Furthermore, several studies demonstrating improvements speed of movement or force production utilized different tasks such as countermovement and vertical jumps.[54,220,228] As such, it could be that the MVIC used in this study was not sensitive or dynamic enough to detect differences between conditions. Future studies should consider evaluating other tasks where the rate of torque development is considered crucial.

There are limitations to address when interpreting the results of this study. Firstly, a single session of vibration therapy likely does not produce lasting effects on muscle function. Furthermore, we propose that this treatment would be suitable to aid in rehabilitation to prevent

or delay the progression of knee OA. However, given the short-term nature of this study, we were unable to assess knee OA progression. Future studies should determine if vibratory treatments are appropriate to elicit a reduction in knee OA prevalence among patients with ACLR. Finally, while we observed an increase in quadriceps peak torque and EMG, the mechanisms of WBV and LMV are unclear. Future studies should evaluate the mechanisms that govern changes in muscle function following WBV and LMV, such as changes in corticospinal excitability. WBV and LMV may influence the neuromuscular system differentially, thus these differences should continue to be investigated.

Conclusion

Our findings indicate that WBV and LMV improve quadriceps peak torque and EMG amplitude in patients with ACLR. WBV and LMV had no effect on quadriceps RTD. Overall, our findings suggest that WBV and LMV are appropriate methods to acutely increase quadriceps function, and could be useful to aid in restoring quadriceps strength in patients with knee pathologies. Future studies should evaluate the effects of repeated exposure to vibratory stimuliand the effects of adding vibration to strengthening exercises. Finally, future research should continue to explore the differences between WBV and LMV, as LMV may provide a cost effective alternative to WBV if it provides similar effects.

CHAPTER 7: MANUSCRIPT 3

The Effects of Whole Body and Local Muscle Vibration on Quadriceps Corticomotor Excitability, Spinal Neuron Excitability, and Voluntary Muscle Activation in Healthy Young Adults

Overview

Context: Whole body vibration and local muscle vibration acutely improve muscle function, and may be suitable tools in performance enhancement and injury rehabilitation. However, the mechanisms underlying these improvements are unclear, and the efficacy of these treatments has not been compared. **Objective:** To compare the effects of whole body and local muscle vibration on quadriceps function in healthy young adults. **Design:** Single blind randomized controlled trial. **Setting:** Laboratory **Patients or Other Participants:** Sixty healthy and recreationally active young adults. **Interventions:** Subjects were randomized to one of three groups (WBV, LMV and control) and data were collected in a single session. Subjects completed testing of quadriceps corticomotor excitability, spinal neuron excitability, and voluntary activation and then completed an intervention based on group assignment. Subjects repeated the assessment immediately, ten minutes, and twenty minutes following the intervention. **Main Outcome Measures:** Corticomotor excitability was assessed using active motor threshold (AMT) and motor evoked potential (MEP) amplitude. Spinal neuron excitability was assessed using Hoffmann (H) reflex. Voluntary activation was assessed using the central activation ratio (CAR). **Results:** Data were analyzed using 3(goup) by 4(time) ANOVA. The group by time interaction was significant for AMT, MEP amplitude, and CAR,

but not for H-Reflex. Subjects in the WBV group improved in AMT, MEP amplitude, and CAR. Subjects in the LMV group improved in AMT. No effect was observed on H-Reflex. **Conclusions:** These findings suggest that whole body and local muscle vibration improve corticomotor excitability, and whole body vibration also improves voluntary quadriceps activation. As such, vibratory stimuli – in particular whole body vibration – may be an appropriate tool to acutely improve quadriceps function in healthy individuals.

Introduction

Vibratory stimuli have practical applications to strength and conditioning, and injury rehabilitation, as they acutely increase muscle strength,[183,212] power,[41] and activation[178,212,214] during and following cessation of treatment.[214] Furthermore, these treatments improve functional tasks such as vertical and countermovement jumps.[54] Despite a preponderance of evidence linking muscle vibration to enhanced muscle function, there is still uncertainty regarding the mechanisms underlying the observed improvements. Previous work suggests that improvements in muscle function are a result of enhanced reflexive activity from stimulation of the muscle spindle system.[50] Essentially, discharge of the primary endings of the muscle spindle (Ia afferent) from repeated muscle lengthening invokes what is known as the tonic vibratory reflex (TVR).[51,52] However, the TVR only accounts for alterations in muscle function that occur during vibration, and does not account for improvements following the cessation of treatment. For example, Pamukoff et al.[214] demonstrated that quadriceps EMG activity during a knee extensor maximal voluntary contraction remained elevated at least 5 minutes following local muscle vibration. Furthermore, some studies indicate a suppression of spinal neuron excitability following vibration in healthy individuals[57] and in patients with spinal cord injury.[58] These

findings suggest that improvements in muscle function following vibration are not likely attributed to gains in spinal neuron activity.

What remains unclear is the role of supraspinal structures in mediating muscle function following vibration treatment. Afferent input from muscles is a major contributor to motor control, and muscle vibration stimulates various areas of the cerebral cortex.[61] There is some evidence to suggest that muscle vibration enhances cortical neuron excitability,[64,65,171] which may be responsible for persisting improvements in muscle function. Specifically, motor evoked potential (MEP) amplitude measured using single pulse transcranial magnetic simulation is augmented in response to muscle vibration. For example, Mileva et al.[64] found that tibialis anterior MEP amplitude was augmented during and following whole body vibration, and Sigglekow et al.[65] found that extensor carpi radialis MEP amplitude increased during local muscle vibration. Overall, these findings suggest that adaptations from muscle vibration are not restricted to spinal reflex and peripheral activity, but also involve cortical processes. However, these studies have used small samples, and have not concurrently evaluated the effects on cortical neuron excitability, spinal neuron excitability, and voluntary muscle activation. Additionally, these studies have used different kinds of vibration – whole body vibration (WBV) vs. local muscle vibration (LMV) - and it is unclear if these modalities yield similar results. WBV platforms are costly, and LMV may be a portable and cost-effective alternative. Furthermore, the efficacy of these modalities may vary. During WBV, the vibration signal is applied at the feet and dampened as it passes to proximal structures (e.g. the quadriceps). However, the reduction in energy from the vibration signal could be less if it were applied directly to the muscle of interest via LMV. In contrast, WBV may have a larger effect since it stimulates additional sensory receptors throughout the lower extremity that may influence

muscle activity.[215] Lastly, these studies have only evaluated MEP amplitude during application of the vibratory stimulus, and it is unclear if the effects persist following the cessation of treatment.

The purpose of this study was to evaluate and compare the effects of WBV and LMV on spinal neuron excitability, corticomotor excitability, and voluntary muscle activation. A secondary purpose was to determine with the effects persisted for up to 20 minutes.

Methods

Experimental Design

A single blind randomized controlled trial design was used in this study in which subjects were randomized to 1 of 3 groups to receive either WBV, LMV, or control interventions (n = 20 per group) following pre-test assessments of quadriceps function. All subjects completed 3 testing visits (spinal neuron excitability, corticomotor excitability, and voluntary muscle activation) in a block randomized order separated by 1-week washout periods. During each session subjects completed a baseline test, received an intervention, and completed follow-up testing immediately, 10 minutes, and 20 minutes following the intervention. Prior to testing, subjects completed a familiarization session of all testing and intervention procedures to reduce the possibility of a learning effect. The investigator conducting all analyses was blinded to group assignment.

Subjects

Descriptive statistics are presented in Table 7. An *a priori* power analysis based on previous data[214] suggested that 16 subjects per group (N=48, $f_2 = 0.43$, $\alpha = 0.05$, power = 0.8) would be necessary to detect a significant difference in quadriceps function between groups.

Therefore, 60 healthy individuals were recruited (Table 7) to ensure adequate power. To be eligible for participation, subjects were required to be recreationally active, defined as participation in physical activity for 30 minutes at least 3 times per week. Subjects were excluded for a history of musculoskeletal injury within 6 months prior to testing, lower extremity surgery, neurological disorder, cardiovascular disease, hypertension, diabetes mellitus, concussion or head injury, stroke, epilepsy, peripheral neuropathy, migraine headaches, cranial neural surgery, cancer in the brain or thigh musculature, cardiac pacemaker, implanted foreign metal object, or diagnosed psychiatric disorder.

Hoffmann Reflex

Hoffmann (H) reflex was used to assess excitability of the quadriceps alpha motoneuron pool (i.e. spinal neuron excitability). H-reflex and M-wave measurements of the vastus medialis (VM) were collected with surface electromyography (EMG). All measurements were recorded in the dominant limb, defined as the limb one would use to kick a ball. Subjects lay supine on a padded table with their arms placed comfortably at their sides, their heads resting on a pillow, and their knees slightly flexed (15º) with a bolster. Reflexes were elicited with a STMISOLA Constant Current and Constant Voltage Isolated Linear Stimulator (STMISOLA, BIOPAC Systems, Inc). A bipolar stimulating bar electrode (EL351, BIOPAC Systems Inc) was positioned over the femoral nerve, and a 1ms square wave stimulus was delivered to the femoral nerve. The electrical stimulus was increased in 0.2 Volt increments until a maximum H- reflex was elicited, and then 5 maximal H-reflexes were obtained at that voltage. The stimulus was then further increased until a maximal M-wave was elicited. EMG data were sampled at 2 KHz. H-max and M-max were re-established for the post-intervention assessments to account for

potential local effects of the vibratory stimuli on EMG characteristics (e.g. a "warmup" effect). The ratio of maximal H-wave to maximal M-wave was used for analysis.

Corticomotor Excitability

Corticomotor excitability was assessed via active motor threshold (AMT) and MEP amplitude using transcranial magnetic stimulation. This method involves introducing a brief, non-painful magnetic stimulus that excites neurons in the motor cortex associated with a specific muscle, and subsequent nervous system pathways are activated causing a contraction of the targeted muscle. These small contractions, MEPs, are measured to determine function of the cortical neurons and corresponding neural pathways that dictate muscle activation. MEPs were measured in the VM via EMG electrodes in the dominant limb. Subjects were seated in a dynamometer with the knee in 60° of flexion, and were asked to produce 5% of their maximal voluntary isometric contraction (MVIC) during active motor threshold/MEP testing to standardize the level of effort. A computer screen depicting real-time feedback of subject's torque output was used to ensure this criterion was met. The motor cortex was mapped to identify the location that elicited the greatest MEP in the VM. A lycra swim cap was placed over the subject's head, and the TMS coil was moved until a maximal response was found. The lycra swim cap featured a grid that was used to systematically and reliably stimulate portions of the motor cortex in 1cm intervals (Figure 11). The coil was moved about each grid point until the location that elicited the largest response was found. The point that elicited the greatest MEP during stimulation was marked for use during the remainder of the testing session. AMT was determined as the lowest stimulator intensity required to elicit a measureable MEP (>100μV) in at least 5 out of 10 trials. MEP responses were then elicited at 120% of AMT, and eight MEPs

were recorded, averaged, and normalized to a maximal M-wave recorded at the beginning of the session for analysis.

Voluntary Activation

Voluntary activation was assessed via the central activation ratio (CAR) during a maximal voluntary isometric knee extension. A brief electrical stimulus (10-pulse train, 600μs duration, 100Hz, 125V) was manually delivered via two adhesive electrodes placed on the proximal and distal quadriceps following plateau of the MVIC using an isolated stimulator (Grass Telefactor model SK48). Subjects completed this test prior to the intervention, and immediately, 10 minutes, and 20 minutes following the intervention. CAR was calculated as the ratio of peak voluntary torque to the torque increment resulting from the electrical stimulus (Figure 10). The mean of 3 trials at each time point (pre and post) was used for analysis.

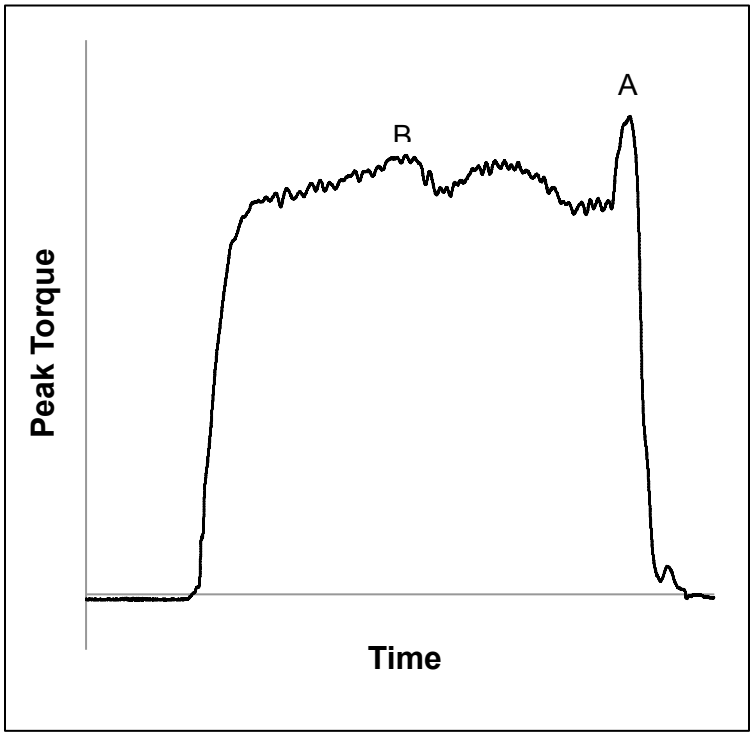

Figure 10: The central activation ratio was used to quantify voluntary quadriceps activation during an MVIC. Subjects received an electrical stimulus upon reaching their voluntary peak torque production. The ratio of voluntary torque to torque produced from the superimposed stimulus (A/B x 100) was used for analysis.

Intervention

Following baseline testing, subjects were randomized to LMV, WBV, or control groups. The LMV group received 6 bouts of 60 seconds vibration with 2 minutes rest between each bout

while standing with the knees flexed approximately 60°. A custom-made LMV device was placed on the quadriceps tendon (Figure 5, right). Subjects randomized to the WBV group stood with the knees flexed approximately 60° on a vibrating platform (PowerPlate, Performance Health Systems, Northbrook, IL) that provided a similar stimulus (Figure 5, left). The LMV and WBV stimuli were held constant at 2*g* of acceleration at a frequency of 30Hz. The control group performed the same procedures but did not receive vibration. These parameters were the same as in prior studies [212,214] demonstrating similar effects between LMV and WBV on voluntary muscle activation.

Statistical Analyses

All data were confirmed as being normally distributed using the Shapiro-Wilk test. All dependent variables (AMT, MEP amplitude, H:M ratio, CAR) were compared between groups at baseline using one-way ANOVA. The effects of the interventions on each dependent variable were evaluated via separate 3 (Group: WBV, LMV, Control) x 4 (Time: Baseline and Immediately, 10 min, and 20 min post-intervention) repeated measures ANOVA. The level of significance was set to $\alpha = 0.05$ and Bonferroni *post hoc* adjustments (0.05/18 = 0.003)were used to evaluate significant ANOVA models.

Results

Data were found to be normal via the Shapiro-Wilk test and evaluation of skewness and kurtosis. No outliers were identified and thus all cases were used for analyses, and no differences were found at baseline between groups. The group by time interaction was significant for AMT (Table 13, $F_{2,57} = 13.39$, $p<0.001$), MEP amplitude (Table 14, $F_{2,57}=4.21$, $p=0.001$), and CAR (Table 15, $F_{2,57} = 2.86$, $p = 0.011$), but not for H-reflex amplitude (Table 16, $F_{2,57} = 0.79$, $p = 0.619$).

Table 13: Healthy Cohort AMT Results (mean (SD))

AMT (%)	Pre	Post	10 min Post	20 min Post	*P* (group x time)
Control (n=20)	42.7 (8.6)	42.7 (9.0)	43.0 (8.9)	43.1 (8.6)	
WBV (n=20)	45.4 (7.7)	42.9 (8.2)*	43.1 (8.3)*	43.4 (7.9)*	<0.001
LMV (n=20)	46.3 (11.5)	44.0 (11.5)*	44.0 (11.3)*	44.7 (11.3)*	

*indicates significantly less than pre test (p<0.003)

Table 14: MEP Results (mean (SD))

MEP amplitude	Pre	Post	10 min Post	20 min Post	*P* (group x time)
Control (n=20)	0.060 (0.044)	0.058 (0.042)	0.059 (0.043)	0.058 (0.045)	
WBV (n=20)	0.045 (0.029)	0.068 (0.040)*	0.062 (0.036)*	0.068 (0.039)*	0.001
LMV (n=20)	0.047 (0.024)	0.060 (0.044)	0.065 (0.050)	0.060 (0.043)	

*indicates significantly less than pre test (p<0.003)

Table 15: CAR Results (mean (SD))

CAR (%)	Pre	Post	10 min Post	20 min Post	*P* (group x time)
Control (n=20)	93.1 (3.9)	90.9 (5.7)	90.4 (6.6)	89.7 (6.4)	
WBV (n=20)	91.9 (4.6)	94.4 (3.9)* Ŧ	90.9 (6.5)	92.0 (5.9)	0.011
LMV (n=20)	91.9 (3.2)	92.2 (3.9)	87.5 (8.8)	87.4 (8.7)	

*indicates significantly less than pre test (p<0.003)
Ŧ indicates significantly greater than control (p<0.003)

Table 16: H-Reflex Results (mean (SD))

H-Reflex (H:M)	Pre	Post	10 min Post	20 min Post	*P* (group x time)
Control (n=20)	0.27 (0.19)	0.26 (0.16)	0.25 (0.16)	0.25 (0.14)	
WBV (n=20)	0.26 (0.15)	0.20 (0.15)	0.23 (0.17)	0.23 (0.17)	0.619
LMV (n=20)	0.28 (0.17)	0.23 (0.15)	0.24 (0.15)	0.23 (0.15)	

Post hoc analyses revealed a significant increase in CAR immediately post-treatment in the WBV group (+2.9%, p<0.01), a significant reduction in AMT immediately post-treatment in the WBV (-2.6%, p<0.001) and LMV (-2.1%, p<0.001) groups, and a significant increase in MEP amplitude in the WBV group (+0.03, p=0.001) immediately post-treatment. The WBV group had a greater CAR compared to the control group immediately post- treatment (+3.51%,

$p<0.0026$). There was no difference in CAR between the WBV group and LMV group immediately post-treatment.

The reduction in AMT was significant 10 minutes following WBV (-2.3%, $p<0.001$) and LMV (-2.3%, $p<0.001$), and 20 minutes following WBV (-2.4%, $p<0.001$) and LMV (-1.6%, $p<0.001$). The increase in MEP amplitude was significant 10 minutes following treatment (+0.02, $p=0.001$) and 20 minutes following treatment in the WBV group (+0.02, $p=0.001$). No differences were observed in CAR in any group at 10 or 20 minutes post-treatment.

Discussion

The main findings of this study were that both WBV and LMV improved quadriceps function via an improvement in corticomotor excitability rather than from enhanced spinal neuron activity. Furthermore, the effects may be more pronounced following WBV compared to LMV, as there was an increase in voluntary quadriceps activation (CAR) in the WBV group only. Lastly, the effects of muscle vibration on AMT and MEP amplitude may persist for up to 20 minutes following treatment. Interestingly and in contrast to our hypotheses, we found no change in spinal motorneuron activity.

Improvements in muscle function following vibration are speculated to result from improved neural excitation through enhanced reflex activation[51,52] and/or enhanced cortical processes.[64,65] Vibration applied to a muscle or tendon is thought to excite the primary spindle endings, and thus stimulate the alpha motoneuron pool within the spinal cord causing a reflexive contribution to muscle force production. However, prior research shows that the H-reflex is depressed during LMV[229] and WBV,[57,58] suggesting that other mechanisms contribute to improved muscle function following vibration. The suppression of the H-reflex amplitude is likely due to presynaptic inhibition.[230,231] Repetitive muscle contractions in response to vibration

may contribute to neurotransmitter depletion in the presynaptic terminals, and thus reduce postsynaptic output.[57] Interestingly, our study found no influence of WBV or LMV on H-reflex amplitude, which was contrary to our hypotheses, but in agreement with previous research.[218,232] Given the discrepancy in the literature regarding the influence of vibration on the H-reflex, it could be that the effects of vibration on reflexive activity are limited to while the stimulus is applied, rather than following it. We evaluated H-reflex an average of 2 minutes and 37 seconds following treatment, and the effects on the alpha motoneuron pool within the spinal cord may have dissipated by that time. Ritzmann et al.[57] reported a reduction of the soleus H-reflex while standing during WBV that persisted for 5 minutes but less than 10 minutes following exposure. We attribute the difference in findings to a different muscle studied (quadriceps vs. soleus), testing position (standing vs. supine), and the vibratory stimulus parameters (frequency = 22 Hz, amplitude = 4mm).

Our findings are in agreement with previous studies regarding the effect of WBV and LMV on quadriceps MEP amplitude.[64,65] The reduction in active motor threshold observed in this study is novel, yet not unexpected. Cortical areas within the brain receive and process afferent input from muscles, and generate evoked cortical potentials in response to vibration.[61] Afferent input from muscles contributes to neuromuscular control,[62] and facilitation from muscle afferents contributes nearly one third of overall central motor drive.[233] Alterations in afferent input from the muscle spindles change the excitability of the corticospinal pathway,[234] and activation of the corticomotor region.[235] Therefore, it is reasonable that vibration augments muscle function via alterations in cortical processes (increase in MEP amplitude, reduction in AMT).

Next, we observed an increase in voluntary quadriceps activation (CAR) in the WBV group. This is in agreement with previous studies evaluating the effects of WBV on CAR.[212] Given that we observed no changes in spinal motor neuron excitability as measured by the H-reflex amplitude, the improvement that we saw in CAR is likely due to the enhancement in corticomotor excitability. Interestingly, we only observed an improvement in CAR in the WBV group, which is in contrast to previous research.[212] However, that study[212] utilized a group of individuals with artificial knee effusion, and the effects observed in that study could also be due to saline effusion from the knee joint. Additionally, while both LMV and WBV stimulate the muscle spindle system, WBV also stimulates other sensory receptors throughout the lower extremity, such as cutaneous receptors in the foot known to influence motor control.[215,217] As such, it could be that the reduction in AMT following LMV is not on its own sufficient to cause an improvement in CAR in healthy individuals. We did consider that a change in quadriceps CAR could be attributable to a reduction in hamstrings co-contraction, and as such, we measured hamstrings EMG simultaneously to verify our interpretation of the findings. We did not observe a change in biceps femoris ($F_{2,57}$= 0.72, p=0.63) or medial hamstrings ($F_{2,57}$= 0.88, p=0.51) EMG during the assessment of quadriceps CAR.

Finally, we observed an effect on AMT and MEP amplitude that persisted for up to 20 minutes following the cessation of treatment in the WBV group. Previous studies suggest that the effects of vibration last between 5 and 30 minutes,[54,214] thus our findings are in agreement. Although the improvement in corticomotor excitability persisted for up to 20 minutes, we did not observe a similar effect on CAR. Furthermore, a warm-up effect and increased muscle temperature may also contribute to the improvement in CAR following vibration.[69,168,211] However, we observed no evidence of a change in M-wave amplitude (group x time interaction

effect $F_{2,57}$=1.95, p=0.12), indicating that improvements in quadriceps function were likely due to enhanced corticomotor excitability.

There are limitations to address when interpreting the findings of this study. Firstly, our study group was healthy with no known deficits in quadriceps activation. Therefore, our results may indicate a ceiling effect, and greater improvements may be seen in individuals with reductions in quadriceps activation, such as patients with knee pathologies. Future studies should evaluate the effects of muscle vibration in pathologic populations, and on activities of daily living requiring normal quadriceps function such gait or stair ascent. Secondly, we assessed each outcome variable on different days in order to test the duration of the effect. It is possible that the effects differed by day. However, testing occurred at the same time of day (± 2 hours) for each subject, and the order of the testing sessions was randomized. Future studies should consider evaluating these measures concurrently on the same day if time permits.

Conclusion

Overall, findings from this study indicate that quadriceps function improves following vibration via an augmentation in corticomotor excitability. Furthermore, we found no change in spinal neuron activity, indicating that the effects of vibration on reflexive activity as previously reported may be limited to the time when the treatment is applied or very shortly thereafter. As such, vibratory stimuli – particularly WBV – may provide a suitable treatment for those individuals with deficits in quadriceps function. Future studies should investigate the effects of vibratory stimuli in pathologic populations, as the magnitude of the effects could be larger in those with underlying deficits.

CHAPTER 8: MANUSCRIPT 4

The Effects of Whole Body and Local Muscle Vibration on Quadriceps Corticomotor Excitability, Spinal Neuron Excitability, and Voluntary Activation in Patients with Anterior Cruciate Ligament Reconstruction

Overview

Context: Individuals with anterior cruciate ligament reconstruction (ACLR) have deficits in quadriceps function from alterations in neuromuscular function that may contribute to the development of knee osteoarthritis. Whole body vibration and local muscle vibration acutely improve muscle function, and may be suitable tools in injury rehabilitation. **Objective:** To compare the effects of whole body and local muscle vibration on quadriceps function in individuals with ACLR. **Design:** Single blind, single group, crossover **Setting:** Laboratory **Patients or Other Participants:** Twenty individuals with ACLR. **Interventions:** Subjects completed an assessment of quadriceps corticomotor excitability, spinal neuron excitability, and voluntary activation, and then received a treatment of whole body vibration, local muscle vibration, or control. Subjects repeated the assessment immediately following the intervention. Subjects completed the remaining treatment conditions in separate sessions. **Main Outcome Measures:** Corticomotor excitability was assessed using active motor threshold (AMT) and motor evoked potential (MEP) amplitude. Spinal neuron excitability was assessed using Hoffmann (H) reflex. Voluntary activation was assessed using the central activation ratio (CAR). **Results:** Data were analyzed using 3(condition) by 2(time) ANOVA. The group by time interaction was significant for AMT and CAR, but not for MEP amplitude or H-reflex. Post hoc

analyses indicated a significant decrease in AMT, and a significant increase in CAR following in the WBV and LMV conditions relative to the control condition. **Conclusions:** These findings suggest that whole body and local muscle vibration improve voluntary quadriceps activation in individuals with ACLR. Furthermore, the increase in CAR is likely attributable to an increase in corticomotor excitability. These treatments may alleviate quadriceps dysfunction attributable to deficits in neuromuscular function. As such, vibratory stimuli may be appropriate to improve the efficacy of rehabilitation protocols and reduce the risk of knee osteoarthritis following ACLR.

Introduction

Individuals who experience ACL reconstruction (ACLR) are 3-5 times more likely to develop knee osteoarthritis (OA) compared to healthy controls.[6,9] Despite reconstruction, patients with ACL injury show evidence of knee OA as soon as 1 year following reconstruction.[221] When considering the additional of cost of knee OA, the annual lifetime burden of ACL injury is nearly $8 billion when treated with reconstruction, and nearly $18 billion when treated with rehabilitation only.[4,5,19] OA also contributes to comorbidities such as physical disability, cardiovascular disease, diabetes, and reduced quality of life.[17,18]

Quadriceps weakness following ACL injury is common and may contribute to the development of knee OA.[1,20,104] Alterations in afferent input to the central nervous system decrease the excitability of the quadriceps alpha motoneuron pool.[1] This leads to an inability to fully activate the quadriceps, termed arthrogenic muscle inhibition (AMI). Interestingly, individuals with ACLR display activation deficits in the contralateral limb,[118] suggesting central influences on AMI such as reduced cortical and spinal neuron excitability. Quadriceps AMI contributes to reduced knee extensor strength, which predicts knee OA progression and severity.[24,28,30] Knee OA is considered a mechanically driven disease, and alterations in joint

loading influence disease progression. The quadriceps act as a shock absorber during the early stance phase of gait, and failure to adequately absorb energy caused by impact with the ground may alter the loading characteristics of articular cartilage.[99] Patients with ACL injury display lesser knee extensor moments, potentially contributing to greater cartilage loading and development of OA.[34-36]

Unfortunately, restoring quadriceps function following ACL injury is challenging, as persistent AMI presents a barrier to effective rehabilitation.[38,39] Therefore, novel strategies are necessary to improve the efficacy of strengthening protocols for the quadriceps. Vibration therapy (VT) is an increasingly popular mode of exercise with reports of improved muscle strength,[183] power,[41] electromyography,[178,214] and physical function.[54] Furthermore, VT improves voluntary quadriceps activation in individuals with artificially induced quadriceps AMI.[212] Therefore, VT may be a suitable adjunct treatment for patients with ACL injury. However, it is unclear if VT influences quadriceps function in individuals with ACL injury. Importantly, presynaptic mechanisms such as impaired corticospinal excitability also contribute to AMI.[25,26] There are also reports of enhanced corticospinal excitability during VT,[64,65] thus VT may be a suitable treatment for quadriceps AMI. Unfortunately, these studies have utilized small samples and healthy cohorts. Lastly, VT is commonly delivered using whole body (WBV) platforms which are costly and lack portability. Local muscle vibration (LMV) also improves quadriceps function[212-214] and is potentially a portable and cost-effective alternative. However, no investigations have compared the effects of WBV and LMV on corticospinal excitability, spinal motorneuron excitability, and voluntary quadriceps activation in patients with ACLR.

The purpose of this study was to compare the effects of WBV and LMV on corticospinal excitability, spinal motorneuron excitability, and voluntary muscle activation in individuals with

ACLR. We hypothesized that LMV and WBV would enhance corticospinal excitability and voluntary activation, but attenuate spinal motorneuron excitability, relative to a control condition, but that the magnitude of improvement would not differ between WBV and LMV.

Methods

Experimental Design

A single-group, repeated measures, single-blind crossover design was used in this study. Data collection occurred during 3 testing visits (WBV, LMV, control) separated by 1-week washout periods. Subjects completed a baseline test, received an intervention, and immediately completed follow-up testing. Prior to testing, subjects completed a familiarization session of all testing and intervention procedures to reduce the chance of a learning effect. The order of the testing sessions was counterbalanced via a Latin square to reduce the chance of a learning or order effect. The order of assessments within each testing session was fixed (H-Reflex, CAR, AMT, MEP amplitude at pre-test, and CAR, AMT, MEP amplitude, H-reflex at posttest) rather than randomized. Assessment of the H-reflex required a private and quiet testing setting, while other assessments took place in the same location within the laboratory while seated on a dynamometer. Furthermore, peak torque was evaluated during the CAR assessment which provided us with a standardized activation level for subsequent AMT and MEP testing. Finally, AMT was required to determine a standardized stimulating intensity to elicit MEPs for measurement. For these reasons, it was necessary to use a standard rather than random testing order. The tester completing all analyses was blinded to group assignment, and all interventions were delivered by research assistants.

Subjects

An *a priori* power analysis based on previous data [212,214] suggested that 14 subjects (f_2 = 0.43, $\alpha = 0.05$, power = 0.8) would be necessary to detect a significant difference in quadriceps function in a crossover design. Therefore, 20 patients with unilateral ACLR were recruited (mass = 77.2 ± 17.1 kg, height = 170.7 ± 11.1 cm, males = 6, age = 21.1 ± 1.2 years, time since ACLR = 50.7 ± 21.3 months, patellar tendon autograft = 16, hamstring autograft = 3, allograft = 1, Tegner Score=6.8 ± 1.6) to ensure adequate statistical power since baseline data was based on quadriceps EMG amplitude following vibration. To be eligible for participation, subjects were required to have unilateral ACLR, be cleared by a physician for participation in physical activity, and be recreationally active, defined as participation in physical activity for 30 minutes at least 3 times per week. Subjects were excluded for any re-injury or revision surgery for the injured limb, a history of lower extremity musculoskeletal injury within 6 months prior to testing, lower extremity surgery (other than ACLR), neurological disorder, cardiovascular disease, hypertension, diabetes mellitus, concussion or head injury, stroke, epilepsy, peripheral neuropathy, migraine headaches, cranial surgery, cancer in the brain or thigh musculature, cardiac pacemaker, implanted foreign metal object, or diagnosed psychiatric disorder.

Hoffmann Reflex

Hoffmann reflex (H-reflex) was used to assess excitability of the quadriceps alpha motoneuron pool (i.e. spinal motorneuron excitability). H-reflex and M-wave measurements of the vastus medialis (VM) were collected with surface electromyography (EMG) from the injured limb. Subjects lay supine on a padded table with their arms placed at their sides, their heads resting on a pillow, and their knees slightly flexed (~10-15º) with a bolster. Reflexes were elicited with a STMISOLA Constant Current and Constant Voltage Isolated Linear Stimulator

(STMISOLA, BIOPAC Systems, Inc). A bipolar stimulating bar electrode (EL351, BIOPAC Systems Inc) was positioned over the femoral nerve where a 1ms square wave stimulus was delivered. The electrical stimulus was increased in 0.2 Volt increments until a maximum H-reflex was elicited, and 3 maximal H-reflexes were collected at that voltage. The stimulus was then increased until a maximal M-wave was elicited. EMG data were sampled at 2 KHz. H-max and M-max were re-established for the post-intervention assessments to account for local "warm-up" effects of the vibratory stimuli on EMG characteristics. The ratio of maximal H-wave to maximal M-wave was used for analysis.

Voluntary Activation

Voluntary activation was assessed via the central activation ratio (CAR) during a maximal voluntary isometric knee extension. A brief electrical stimulus (10-pulse train, 600μs duration, 100Hz, 125V) was delivered via two adhesive electrodes placed on the proximal and distal quadriceps following plateau of the MVIC using an isolated stimulator (Grass Telefactor model SK48). CAR was calculated as the ratio of peak voluntary torque to the peak torque resulting from the electrical stimulus (Figure 11). The mean of 3 trials at each time point (pre and post) was used for analysis.

Corticomotor Excitability

Corticomotor excitability was assessed via active motor threshold (AMT) and amplitudes of motor evoked potentials (MEPs) using transcranial magnetic stimulation (TMS). This method involves introducing a brief, non-painful magnetic stimulus that excites neurons in the motor cortex associated with a specific muscle, and subsequent nervous system pathways are activated causing a contraction of the targeted muscle. These small contractions, MEPs, are measured to determine excitability of the cortical neurons and corresponding neural pathways that dictate

muscle activation. MEPs were measured in the VM via EMG electrodes. Subjects were seated in a dynamometer with the knee in 60° of flexion, and were asked to produce 5% of their maximal voluntary isometric contraction (MVIC) to standardize the level of effort. A computer screen depicting real-time feedback of subject's torque output was used to ensure this criterion was met.

The motor cortex was mapped to identify the location that elicited the greatest MEP response in the VM. A lycra swim cap with a 1x1 cm grid was placed over the subject's head (Figure 11), and the TMS coil was moved along the grid until the location that elicited a maximal response was identified. This point was marked for use during the remainder of the testing session. AMT was determined as the lowest stimulus intensity required to elicit a measureable MEP (>100μV) in at least 5 out of 10 trials, and 8 MEP responses were elicited at 120% of AMT and normalized to a maximal M-wave for analysis.

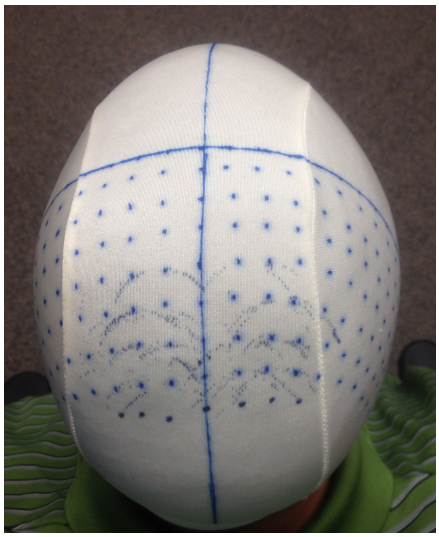
Figure 11: Lycra Swim Cap

Intervention

Following baseline testing, subjects received LMV, WBV, or a control intervention. Subjects completed the remaining two interventions on subsequent days in a counterbalanced order. The LMV intervention consisted of 6 bouts of 60 seconds vibration with 2 minutes rest between each bout while standing with the knees flexed approximately 60°. A custom-made LMV device was placed on the quadriceps tendon (Figure 5, right). The WBV intervention consisted of similar treatment parameters (duration and position), however subjects stood with

the knees flexed approximately 60° on a vibrating platform (PowerPlate, Performance Health Systems, Northwood, IL) that provided a similar stimulus (Figure 5, left). The LMV and WBV stimuli were held constant at 2*g* of acceleration at a frequency of 30Hz. The control intervention consisted of the same procedures but without vibration. These parameters were the similar to previous studies [212,214] demonstrating effects of LMV and WBV on voluntary muscle activation.

Statistical Analyses

All data were confirmed as being normally distributed using the Shapiro-Wilk test and skewness an kurtosis statistics. All dependent variables (MEP amplitude, AMT, H:M ratio, CAR) were compared between conditions at baseline using one-way repeated measures ANOVA. The effects of the interventions on the dependent variables were evaluated via 3x2 (condition x time) repeated measures ANOVA. The level of significance was set to $\alpha = 0.05$ and Bonferroni *post hoc* adjustments ($\alpha = 0.05/6 = 0.0083$) were used to evaluate significant ANOVA models.

Results

Data were found to be normal via the Shapiro wilk test and evaluation of skewness and kurtosis. No outliers were identified and all 20 subjects were included for analyses. Baseline values for the dependent variables did not differ between conditions (Table 17). The condition by time interaction was significant for AMT (Figure 12, $F_{2,17} = 29.47$, $p<0.001$) and CAR (Figure 13, $F_{2,17} = 13.31$, $p<0.001$), but not for MEP amplitude (Figure 14, $F_{2,17} = 1.25$, $p = 0.30$) or H-reflex amplitude (Figure 15, $F_{2,17} = 0.1.41$, $p = 0.26$).

Table 17: ACLR Baseline Characteristics (mean (SD))

Variable	Control	WBV	LMV	*p*
AMT	44.2 (9.3)	43.5 (8.9)	44.1 (9.2)	0.53
MEP	0.07 (0.04)	0.09 (0.06)	0.08 (0.05)	0.09
CAR	82.7 (11.1)	80.9 (11.0)	80.8 (10.8)	0.86
H-Reflex	0.24 (0.18)	0.24 (0.19)	0.24 (0.14)	0.83

Post hoc analyses indicated significant reductions in AMT in the WBV (-3.1%, $p<0.001$) and LMV (-2.9%, $p<0.001$) conditions from pre-test to post-test. AMT was also less than in the control condition at post-test in the WBV ($p<0.001$) and LMV conditions ($p<0.001$). Similarly, significant increases in CAR were observed for the WBV (+4.9%, $p = 0.001$) and LMV (+2.7%, $p = 0.001$) conditions, and CAR in the WBV condition was greater than the control condition at post-test ($p = 0.005$). CAR in the LMV condition was greater than in the control condition (4.11%, $p = 0.007$). Finally, WBV did not differ from LMV at post-test for AMT or CAR.

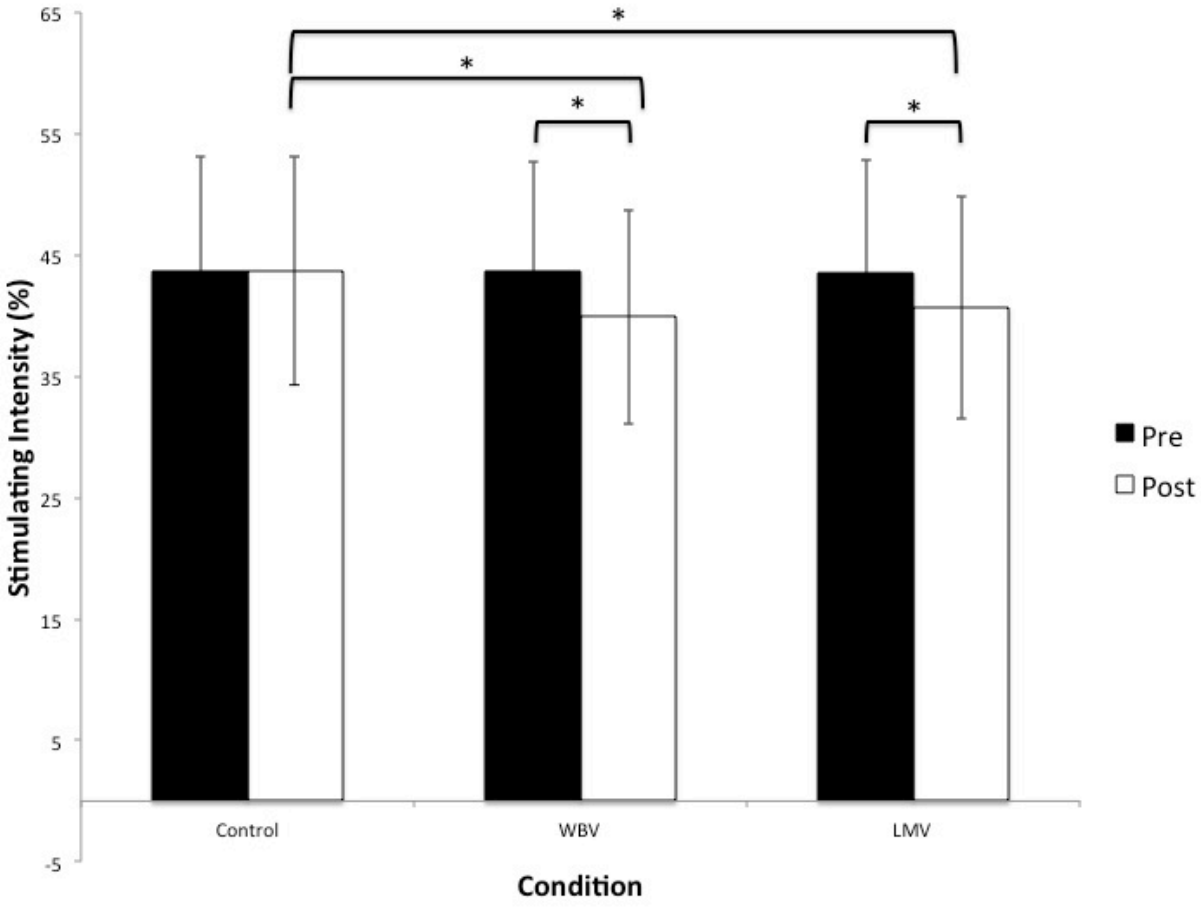

Figure 12: ACLR cohort active motor threshold condition by time interaction, $p<0.001$; * indicates $p<0.0087$

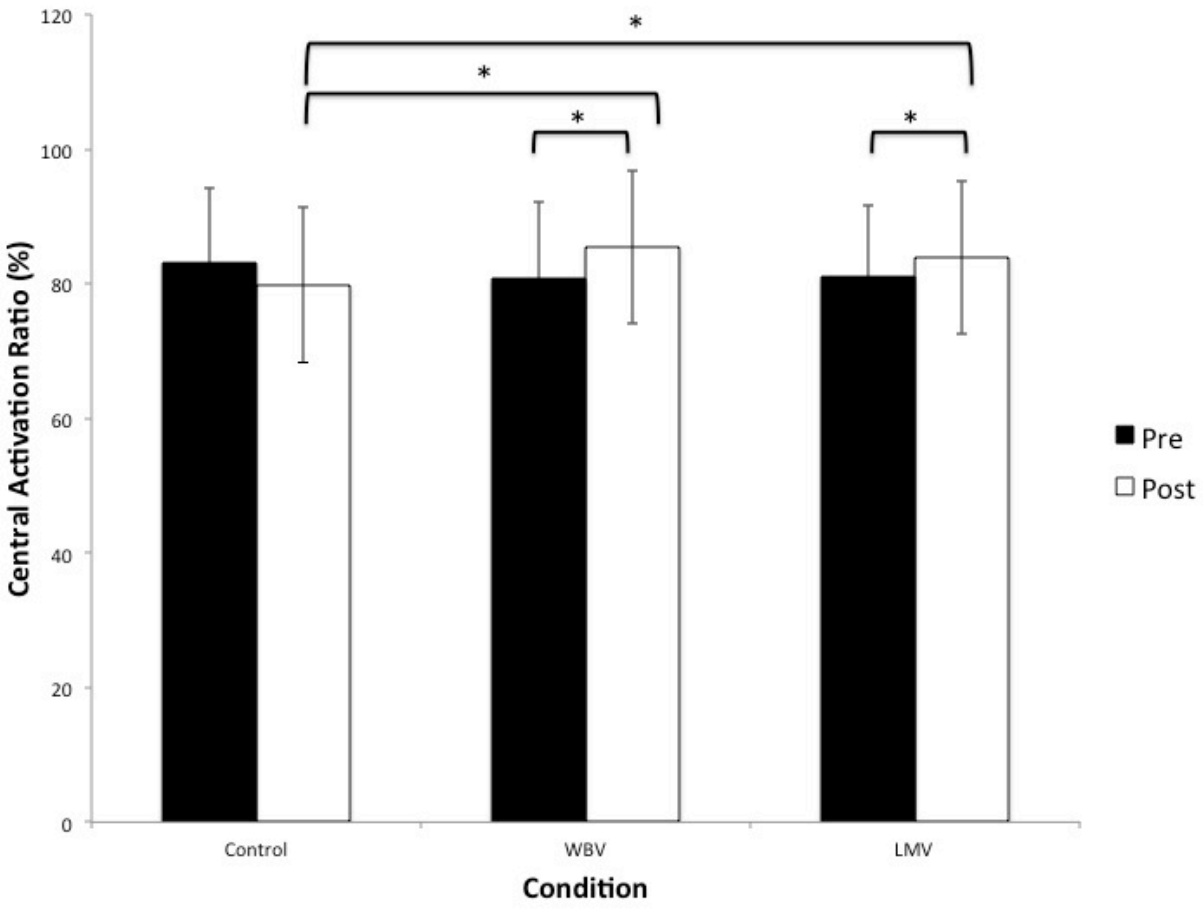

Figure 13: ACLR cohort central activation ratio condition by time interaction, $p<0.001$; * indicates $p<0.0087$

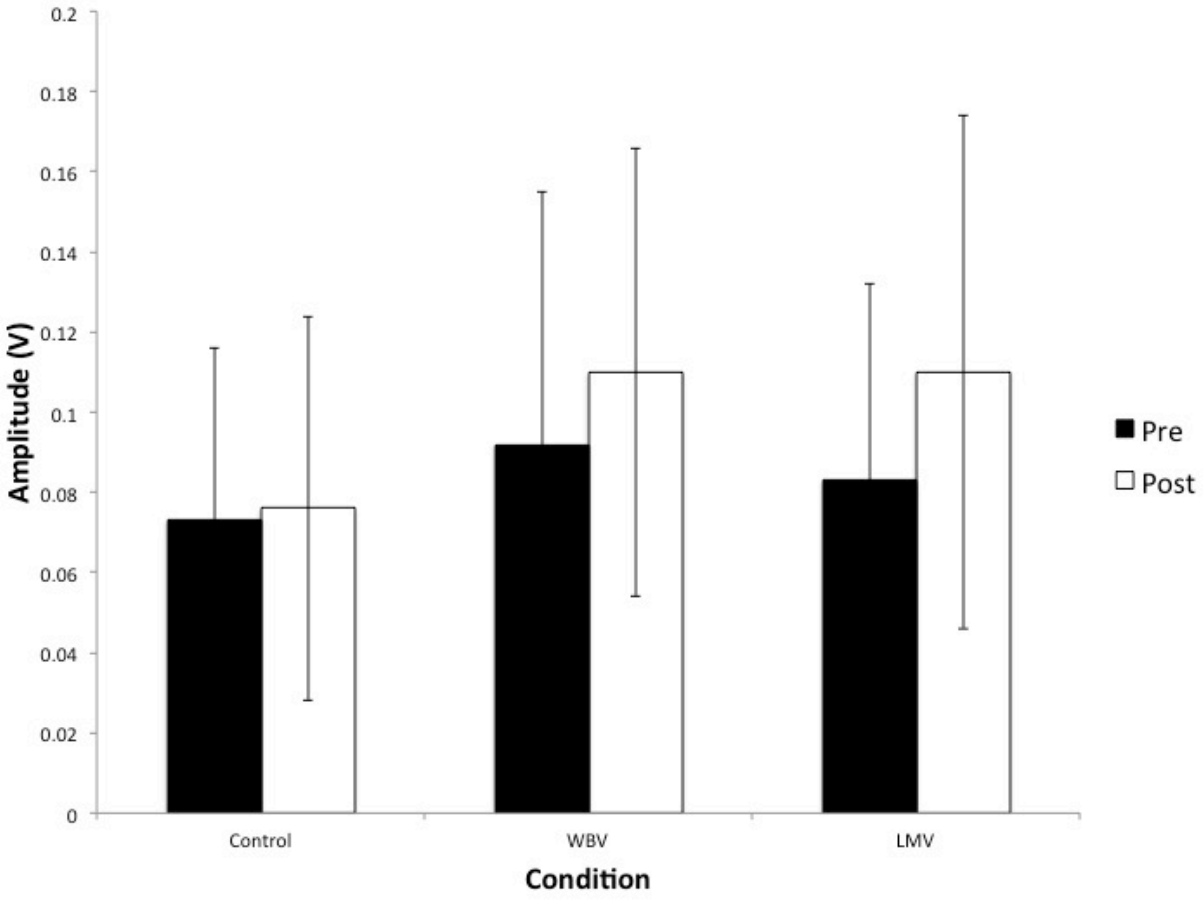

Figure 14: ACLR cohort motor evoked potential amplitude condition by time interaction, p=0.30

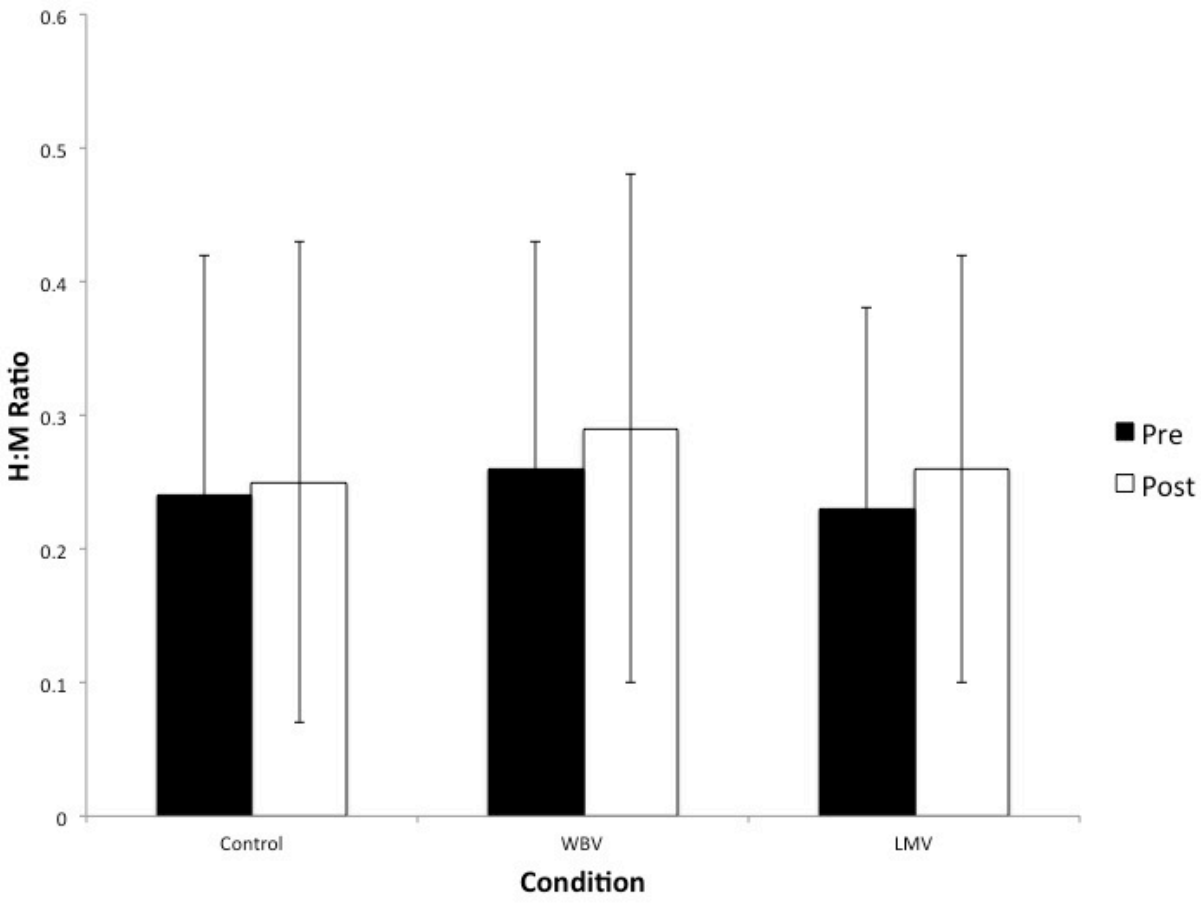

Figure 15: Hoffman's reflex condition by time interaction, p=0.26

Discussion

The main findings of this study were that WBV and LMV increased corticomotor excitability (AMT) and voluntary activation (CAR). Furthermore, the magnitudes of the increases caused by WBV and LMV did not differ, suggesting that these treatments produce equivalent effects. Finally, we found no effect of WBV or LMV on spinal neuron excitability (H-reflex).

Our findings are in agreement with previous research regarding improvement in corticomotor excitability with WBV[64] and LMV.[65] However, this is the first study to our knowledge to report these effects in individuals with ACLR. Muscle vibration primarily

stimulates the Ia afferents of the muscle spindles, resulting in a reflexive contribution to muscle force production (i.e. the tonic vibratory reflex).[50] While this mechanism accounts for improvements in muscle function during the stimulus, it does not likely explain enhancements in quadriceps function following the treatment as evidenced by the lack of influence on the H-reflex in our subjects. Cortical areas receive and process sensory information and generate motor commands in response to vibration.[61] Given that afferent input to the motor cortex contributes to motor control, it is plausible that enhanced muscle function could result from cortical stimulation via WBV and LMV.[62] The reduction in AMT following WBV and LMV suggests greater corticomotor excitability, which may reduce the recruitment threshold.[171]

Interestingly, we did not see a concurrent elevation in MEP amplitude. However, we attribute the lack of significant findings to the order of testing. Unfortunately we were not able to randomize the order of testing, and MEP amplitude was always assessed following CAR, and AMT. Previous studies indicate that the effects of vibration on muscle function last approximately 5 minutes.[54,214] Therefore, the effects of vibration likely diminished by the time MEP amplitude was assessed. Future studies should evaluate MEP amplitude shortly after the cessation of treatment, and evaluate the precise duration of the effect from vibration.

We also observed a significant increase in CAR in both the WBV and LMV conditions. These findings are in agreement with a previous study in individuals with artificial arthrogenic muscle inhibition from experimental knee effusion.[212] Given that we did not observe an increase in spinal neuron excitability, it seems reasonable that the improvement in CAR is due to the enhancement in corticomotor function. Quadriceps CAR could increase from reduced hamstring activity, thus we measured hamstring EMG simultaneously to verify our interpretation of the results. However, we observed no changes in biceps femoris ($F_{2,16}$= 0.93, p=0.41) or medial

hamstrings ($F_{2,16}$= 0.28, p=0.75) activity with the interventions. Similarly, while not an aim of this study, we also examined the quadriceps M-wave amplitude and found no effect of WBV or LMV ($F_{2,16}$ = 0.397, p = 0.68). This suggests that improvements in quadriceps function are not due to a local warmup effect, potentially supporting effects of WBV and LMV on corticospinal excitability. This is a relevant finding as patients with ACLR have deficits in voluntary quadriceps activation[104] from AMI that may stem from impaired supraspinal control.[26] These deficits likely contribute to the development of posttraumatic osteoarthritis following ACL injury,[104] and also limit the effectiveness of rehabilitation.[38,163] Traditional strengthening exercises are ineffective in patients with knee pathologies because AMI prevents sufficient muscle activity to stimulate strength gains.[39] Therefore, alternative methods of strengthening are required to improve the efficacy of rehabilitation. Our findings indicate that WBV and LMV may be suitable adjunct treatments to acutely increase quadriceps activation prior to strengthening exercises.

Finally, we observed no effect of WBV or LMV on H-reflex amplitudes. Previous results are ambiguous regarding the effect of vibration on the H-reflex. For instance, some studies indicate no effect of vibration on the H-reflex in healthy populations,[218,232] while others indicate a suppression[57] or even facilitation[169,174] of the H-reflex during and following vibration. Previous studies[57,58,218] that have found an effect of vibration on the H-reflex have primarily investigated the triceps surae complex, whereas we investigated the H-reflex in the quadriceps. A previous study[232] utilizing similar WBV parameters reported equivocal findings. Therefore, it could be that the H-reflex of the quadriceps responds in a different manner to vibratory stimuli compared to the triceps surae. Secondly, the testing position for H-reflex was not the same as the

intervention position or testing position for TMS and CAR. As such, the change in position and quadriceps muscle length may have influenced the H-reflex data.[236,237]

There are limitations to address when interpreting the results of this study. Firstly, we were not able to randomize the order of testing within sessions due to laboratory constraints, thus an order effect cannot be ruled out and future studies should evaluate each of these outcomes independently to capture the duration of the effect for each measure. The lack of effect on H-reflex could be explained by the order of testing. The H-reflex was assessed after dynamometry assessments (CAR, AMT, MEP amplitude) following the intervention, and may have returned to its baseline level by this time. This seems in line with previous studies indicating that effects of vibration on the H-reflex seem to last at least 5 minutes, but less than 10 minutes.[57,58] Additionally, we only assessed AMT, and MEP amplitude at 120% of AMT. These measures are indicative of overall corticomotor function, and do not reveal changes in intracortical inhibitory and facilitatory processes. Future studies are necessary to ascertain the specific neurophysiologic mechanisms underlying the alteration in muscle function following WBV and LMV.

Conclusions

This study demonstrated a reduction in AMT and increase in CAR following WBV and LMV in a sample of patients with ACLR. These findings indicate that WBV and LMV are appropriate methods to acutely increase quadriceps function, and could be useful rehabilitative tools for patients with deficits in quadriceps function. Future studies are needed to determine if implementing WBV and LMV with traditional strengthening leads to improved quadriceps function, and if these treatments lessen the risk of posttraumatic OA.

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