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TEMPORAL NEUROMUSCULAR ALTERATIONS OF THE QUADRICEPS AFTER UNILATERAL ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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TEMPORAL NEUROMUSCULAR ALTERATIONS OF THE QUADRICEPS AFTER UNILATERAL ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

DISSERTATION

Submitted as partial fulfillment of the requirements for
the degree of Doctor of Philosophy in the
Department of Rehabilitation Sciences

By

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Lexington, Kentucky

2016

ABSTRACT

TEMPORAL NEUROMUSCULAR ALTERATIONS OF THE QUADRICEPS AFTER UNILATERAL ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

Objective: The primary aim of this research was to examine the temporal pattern of neuromuscular quadriceps deficits in both the involved and uninvolved limbs of patients assigned to the control group after anterior cruciate ligament reconstruction (ACLr), by assessing quadriceps strength, voluntary activation, and corticomotor excitability prior to surgery (baseline), three months after ACLr, and six months after ACLr. A secondary aim of this research was to determine whether quadriceps strength, voluntary activation, and/or corticomotor excitability assessed in patients prior to ACLr and/or at three months after surgery, is predictive of lower extremity postural control and/or self-reported function at six months after ACLr. Lastly, a tertiary aim of this research was to determine if a 12-week home-based neuromuscular electrical stimulation (Home-NMES) program elicits greater bilateral improvements in quadriceps strength, voluntary activation, and corticomotor excitability of patients at three and six months after ACLr compared to a 12-week standard home-exercise program (control group). Participants: Fifty patients scheduled to undergo unilateral ACLr were randomly allocated to the home-NMES group (19 Female, 6 Male; age: 18.9 ± 5.4 years; height: 170.8 ± 9.7 cm; weight: 74.6 ± 18.5 kg; 28.0±20.0 days-post-injury) or control group (14 Female, 11 Male; age: 19.4 ± 4.5 years; height: 171.1 ± 11.5 cm; weight: 70.7 ± 11.9 kg). Methods: A randomized clinical trial design was used in this study. Prior to ACLr, isometric quadriceps strength and voluntary quadriceps activation were assessed in both limbs of patients, and corticomotor excitability was assessed in the involved limb. Three days after ACLr, both groups were instructed to begin their allocated interventions. The Home-NMES group administered NMES to their involved limb's quadriceps three sessions a day for 15 minutes, and five days a week for 12 weeks using a portable NMES device. The control group was treated according to the current standard-of-care, but they were also instructed to perform volitional isometric quadriceps contractions for the same duration and frequency as the Home-Based NMES protocol. The outcomes measures were reassessed in both groups at three and six months post-ACLr. Main Outcome Measures: Quadriceps strength and voluntary activation were assessed using maximal voluntary isometric contractions and the superimposed burst technique, respectively. Normalized

peak knee extension torque and central activation ratio were used to quantify isometric quadriceps strength and activation, respectively. Corticomotor excitability was evaluated with transcranial magnetic stimulation, and quantified with active motor threshold). The Y-balance test anterior reach (YBT-A) and Knee Injury and Osteoarthritis Outcome Score (KOOS) were used to assess the patients lower extremity knee function at six months post-ACLr. Statistical Analyses: Specific Aim 1: A 2x3 (limb x time) mixed model, ANOVA with repeated measures was performed in the control group to assess differences between the involved limb and the uninvolved limb for isometric quadriceps strength, and voluntary quadriceps activation over time. A one-way mixed model, ANOVA with repeated measures was performed in the control group to assess differences in corticomotor excitability over time. Post-hoc comparisons were performed when appropriate. Specific Aim 2: Separate, mixed model, linear regression analyses were performed in the control group (involved limb) to determine the effect that the neuromuscular quadriceps outcome measures assessed at baseline and 3 months post-ACLr, had on lower extremity knee functional outcome measures assessed at 6 months post-ACLr. Specific Aim 3: A 2x2x3 (group x limb x time) mixed model, ANOVA with repeated measures was performed to assess group differences between the involved limb and the uninvolved limb in isometric quadriceps strength, and voluntary quadriceps activation over time. A 2x3 (group x time) mixed model, ANOVA with repeated measures was performed to assess group differences in corticomotor excitability over time. Post-hoc comparisons were performed when appropriate. Results: Aim 1: Patients demonstrated lower quadriceps strength on their involved limb compared to their uninvolved limb at baseline, three months post-ACLr, and six months post-ACLr. Quadriceps strength progressively decreased in the involved limb of patients from baseline to 3 months post-ACLr, baseline to 6 months post-ACLr, and increased from 3 months to 6 months post-ACLr. Quadriceps strength was also decreased in the uninvolved limb of patients from baseline to 6 months post-ACLr.). Irrespective of when it was assessed, voluntary quadriceps activation was higher in the involved limb of patients compared to their uninvolved limb. There were no changes in corticomotor excitability of the involved limb over time. Specific Aim 2: The quadriceps strength of patients at three months post-ACLr had a significant positive effect on their 6-month YBT-A performance KOOS score.). Neither voluntary quadriceps activation or corticomotor excitability or AMT (at baseline or 3-month post-ACLr) had a significant effect on any of the 6-month lower extremity functional outcome measures**.** Specific Aim 3: Irrespective of limb or when it was assessed, quadriceps strength was higher in the control group compared to the Home-NMES group. Both groups demonstrated lower quadriceps strength on their involved limbs compared to their uninvolved limbs at baseline, three months post-ACLr, and six months post-ACLr. Quadriceps progressively decreased in the involved limbs of both groups from baseline to three months post-ACLr and baseline to six months post-ACLr, and increased from three months to six months post- ACLr. At baseline, voluntary quadriceps activation was higher in the involved limbs of both groups compared to their uninvolved limbs. There were no

group differences or changes over time observed in the involved limb of both groups with corticomotor excitability. Conclusion: Although quadriceps weakness is more apparent in the involved limb of patients after ACLr, the quadriceps strength of their uninvolved limb was also affected. Clinicians are encouraged to not rely on a quadriceps strength limb symmetry index when making return-sport-decisions for their patients after recovering from ACLr. The quadriceps in the uninvolved limb of patients demonstrated more inhibition, which may explain the quadriceps strength deficits observed in the uninvolved limb of patients following ACLr. To reduce the risk of subsequent injury upon return-to-sport and protect against the development of knee OA, we recommend that clinicians incorporate bilateral interventions aimed at restoring quadriceps strength and disinhibiting the quadriceps. Intensive quadriceps strengthening should be performed in the early stages of ACLr rehabilitation, so that lower extremity function can be improved in patients later on. Lastly, the effectiveness of home-based NMES as a modality for restoring quadriceps strength and activation in patients after ACLr is inconclusive. Home-based NMES provides patients with the ability to receive higher doses of NMES to the quadriceps; but its effectiveness may be limited by low contraction intensities and poor treatment compliance in patients.

Keywords: anterior cruciate ligament reconstruction, quadriceps, neuromuscular, electrotherapy

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April 29th, 2016

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To whomever reads this,
I hope that you find the information to be of some value,
and that the degree of disuse atrophy and myopia that I incurred while writing this
is evidenced by the comprehensiveness

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GOD: You know that there were times when I failed to put you first during this stage of my life. Thank you for being patient with me. I would be nothing without you.

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LIST OF ABBREVIATIONS

%ACT……Percent Activation
ACL……Anterior Cruciate Ligament
ACLr……Anterior Cruciate Ligament Reconstruction
AMI……Arthrogenic Muscle Inhibition
aMN……Alpha Motoneuron
AMT……Active Motor Threshold
CAR……Central Activation Ratio
CSA……Cross-Sectional Area
EMG……Electromyography
EMGBF……Electromyographic-Biofeedback
ES……Effect Size
GTO……Golgi Tendon Organ
H:M……H_{max}:M_{max}
H_{max}……Maximal H-reflex
H-reflex……Hoffman-Reflex
ICC……Intraclass Correlation Coefficient
IKDC……International Knee Documentation Committee
ITT……Interpolated Twitch
KET……Knee Extension Torque
KOOS……Knee Injury and Osteoarthritis Outcome Score
LMV……Local Muscle Vibration
LSI……Limb Symmetry Index
MDC……Minimal Detectable Change
MEP……Motor Evoked Potential
M_{max}……Maximal M-wave
MRI……Magnetic Resonance Imaging
MVIC……Maximal Voluntary Isometric Contraction
NMES……Neuromuscular Electrical Stimulation
NQD……Neural Quadriceps Dysfunction
OA……Osteoarthritis
OR……Odds Ratio
PRO……Patient Reported Outcome
QAF……Quadriceps Activation Failure
SEM……Standard Error of Measure
SIB……Superimposed Burst
SLH……Single-Leg Hop
sTMS……Single-Pulsed Transcranial Magnetic Stimulation
TENS……Transcutaneous Electrical Nerve Stimulation
TES……Transcranial Electrical Stimulation
TMS……Transcranial Magnetic Stimulation
WBV……Whole-Body Vibration
WDR……Wide Dynamic Range
yMN……Gamma Motoneuron

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Anterior cruciate ligament (ACL) injuries are one of the most common knee-joint injuries seen in orthopaedics, with up to one quarter of a million of these injuries occurring in the United States each year.[1] The majority of ACL injuries occur in young athletes who participate in high-risk sports, such as football, soccer, basketball, and skiing. ACL reconstruction (ACLr) is the recommended treatment for patients diagnosed with ACL injuries in effort to restore knee-joint stability, preserve the menisci, and allow patients to return to their desired levels of physical activity. The Centers for Disease Control and Prevention estimated that over 100,000 ACL surgeries are performed annually.[2] However, there are several postoperative side effects observed in patients following ACLr that must be considered.

Compared to healthy individuals, patients who have had previous ACLr have demonstrated decreased functional performance,[3-10] and reported reduced levels of function and quality of life.[8,9,11,12] Schmitt and colleagues[8] reported that in patients who were cleared to return to sport after unilateral ACLr demonstrated greater limb asymmetry on functional hop test, and lower self-reported function compared to healthy athletes of similar age, height, and weight. In addition, unilateral ACLr has been repeatedly shown to alter lower extremity biomechanics in patients during walking,[13] running,[14,15] and jumping/landing tasks.[16-20] Lastly,

ACLr does not protect patients from the development of knee osteoarthritis (OA), an unforgiving and incurable disease that is associated with both disability and mortality.[21,22] Within the first decade after ACLr, it has been reported that over one third of patients develop knee OA, and this prevalence approaches 50% by the second decade.[23] Furthermore, patients who undergo ACLr are found to have a 29% higher odds of developing knee OA compared to those who are ACL-deficient.[23]

Perhaps the most apparent side effect that is observed in patients after ACLr is a persistent quadriceps strength deficit in the involved limb. Although quadriceps weakness is also present in patients after ACL injury, it is further exacerbated after they undergo ACLr.[3,24-31] Studies have reported quadriceps strength deficits in patients beyond 12 months and up to 20 years after ACLr.[5,11,25,32-50] Kuenze et al.[48] recently compared the quadriceps strength limb symmetry indices (LSI) of 22 patients who were an average of 2.5 years removed from primary ACLr, and 24 matched, healthy controls. They reported significant group differences in quadriceps strength, with the healthy controls demonstrating nearly symmetrical quadriceps strength (LSI = 97 ± 14%), and the ACLr patients still exhibiting persistent asymmetry beyond 2 years after surgery (LSI = 85 ± 21%). Furthermore, growing evidence demonstrates that the quadriceps strength deficits observed in patients after unilateral ACLr are not specific to the involved limb, but are observed in the uninvolved limb as well.[32,42,45,51,52] Chung et al.[45] recently assessed the temporal changes in bilateral quadriceps strength of 75 patients up to 24 months after unilateral ACLr, and compared their values to 75

matched, healthy controls. As expected, the quadriceps strength on the involved limb was significantly lower than that of the uninvolved limb at each postoperative time point leading up to 24 months ($p < 0.05$), but when these values were compared to that of the healthy control group, both the involved and uninvolved limbs of the ACLr group demonstrated significantly lower quadriceps strength at each time point. Although a LSI is typically used to quantify quadriceps strength deficits in the involved limbs of patients after ACLr, reports such as these suggest that using the uninvolved limb as the reference may deceive clinicians by underestimating the true magnitude of quadriceps weakness that is present. Therefore, it may be more beneficial for clinicians to individually compare the postoperative quadriceps strength of both limbs to the quadriceps strength of the uninvolved limb measured prior to ACLr.

Restoring quadriceps strength in patients after ACLr is a primary focus for clinicians during rehabilitation, due to the association quadriceps weakness has with the aforementioned side effects of ACLr. A number of studies have demonstrated the negative effect quadriceps weakness has on functional performance and self-reported function in patients after ACLr.[3,7-9,11,28,39,48,53-65] Quadriceps strength has been shown to predict 25% ($r^2 = 0.25$) of the variance in single-leg hop distance,[54] and over 60% ($r^2 = 0.61$) of the variance in self-reported function of patients with a prior history of ACLr.[61] Several studies have also demonstrated that quadriceps weakness contributes to the biomechanical alterations observed during dynamic tasks.[54,63,66-72] Ithburn and colleagues[63] recently conducted a study comparing the quadriceps strength and single-leg

drop-landing biomechanics of 93 patients who were eight months post-ACLr, and 47 age-matched healthy controls. They subdivided patients into high-strength and low-strength groups, and then compared the biomechanical data between the three groups. They not only found that both the ACL groups demonstrated greater knee-joint biomechanical asymmetries during landing compared to the healthy controls, but that these asymmetries were even more pronounced in the low-strength ACLr group compared to the high-strength ACLr group.

Perhaps the most detrimental effect quadriceps weakness has is on the knee-joint health of patients after ACLr. During normal gait, three to four times of an individual's bodyweight is transmitted through their knee-joint.[73] To limit excessive joint loading, the quadriceps serve as the primary shock absorber for the knee-joint. During ground contact (weight acceptance), the quadriceps eccentrically contract to absorb the majority of external forces at the knee.[73-75] As a result, the forces transmitted through the knee-joint become dissipated, and minimal stress is placed on articular cartilage.[76,77] Conversely, weakness of the quadriceps would cause higher loads to be transmitted at the knee-joint, and expose the articular cartilage to more contact. Therefore, it has long been hypothesized that quadriceps weakness contributes to the onset and progression of knee OA in patients following ACLr.

Within the past decade, several studies have been able to support this hypothesis through longitudinal investigations.[78-83] Tourville and colleagues[79] prospectively assessed tibiofemoral joint space narrowing and isokinetic knee extension torque (KET) in 38 patients prior to ACLr and 4 years postoperatively.

After follow-up testing, the authors separated patients into narrow and normal joint space groups based upon their 4-year radiographs, and compared the ACLr patients' quadriceps strength to that of 32 healthy controls. At baseline, the quadriceps strength in both ACLr groups was lower than that of healthy controls. However, the peak KET of the narrow ACLr group's was also significantly lower than that of the normal ACLr group. Four years after ACLr, the quadriceps strength of the normal ACLr group improved and was not significantly different compared to healthy controls, while the narrow ACLr group's quadriceps strength remained lower than both the normal ACLr group and healthy controls. Furthermore, a recent systematic review and meta-analysis reported that patients who exhibit early quadriceps weakness have a 65% higher odds of developing knee OA years later (OR = 1.65).[78]

In addition to the quadriceps strength deficits that are observed in patients after ACLr, there are concurrent neural alterations occurring throughout various levels of the central nervous system that result in neural quadriceps dysfunction (NQD). The most evident type of NQD that patients exhibit following ACLr is the inability to voluntary activate the quadriceps on the involved limb.[32,34,51,84-86] This decreased voluntary activation can be explained by a diminished ability to fully recruit the motor units innervating the quadriceps and a reduced motor neuron firing frequency.[87] Healthy individuals without a history of knee injury or surgery have the ability to volitionally activate at least 95% of the available motor units innervating the quadriceps.[88] Therefore, a volitional activation of 95% has been generally accepted as the cutoff value for determining whether or not a patient

has neural inhibition of their quadriceps after ACLr.[89,90] Like quadriceps weakness, quadriceps inhibition has been reported to exist bilaterally in patients after unilateral ACLr, with the nonsurgical limb being equivalent to that of the surgical limb. [32,51,91]

One of the more recent types of NQD that has been observed in patients after ACLr is a modified corticomotor excitability associated with the quadriceps.[34,51,84] Corticomotor excitability is typically assessed by applying transcranial magnetic stimulation (TMS) to the area of the motor cortex where the quadriceps are most represented, and measuring the resulting neuromuscular responses at the quadriceps through surface electromyography (EMG).[92-95] As opposed to quadriceps weakness and inhibition, modifications in corticomotor excitability are not observed immediately after unilateral ACLr.[51] Lepley and colleagues[51] longitudinally assessed the changes in corticomotor excitability of 20 patients before and after undergoing unilateral ACLr. When compared to healthy controls, no differences in corticomotor excitability were found preoperatively or at two weeks postoperatively, but it was lower in patients at six months post-ACLr. However, it remains unknown whether changes in corticomotor excitability occur in patients during the first several months following ACLr, demonstrating the need for more longitudinal studies to assess this outcome.

1.2 SIGNIFICANCE

After knee-joint injury and/or surgery, the knee becomes immobilized due to pain and swelling, causing the quadriceps to atrophy and weaken. As

mentioned above, quadriceps weakness can lead to altered lower extremity mechanics and reduced function, which may predispose patients to future injury such as knee OA. However, the problem is that a majority of studies assessed the correlation between quadriceps strength and observed sequelae (i.e., altered biomechanics, reduced function, knee OA, etc.) in patients cross-sectionally after they returned to sport activity, and were unable to determine whether earlier quadriceps strength deficits explained the sequelae observed in patients later on after ACLr. Answering this question would provide further evidence for clinicians to focus on quadriceps strengthening in patients during the early stages of ACLr rehabilitation.

NQD has been thought to be a driving factor behind the cyclical sequelae (see Figure 1.1).[96] NQD has been shown to explain nearly half of the variance in quadriceps strength of patients after ACLr.[97] Therefore, NQD is thought to contribute to altered lower extremity biomechanics, reduced function, and early knee OA that are observed in patients with quadriceps weakness. However, little to no research has been able to confirm the effect of NQD on these postoperative sequelae. Furthermore, since NQD is believed to limit the ability of patients to regain quadriceps strength after ACLr, postoperative rehabilitation protocols should involve methods to properly target NQD. Traditional rehabilitation protocols that consist of isometric or concentric modes of exercise to enhance quadriceps strength in patients after ACLr have been largely ineffective.[98,99] This led to the introduction and development of disinhibitory interventions. Disinhibitory interventions consist of therapeutic modalities that

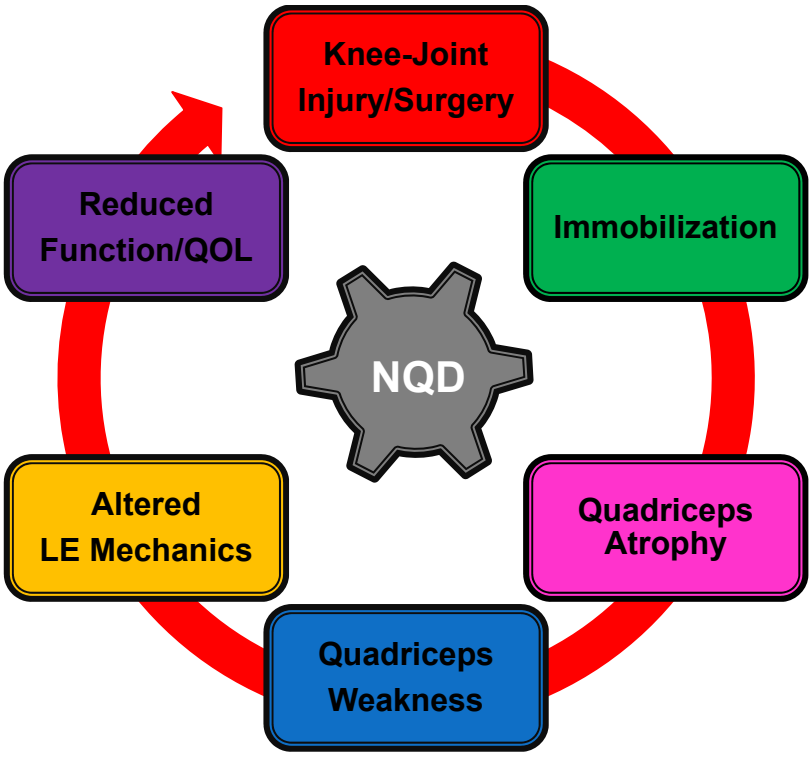

Figure 1.1. Cyclical sequelae of knee-joint injury/surgery. An adapted paradigm from Stokes and Young, 1985, Clinical Science, 67, 7-14.[96]

have been shown to successfully mediate NQD in patients with a history of knee-joint injury/surgery by targeting its underlying mechanisms.[100-102]

Neuromuscular electrical stimulation (NMES) is a motor-based modality which elicits muscle contractions by directly activating the intramuscular nerve branches through surface electrodes at the skin.[103] NMES has been well established in the literature as an effective modality for restoring quadriceps strength in patients after ACLr.[70,104-110] Although these strength improvements can be easily attributed to the muscle hypertrophy,[111-115] it is believed that neural adaptations elicited by NMES are partly responsible for the increases in muscle strength.[111-113,116,117] However, there is conflicting evidence concerning the disinhibitory effects of NMES on removing NQD in patients after knee

injury/surgery. Several studies have reported improvements in the voluntary quadriceps activation of patients with NMES interventions.[116,118-122] Stevens et al.[118] assessed the effect of a quadriceps exercise program supplemented with NMES for patients after total knee arthroplasty. Compared to those patients who did not receive supplemental NMES, the group who received NMES with exercise demonstrated significant improvements in voluntary quadriceps activation at three weeks, six weeks, and six months postoperatively.[101] Other studies have negated the disinhibitory effects of NMES,[123-128] but no study has investigated the disinhibitory effect of NMES in patients after ACLr. Furthermore, portable NMES units have demonstrated promising results in regard to improving outcomes.[129-131] The higher volume of NMES combined with the convenience of home-based NMES, make these units an attractive modality for postsurgical patients. Therefore, research is needed to assess the effect of home-based NMES on improving neuromuscular quadriceps function in patients after ACLr.

1.3 SPECIFIC AIMS

1. **To examine the temporal pattern of neuromuscular quadriceps deficits in both the involved and uninvolved limbs of the patients assigned to the control group after ACLr, by assessing quadriceps strength, voluntary activation, and corticomotor excitability prior to ACLr (baseline), three months after ACLr, and six months after ACLr.** We hypothesized that quadriceps strength and voluntary activation would be lower in the involved limb compared

to the uninvolved limb at each time point. We believed this because previous reviews have demonstrated side-to-side quadriceps strength differences in patients after ACLr at similar time points.[98,132] Secondly, we expected that quadriceps strength and voluntary activation would decrease in the involved limb at three months post-ACLr compared to baseline, and return to baseline values at six months post-ACLr. We believed this because neuromuscular quadriceps function has been found to be more affected within the first few months after ACLr compared to ACL injury,[3,24,27,31,133] and it begins to return to preoperative levels around six months post-ACLr.[24,51] We expected that the corticomotor excitability of the involved limb's quadriceps would progressively decrease over time, and be most pronounced at six months in accordance with the recent findings from Lepley et al.[51] Lastly, we expected that the quadriceps strength and voluntary activation of the uninvolved limb to progressively decrease over time, because recent studies have shown that these two measures are decreased in both limbs of patients after unilateral ACLr.[34,42,45,51,84,91]

2. **To determine whether quadriceps strength, voluntary activation, and/or corticomotor excitability assessed in patients prior to surgery and/or at three months after ACLr, can predict lower extremity postural control and/or self-reported function at six months post-ACLr.** We hypothesized that the patients' quadriceps strength and activation assessed at baseline and three months after

ACLr would significantly influence the lower extremity postural control and self-reported function at six months post-ACLr. We believed this because these measures are sensitive to change within the first few months after ACL injury and reconstruction,[3,24,27,31,133] and they have previously been reported to affect knee function in patients.[53-55,60-62,72,134] Secondly, we expected that corticomotor excitability would have an insignificant influence on these same outcomes, mainly because this measure has been found to be less affected within the first few months after ACL injury and reconstruction.[51]

3. **To determine if a 12-week home-NMES program elicits greater bilateral improvements in quadriceps strength, voluntary activation, and corticomotor excitability of patients at three and six months after ACLr compared to a 12-week standard home-exercise program (control group).** We hypothesized that patients who performed the home-NMES program would demonstrate greater bilateral improvements in quadriceps strength, voluntary activation, and corticomotor excitability at both three and six months post-ACLr compared to patients in the control group. We believed this because of the previous literature that has demonstrated neuromuscular improvements in the quadriceps of patients after NMES interventions,[105,106,118,122] the evidence of NMES targeting cortical areas of the brain,[116,135-137] and the phenomenon of cross-education

that has been observed in the contralateral limb after ipsilateral NMES treatments.[111,138,139]

CHAPTER 2: REVIEW OF LITERATURE

2.1 INTRODUCTION

2.1.1 Evidence of Quadriceps Weakness

Quadriceps weakness is the most prevalent neuromuscular deficit observed in the involved limbs of patients following ACL injury and ACLr. The incidence and progression of quadriceps weakness has been well documented in the literature.[3,5,8,11,24-49,51,52,56,57,59,64,65,86,91,98,132,133,140-179] As a result, quadriceps weakness has become an expected side effect of knee-joint trauma amongst clinicians. Although ACLr is the recommended treatment to restore knee-joint stability and improve function in patients with ACL injuries, it is not an effective treatment for restoring quadriceps strength. In fact, quadriceps weakness is further exacerbated in patients after ACLr compared to when they were without an intact ACL (ACL-deficient).[3,24-31] Moreover, the amount of quadriceps weakness a patient exhibits prior to ACLr has been reported to be directly related to the magnitude of quadriceps strength that will be further lost after ACLr.[27,56,64,147] Therefore, it is important for clinicians to focus their rehabilitation on restoring quadriceps strength in patients both before and after ACLr.

Quadriceps strength is typically assessed by having the patient perform a maximal voluntary contraction of the quadriceps during an open kinetic chain, knee extension task. This can be performed either isometrically (fixed knee-joint angle) or isokinetically (fixed angular velocity), with peak KET being the primary measure of interest (measured in Nm or ft·lbs). An LSI is commonly used to

quantify quadriceps weakness in patients after ACLr, which involves dividing the peak KET produced in the involved limb by the peak KET produce in the uninvolved limb (often reported as a percentage). Previous literature reviews have reported that the average quadriceps strength LSI observed in patients after ACLr was less than 80% at six months post-ACLr,[98,132] and less than 90% at 12 months post-ACLr.[132] A criterion that is regularly used by clinicians when determining whether a patient is ready to return to activity/sport after ACLr, is if their quadriceps strength LSI is equal to or greater than 90%.[8,28,68,180,181] However, most patients are discharged from rehabilitation and receive medical clearance to return to their pre-injury physical activities or sports between six and 12 months after their ACLr.

This incongruity is most likely the result of the clinical methods used to assess quadriceps strength in these patients. An isokinetic dynamometer is referred to as the “gold standard” tool for measuring KET attributed to quadriceps strength. However, these devices are rarely available in physical therapy clinics due to their high financial cost. Therefore, most clinicians resort to manual muscle tests or leg extension machines, which can compromise the validity and reliability of the quadriceps strength assessment. In addition, quadriceps strength LSI is known to be affected by angular velocity used during isokinetic assessments. Several studies have reported insufficient quadriceps strength symmetry (LSI ≤90%) in patients after ACLr when testing (concentrically) at an angular velocity of 60°/s, but when testing at angular velocities of 120°/s or faster, these same patients were able to meet the criterion (LSI

≥90%).[30,31,57,132,133,142,168,178,179] Most recently, Hsiao et al.[31] assessed quadriceps strength LSI in patients after ACLr using a variety of angular velocities (isokinetic) as well as knee-joint angles (isometric). When compared to the pre-ACLr values, significant decreases in quadriceps strength LSI were only observed at the slower angular velocities (concentric at 50°/s and 100°/s) and the larger knee flexion angles (70° and 90°). Although this phenomenon has yet to be fully understood from a physiological standpoint, it must be considered by clinicians when performing quadriceps strength assessments on these patients. Current evidence suggests that quadriceps strength should be tested isometrically at 70-90° of knee flexion,[31] and/or isokinetically at an angular velocity of 60°/s (concentric) in order to detect asymmetries in patients following ACLr.[98,132]

The length of time quadriceps weakness has been found to persist in patients following ACLr is of equal concern. Studies have reported quadriceps strength deficits in patients beyond 12 months and up to 20 years after ACLr.[5,11,25,32-50] Kuenze et al.[48] recently compared the quadriceps strength LSI of 22 patients (average of 2.5 years removed from primary ACLr), and 24 matched, healthy controls of comparable age, height, and weight ($p > 0.05$). After assessing isometric quadriceps strength (90° of knee flexion) bilaterally in both groups, they reported significant group differences in quadriceps strength LSI ($p = 0.03$). The healthy controls demonstrated nearly symmetrical quadriceps strength (LSI = 97 ± 14%), whereas the ACLr patients still exhibited persistent asymmetry beyond two years after surgery (LSI = 85 ± 21%). The persistent quadriceps weakness that is observed in patients with a history of ACLr is likely the result of a

combination of multiple factors. First, this may mean that patients are being released from rehabilitation prematurely and the current quadriceps strengthening interventions used in rehabilitation are not efficacious. Secondly, patients may have achieved the recommended 90% LSI for quadriceps strength at their date of clearance to return to activity/sport, but they failed to maintain that symmetry years after their ACLr. Lastly, patients may have developed sequelae such as patellofemoral pain or early knee osteoarthritis, which have also been associated with quadriceps strength deficits.[59,182]

It must be mentioned that the attenuation of quadriceps strength that has been consistently observed in the involved limbs of patients after unilateral ACLr, has also been reported in these patients' uninvolved limbs.[32,42,45,51,52] Although more research is needed to understand the manifestation of contralateral quadriceps weakness in patients after unilateral ACLr, the available evidence relative to this matter is sufficient to deserve clinical consideration. Chung et al.[45] recently assessed the temporal changes in bilateral isokinetic quadriceps strength (concentric at 60 deg/s) of 75 patients at three, six, 12, and 24 months after unilateral ACLr. In addition, they compared the peak KET values of the ACLr patients to 75 healthy controls who were of equal age, sex, height, weight, and pre-injury physical activity level (via Tegner activity scale). In the ACLr group, the uninvolved limb's peak KET was significantly higher than that of the involved limb at three (266.1 ± 43.7 Nm vs. 178.8 ± 51.2 Nm), six (276.4 ± 42.7 Nm vs. 224.2 ± 58.5 Nm), 12 (276.7 ±44.9 Nm vs. 235.4 ± 56.9 Nm), and 24 months (276.6 ± 42.8 Nm vs. 242.8 ± 55.5 Nm) after ACLr ($p < 0.05$). However,

when these values were compared to that of the healthy control group (290.9 ± 40.1 Nm), both the involved and uninvolved limbs of ACLr group demonstrated significantly lower peak KET at each follow-up time point ($p < 0.05$). Evidence such as this suggests that using the uninvolved limb as the reference when assessing quadriceps strength in patients after unilateral ACLr may underestimate the magnitude of quadriceps strength deficits. Therefore, the quadriceps strength LSI could mask true quadriceps weakness and deceive clinicians when making the decision to return patients to their pre-injury activity/sport after ACLr. For example, a patient may demonstrate greater than 90% quadriceps strength LSI, but if the quadriceps strength of their uninvolved limb has also declined since the initial ACL injury, then the recovery of quadriceps strength on the involved limb may be overestimated by an LSI.

Clearing a patient to return to their pre-injury activity/sport prior to restoring bilateral quadriceps strength may place both of their limbs at risk for subsequent knee-joint injury, and expose the knee to increased contact forces due to the decreased force absorption capabilities from the quadriceps. To unmask the quadriceps strength deficits in the involved limbs of patients and account for the potential deficits of their uninvolved limbs, clinicians are encouraged to not depend on an LSI when assessing the recovery of quadriceps strength in patients after unilateral ACLr. Alternatively, it is recommended that clinicians compare the bilateral peak KET data of their ACLr patients to those of healthy individuals who are of similar age and stature (preferably normalized to bodyweight: Nm/kg or Ft·lbs/lbs). If data from healthy individuals are not

available to clinicians, the second best alternative is to compare the patients' postoperative bilateral quadriceps strength to the preoperative quadriceps strength of their uninvolved limbs after the initial ACL injury. Although acute ACL injury is known to elicit deficits in ipsilateral quadriceps strength, there is no evidence to suggest that acute ACL injury affects quadriceps strength in the contralateral limb. Using these alternative comparison strategies provides clinicians with a clearer representation of quadriceps strength recovery in the involved limbs of patients after ACLr, and allows clinicians to determine if postoperative quadriceps weakness is present in the uninvolved limbs so that adjustments can be made in rehabilitation to correct bilateral quadriceps strength deficits.

2.1.2 Consequences of Quadriceps Weakness

Given the ubiquitous nature of quadriceps weakness in patients who have undergone ACLr, and its tendency to remain years after surgery, it is important to understand the consequences of persistent quadriceps weakness. Since the quadriceps are the largest muscle group of the lower extremity, which function to facilitate movement and absorb external forces, it is expected that weakness in this muscle group would lead to functional limitations in patients after ACLr. The following section will discuss the consequences of quadriceps weakness on the functional performance, self-reported function, lower extremity biomechanics, knee-joint health, and general health of individuals.

Functional Performance

Single-leg hop (SLH) testing is one of the more common methods used by clinicians to assess lower extremity functional performance in patients after ACLr. This testing consists of either a single hop for distance,[183-185] a timed 6-meter hop,[183] a straight triple hop for distance,[185] a cross-over triple hop for distance,[185] or a combination of the four. SLH testing is regularly used in conjunction with quadriceps strength testing for return to activity/sport decision making, with the same criteria (≥ 90% LSI) being used to determine a patient's physical readiness to return to their pre-injury level of physical activity. In fact, growing evidence has shown that quadriceps strength and SLH performance is higher (or more symmetrical) in patients who return to activity/sport after ACLr compared to those who do not.[180,186,187]

Numerous studies have reported that quadriceps weakness negatively affects a patient's performance on SLH tests after ACLr.[3,7-9,28,39,53-59] Keays et al.[28] assessed the isokinetic peak KET (concentric at 60 and 120 deg/s), single hop for distance, triple hop for distance, and performance on several agility tests in 31 patients before unilateral ACLr and at their 6-month postoperative follow-up. The authors then sought to determine whether quadriceps strength was correlated with functional performance before and after ACLr. Before ACLr, significant correlations were observed between isokinetic quadriceps strength (at both speeds) and performance on single (60 deg/s: $r = 0.55$, 120 deg/s: $r = 0.53$; $p < 0.01$) and triple hop tests (60 deg/s: $r = 0.55$, 120 deg/s: $r = 0.59$; $p < 0.01$). However, significant correlations were reported for the agility tests at six months after ACLr (60 deg/s: $r = 0.47 – 0.53$, 120 deg/s: $r = 0.46 – 0.52$; $p \leq 0.01$), and

stronger correlations were also observed between quadriceps strength and the single (60 deg/s: r = 0.66, 120 deg/s: r = 0.74; p < 0.00) and triple hop tests (60 deg/s: r = 0.62, 120 deg/s: r = 0.74; p < 0.001). This study not only demonstrated the relationship between quadriceps strength and lower extremity functional performance, but that this relationship is even stronger in patients following ACLr. A recently published study by Palmieri-Smith and colleagues[54] reported that isokinetic quadriceps strength LSI (concentric at 60 deg/s) significantly predicted 25% (r^2 = 0.25; p < 0.002) of the SLH for distance LSI in patients six to eight months removed from ACLr.

There is also some evidence to suggest that postoperative quadriceps strength is related to vertical jump height in patients after ACLr.[4,7] Laudner et al.[4] recently assessed isokinetic peak KET (concentric at 60 and 300 deg/sec), and both single and double leg vertical jump height in 26 patients who were an average of eight (7.8 ± 1.9) months post-ACLr and 26 healthy controls (matched by height and weight). The bilateral differences in single leg vertical jump height and peak KET (at both speeds) were significantly greater in patients than in the healthy controls (p = 0.001). Furthermore, they found that isokinetic peak KET was significantly correlated with both single (60 deg/s: r = 0.71, 300 deg/s: r = 0.74; p < 0.05): and double leg (60 deg/s: r = 0.64, 300 deg/s: r = 0.63; p < 0.05) vertical jump height in patients. This data suggest that quadriceps weakness not only mitigates single-leg jump performance in the horizontal direction, but in the vertical direction as well.

Altogether, this evidence demonstrates the importance of restoring quadriceps strength in patients after ACLr in regards to improving lower extremity functional performance and preparing them to return to activity/sport. Therefore, clinicians should continue to emphasize quadriceps strengthening in the later stages of rehabilitation to facilitate improvements in lower extremity function.

Self-Reported Function

Self-reported function is another outcome used by clinicians to determine how well patients perceive their knee-joint pain, symptoms, and function following ACLr. It is used to determine how successful ACLr and postoperative rehabilitation are as treatments for ACL injuries. Questionnaires are used to assess self-reported function and collect data on patients before and/or after ACLr. The questionnaires that are currently used to assess self-reported function in patients who have undergone ACLr are the International Knee Documentation Committee (IKDC) form and Knee Osteoarthritis Outcome Score (KOOS). The IKDC is a valid and reliable questionnaire for assessing self-reported function in patients after ACL injury or reconstruction.[188,189] The KOOS consists of 18 questions that pertain to knee-joint symptoms, and performance during dynamic and daily activities. Excellent validity and reliability has been reported for the KOOS in both ACL injury and ACLr patient populations.[190-193] It consists of 42 questions that are categorized into five domains: knee-joint symptoms, knee-joint pain, function with activities of daily living, function with sports/recreation, and quality of life. Both the IKDC and KOOS (total) are scored on a 0-100 scale, with 100 representing the highest self-reported function. However, clinicians are

urged to analyze and interpret each domain of the KOOS separately. Therefore, each KOOS domain is typically scored separately on a 0-4 scale and transformed into a percentage (0-100%).

Both the IKDC and KOOS,[8,48,55,60-63] as well as other questionnaires pertaining to self-reported function (Cincinnati Knee Score, Lysholm, and Tegner activity scale),[11,39,64,65] have been shown to be related to quadriceps strength of patients after ACLr. Perhaps the most impressive study that supported this relationship was that done by Pietrosimone and colleagues.[61] They assessed isometric peak KET (at 90° of knee flexion) and IKDC scores in 15 patients who were an average of 54.4 (± 40.9) months removed from ACLr, and performed a linear regression analysis to determine the amount of variability in self-reported function that could be explained by their quadriceps strength. They discovered that isometric quadriceps strength predicted over 60% ($r^2 = 0.61$; $p = 0.01$) of the variance in the IKDC scores of patients who have a history of ACLr. This finding demonstrates that the majority of self-reported function (via IKDC) in patients after ACLr can be explained by their quadriceps strength, and that quadriceps weakness can severely limit these patients' perceived function.

Lower Extremity Biomechanics

Assessing a patient's lower extremity biomechanics after ACLr is also important to determine whether there are kinematic and/or kinetic patterns that give insight into specific weaknesses or place patients at risk for subsequent injury. 3-D motion analyses are known as the gold standard for assessing biomechanical patterns in individuals. They can provide information relative to

joint angles, joint moments (internal and external), and vertical ground reaction forces during various dynamic tasks (i.e., walking, running, jumping, etc.). Although 2-D motion analyses are less expensive and can provide similar information, they do not possess the same level of validity and reliability as 3-D motion analyses. Therefore, a 3-D motion analysis is typically used by researchers when assessing lower extremity biomechanics in patients before and/or after ACLr.

Unilateral ACLr has been repeatedly shown to alter lower extremity biomechanics in patients during walking,[13] running,[14,15] and jumping/landing tasks.[16-20] However, several studies have demonstrated that quadriceps weakness contributes to the biomechanical alterations observed during these tasks.[54,63,66-72] Ithburn and colleagues[63] recently conducted a study comparing the isometric quadriceps strength LSI (at 60° of knee flexion) and single-leg drop-landing biomechanics of 93 patients (mean age, 17.3 years) who were eight months post-ACLr, and 47 age-matched healthy controls (mean age, 17.0 years). After assessing the quadriceps strength of the ACLr group, they subdivided patients into high-strength (≥ 90% LSI) and low-strength (< 80% LSI) groups, and then compared the biomechanical data between the three groups (high-strength ACLr, low-strength ACLr, and healthy control). They reported that both ACL groups demonstrated greater knee-joint biomechanical asymmetries during landing compared to the healthy controls. Specifically, decreased knee flexion excursion (low-strength, $p < 001$; high-strength, $p = 0.02$) and peak internal knee extension moments (low-strength, $p < 001$; high-strength, $p < 0.01$), and peak

increased trunk flexion angle (low-strength, $p < 001$; high-strength, $p = 0.03$) were observed in the involved limbs of the ACLr groups. However, knee flexion excursion ($p = 0.03$) and peak internal knee extension moments ($p = 0.03$) were further decreased, and peak trunk flexion angle was increased ($p < 0.01$) in the involved limbs of the low-strength ACLr group compared to the high-strength ACLr group. The authors also performed a linear regression analysis, and reported that isometric quadriceps strength LSI was a significant predictor for knee flexion excursion ($r^2 = 0.12$, $p < 0.001$), peak internal knee extensor moment ($r^2 = 0.10$, $p < 0.001$), and peak trunk flexion angle ($r^2 = 0.15$, $p < 0.001$). Similar results have been previously reported by Lewek et al.[68] They discovered that quadriceps strength LSI in patients after ACLr significantly predicted peak knee flexion angles ($r^2 = 0.25$, $p < 0.05$) and peak internal knee extension moments ($r^2 = 0.38$, $p < 0.01$) during a jogging task.

In another study by Schmitt et al.,[67] they reported that external biomechanical forces are also distributed differently between the limbs of patients at the time of return to activity/sport after unilateral ACLr. Similar to Ithburn et al.,[63] they divided patients into high (≥ 90% LSI) and low-strength (< 85% LSI) groups, and compared biomechanical data to that of an age-matched, healthy control group. However, instead of performing single-leg landing task, the participants performed a double-leg drop vertical jump task. Compared to the high-strength ACLr and healthy control groups, the low-strength ACLr group demonstrated greater asymmetry in peak external knee flexion moments ($p < 0.001$, $p < 0.001$, respectively), peak vertical ground reaction forces($p < 0.001$, p

< 0.001, respectively), and peak loading rates ($p < 0.01$, $p < 0.05$, respectively). Specifically, all three biomechanical measures were significantly lower in the involved limbs and higher in the uninvolved limbs of the low-strength ACLr group. There were no significant differences between the high-strength ACLr group and healthy control group in regards to biomechanical limb symmetries ($p < 0.05$).

Knee-joint excursion and internal knee extension moments are biomechanical measures that are believed to be controlled through an eccentric contraction of the quadriceps.[68] Therefore, a reduction of these two measures may be an indicator of quadriceps weakness. The increased trunk flexion angle observed in ACLr patients is said to be a compensatory biomechanical strategy to accommodate for quadriceps weakness by shifting ground reaction forces anterior to the knee.[16] Furthermore, the asymmetrical distribution of external forces between limbs of patients who exhibit quadriceps weakness after ACLr has been theorized to place both knee-joints at risk for subsequent knee-joint injury.[67,194] While the ipsilateral quadriceps weakness exhibited in patients after unilateral ACLr may decrease their ability to absorb shock at the surgical knee-joint, their increased reliance on the contralateral limb may also overload the nonsurgical knee-joint. Although ACLr alone has an effect on lower extremity biomechanics, quadriceps weakness seems to further contribute to biomechanical alterations in these patients.

Knee-Joint Health

The development of knee OA is a common side effect in patients who sustained ACL injuries.[195,196] Although ACLr is a successful treatment for

restoring knee-joint stability in these patients, it is largely ineffective at preventing the development of knee OA. Within the first decade after ACLr, it has been reported that over one third of patients develop knee OA, and this prevalence approaches 50% by the second decade.[23] Furthermore, patients who undergo ACLr are found to have a 29% higher odds of developing knee OA compared to those who are ACL-deficient.[23] These statistics are interesting given that ACLr has also been shown to exacerbate quadriceps weakness in patients who sustain ACL injuries, which is why many researchers have hypothesized quadriceps weakness to be a risk factor for the onset and progression of knee OA in these patients.[73-75,197]

During normal gait, three to four times the bodyweight of a healthy individual is transmitted through their knee-joint.[73] To limit excessive joint loading, the quadriceps serve as the primary shock absorber for the knee-joint. During ground contact (weight acceptance), the quadriceps contract eccentrically to absorb the majority of external forces at the knee.[73-75] As a result, the forces transmitted through the knee-joint become dissipated, and minimal stress is placed on articular cartilage.[76,77] Therefore, weakness of the quadriceps would likely cause higher loads to be transmitted at the knee-joint, and expose the articular cartilage to more contact. Two studies[76,198] used a femoral nerve block to temporarily paralyze the quadriceps of healthy individuals, and assessed the change in loading rate at the knee during gait. After quadriceps paralysis, the loading rate at the knee during heel-strike increased to more than twofold in these individuals. The authors concluded that the increase in knee-joint loading

was a direct reflection of the inability of the quadriceps to absorb external forces during weight acceptance.

Since quadriceps weakness was first hypothesized to be related to the onset and progression of knee OA, considerable research has been devoted to determining the legitimacy of this relationship. As of today, there are numerous studies that have been able to establish an association between quadriceps weakness and knee OA in patients.[78-83,182,199-214] Slemenda and colleagues[212] were one of the first groups to demonstrate the integral role quadriceps strength has on lowering the risk of knee OA in patients. They assessed isokinetic KET (concentric at 60 deg/s) and radiographic tibiofemoral knee OA in 462 individuals who were over the age of 65 years. Those individuals with Kellgren-Lawrence grades greater or equal to 2 were classified as having knee OA, and those who graded less than 2 were classified as healthy controls. Compared to the healthy controls, those individuals with radiographic knee OA had approximately 20% less quadriceps strength ($p < 0.01$). In addition, they reported that for every 10 ft·lb increase in isokinetic KET, there was a 20% lower odds of radiographic knee OA (OR = 0.80, CI = 0.71-0.90) and 29% lower odds of symptomatic knee OA (OR = 0.71, CI = 0.59-0.87). Thus, higher quadriceps strength served as a protector against knee OA in older individuals. These results were later supported by Baker et al.,[210] who reported high isometric KET (at 90° of knee flexion) to be a significant protector against mixed knee OA (tibiofemoral and patellofemoral) in patients who were 60 years or older (OR = 0.4-0.5, CI = 0.3-0.8).

However, the limitation of these two studies is that their assessments were cross-sectional, which is the case for the majority of studies in this area.[199-203,205,207-209,211,213,214] In other words, these studies are unable to discern whether OA precedes quadriceps weakness, or quadriceps weakness precedes OA. Therefore, longitudinal follow-up studies are ideal for determining the true effect quadriceps weakness has on the onset and progression of knee OA. There have been a handful of longitudinal studies that have been able to demonstrate that quadriceps weakness is a significant contributor to the onset of knee OA in patients.[78-83,212] Tourville and colleagues[79] assessed tibiofemoral joint space narrowing and isokinetic KET (concentric at 60 deg/s) in 38 patients prior to ACLr (baseline) and four years postoperatively. After follow-up testing, the authors separated patients into narrow and normal joint space groups based upon their 4-year radiographs. They also compared the ACLr patients' quadriceps strength to that of 32 healthy controls of similar age, body mass index, and physical activity level. At baseline, the quadriceps strength in both ACLr groups was lower than that of healthy controls ($p < 0.001$). However, the quadriceps strength of the narrow ACLr group's peak KET was also significantly lower than that of the normal ACLr group ($p = 0.04$). Four years after ACLr, the quadriceps strength of the normal ACLr group (95 ± 10.3% LSI) improved and was not significantly different compared to healthy controls (99 ± 11.6% LSI, $p > 0.05$), while the narrow ACLr group's quadriceps strength (83 ± 23.1% LSI) remained lower than both the normal ACLr group ($p = 0.04$) and healthy controls ($p = 0.01$). A more recent systematic review and meta-analysis by Oiestad et al.[78] reported that

initial quadriceps weakness increased the odds of patients developing knee OA (radiographic and/or symptomatic) by 65% (OR = 1.65, CI = 1.23-2.21). While this study concluded that quadriceps is a significant risk factor of knee OA, their analyses only consisted of five longitudinal studies.[82,83,212,215,216]

Compared to the handful of longitudinal studies that have been able to support that the onset of knee OA in patients is related to a history or quadriceps weakness, there are even fewer longitudinal studies available that demonstrate that quadriceps weakness influences the progression of knee OA.[204,206] Both studies assessed initial isokinetic peak KET (concentric at 60 deg/s) in patients diagnosed with knee OA, and divided them into tertiles according to quadriceps strength (low, med, and high strength). At 30-month follow-up, the severity of knee OA was assessed in both studies to determine whether initial quadriceps strength contributed to the progression of knee OA. In the earlier study, Amin and colleagues[206] reported that compared to the patients in the lowest tertile of quadriceps strength at baseline, the patients in the highest tertile had a 60% lower odds of progressive patellofemoral osteoarthritis 30 months later (OR = 0.40, CI = 0.2-0.9). A later study, by Segal et al.,[204] reported that women in the lowest tertile of quadriceps strength at baseline had a 69% odds of having tibiofemoral joint-space narrowing at their 30-month follow-up (OR = 1.69, CI = 1.26-2.28). Although these results are impactful, more studies are needed to confirm the influence quadriceps weakness has on both the onset and progression of knee OA in patients.

General Health

In addition to quadriceps weakness being associated with poor knee-joint health, there is also some evidence showing that quadriceps weakness affects the general health of individuals.[217-220] The progressive loss of quadriceps strength over a period of 11 years has been reported to increase the risk of fragility fracture in men and women who are over 60 years of age.[217] Furthermore, quadriceps strength has been shown to protect against mortality in patients with chronic obstructive pulmonary disorder because it is believed to improve their exercise capacity.[218] Evidence such as this portrays the importance of restoring quadriceps strength in patients after ACLr in order to improve their quality of life and longevity.

2.2 EXPLAINING QUADRICEPS WEAKNESS

Although age, physical activity level, and surgical factors can affect quadriceps strength in patients after ACLr, there are several neuromuscular changes that occur in the quadriceps that can explain the persistent quadriceps weakness observed in this patient population. The remainder of this review will be devoted to the providing evidence on the neuromuscular changes that occur in the quadriceps after ACLr, understanding the mechanisms and ramifications of these changes, and discussing the disinhibitory interventions that can be used to correct these changes and restore quadriceps strength in patients after ACLr.

2.2.1 Modified Quadriceps Morphology

Evidence of Quadriceps Atrophy

Along with quadriceps weakness, atrophy of the quadriceps can be just as evident on the involved limbs of patients following unilateral ACLr. Quadriceps atrophy has been consistently reported in the literature for patients who have sustained an ACL injury and/or have undergone subsequent ACLr. Thigh circumference,[47,221-226] quadriceps cross-sectional area (CSA) and volume are all measures that have been shown to decrease following knee-joint trauma in these patient populations.[33,47,52,91,169,170,225,227-235] Quadriceps CSA and volume are typically assessed using magnetic resonance imaging (MRI) or computed tomography (CT), whereas thigh circumference is typically assessed using a cloth tape measurer. Of these measures, quadriceps CSA and volume are the gold standard for assessing quadriceps atrophy, because unlike thigh circumference, they can partition out adjacent musculature, bone, and adipose tissue. However, the elevated financial costs associated with using an MRI or CT to assess quadriceps CSA and volume are not as economically or clinically feasible as a thigh circumference assessment. A tool that may provide a middle-ground between sensitivity and economy when it comes to assessing quadriceps atrophy is that of diagnostic ultrasound. Diagnostic ultrasound has recently been shown to detect differences in muscle thickness at the quadriceps of patients after ACLr.[236] Its lower cost compared to an MRI and CT, combined with its higher sensitivity compared to thigh circumference make diagnostic ultrasound an attractive alternative tool, yet more research is needed to determine the validity and reliability of diagnostic ultrasound for the assessment of quadriceps atrophy.

Although it is the recommended treatment for restoring knee-joint stability in patients who have sustained ACL injuries, unilateral ACLr does not seem to be an effective treatment to attenuate quadriceps atrophy. Lindstrom et al.[230] recently assessed quadriceps CSA (combining the four quadriceps muscles) in male and female patients who had a history of ACL-deficiency and underwent a subsequent unilateral ACLr. Prior to surgery, the quadriceps CSA was significantly smaller on the involved limb (males: 616.5 ± 24.4 cm^2, females: 441.1 ± 12.5 cm^2) compared to the uninvolved limb (males: 638.4 ± 21.7 cm^2, females: 474.4 ± 12.7 cm^2; $p < 0.001$) of patients. Quadriceps CSA was reassessed in patients one year after unilateral ACLr, and significant quadriceps atrophy was still observed in the involved limb (males: 616.7 ± 24.7 cm^2, females: 433.9 ± 18.6 cm^2) when compared to the uninvolved limb (males: 644.7 ± 20.7 cm^2, females: 473.5 ± 17.9 cm^2; $p < 0.001$). Several studies have supported these findings, demonstrating ipsilateral quadriceps atrophy in patients who are one year or more removed from unilateral ACLr.[47,221,227,236] In fact, Arangio et al.[47] reported differences in quadriceps CSA (averaging the four quadriceps muscles) between limbs in patients who were an average of four years (48.7 months) removed from unilateral ACLr (involved: 51.3 ± 1.3 cm^2, uninvolved: 55.8 ± 1.27 cm^2; $p < 0.001$).

Interestingly, significant quadriceps atrophy has not been consistently observed in patients who are ACL-deficient.[231] Within the past decade, several studies have been performed to determine whether or not differences in quadriceps atrophy exist between ACL-deficient patients who are classified as

non-copers and those classified as copers.[228,231,232] Non-copers represent the majority of ACL-deficient patients. They are defined as patients who report recurrent episodes of knee-joint instability and reduced physical function. Therefore, these patients often undergo ACLr to restore knee-joint stability and improve their physical function. Conversely, copers represent a small cohort of ACL-deficient patients who are able to maintain their pre-injury physical function, without experiencing episodes of knee-joint instability.[237-240] Copers are said to adopt neuromuscular strategies that effectively compensate for their ACL-deficiency, and allow them to return to their pre-injury levels of physical function without requiring ACLr.[231,238,240] A study done by Williams et al.[231] compared quadriceps volume and CSA between ACL-deficient non-copers, ACL-deficient copers, and healthy controls. In ACL-deficient non-copers, quadriceps volume ($p = 0.003$) and CSA ($p = 0.017$) were significantly smaller on the involved limb compared to the uninvolved limb. However, between-limb differences in quadriceps volume and CSA were not observed in either the ACL-deficient copers or healthy controls. When comparing quadriceps volume and CSA limb symmetries (involved/uninvolved) between the three groups, quadriceps volume was significantly smaller in the ACL-deficient non-copers (0.90 ± 0.09) compared to both the ACL-deficient copers (1.01 ± 0.16) and healthy controls (1.01 ± 0.06). These findings suggest that ACL-deficient copers not only adopt neuromuscular strategies to maintain physical function, but they are able to avoid the development of significant quadriceps atrophy. Therefore, the ability of ACL-deficient copers to bypass ACLr may also help to reduce their risk of developing

quadriceps weakness and atrophy that are commonly observed in patients after ACLr.

Evidence of Fiber-Type Changes

Along with muscle atrophy, variations in muscle fiber type have also been demonstrated in the quadriceps of patients following ACL injury or ACLr. Skeletal muscles consists of two primary muscle fiber types: slow-twitch muscle fibers (type I) and fast-twitch (type II) muscle fibers. Type I muscle fibers are slow-oxidative fibers, and they are believed to be responsible for muscle endurance and posture maintenance due to their high resistance to fatigue. Type II muscle fibers can be subdivided into fast-oxidative-glycolytic fibers (type IIa) and fast-glycolytic fibers (type IIx). Both of these type II fiber subtypes are less resistant to fatigue than type I fibers, but type IIa fibers are more resistant to fatigue than type IIx fibers due to their oxidative characteristics. As a whole, type II fibers are believed to be responsible for rapid and powerful muscle contractions, with type IIx being the faster of the two subtypes.

The gold standard for analyzing skeletal muscle fiber types in humans is by taking muscle biopsies and performing immunohistochemical analyses. Muscle biopsies of the quadriceps are typically performed on patients during their arthroscopic ACLr, where muscle samples can be taken from the vastus medialis oblique and/or vastus lateralis muscles while the patient is under anesthesia. These muscle samples are then cross-sectioned and mounted on glass slides. Immunohistochemical analyses are performed to differentiate muscle fiber types under the microscope. This involves staining the muscle samples with antibodies

so that the myosin heavy-chain isoforms associated with slow-twitch and fast-twitch muscle fibers can be correctly identified. Since most quadriceps muscle biopsies are taken from patients during their ACLr procedure, the majority of these data has come from patients with an ACL-deficiency.[235,241-244] Both slow and fast twitch fibers have been reported to be atrophied in the quadriceps of patients who have previously sustained and ACL injury.[235,241-244] However, the majority of the evidence demonstrates that type II fibers within the quadriceps are selectively atrophied more than type I fibers in this patient population.[241-243]

An alternative method that has been used to assess skeletal muscle fiber type changes within the quadriceps of patients after ACL injury and ACLr is EMG median frequency analyses. Although this method is a more crude assessment of muscle fiber type compared to a muscle biopsy, it is much less invasive and more comfortable for patients. A Fast Fourier Transform analysis is performed to convert the EMG signals during an MVIC into a frequency domain, and a power density spectrum is calculated. The power density spectrum is then divided into two regions of equal power to determine the median frequency of motor unit action potentials within the muscle/s of interest. Type I motor units innervate type I (slow-twitch) muscle fibers, and type II motor units innervate type II (fast-twitch) muscle fibers. Type I motor units fire at a lower frequency than Type II motor units, and are the first to be recruited during a voluntary muscle contraction. Therefore, assessing the median frequency of the quadriceps during an MVIC provides information regarding the distribution of muscle fiber types in patients after ACL injury or ACLr, and whether they differ from healthy individuals. Due to

its noninvasiveness, EMG median frequency analyses can conveniently be performed on patients before or after they undergo ACLr. Therefore, as opposed to muscle biopsies, there is much more data from EMG median frequency analyses on patients following ACLr. Furthermore, the evidence has demonstrated a distinct pattern of lower EMG median frequency in the quadriceps on the involved limbs of patients who are ACL-deficient and/or have undergone ACLr.[56,65,86,223] Drecshler et al.[86] compared EMG median frequencies in the quadriceps of patients post-ACLr to those of healthy (sport-matched) controls. They reported a significantly lower mean EMG median frequency in the ACLr group compared to the control group at both one and three months after ACLr ($p < 0.05$). Other studies have reported reduced quadriceps EMG median frequencies in the involved limbs of patients who were six months or longer removed ACLr compared to their uninvolved limbs.[56,65] The reduced quadriceps EMG median frequency observed on the ACLr limb suggests that type II motor units are less activated in these patients, and that the EMG median frequency is predominately represented by the activation of type I motor units. This interpretation may help to explain the findings from the aforementioned muscle biopsy studies as to why type II muscle fibers are selectively atrophied in the quadriceps of patients.

Mechanisms of Modified Quadriceps Morphology

Muscle atrophy can be commonly categorized into two types: disuse atrophy and neurogenic atrophy. Disuse atrophy, given its name, is caused by a period of physical inactivity that results in muscle wasting. This type of atrophy is

commonly seen in patients who are bedridden, or in those who undergo period of joint immobilization, where the surrounding joint musculature is neglected and atrophies. Neurogenic atrophy is more serious than disuse atrophy because it involves the nerve supplying innervation to the involved muscle. Neurogenic atrophy occurs when there is an injury, or disease, of the innervating nerve resulting in an inhibition of the muscle and subsequent atrophy. Disuse atrophy is the type of atrophy that is most likely present in patients following ACLr; however, neurogenic atrophy may also be involved due to the NQD observed in these patients; at topic which will be discussed later in this chapter.

Research efforts of the 21st century have made substantial progress in uncovering the complex physiology behind muscle atrophy and hypertrophy. Both muscle atrophy and hypertrophy are found to involve multiple signaling pathways and molecular mediators, but in general, these processes are regulated by protein turnover within the muscle fibers.[245-247] With muscle hypertrophy, the diameter of muscle fibers are increased through protein synthesis (or decreased protein degradation) and the addition of contractile proteins (in parallel) within muscle fibers. Conversely, muscle atrophy is the result of protein degradation (or decreased protein synthesis), which elicits a breakdown of these contractile proteins, and ultimately, a reduction in the diameter of muscle fibers. A recent study by Mendias et al.[26] sought to assess the fluctuations in pro-atrophy biomarkers circulating in the blood of patients both before and after ACLr. Blood draws were performed on 18 patients prior to surgery and multiple time points after ACLr (3 days, 2 weeks, 5 weeks, 12

weeks, 18 weeks, and 26 weeks). The primary pro-atrophy biomarkers of interest were myostatin and transforming growth factor-β. Both of these cytokines have been shown to directly induce muscle atrophy and reduce muscle force production.[246,248] The authors reported elevated levels of myostatin in patients at three days post-ACLr, and elevated levels of both myostatin and transforming growth factor-β at 2-weeks post-ACLr. Both myostatin and transforming growth factor-β returned to baseline levels at 5-weeks post-ACLr, and they remained stable until 26 weeks post-ACLr. These results indicate that ACLr has an acute excitatory effect on these pro-atrophy biomarkers, which may explain why these patients have persistent quadriceps atrophy and difficulty restoring quadriceps strength.

The mechanisms behind the muscle fiber type variations observed in the quadriceps of patients after ACL injury and/or ACLr is less understood. Stockmar et al.[241] assessed the metabolic profiles (oxidative vs. glycolytic activity) within the vastus medialis oblique muscle biopsies of six patients with ACL-deficiency in addition to immunohistochemical analyses. They reported a decreased muscle fiber diameter that was similar between type I (88.7%, $p < 0.008$) and type II muscle fibers (85.9%, $p < 0.015$) within the quadriceps on the involved limb compared to the uninvolved limb. However, a reduction in glycolytic activity and an oxidative shift was observed within the muscle fibers of the vastus medialis oblique on the involved limb compared to the uninvolved limb. This oxidative shift suggests that a number of type II (fast twitch) muscle fibers either shifted to a type IIa (fast-oxidative) profile, or they transformed into type I (slow twitch)

muscle fibers (less likely). Either way, the fast force production of the quadriceps was sacrificed in these patients.

An alternative (and perhaps combined) mechanism that may explain the differences in muscle fiber type behavior observed within the quadriceps of patients after ACL injury and/or ACLr, is a reduced sensitivity of Ia afferents located at the muscle spindles. Adequate feedback from Ia afferents is necessary for the recruitment of high-threshold (type II) motor units at the quadriceps.[249-252] Therefore, an attenuation of Ia afferent feedback from the muscle spindles within the quadriceps, may contribute to the selective atrophy of type II muscle fibers that has been reported in these patients due to the prolonged inhibition of type II motor units. Reduced Ia afferent sensitivity within the muscles spindles of the quadriceps is believed to be the result of gamma loop dysfunction and/or presynaptic inhibition that occurs in patients after ACL injury and ACLr. Gamma loop dysfunction is believed to occur in these patients as a result of damage to the mechanoreceptors located within the knee-joint capsule and ACL. The afferent feedback from these knee-joint mechanoreceptors are thought control the activation of gamma motor neurons located within the spinal cord that function to regulate the tautness of the muscle spindles. The extensive work done by Konishi and colleagues[52,221,253] has confirmed the presence of gamma loop dysfunction in the quadriceps of patients who have undergone unilateral ACLr. By delivering a vibratory stimulus to the patellar tendon, a reduction in quadriceps strength is observed in healthy individuals due to slackening of the muscle spindles and desensitization of Ia afferents, which inhibits their ability to

recruit type II motor units. However, when the same vibratory protocol is performed on patients after ACLr, the force producing capability of their quadriceps is unchanged compared to their pre-vibratory state. These findings suggest that gamma loop dysfunction exists within the quadriceps of these patients because the damage done to knee-joint mechanoreceptors disrupts gamma motor neuron activation, leading to a persistent slackening of muscles spindles and a desensitization of Ia afferents. As a result, the ability of these patients to recruit fast force producing, type II motor units is reduced, and selective atrophy of type II muscle fibers may be observed due to prolonged disuse.[253]

Pre-synaptic inhibition is a potential mechanism for the quadriceps inhibition that is commonly observed in patients after knee-joint trauma, but it may also contribute to selective atrophy of type II muscle fibers within the quadriceps. Pre-synaptic inhibition pertains to a diminished synaptic feedback from Ia afferents that prevent the activation of alpha motor neurons within the spinal cord. It is believed to be induced by a repetitive activation of Ia afferents,[254] which depletes the amount of neurotransmitters released at the spinal cord.[255-257] Interestingly, the depolarization of joint afferents has also been shown to influence the pre-synaptic behavior of Ia afferents.[258-260] Therefore, it is possible that ACL injury and/or ACLr induces pre-synaptic inhibition due to the disruption of knee-joint mechanoreceptors. If this is true, then pre-synaptic inhibition may work in conjunction with gamma loop dysfunction as a mechanisms of the selective atrophy of type II muscle fibers observed within the

quadriceps of these patients. A further description of the neurophysiology behind gamma loop dysfunction and pre-synaptic inhibition will be discussed later in this chapter.

Ramifications of Modified Quadriceps Morphology

The quadriceps weakness that is observed in the involved limb of patients following ACLr may be partially attributed to these morphological changes that occur within quadriceps. Since muscle hypertrophy improves muscle force output, it is logical to assume that muscle atrophy would lead to strength deficits. Several studies have confirmed the relationship between quadriceps atrophy and quadriceps strength in patients with ACL-deficiency[232] or in those who have undergone ACLr.[40,47,57,91,230] A recent study by Thomas et al.[91] assessed isometric quadriceps strength (at 90° of knee flexion) and quadriceps CSA in 20 patients who were recently cleared to return to full physical activity after undergoing unilateral ACLr (Mean ± SD = 212.89 ± 31.62 days post-ACLr). Both quadriceps strength (148.39 ± 37.91 Nm vs. 212.98 ± 62.57 Nm; $p < 0.001$) and quadriceps CSA (68.81 ±17.8 cm^2 vs. 81.1 ± 21.58 cm^2; $p < 0.001$) were significantly decreased on the surgical limbs of patients compared to their non-surgical limbs. The authors then used a linear regression analysis to determine the association between quadriceps atrophy and quadriceps strength in these patients. The analysis revealed that quadriceps CSA explained nearly 31% of the variance in isometric quadriceps strength in patients following ACLr ($r^2 = 0.307$; $p = 0.011$).

Furthermore, the amount of quadriceps atrophy observed in patients after ACLr has also been correlated with functional tests commonly used by clinicians to determine an athlete's readiness to return to sport.[230] Lindstrom and colleagues[230] assessed quadriceps CSA and one-leg hop function in 37 patients prior to unilateral ACLr and at one year following surgery. Quadriceps CSA was significantly smaller in the involved limb than the uninvolved limb at both pre-ACLr (involved/uninvolved = 0.96 ± 0.01; $p < 0.001$) and one year post-ACLr (0.95 ± 0.02; $p < 0.001$), with no significantly changes being observed across time. One-leg hop distance improved from pre-ACLr to post-ACLr in both the involved (102.6 ± 7.0 cm to 136.9 ± 6.9 cm; $p < 0.001$) and uninvolved limbs (123.4 ± 6.7 cm to 146.7 ± 6.5 cm; $p < 0.001$) of patients, with improvements in the involved limb being greater than the uninvolved limb ($p = 0.001$). The most interesting finding was the significant correlations observed between quadriceps CSA and one-leg hop function of patients. At one year post-ACLr, the involved/uninvolved quadriceps CSA ratio were strongly correlated with one-leg hop distance involved/uninvolved leg ratio ($r = 0.63$; $p < 0.001$), triple-hop distance involved/uninvolved leg ratio ($r = 0.68$; $p < 0.001$), and 6-m timed-hop involved/uninvolved leg ratio ($r = 0.7$; $p < 0.001$). Therefore, the negative effect that quadriceps atrophy has on a patient's quadriceps strength after ACLr may translate to decreased performance during physical activities that involve explosive movements.

There is much less evidence demonstrating the association between muscle fiber type changes and quadriceps strength in patients after ACL injury

and/or ACLr. This is largely due to the difficulty of translating microscopic cellular changes to a macroscopic level. However, the available evidence on the ramifications of EMG median frequency changes in quadriceps of these patients does hold some merit. In an older study by McNair and Wood,[261] they assessed for differences in quadriceps EMG median frequency between patients with ACL-deficiency who demonstrated different quadriceps strength profiles. Seventeen patients with chronic ACL-deficiency were separated into minimal quadriceps weakness and maximal quadriceps weakness groups. After analyzing each patient's quadriceps EMG median frequency (vastus lateralis) on their involved limb, a significantly higher EMG median frequency was observed in the minimal quadriceps weakness group compared to the maximal quadriceps weakness group ($p < 0.05$). The authors concluded that the group differences were due to a greater degree of type II muscle fiber atrophy present within the maximal quadriceps weakness group. A later study by McHugh and colleagues[56] found that preoperative quadriceps EMG median frequency was moderately correlated with postoperative isometric quadriceps strength in patients who were six months removed from ACLr ($r = 0.54$, $p < 0.001$). Surprisingly, this same study found preoperative quadriceps EMG median frequency to be significantly correlated with one-leg hop distance in patients at six months post-ACLr ($r = 0.35$; $p < 0.05$). These findings are supported by a more recent study that reported moderate correlations between knee function (via Cincinnati Knee Score) and EMG median frequency limb symmetries (involved/uninvolved) of the vastus lateralis ($r = 0.48$; $p = 0.018$) and vastus medialis oblique ($r = 0.67$; $p = 0.001$) muscles in thirteen

athletes who were six to nine months removed from unilateral ACLr an cleared to return to sport.[65] More studies are necessary to determine the global impact muscle fiber type changes have on both the quadriceps function and lower extremity function of patients following ACLr.

2.2.2 Neural Quadriceps Dysfunction

Evidence of Quadriceps Inhibition

In addition to the morphological alterations taking place in the quadriceps after ACLr, there are concurrent neural alternations occurring both within the quadriceps and throughout various levels of the nervous system. The most evident neural deficit observed in patients after ACLr is their inability to voluntary activate the quadriceps on the involved limb.[32,34,51,84-86] The decrease in voluntary activation can be explained by a diminished ability to fully recruit the motor units innervating the quadriceps and a reduced motor neuron firing frequency.[87] Healthy individuals without a history of knee injury or surgery have the ability to volitionally activate at least 95% of the available motor units innervating the quadriceps.[88] Therefore, a volitional activation of 95% has been generally accepted as the cutoff value for determining whether or not a patient has neural inhibition of their quadriceps following ACLr.[89,90]

Force-based measurements are the preferred method for assessing voluntary muscle activation in a healthy or pathological population.[262,263] As an individual performs a maximal voluntary isometric contraction (MVIC) of their quadriceps, supramaximal, electrical stimulation is percutaneously applied over the femoral nerve trunk or intramuscular nerve branches to elicit a superimposed

twitch. An individual's voluntary quadriceps activation level is determined by assessing the extent in which the electrical stimulation increases their peak KET during a MVIC (typically expressed as a percentage).[262,263] Theoretically, if the electrical stimulus evokes little to no increase in KET during the MVIC, then that participant is considered to have full quadriceps activation (≥95%).[90,264] Conversely, if there is a large increase in torque after the electrical stimulus has been delivered to the quadriceps, then it is assumed that the participant has some level of inhibition present at their quadriceps (<95% of quadriceps activation).[90,264]

Decreased volitional quadriceps activation that is present in patients following ACLr can be labeled as either arthrogenic muscle inhibition (AMI) or quadriceps activation failure (QAF). Arthrogenic, in its Greek form, translates to "generated (-genic) from the joint (arthro-)". Thus, the term AMI pertains to inhibition of surrounding joint musculature that is due to the distention or damage present within the joint.[265] AMI of the quadriceps can be observed in patients immediately after ACL injury or reconstruction even though there is no structural damage imposed to the muscle or innervating nerve. AMI has been theorized to be a reflexive neural phenomenon that is organically built in as a protective mechanism after joint injury.[96] In other words, AMI is intended to prevent individuals from causing further joint damage after initial injury by inhibiting the primary muscle acting on the involved joint.

AMI has been known primarily as a lower extremity event occurring in those muscles involved in weight bearing tasks. The majority of AMI has been

observed in the muscles surrounding the knee or ankle after joint-injury.[172,266-270] While it is well known that the quadriceps are the main upper-leg muscle group to become inhibited after knee-joint injury, the lower-leg muscles most inhibited after ankle-joint injury are less specific. Of the muscles surrounding the ankle-joint, the tibialis anterior and fibularis (peroneals) muscles have been found to demonstrate AMI the most in patients with chronic ankle instability or acute ankle sprain,[268-270] but there is no consensus on which muscle group is predominantly inhibited. An explanation of why AMI is less specific after ankle-joint injury versus knee-joint injury may be due to the structural differences between the two joints. The knee-joint (tibiofemoral joint) is primarily a hinged-joint constructed for the movements of flexion and extension. Since the neuromuscular function of quadriceps are a key component during weight-bearing activities, it is intuitive that they are the primary upper-leg muscle group to fall prey to AMI after knee-joint injury. Conversely, the ankle-joint is actually made up of two joints: a hinged-joint (talocrural joint) that allows for ankle plantarflexion and dorsiflexion, and a condyloid-joint that allows for ankle inversion and eversion. Therefore, the multi-jointed structure of the ankle-joint may explain why more than one lower-leg muscle group demonstrates AMI after ankle-joint injury.

QAF is similar to AMI in that it pertains to quadriceps inhibition observed in patients after knee-joint trauma. However, the term QAF is used to describe those patients who persistently exhibit quadriceps inhibition long after the joint damage has subsided. There have been several studies that have reported persistent quadriceps inhibition in patients who are more than two years from

ACLr.[32,34,84,97,271] In a recent study by Pietrosimone et al.,[34] they reported residual neural quadriceps deficits present in patients who were an average of 4 years (48 ± 36.2 months) removed from unilateral ACLr. They discovered that the patients' ability to voluntary activate the ipsilateral quadriceps remained inhibited (88 ± 12%) and was significantly lower than that of healthy controls 4 years post-ACLr. At this time period after ACLr, it is expected that patients' should be relatively asymptomatic unless they have developed a subsequent knee-joint pathology. Therefore, using QAF instead of AMI to describe these patients is more appropriate because their quadriceps inhibition is no longer arthrogenic in nature, but a habitual inhibition. There is less evidence for QAF than there is for AMI, but this is mainly due to the longer follow-up studies that are needed to capture QAF. In addition, it is difficult to find patients with true QAF, because many patients who have a history of knee-joint injury or surgery express lingering orthopaedic symptoms and/or go on to develop subsequent knee-joint pathologies (i.e., anterior knee pain, early-onset OA, etc.). In this scenario, AMI is still considered to be the culprit of the quadriceps inhibition observed in these patients because their knee-joints are currently symptomatic and/or re-injured.

The evidence supporting the existence of quadriceps inhibition in patients following ACLr has been well documented over the past 15 years with the use of the aforementioned force-based measurements. Prior to this time period, it was well established that the incidence of a knee-joint injury such as an ACL injury elicits a neural inhibition of the quadriceps on the involved limb.[90,264,267] Therefore, it is logical to assume that the surgical knee-joint trauma imposed by

ACLr would resemble the neural inhibition observed in the quadriceps after the initial ACL injury. Urbach and colleagues[32] were the first to demonstrate true neural inhibition (<95% voluntary quadriceps activation) in the quadriceps of patients after ACLr using the IT technique. They longitudinally assessed the voluntary quadriceps activation in 12 patients with ACL injuries prior to ACLr, and assessed the same sample of patients two years after having undergone ACLr. The mean (± SD) quadriceps activation of the patients prior to ACLr was 74.9% (± 3.5). At two years after ACLr, the patients' quadriceps activation improved to 85.3% (± 2.5), demonstrating that neural activation had recovered, but an inhibition of approximately 15% still remained.

An observation that most researchers did not foresee when first assessing voluntary quadriceps activation in patients after unilateral ACL injury or ACLr was the presence of quadriceps inhibition in the contralateral (uninvolved) limb. A bilateral quadriceps activation deficit after ACL injury and subsequent ACLr has been consistently reported in the literature and is now considered to be a natural neural response in patients after unilateral knee-joint injury.[32,51,90,91,145,172] Furthermore, the amount of neural inhibition present within the quadriceps of the contralateral limb has been reported to be equivalent to that of the ipsilateral (involved) limb following unilateral ACLr. In a recent study by Thomas et al.,[91] voluntary quadriceps activation was assessed bilaterally in the limbs of patients who were seven months removed from ACLr. The mean voluntary quadriceps activation level of the patients' involved limbs was 87% (± 12), while the uninvolved limbs demonstrated a quadriceps activation level of 85% (± 14).

Therefore, the joint trauma present within the surgically reconstructed knee-joint of these patients was modulating the neural quadriceps activation of their healthy limb to the same extent as the quadriceps of their reconstructed limb. Scientists have yet to fully explain the reason for the bilateral neural quadriceps inhibition observed after unilateral ACLr. The most popular explanation is that of a neural crossover effect that occurs in the central nervous system due to altered afferent information being transmitted from the involved knee-joint.[42,145,272] Due to this bilateral deficit, physicians are cautioned when using a patient's uninvolved limb as a comparison when assessing the recovery of neuromuscular quadriceps function in the involved limb and making return-to-activity decisions after ACLr. Consequently, physicians should be advised to consider a healthy-matched control as a comparison, and clinicians should place further attention on the uninvolved limb during the rehabilitation of patients following ACLr.

Evidence of Reduced Spinal-Reflexive Excitability

Another neural deficit that has been observed in patients following ACLr is a reduction in spinal-reflexive excitability at the quadriceps.[34,51,273] The gold standard for accessing the spinal-reflexive excitability of a muscle is the Hoffman reflex (H-reflex) technique.[274,275] In its basic form, the H-reflex is the electrical variant to the mechanically induced stretch-reflex.[274] However, the H-reflex technique better isolates the monosynaptic reflex and allows for more specific assessment of spinal-reflexive activity. Unlike the stretch-reflex, the H-reflex technique bypasses the muscle spindle by applying a submaximal electrical stimulus at the muscle's peripheral nerve. The stimulation of the nerve activates

Ia afferent (sensory) fibers that transmit signals to the spinal cord, causing a depolarization of alpha motor neurons (aMN) and efferent (motor) fibers.[274,276-278] The end result is myoelectric response observed at the muscle, labeled as the H-reflex. A muscle's H-reflex activity is quantified via voltage amplitudes on surface EMG. A reduced H-reflex that is observed in the quadriceps of patients following ACLr signifies that there are inhibitory mechanisms present within the spinal cord that are partially responsible for the NQD.[259,260,265,279] Therefore, the quadriceps H-reflex has become a valuable measure for accessing the spinal-reflexive behavior in patients before and/or after they have undergone ACLr.

Although the H-reflex has been used in research for over a century,[280] there have only been a handful of studies that have used the H-reflex to assess the spinal-reflexive excitability of the quadriceps in patients following ACLr.[34,51,84,97,273,281] The majority of quadriceps H-reflex assessments have been reported in studies that used an artificial knee effusion model by injecting saline fluid into the knee-joint capsule of healthy participants.[259,260,282-284] It has been well established that artificial knee-joint effusion inhibits the quadriceps H-reflex in healthy individuals. This is a widely accepted model for demonstrating the neural effect that knee-joint effusion has on spinal-reflexive excitability, but it fails to represent the additional structural damage, inflammation, and pain that is present after true knee-joint trauma such as ACLr. Therefore, the few studies that have assessed the quadriceps H-reflex in patients after ACLr are particularly important to understanding the impact that the surgery has on spinal-reflexive excitability.

There have been a total of six published studies that have assessed the quadriceps H-reflex in patients following ACLr.[34,51,84,97,273,281] Of these six studies, Lepley et. al.,[51] were the only group to demonstrate a reduced quadriceps H-reflex in the involved limbs of patients post-ACLr compared to a healthy control group. Conversely, there were also two separate studies that have reported an increased quadriceps H-reflex in ACLr patients compared to healthy controls.[34,97] The primary difference between these two studies and the aforementioned study is the timing of when the postoperative H-reflex assessments were performed. The two studies that reported an elevated quadriceps H-reflex performed their assessments on patients who were an average of four years removed from ACLr.[34,97] Whereas, the patients in the study by Lepley et al., performed H-reflex assessments only two weeks after undergoing ACLr.[51]

These findings demonstrate that there may be a difference in spinal-reflexive excitability of patients who are in the acute stage after ACLr compared to those who are in the chronic stage after ACLr. Studies that have used the artificial knee effusion model concur that quadriceps H-reflex is acutely suppressed following knee-joint trauma because they reported reductions in the quadriceps H-reflex immediately after injecting the knee-joint capsule with saline fluid.[259,260,282-284] Artificial knee effusion models cannot support the elevated spinal-reflexive excitability observed in the quadriceps patients who are in the chronic stage after ACLr because the majority of the patients do not present with knee-joint effusion. It has been theorized that heightened spinal-reflexive excitability observed in these patients after ACLr may be a neural adaptation that

progressively develops to compensate for their persistent quadriceps dysfunction.

It must be noted that half of the studies which have assessed spinal-reflexive excitability in patients after ACLr did not report significant differences in H-reflex compared to healthy controls.[84,273,281] This demonstrates that the science is still far away from determining if and how spinal-reflexive excitability is modulated after ACLr in humans, and additional studies assessing the quadriceps H-reflex in these patients are needed to progress this area of research. It is important to determine if the spinal-reflexive excitability is suppressed in patients after ACLr because it not only impedes their recovery of neuromuscular function, but it may put them at risk for future injury. A reduced spinal-reflex may hinder a patient's neuromuscular system to appropriately respond to environmental stimuli. For example, if this patient were walking and experienced an external perturbation causing their surgical knee to collapse into knee flexion, their quadriceps may not appropriately contract in response to being rapidly stretched due to the reduced spinal-reflexive excitability. Therefore, the patient may be at a higher risk for straining a muscle or falling.

Evidence of Corticomotor Excitability Alterations

One of the more recent neural adaptations that is beginning to gain traction in this area of research is the modified cortical activity that is observed in patients after ACLr. Specifically, corticomotor excitability associated with the quadriceps has been shown to be altered in patients following unilateral ACLr.[34,51,84] Corticomotor excitability is typically assessed by applying single-

pulse transcranial magnetic stimulation (sTMS) to the area of the primary motor cortex where the majority of the MNs projecting to quadriceps via the corticospinal tract are represented, and measuring the subsequent motor evoked potential (MEP) observed at the quadriceps through surface EMG.[92-95] The corticomotor excitability measures most commonly used with sTMS are motor thresholds and MEP recruitment curves. Both of these measures provide slightly different information, yet complement each other in regards to the corticomotor excitability of the MNs in the motor cortex representing a given muscle group. Motor thresholds are believed to reflect membrane excitability and local density of a central core of pyramidal neurons and interneurons.[92,95,285] As the activation threshold of these neural elements increases, more sTMS output is needed for the motor threshold to be reached. Therefore, an increased motor threshold is interpreted as a decreased corticomotor excitability in that region of the motor cortex. MEP recruitment curves are thought to demonstrate the extent in which the alpha-motor neuron pool is activated with increasing sTMS intensities, as well as the spatial distribution of neural elements within a region of the motor cortex.[94,286,287] The steepness of the MEP recruitment curve is attributed to the extent of motor representation for a given muscle group (steeper the curve = greater representation of muscle group, and vice versa).

The majority of studies assessing corticomotor excitability in patients after ACLr have used motor thresholds to quantify the magnitude and/or change of excitability in the area of the motor cortex represented by the quadriceps.[34,51,61,84,97,288] As opposed to the aforementioned types of NQD,

modifications in corticomotor excitability relative to the quadriceps of patients do not seem to arise until at least six months after unilateral ACLr.[51] Lepley and colleagues[51] have provided the only research to date that has longitudinally assessed the changes in corticomotor excitability of patients before and after undergoing unilateral ACLr. Bilateral assessments of motor thresholds of the quadriceps were measured in 20 patients over three time points: five weeks prior to ACLr, two weeks post-ACLr, and six months post-ACLr. Prior to surgery, there were no differences in motor thresholds between limbs or when compared to healthy controls. The motor thresholds were significantly increased (corresponding to decreased corticomotor excitability) in both limbs two weeks after ACLr, but were no different compared to the control group. However, the motor thresholds in both limbs were significantly higher than the healthy controls at 6 months post-ACLr, as well as when compared to the threshold values expressed before surgery and two weeks post-ACLr. The corticomotor excitability of the patient's uninvolved limbs seemed to follow the same time trajectory after unilateral ACLr as the surgical limb, which further supports the existence of a neural cross-over effect. These patients not only demonstrated a reduced corticomotor excitability associated with the quadriceps of patients recovering after ACLr, but these attenuations were not truly evident until 6 months after surgery. The absence of corticomotor excitability attenuations after acute knee-joint disruption is not completely unexpected. In a previous study by Lepley et al.[288], an artificial knee-joint effusion elicited an immediate reduction in voluntary quadriceps activation, while it failed to attenuate corticomotor excitability. These

findings suggest that more time is needed for neural changes to be observed in supraspinal regions of the nervous system compared to spinal regions.

Two additional studies have reported decreases in corticomotor excitability in relation to the quadriceps of patients following unilateral ACLr,[34,84] but their motor threshold assessments were conducted years after the patients underwent surgery. However, both of these studies reported significant differences between limbs at this extended time point, with lower corticomotor excitability being exhibited in the quadriceps of the surgical limb.[34,84] This finding suggests that although the corticomotor excitability of the contralateral quadriceps demonstrates similar reductions as the ipsilateral quadriceps after unilateral ACLr, this neural deficit may not persistent for as long in the contralateral limb and it naturally recovers. An alternative theory is that the corticomotor excitability of the contralateral limb is improved over time after unilateral ACLr because patients tend to place more reliance on this limb during ambulatory tasks. Conversely, the mechanics and postural control of the surgical limb is modified in patients after unilateral ACLr, which may explain the cortical reorganization and reduced corticomotor excitability of the ipsilateral quadriceps. More prospective studies assessing longitudinal corticomotor excitability in patients recovering from ACLr are needed to better determine when these neural alterations begin to arise, and understand how long they tend to persist and/or resolve in both limbs.

Timeline of Neural Quadriceps Dysfunction post-ACLr

The temporal manifestation of NQD that is observed in ACL-injured patients before and after they have undergone ACLr has yet to be fully

understood and agreed upon among researchers. However, a general timeline of the neural quadriceps deficits observed after ACLr can be developed via a thorough review of the literature. The evidence regarding the onset and progression of quadriceps inhibition that is observed in patients after ACL injury and reconstruction is the most mixed in the literature compared to the other neural quadriceps deficits. This can be partially attributed to the different techniques used to assess voluntary quadriceps activation. As mentioned previously, the SIB and IT techniques are the most common methods for assessing quadriceps activation, but each uses a different equation to calculate activation, and can therefore provide slightly different information in regards to the amount of inhibition present within the quadriceps of these patients.

Significant deficits in bilateral voluntary quadriceps activation (54-83%) has been reported patients after ACL injury,[32,51,99,145,264,266,289] but some studies have reported quadriceps activation levels in these patients approaching those of healthy individuals (~ 95%).[24,27,89,172,290] Likewise, deficits in bilateral voluntary quadriceps activation (75-88%) have been reported in patients after ACLr,[27,32,34,48,91,97,291,292] while other studies have reported little to no voluntary quadriceps activation deficits in patients after ACLr (~95%).[24,51,55,86,290,293,294] This mixed evidence may be solely due to differences in measurement techniques used to assess voluntary quadriceps activation. However, it may also be due to differences in when voluntary quadriceps activation was assessed in patients. In general, the majority of studies that reported deficits in voluntary quadriceps activation,[32,34,48,97,99,264,292] assessed patients who were more than one year

removed from ACL injury or reconstruction; whereas the majority of studies that reported little to no deficits in voluntary quadriceps activation,[24,27,51,55,86,89,172,232,290] assessed patients who were less than eight months removed from ACL injury or reconstruction. It can be expected that some level of quadriceps inhibition is present in patients immediately after ACL injury and reconstruction based on the principles of AMI. During this acute state of joint trauma, the effusion, pain, and inflammation present within the knee-joint is sufficient to inhibit the involved limb's quadriceps, and cross-over to the uninvolved limb as well. However, force-based measures of voluntary quadriceps activation are typically contraindicated in the involved limb of patients within the first two months after ACL injury and reconstruction due to increased pain, inadequate range-of-motion, and/or post-surgical guidelines that are enforced to protect the graft from being stressed prematurely (post-ACLr only). AMI of the quadriceps seems to resolve during the first few months after ACL injury and reconstruction, with voluntary quadriceps activation approaching near normal levels in patients at one year post-injury/surgery. However, voluntary quadriceps activation seems to relapse into an inhibited state years later. This delay in quadriceps inhibition may described as presence QAF, or it could be quadriceps inhibition that is due to the insidious onset of a subsequent knee-joint pathology, such as knee OA. Like patients after ACL injury or reconstruction, patient with knee OA have been reported to exhibit bilateral deficits in voluntary quadriceps activation.[295] However, further research is need to explore this theory, and to

determine whether deficits in voluntary quadriceps activation after ACL injury and reconstruction are truly time-dependent.

The time course of spinal-reflexive alterations that occur in patients before and after ACLr has been described more consistently throughout the literature. Lepley et al.[51] has been the only study to assess the H-reflex in patients both before and after ACLr. Compared to their preoperative assessment, the H-reflexes of patients two weeks after undergoing unilateral ACLr was lower in both limbs; therefore, implying that the joint damage caused by the surgery attenuated spinal-reflexive excitability to a greater extent than the ACL injury itself. This observation is similar to the differences seen in patients' voluntary quadriceps activation before and after ACLr, with the surgery inflicting more quadriceps inhibition than the injury. Unlike the time course observed with quadriceps inhibition after ACLr, the recovery of spinal-reflexive excitability in patients seems to be more rapid. Studies have found that the quadriceps H-reflex of patients three to six months after ACLr is not only higher than that of more acute assessments (2-4 weeks post-ACLr),[51,273] but it is no different than that of healthy matched controls as well. Furthermore, four years removed from ACLr, patients have higher spinal-reflexive excitability than healthy individuals.[34,84] These findings demonstrate that although the quadriceps H-reflex is reduced bilaterally in patients acutely following unilateral ACL injury and ACLr, it seems to rapidly recover and heighten over time. This heightened spinal-reflexive excitability observed in patients who are years removed from ACLr may serve as a

compensatory mechanism for the additional neuromuscular deficits that are exhibited in these patients.

There have not been enough longitudinal studies to draw a conclusion on the time course of corticomotor excitability alterations in patients after ACL injury and reconstruction. However, a general pattern of time can begin to be observed by combining studies that have assessed corticomotor excitability. Corticomotor excitability changes have been demonstrated bilaterally in patients after unilateral ACLr,[34,51,84,97] but these changes have not been apparent until at least six months post-surgery.[51] Corticomotor excitability in the uninvolved limb has been shown to return to baseline in patients who are over a year removed from unilateral ACLr, whereas the corticomotor excitability in the surgical limb remains decreased.[34,84] Decreased corticomotor excitability is one of the few neural quadriceps deficits that has been shown to remain in patients after ACLr. However, the clinical importance of corticomotor excitability and the effect it has on the recovery of quadriceps function in patients after ACLr has yet to be determined. Therefore, more research is needed to determine the temporal behavior of cortical excitability and how it contributes to other neuromuscular quadriceps deficits observed in patients after ACLr.

The corticomotor excitability changes that have been reported in patients prior to ACLr is not as clear as what has been reported after ACLr. Lepley et al.[51] assessed corticomotor excitability in patients who were five weeks from initial ACL injury. The motor thresholds of these patients were no different between limbs or when compared to healthy controls, signifying that corticomotor

excitability was unaffected by the acute knee-joint injury. An earlier study conducted by Heroux and Tremblay[296] reported opposing findings in a group of ACL-deficient patients. They bilaterally assessed corticomotor excitability associated with the quadriceps of 10 patients who previously sustained a unilateral ACL injury without undergoing subsequent ACLr. They found the motor thresholds of the injured limb to be significantly lower (higher corticomotor excitability) than that of the uninjured limb, whereas no differences were observed between limbs in the healthy control group. Although these findings contradict those of Lepley et al.,[51] there are two methodological differences that may explain their lack of agreement. To begin with, Heroux and Tremblay[296] assessed motor thresholds with the patients' quadriceps being in a relaxed state, while Lepley et al.[296] assessed motor thresholds during a slight quadriceps contraction (5% of MVIC). This procedural variation between studies may have influenced the dependent variables enough to result in conflicting results. The second and more promising explanation is that the patients were assessed at different time points after initial ACL injury. As stated above, Lepley et al.[51] assessed preoperative corticomotor excitability at an average of five weeks after ACL injury; where, Heroux and Tremblay[296] assessed patients who were nearly two years (median = 22 months) removed from ACL injury. Therefore, the heightened corticomotor excitability demonstrated in the involved limb of patients who participated in the study by Heroux and Tremblay may have been a result of time itself. The authors hypothesized that because their patients were ACL-deficient for an extended period of time, more cortically-driven control over the

knee musculature was required to manage the external demands of daily activities and maintain knee-joint stability.[296] Therefore the increased corticomotor excitability associated with the injured limb's quadriceps may serve as a coping mechanism for individuals with ACL-deficiency.

Although a general timeline can be developed to portray the expected onset and duration of the aforementioned neural quadriceps deficits in patients following ACLr, clinicians must interpret it with caution. Like any disease, there will be outliers that fall outside the expected, "normal" timeframe of symptoms. Therefore, clinicians must remember to take an individualistic approach when treating neural quadriceps deficits in patients after ACLr. These deficits may manifest and progress differently between patients, making it important for clinicians to treat patients until neural quadriceps function is restored. The presence of bilateral neural quadriceps deficits in patients after unilateral ACLr provides additional justification for clinicians to incorporate both limbs when designing rehabilitation protocols, and to not rely on a bilateral comparison alone when making return-to-activity decisions. Comparing a patient's post-operative neuromuscular function to that of a healthy, matched control is preferred when determining readiness to return-to-activity. Furthermore, there are multiple factors that contribute to the persistent quadriceps weakness observed in patients after ACLr. Once NQD has been resolved in patients, clinicians should continue to target any structural modifications that remain within the quadriceps in efforts to restore the muscle mechanics and strength to a healthy state.

Mechanisms of Neural Quadriceps Dysfunction

The underlying mechanisms of NQD are multi-faceted, and there has been a growing body of research within the past decade dedicated to exploring this area. Since NQD was first determined to be a natural condition that occurs in patients after ACLr, researchers have developed and tested theories in attempts to explain the neurophysiology behind the observed neural quadriceps deficits. Because of this research, understanding of NQD has evolved and improved over the years. Therefore, the neural mechanisms that have been most supported by research will be highlighted and described in this review.

Before the mechanisms of NQD can be discussed, it is important to establish an understanding of the various sensory receptors located within the knee-joint. These sensory receptors are commonly divided into two main groups, those that are innervated by larger, myelinated afferents, and those that are innervated by small, unmyelinated (or lightly myelinated) afferents.[102,297] Large, myelinated afferents hold precedence over small, unmyelinated (or lightly myelinated) afferents due to their lower activation thresholds and higher conduction velocities. Therefore, the hierarchy of knee-joint afferents can be appreciated by their numerical classification type.

Type Ia and Ib afferents are at the top of the large, myelinated afferent group because they have the largest fiber diameters and highest conduction velocities. Type Ia afferents innervate muscle spindles and are depolarized after a rapid muscle stretch. Type Ib afferents innervate Golgi tendon organs and are typically depolarized following a strong muscle contraction. Type II afferents also fall under the large, myelinated afferent group, and are depolarized by

mechanical pressure and tension.[297-299] In the muscle, type II afferents innervate intrafusal fibers (nuclear chain) and respond to stimuli in the absence of muscle length changes (non-adaptive). Since they respond to instantaneous muscle length and not change, they are thought to contribute to an individual's joint position sense. The sensory receptors innervated by Type II afferents include Ruffini endings, Pacinian corpuscles, and Golgi-like endings. Although they have also been found to exist in the human knee-joint, the proportion of Type II afferents in the knee-joint is unknown and is believed to be relatively small based on data from animal studies.[298]

Type III and IV afferents fall under the small, unmyelinated (or lightly myelinated) variety, and they innervate the second group of knee-joint receptors.[297,298,300] The articular branch of the tibial nerve is the largest articular nerve supplying the human knee-joint.[300] Of the sensory fibers comprised in the articular branch of the tibial nerve, 70% of them are reported to be Type IV afferents.[300] Both Type III and IV afferents innervate free nerve endings possessing high activation thresholds, which respond to strong mechanical, thermal, or chemical stimuli. Therefore, the primary function of Type III and IV afferents is believed to be nociceptive in nature. However, animal studies have found that a portion these afferents can be activated by non-painful, passive knee-joint motion, suggesting that these findings may be observed within the human knee-joint as well.[301]

Gamma Loop Dysfunction

The gamma loop comprises the monosynaptic reflex and is thought to be dysfunctional within the quadriceps of patients after ACLr.[133,150,221,253] The function of the gamma loop is to monitor the rate of change in a muscle's length and recruit high-threshold (type II) aMNs during an MVIC. Gamma motoneurons (yMNs) within the spinal cord regulate the tautness of the muscle spindles within the intrafusal fibers of skeletal muscle. The tautness of the muscles spindles correspond to the sensitivity of the Ia afferents. As a muscle is rapidly stretched, the muscles spindles depolarize Ia afferents, which transmit signals to the spinal cord to activate aMNs and induce a reflexive contraction within the muscle. The sensitivity of the Ia afferents at the muscle spindles also dictate the recruitment of high-threshold motor units during an MVIC.[249-252,302] Therefore, it is considered to be physiologically impossible to recruit type II aMNs during an MVIC without a functional gamma loop.

Joint afferents are thought to influence aMN recruitment by controlling the activity of yMNs within the spinal cord.[303] Therefore, damage to the mechanoreceptors within the knee-joints of patients after ACLr could be responsible for the observed gamma loop dysfunction. The mechanoreceptors located within both the knee-joint and ACL are thought to directly influence the activation of the yMNs associated with the muscle spindles located within the quadriceps.[303] After the ACL has been ruptured and subsequently reconstructed, the consequent damage to the mechanoreceptors attenuates the activity of yMNs, and the recruitment of high-threshold aMNs is inhibited due to the reduced sensitivity of Ia afferents. Thus, the persistent quadriceps weakness that is

exhibited in patients following ACLr has been partially attributed to gamma loop dysfunction.[133,150,221,253] Furthermore, the selective atrophy of type II muscle fibers combined with the lack of force attenuation after quadriceps fatiguing exercise,[56,65,86,292,304] which have been observed in these patients, may be explained by Ia desensitization.

Dr. Yu Konishi has done the majority of work in this area, and his research largely supports the above hypothesis.[133,221,253,272,305] In one of his earlier studies,[305] he worked to determine the effect that altered knee-joint afferents had on neuromuscular quadriceps function. His group assessed MVIC and EMG activity of the quadriceps in three groups: patients with ACL deficiency, healthy participants with anesthetized joints (via lidocaine injection), and in healthy controls. These neuromuscular assessments were performed both before and after each group had vibratory stimuli applied to their infrapatellar tendon. In the control group, the prolonged tendon vibration caused an immediate reduction in both MVIC and EMG activity. However, the same vibratory protocol failed to elicit neuromuscular reductions in both the ACL-deficient and anesthetized groups. Exposing the tendon to a prolonged vibration creates a physiological, habitual response within the gamma loop by increasing the activation threshold of yMNs, slackening the muscle spindles, decreasing the sensitivity of the Ia afferents, and consequently inhibiting the activation of high threshold (type II) aMNs.[250,252,306,307] At the same time, the prolonged vibratory stimulus is thought to further reduce the sensitivity of Ia afferents by increasing their respective activation thresholds and/or depleting neurotransmitters at their terminal endings;[307] thus, preventing

the recruitment of type II aMNs. As a result, the reduced neuromuscular output from the quadriceps is the expected response after prolonged infrapatellar tendon vibration. Conversely, the lack of reduced neuromuscular output observed in the quadriceps of the ACL-deficient and anesthetized groups post-vibration indicated that gamma loop dysfunction was present in those individuals, confirming the hypothesis that altered afferent signaling from within the knee-joint disrupts gamma loop function. Although physiology of gamma loop dysfunction can be debated, some researchers believe that damage to the ACL causes a reduction in excitatory feedback from ligamentous mechanoreceptors to yMNs and/or supraspinal centers which diminishes the alpha-gamma coactivation during and MVIC.[264,303,305,308] However, the sparse innervation of sensory receptors within the ACL compared to other knee-joint structures has raised uncertainty.[298,299] An alternative theory that may also work in conjunction is that the afferent discharge of nociceptive originating from the knee-joint after trauma contributes to gamma loop dysfunction. Animal studies have discovered that prior depolarization of Type IV afferents within the knee-joint suppresses any ensuing excitatory feedback from other sensory receptors to yMNs.[309] In order for this theory to gain legitimacy, these findings must be replicated in humans.

There have been several follow-up studies that have been able to reproduce the above findings within the quadriceps of an ACLr patient population.[133,150,221,253] Similar to the bilateral quadriceps inhibition that is observed in patients after ACLr,[90,145,266] gamma loop dysfunction has been found to exist bilaterally in the quadriceps of patients following unilateral ACLr.[221]

However, the gamma loop dysfunction in the contralateral quadriceps was only present for 12 months post-ACLr, whereas this dysfunction persisted in the ipsilateral quadriceps beyond 18 months. It is thought that the disruption of afferent signaling present in the ipsilateral knee-joint after ACLr has an effect on both spinal and supraspinal centers.[221,272,303] As a result, the gamma loop dysfunction observed in the contralateral quadriceps after unilateral ACLr may be due to descending inhibitory signals projecting towards the contralateral limb.

Furthermore, Konishi and colleagues[133] recently compared the extent of gamma loop dysfunction between patients with unilateral ACL ruptures, patients with unilateral ACLr, and healthy controls. The MVIC and EMG activity was significantly decreased after infrapatellar vibration in the control group's involved quadriceps. However, these same neuromuscular measures remained unchanged post-vibration in both limbs of the ACL-ruptured group and ACLr group. Although the percentage change in MVIC and EMG activity between the ipsilateral quadriceps of both groups was not significantly different, the ACL-ruptured group's contralateral quadriceps showed a greater change than that of the ACLr group's contralateral quadriceps. This finding suggests that ACLr further disrupts gamma loop function of the contralateral quadriceps compared to an ACL rupture. Therefore, the initial ACL rupture induces bilateral gamma loop dysfunction in the quadriceps of patients, but the invasion of additional knee-joint structures (i.e., skin, capsule, menisci, etc.) via surgery further compounds the dysfunction present within the contralateral quadriceps via central mechanisms.[133,303,310] The duration gamma loop dysfunction persists after ACLr

remains unknown because there has not been another study that has assessed this outcome in patients who are beyond 18 months post-ACLr. Since gamma loop dysfunction tends to linger in patients after ACLr, it may explain the persistent quadriceps weakness and QAF observed in this patient population as well.

Nonreciprocal (Ib) Inhibition

Nonreciprocal (Ib) inhibition pertains to the group of interneurons located in lamina VI and VII of the spinal cord.[311] This group of interneurons receives input from the Ib afferents transmitted from Golgi tendon organs (GTOs) that originate within the musculotendinous junction. GTOs are proprioceptive sensory receptors that function to monitor changes in muscle tension.[312] As a muscle begins to contract, the tension at the musculotendinous junction increases, causing a deformation of the GTOs housed within the junction.[313] The deformation of GTOs elicits a depolarization of Ib afferents which propagate signals to the spinal cord. Ib afferents then synapse with Ib inhibitory interneurons, that also project information to supraspinal centers, and an inhibitory reflex is elicited at the muscle.[313,314] This inhibitory reflex suppresses efferent activity to promote elongation of the muscle,[315] and is best characterized as a sudden relaxation of a muscle after experiencing a state of high tension.

Interestingly, Ib interneurons have also been found to receive input from a variety of knee-joint afferents. Through the use of animal models, researchers have been able to demonstrate that a polysynaptic pathways exists between knee-joint afferents and Ib interneurons.[316,317] This research has been supported

in humans through the work of Iles and colleagues.[318] They used an artificial knee-joint effusion model by infusing saline into the knee-joint capsules of healthy individuals. Through the use of a spatial facilitation technique, they concluded that capsular pressure caused by the effusion depolarized type II afferents and triggered nonreciprocal (Ib) inhibition of the quadriceps H-reflex. It remains unknown whether pathways also exist between type III and IV knee-joint afferents and Ib interneurons in humans, but nonreciprocal (Ib) inhibition is still considered to be a potential mechanism of the NQD observed in patients after ACLr.[102]

Flexion Reflex

The presence of AMI in the quadriceps of patients after knee-joint injury has been well supported throughout the literature. However, several studies have also reported increased neural activity in the hamstrings of these patients,[319-321] described as a flexion reflex. The flexion reflex is characterized as a facilitation of flexor muscles and an inhibition of extensor muscles after joint injury.[322] Although it is considered to be a natural phenomenon, the neural pathways associated with the flexion reflex have not been fully explored. Wide dynamic range (WDR) interneurons are thought to play a key role in mediating the flexion reflex.[323,324] These interneurons originate in lamina V of the spinal cord and receive nociceptive input from a variety of peripheral receptors, including free nerve endings within knee-joints.[325] The influx of inflammation and pain that is present after knee-joint injury activates free nerve endings, triggering a discharge of input from type III and IV afferents to the WDR interneurons. As inflammation and pain

continue to reside in the knee-joint, the free nerve endings and WDR interneurons become hyperexcitable, and their activation thresholds are lowered.[301,326-328] Not only does this result in a persistent hypersensitivity to noxious stimuli at the knee-joint, but a heightened response to mechanical (non-noxious) stimuli at the joint. This phenomenon is described as a pain sensitization. Specifically, peripheral sensitization pertains to the hypersensitivity of free nerve endings located within the involved joint,[301,326,327] whereas central sensitization pertains to the WDR interneurons.[328] Peripheral sensitization can be observed in patients who exhibit painful reactions to movement with their involved knee-joint, which would otherwise not be perceived as painful.[301,326,327] Central sensitization is a much more complex and widespread condition due to the involvement of WDR interneurons. Patients with central sensitization not only exhibit painful reactions to movement with their involved knee-joint, but non-noxious stimuli from adjacent regions such as the quadriceps are perceived as painful.[328] Therefore, WDR interneurons are believed to contribute to persistent NQD observed in patients after unilateral ACLr, most likely by mediating the flexion reflex.[102]

The flexion reflex was first demonstrated in animal studies which assessed the neuromuscular behavior of the extensor and flexor musculature surrounding the knee-joint after induced knee-joint trauma.[329-331] Furthermore, the flexion reflex has been found to be present following activation of the mechanoreceptors within the ACL of animals. Raunest et al.[330] reported increased EMG amplitudes of the knee flexor muscles, and suppressed

amplitudes in the knee extensor muscles of sheep after shear forces were applied to the ACL. These findings demonstrate that the mechanoreceptors and corresponding afferents within the ACL have both inhibitory and excitatory influences on the neural activity of the quadriceps and hamstrings, respectively.

Although the flexion reflex is well supported in animal studies, the evidence of a flexion reflex in humans is less abundant. However, human studies have shown enhanced activity in the hamstrings of patients with knee-joint injuries compared to healthy controls.[319-321] Additionally, the activity of the hamstrings have been shown to be heightened in patients after ACL injury.[320] The hamstrings function synergistically with the ACL to control anterior tibial translation in the knee-joint; therefore, it is intuitive that their activity be heightened after ACL injury as a strategy to maintain knee-joint stability. The flexion reflex has also been shown to be reestablished in patients after ACLr. By electrically stimulating the ACL grafts of patients with an arthroscopic technique, Tsuda et al.[332] reported that the majority of patients demonstrated increased EMG activity in the hamstrings, suggesting that the ACL grafts underwent sensory re-innervation. The results justify the existence of the flexion reflex in humans, and support that it may also be a potential mechanism of NQD in patients after ACLr.

Pre and Post-synaptic Inhibition

Interneurons account for the majority of all neurons that are located in the spinal cord, and they are key component of the spinal circuitry. The basic function of an interneuron is to relay information between ascending and

descending pathways, as well as to other interneurons. However, interneurons also play an integral role in transmitting excitatory and inhibitory signals to interneurons, aMNs, and yMNs.[333,334] Therefore, it is believed that a portion of NQD that is observed in patients after ACLr is attributed to the neurophysiological behavior of interneurons. Specifically, NQD observed in patients is thought to be a result of inhibitory mechanisms that occur at the pre-synaptic afferent terminals (pre-synaptic inhibition),[259,260,265] and/or at the post-synaptic cleft between interneurons and MNs (post-synaptic inhibition).[335-337] Both of these mechanisms are believed to be under the supraspinal control, which influence activity via descending pathways.[256,338]

Pre-synaptic inhibition is attributed to a decrease of neurotransmitters released from Ia afferent terminal endplates.[255-257] Prior activation of the monosynaptic reflex has been shown to dampen the release of neurotransmitters at the pre-synaptic cleft, resulting in an inhibition of the reflex pathway.[254,339] The attenuated Ia afferent discharge caused be pre-synaptic inhibition may also contribute to the aforementioned gamma loop dysfunction.[102] However, the neurophysiological factors that are specifically responsible for pre-synaptic inhibition are not completely understood. It is thought to involve an interference of the calcium influx at the Ia afferent terminal, possibly due to inhibitory,[257] GABA-ergic interneurons. Calcium plays a key role in the binding of vesicles containing neurotransmitters, which are carried across the pre-synaptic cleft to the interneuronal membrane so that vesicular exocytosis can occur and signals can be transmitted to the appropriate neurons.[257]

The depolarization of joint afferents has also been shown to influence pre-synaptic inhibitory mechanisms.[258-260] Therefore, it can be assumed that knee-joint injury triggers pre-synaptic inhibition through the disruption of joint mechanoreceptors. Palmieri et al.[260] tested this hypothesis by using an artificial knee-joint effusion model in healthy individuals. To determine the effect of knee-joint effusion on spinal-reflexive excitability, H_{max} amplitudes were assessed before and after saline infusion. In addition, they used a modified H-reflex protocol,[340] which consists of applying two stimuli (15% of M_{max}) to the femoral nerve at an 80ms interpulse interval, and then evaluating the H-reflex amplitude elicited from the second stimulus (conditioned reflex) relative to the H-reflex elicited by the first stimulus. If the conditioned reflex is of a lower amplitude, it is referred to as the paired reflex depression and represents the modulation of processes controlling rate-dependent reflex depression and the influence of the reflex activation history. Compared to conditioned reflexes elicited prior to undergoing artificial knee-joint effusion, both the H_{max} and conditioned reflexes observed post-effusion were significantly lower, suggesting that pre-synaptic mechanisms contribute to the reduced spinal-reflexive excitability after knee-joint injury.[260] However, these results should be interpreted with caution due to methodological limitations.

Antidromic signals from efferents have been shown to attenuate the excitability of aMNs in the spinal cord.[337] This phenomenon is defined as post-synaptic (recurrent) inhibition, and it is caused by the activation of recurrent collaterals in the spinal cord that excite a specific group of inhibitory interneurons

known as Renshaw cells.[335,336] While pre-synaptic inhibition is specific to the synapse of Ia afferents,[255] post-synaptic inhibition has a more widespread inhibitory effect on neuronal synapses in the spinal cord. The activation of Renshaw cells not only leads to an inhibition aMNs,[335,336] but it has also been shown to affect Ia inhibitory interneurons and yMNs;[341-343] therefore, making post-synaptic inhibition a potential contributor to gamma loop dysfunction. The net result of post-synaptic inhibition is the reduction of efferent activation in a muscle and its synergists, as well as an excitation of its antagonists.[259,265] However, more research is needed exploring post-synaptic inhibition in humans for it to be considered as a legitimate mechanism of NQD in patients after ACLr.

Supraspinal Mechanisms

The underlying mechanisms of NQD that have been reviewed to this point pertain to the spinal cord and peripheral nervous system. However, knee-joint afferents project input to both spinal and supraspinal centers;[344-346] thus, it is probable that supraspinal mechanisms also contribute to the observed neural dysfunction in patients after ACLr. In particular, supraspinal mechanisms are thought to contribute to the persistent NQD that has been observed in these patients, such as QAF and reduced corticomotor excitability.

Since alterations in corticomotor excitability associated with the quadriceps have only recently been discovered in patients following unilateral ACLr, the research exploring the cortical mechanisms behind this condition is in its infancy. Corticomotor alterations are most likely the result of cortical neuroplasticity after knee-joint trauma. After knee-joint trauma such as that

caused by ACLr, there is an afferent discharge from the knee joint due to the onset of effusion, inflammation, and pain. However, the knee-joint damage elicited during the arthroscopic surgery likely damages (or destroys) mechanoreceptors responsible for joint proprioception.[345] Several studies have reported joint position sense discrepancies in patients after ACLr that are thought to be the result of damage to knee-joint mechanoreceptors.[344,347-349] Therefore, the deprivation of proprioceptive input to the somatosensory cortex may elicit neuroplastic changes in the primary motor cortex pertaining to reduced corticomotor excitability. These neuroplastic changes may involve a reorganization of motor maps in the primary motor cortex, and/or a suppression of corticomotor areas. Cortical reorganization is likely due to compensatory movement strategies that are adopted in patients after ACLr. Numerous studies have reported altered lower extremity biomechanics in patients after primary, unilateral ACLr,[17,350-352] which are thought to be strategies adopted by patients to compensate for neuromuscular deficits, avoid exposing the reconstructed joint to mechanical stress, or the result of pain and effusion. Alternatively, or perhaps concurrently, these avoidance strategies my also result in a long-term depression of corticomotor areas.[353] From a simplistic point of view, as the involved limb's quadriceps continue to be underused in these patients, synapses begin to deteriorate within the primary motor cortex, and their maps become invaded by neighboring muscles; therefore contributing to reduced corticomotor excitability. However, substantial research is needed to test these theories and determine the

exact neural mechanisms of corticomotor alterations observed in patients after ACLr.

The brainstem is also believed to contribute to the mechanisms of NQD in patients after ACLr.[102] The brainstem not only functions to regulate vitals such as heart rate and respiratory rate, but it serves an important role in relaying input from the spinal cord to the cerebrum and cerebellum, and vice versa. The inflammation and pain that is present after joint injury greatly enhances descending input from the brainstem (pain modulation),[354-357] which can both inhibit and facilitate mechanisms at the spinal cord. Based on current evidence, knee-joint pathology is thought to be associated with brainstem dysfunction specific to the modulation of WDR interneurons involved in the flexion reflex.[258,354,356] In addition, the QAF that remains in patients after ACLr has been partly attributed to the brainstem's influence on central sensitization of the WDR interneurons.[102] Nevertheless, supraspinal mechanisms play a significant role in the NQD observed in patients after ACLr, and additional supraspinal regions deserve to be explored to gain a better appreciation of their contributions.

Ramifications of Neural Quadriceps Dysfunction

The ramifications of NQD demonstrated in patients after ACLr are not as well-known in the literature as that of quadriceps weakness. However, within the past decade, clinical research has begun to uncover the contributions NQD has on quadriceps strength, and the resulting consequences it has on physical function and well-being of these patients. The following review will highlight the

correlation and predictive ability of the aforementioned measures of NQD on quadriceps strength, biomechanics, and patient-reported outcomes.

Quadriceps Strength

One of the most established relationships reported in the literature is that between isometric quadriceps strength (MVIC) and voluntary quadriceps activation (via SIB technique) in patients who have sustained knee-joint trauma.[86,97,232,358-364] Significant, strong correlations between these two neuromuscular outcomes in patients post-ACLr have been consistently reported across studies, with Pearson product correlation coefficients ranging from r = 0.67 to r = 0.8.[86,97] Furthermore, voluntary quadriceps activation has been reported to predict up to 87% of the variance in quadriceps MVIC via regression analyses.[358] The relationship between other measures of NQD (spinal-reflexive excitability and corticomotor excitability) and quadriceps strength in patients after ACLr has been underinvested, but recent evidence has shown that relationships may exist.[97,296]

A study conducted by Lepley et al.[97] investigated the predictive capabilities of voluntary quadriceps activation, spinal-reflexive excitability, and corticomotor excitability (AMT) on isometric quadriceps strength (MVIC) in patients who have undergone ACLr. The authors performed the above neuromuscular assessments on patients who were an average of four years removed from primary, unilateral ACLr, and used multiple linear regression analyses to determine the amount of variance in MVIC values that could be explained by the variance in voluntary quadriceps activation, spinal-reflexive

excitability and corticomotor excitability outcome measures. Prior to the regression analyses, they examined correlations within the measures of neural quadriceps function, and between the measures of neural quadriceps function and quadriceps strength. As expected, a strong, positive correlation existed between quadriceps activation and MVIC ($r = 0.78$; $p < 0.001$). There was also a moderate, positive correlation between quadriceps H-reflex and MVIC ($r = 0.66$; $p < 0.05$), and a moderate, negative correlation between quadriceps AMT and MVIC ($r = -0.64$; $p < 0.05$). When all three neural quadriceps measures were entered into the regression model, they were able to predict 49% of the variance in isometric quadriceps strength of patients after ACLr ($r^2 = 0.49$; $p < 0.01$). However, quadriceps activation ($r^2 = 0.37$; $p < 0.001$)) and spinal-reflexive excitability ($r^2 = 0.1$; $p < 0.05$) were the only variables that demonstrated significant predictive capabilities, and quadriceps AMT only increased the predictability of the regression model by 2% ($r^2 = 0.02$; $p = 0.4$).

It should be noted that when correlations were assessed among the neural quadriceps measures in this study,[97] voluntary quadriceps activation and AMT were the only measures to demonstrate a significant correlation ($r = -0.64$; $p < 0.05$); whereas, insignificant correlations existed between quadriceps activation and spinal-reflexive excitability ($r = 0.44$; $p = 0.3$), and spinal-reflexive excitability and AMT ($r = -0.4$; $p = 0.41$). These findings imply that the insignificant predictability of corticomotor excitability on quadriceps strength may be the result of collinearity. Since voluntary quadriceps activation and corticomotor excitability are both central measures of neural quadriceps function, it is intuitive that a

correlation exist between the two, resulting in a potential overlap of their predictive capabilities within the regression model. Conversely, the lack of correlation between voluntary quadriceps activation and spinal-reflexive excitability suggests that they assess different aspects of NQD; therefore, they represent different pieces of the regression model in relation to predictive capabilities on quadriceps strength. However, further research is needed to explore the association of various neural quadriceps measures on quadriceps strength in patients after ACLr.

Biomechanics

Researchers are just beginning to understand the implications of NQD on lower extremity biomechanics following ACLr. To this date, the only publications to investigate the effects of NQD on lower extremity biomechanics have been from studies using an artificial knee-joint effusion model.[282,358,365] Although the artificial knee-joint effusion model is a supported method for inducing NQD, which allows for a controlled assessment of its biomechanical consequences, its clinical validity and generalizability to an ACLr patient population is limited. Therefore, the results from these applied studies must be interpreted with caution.

Several studies have reported altered lower extremity biomechanics after artificially inducing effusions in the knee-joints of healthy individuals.[282,358,365] Torry et al.[365] was the first study to use an artificial knee-joint effusion model to elicit quadriceps inhibition and investigate subsequent biomechanical gait alterations. Compared to the pre-effusion state, the participants demonstrated

increased flexion angles at both the knee and hip during the stance phase of gait. However, there were opposing extensor moments between the knee and hip during the effused state. Knee extensor moments decreased with larger knee-joint effusion indicating that less force from the quadriceps was being applied across the knee-joint during the first half of stance. Conversely, hip extensor moments increased during the first half of stance, suggesting a compensatory strategy at the hip due to quadriceps inhibition.

Palmieri et al.[282] used a similar artificial knee-joint effusion model as Torry et al.,[365] but instead of investigating the effect on gait biomechanics, they assessed single-legged drop landing biomechanics. After saline infusion, there was an immediate reduction in EMG activity of the vastus medialis oblique and vastus lateralis; thus, resulting in a successful induction of AMI in the quadriceps. Compared to a non-effused state, large knee-joint effusion (60 mL of saline) elicited decreased knee-flexion angles, decreased knee-extension moments, and increased vertical ground reaction forces in participants upon landing. Furthermore, regression analyses revealed that quadriceps EMG activity accounted for a significant portion of the variance in the knee-flexion angle (r^2 = 0.29; $p < 0.05$), sagittal plane knee moment (r^2 = 0.37; $p < 0.05$), and the vertical ground reaction force (r^2 = 0.83; $p < 0.05$). In a similar study,[358] quadriceps inhibition (via SIB technique) was reported to explain lower extremity biomechanics during stair descent. Voluntary quadriceps activation significantly explained the variance for both knee-extension moment (r^2 = 0.29; $p < 0.01$) and vertical ground reaction force (r^2 = 0.25; $p < 0.05$). The biomechanical pattern

that has been observed at the knee after joint effusion and quadriceps inhibition is indicative of “quadriceps avoidance” strategy.[282] As the involved limb accepts full support of the body during landing or stair descent, the quadriceps work eccentrically to attenuate forces at the knee-joint. Therefore, the observed decrease in knee-flexion angle and knee-extension moment suggests that the quadriceps are avoiding eccentric activity, which consequently allows for more force to be transferred to the knee-joint as portrayed by the increased vertical ground reaction force.

Based on the ramifications reviewed thus far, NQD may influence the development and/or progression of knee osteoarthritis in patients after ACLr as well. Quadriceps weakness,[78,79,216] altered knee-joint biomechanics,[366-368] and a history ACLr have all been shown to be strongly associated with knee osteoarthritis.[23,369] Therefore, NQD has been hypothesized to increase the risk of knee osteoarthritis in patients after ACLr.[370] However, this connection has yet to be supported by the literature, demanding the need for further research to be done in this area. If researchers are able to establish this connection, the inclusion of disinhibitory interventions in the rehabilitation of patients after ACLr would be warranted to not only combat subsequent NQD, but protect against the development of early knee osteoarthritis as well.

Self-Reported Knee Function

Perhaps the most clinically relevant relationship to discuss is that between NQD and patient-reported outcomes (PROs) after ACLr. PROs are patient-centered assessments that provide insight into a patient’s perceived level

function and quality of life after an injury or intervention. PROs are routinely administered to patients following ACLr as a methodology to determine perceived success. NQD may influence a patient's perception of recovery after ACLr, and therefore, may influence PROs.

The effect of NQD on PROs after knee-joint injury is beginning to be revealed in realms of orthopaedic research.[32,61,84,86,134] Voluntary quadriceps activation has previously been reported to moderate the relationship between quadriceps strength and function in patients with knee osteoarthritis.[134] Fitzgerald et al.[134] assessed quadriceps activation and MVIC, and lower extremity function (Western Ontario and McMaster Universities Osteoarthritis Index combined with Get Up and Go test) in 105 patients with radiographically diagnosed knee osteoarthritis. After performing regression analysis, the authors found that adding the quadriceps activation by MVIC interaction to the regression model resulted in the highest prediction of function ($r^2 = 0.22$; $p < 0.01$); therefore, quadriceps inhibition was believed to serve as a moderator between quadriceps strength and function. For example, patients who exhibited higher levels of quadriceps weakness and quadriceps inhibition, had lower levels of function than those with comparable strength and less inhibition. Conversely, patients who exhibited lower levels of quadriceps weakness and higher levels of quadriceps inhibition, had higher levels of function compared to those of comparable strength and less inhibition. Although the authors could not explain why stronger patients with more quadriceps inhibition had higher levels of function, they hypothesized that if a patient has good quadriceps strength, the presence or absence of quadriceps

inhibition may not play an important role in affecting their function.[134] If a patient has enough strength to function well, they may not need to fully activate their quadriceps. In contrast, if a patient has significant quadriceps weakness and quadriceps inhibition, the combination of the two may be sufficient enough to affect their function. Regardless, this was one of the first studies to demonstrate the effect NQD has on a patient's objective and subjective function after knee-joint injury, which has promoted the significance of restoring neural quadriceps function in patients after ACLr.

To date, there have only been two known studies that have reported a relationship between NQD and PROs in patients following ACLr.[32,48] A prospective study by Urbach et al.[32] assessed the correlation between the recovery of quadriceps activation and restoration of physical activity levels in patients who have undergone ACLr. Voluntary quadriceps activation (via ITT technique) and physical activity level (using the Tegner activity scale) were longitudinally assessed in 12 patients prior to ACLr and at two years post-ACLr. Significant improvements over time were reported for both outcomes, and a strong correlation existed between the two ($r = 0.71$; $p < 0.01$), suggesting that voluntary quadriceps activation has an influence on the restoration of physical activity levels in patients following ACLr. In a more recent study by Kuenze et al.,[48] the authors used receiver-operator-characteristic (ROC) curves as a method to establish clinical thresholds for neuromuscular measures of quadriceps function associated with PROs in patients who were at least six months removed from unilateral ACLr. Interestingly, they found that symmetrical

voluntary quadriceps activation (limb symmetry index > 99.2%; area under curve = 0.67) was more effective than ipsilateral quadriceps activation in identifying patients with better patient-reported function post-ACLr, based on their total Knee Osteoarthritis Outcome Score (KOOS total). The results from this study suggest that near complete voluntary quadriceps activation limb symmetry may be an additional indicator for clinicians to use when determining whether patients are ready to return-to-activity following unilateral ACLr and rehabilitation.

2.3 ASSESSING NEURAL QUADRICEPS DYSFUNCTION

2.3.1 Voluntary Quadriceps Activation

Voluntary muscle activation represents both the extent of motor unit recruitment, and the firing rate of motor units within a given muscle (or muscle group); yet, it does not discern the two. Over the past half-century, force-based measures have been the preferred method for assessing the voluntary muscle activation in both a healthy and clinical population. The force-based assessment of voluntary muscle activation was first described in 1928 by Denny-Brown,[371] and was later tested in 1954 by Merton.[372] By superimposing supramaximal, percutaneous electrical stimuli to the adductor pollicis muscle during an MVIC, Merton[372] observed no differences in force output between superimposed twitch and voluntary contractions from healthy participants. However, when the participants were asked to perform submaximal muscle contractions, the electrical stimuli evoked an increment in twitch force at the adductor pollicis. After plotting the increment of the superimposed twitch force against the force

produced a varying MVIC percentages, he observed a negative linear relationship between the two variables. In other words, as participants approached 100% MVIC, the increment in superimposed twitch force began to diminish. It was determined that complete activation of a muscle can be achieved in healthy individuals when maximal voluntary effort is provided. Conversely, a visible increment in superimposed twitch force during maximal voluntary effort is attributed either to fatigue (central and/or peripheral) or neural inhibition. These results were confirmed in subsequent studies involving the biceps brachii,[373,374] tibialis anterior.[373,375] and quadriceps.[376,377]

More recent evidence has demonstrated that the ability of healthy individuals to completely activate a muscle is less common than what was originally reported by Merton. This discrepancy is mainly attributed to advances in high resolution analyses of voluntary muscle activation. A voluntary quadriceps activation level ≥ 95% has been consistently reported in research on healthy (non-fatigued) individuals; thus, this level is often used as the standard in studies investigating voluntary quadriceps activation in patients after ACLr.[88] The remaining motor units in the quadriceps that are commonly left inactivated (5% or less) by healthy individuals are thought to represent a reserve within the central nervous system that protects muscles from being overloaded. Furthermore, the relationship between voluntary quadriceps activation and quadriceps strength (relative to %MVIC) has been discovered to not be linear, but curvilinear.[263,378] As depicted in Figure 2.1, a sharp incline in quadriceps activation can be observed at the initiation of an MVIC, but the curve then begins to level off at approximately

50% MVIC, and it flattens as 100% MVIC is approached. Therefore, the activation-strength curve is best explained by a 2nd order polynomial.[263,378]

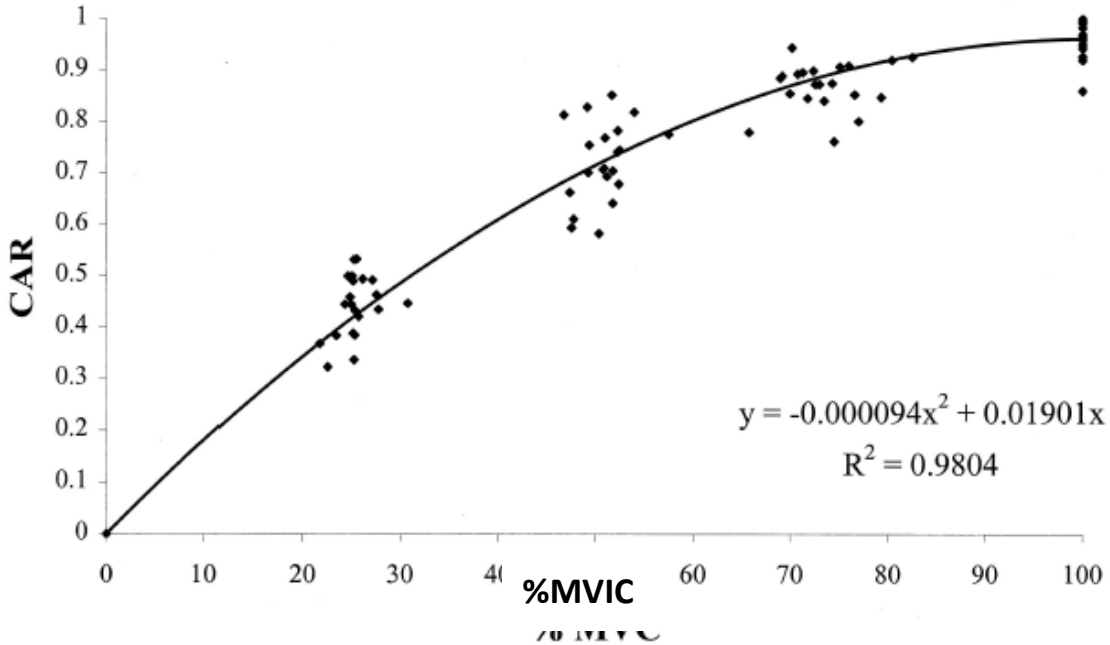

Figure 2.1. Central activation ratio (CAR) data plotted as a function of the percentage of maximum voluntary isometric contraction (% MVIC). The relationship is curvilinear and best fit by a second-order polynomial. Taken from Stackhouse SK, Dean JC, Lee SC, Binder-Macleod SA. Measurement of central activation failure of the quadriceps femoris in healthy adults. Muscle Nerve. 2000;23:1706–1712.[378]

The following review will discuss the force-based techniques corresponding procedures that are used to assess voluntary quadriceps activation. This will include the recommended electrode placement, subject positioning, and parameters for each technique. In addition, the reported reliability of each technique will be discussed.

Procedures

The force-based techniques that are most commonly used to assess voluntary quadriceps activation are the interpolated twitch (ITT) technique and the superimposed burst (SIB) technique.[262,263] Both of these techniques consist of supramaximal, percutaneous electrical stimulation being delivered to the quadriceps to evoke an increase in torque while a subject performs an MVIC of their quadriceps. With the ITT technique, a single stimulus or a pair of stimuli (doublet) is applied over the femoral nerve trunk both at the peak of the subject's MVIC and while they are at rest (either 2-5 seconds before or after the MVIC).[263] Applying an electrical stimulus to a relaxed muscle is a method adopted by the ITT technique intended to assess the peripheral/morphological mechanisms of a muscle or muscle group.[294] This resting stimulus is commonly referred to as the control twitch when quantifying a subject's voluntary quadriceps activation with the ITT technique, because it is used to normalize the superimposed twitch torque increment observed during their MVIC. Conversely, the SIB technique involves a single train of stimuli being applied over the muscle bellies of a subject's quadriceps (via intramuscular nerve branches) at the peak of their MVIC.[262]

Due to the methodological differences between the SIB and ITT techniques, separate calculations are used when quantifying voluntary quadriceps activation with each technique. For the SIB technique, a central activation ratio (CAR) is calculated by dividing the peak torque elicited during the MVIC by the superimposed torque elicited by the train of stimuli (CAR = $[MVIC_{Torque}/SIB_{Torque}] * 100$).[262,378] For the ITT technique, percent activation

(%ACT) is calculated by comparing the ITT torque increment elicited from the single stimulus (or doublet) at peak MVIC to the control twitch torque elicited at rest (%ACT = 1 – [ITT_{Torque}/$Control_{Torque}$]*100).[263,379] The SIB technique and CAR are thought to specifically assess the neural mechanisms (i.e., descending aMN recruitment) underlying voluntary quadriceps activation, whereas the ITT technique and %ACT take into account both the neural and morphological (i.e., potentiation and series elastic components) mechanisms.[294] It is important for researchers not to intermix the procedures and equations associated with the SIB and ITT techniques when assessing voluntary quadriceps activation in attempt to protect the validity of these measures.[380]

Electrode Placement

For the SIB technique, two large electrode pads (self-adhesive or carbon-impregnated) are typically adhered to the participant's skin at the proximal (anode) and distal (cathode) aspects of the quadriceps, and bipolar stimulation is used. The specific electrode placement can either be to a vastus muscle (vastus lateralis and vastus medialis oblique) or rectus muscle (proximal and distal rectus femoris) configuration. No differences in CAR have been discovered between these two electrode configurations when using the SIB technique.[381] The electrode placement for the ITT technique is much more intricate compared to the SIB technique. For the ITT technique, unipolar stimulation is used by adhering a smaller (2x2 inch) active electrode (anode) at the superior-lateral corner of the femoral triangle, and a dispersive electrode (cathode) at the distal quadriceps or posteriorly at the gluteal fold. This electrode configuration is

intended to target the femoral nerve during stimulation because it provides innervation to the quadriceps. Finding the optimal location to stimulate the femoral nerve can be difficult for the examiner; therefore, some researchers have adopted an electrode configuration similar to that used with the SIB technique when using the ITT technique. By placing the electrodes over the muscle bellies of the quadriceps instead of over the femoral nerve, subjects have reported less discomfort with percutaneous electrical stimulation,[382] and higher reliability with %ACT.[263] However, using quadriceps stimulation over nerve stimulation with the ITT technique can be challenged based on methodological grounds regarding its validity. Specifically, twitch torque increments with the ITT technique are shown to be higher with nerve stimulation compared to quadriceps, suggesting that a single stimulus or doublet is not sufficient enough to activate the quadriceps with quadriceps stimulation, and spatial recruitment of motor units at the quadriceps is superior with ITT nerve stimulation.[382] Therefore, femoral nerve stimulation is the preferred electrode configuration when using the ITT technique to assess voluntary quadriceps dysfunction.

Subject Positioning

The recommended subject positioning is identical for both ITT and SIB techniques. When comparing isometric, concentric, and eccentric contraction types in healthy individuals, isometric quadriceps contractions have demonstrated highest voluntary quadriceps activation levels.[383] Subjects are seated on a dynamometer chair with their hip-joints fixed at 85° of flexion and the knee-joint of interest fixed at 90° of flexion. Assessing voluntary quadriceps

activation at 90° of knee-joint flexion has been shown to elicit the highest quadriceps activation levels in healthy subjects;[384-387] thus, optimizing the ability to detect quadriceps inhibition in patients after ACLr. Furthermore, this angle is believed to put less strain on the surgical grafts of patients who are recovering from ACLr, because of the higher anterior shear forces that are generated from the quadriceps at lower knee-joint angles.[388,389]

To help subjects achieve higher knee extension torques when performing MVICs of their quadriceps, they are advised to rapidly push their lower leg against the lever arm pad on the dynamometer at maximal effort, while the examiner simultaneously provides verbal encouragement. In addition, it is important to isolate the subject's quadriceps during their MVIC. Utilizing torso belts to secure the patient to a dynamometer chair helps subjects to maintain an upright posture, which limits paraspinal activity during the MVIC.[390] Subjects should also be instructed to cross their arms over their chest during the MVIC to prevent them from pulling on the chair with their arms.[390] The ITT technique does require subjects to completely relax their quadriceps when the control twitch is applied. Surface EMG can be used to monitor myoelectric activity in the quadriceps and ensure that subjects are fully relaxed prior to delivering the control twitch.

Parameters

The stimulation parameters that are commonly used with ITT can be observed in Table 2.1. To determine the stimulation intensity used with the ITT technique, a control twitch test is commonly performed on subjects before

Table 2.1. Interpolated Twitch Technique Parameters

Parameter	Common Range
# of Stimuli	2
Pulse Duration	0.05 – 1 ms
Interpulse interval	10 ms
Pulse Frequency	50 – 100 Hz
Voltage	400 V

performing ITT trials. The control twitch test consists of delivering a single or paired (doublet) stimulus to the femoral nerve while the subject is at rest, and incrementally increasing the amperage until there is a plateau in twitch torque. The amperage (mA) that produced the highest resting twitch torque in the subject is then used for their subsequent ITT trials. This amperage varies from subject to subject because of the intrinsic differences in muscle morphology between individuals. The control twitch test can be very tedious and uncomfortable for subjects because they are receiving an indefinite number of stimuli at rest prior to performing ITT trials. As a result, some researchers are beginning to promote the use of a standardized amperage when assessing voluntary quadriceps activation with the ITT technique.[380,391] A recent study by Grindstaff et al.[380] assessed differences in control twitch torque at the quadriceps when using various amperages. They reported that using an amperage of 450 mA was sufficient enough to evoke maximum control twitch torque for the majority of participants, whereas 500 mA achieved maximum control twitch torque for all participants. Submaximal amperages have previously been shown to produce %ACT levels in the quadriceps that are comparable to those observed with maximal amperages.[391] Amperages that are 50-90% of the intensity used to produce a maximal control twitch torque have demonstrated valid %ACT levels at the

quadriceps that are no different than those used with maximal amperages.[391] Furthermore, Bampouras et al.[391] reported that 50% of maximal amperage was the lowest intensity to produce a valid %ACT level at the quadriceps, and it was more comfortable for subjects based on a 10mm visual analog pain intensity scale.

The number of stimuli delivered to the femoral nerve when assessing voluntary quadriceps activation with the ITT technique has been a topic of debate within the literature. A single stimulus, doublet, triplet, quadruplet, and quintuplet have all been used to assess voluntary activation, but the differences in %ACT between them are negligible.[263,379,385] However, differences in twitch torque and %ACT have been demonstrated when more than one stimulus is applied to the femoral nerve.[392-394] Compared to using a single stimulus, doublets have been shown to increase superimposed twitch torque during an MVIC,[263] improve the reliability of both twitch torque and %ACT,[392,394] and be less influenced by potentiation.[393] In addition, the post-MVIC control twitch has been recommended over the pre-MVIC control twitch when assessing voluntary quadriceps activation.[395,396] During and after an MVIC of the quadriceps, it is expected that the quadriceps will become potentiated, which increases the superimposed twitch torques and control twitch torques evoked by electrical stimulation. Therefore, the post-MVIC control twitch is recommended when calculating %ACT of the quadriceps based on its validity.[395-398] The post-MVIC control-twitch torque has also been shown to be more reliable than the pre-MVIC control twitch torque,[395,396] which further supporting its use when calculating %ACT.

The stimulation parameters that are commonly used with SIB technique can be observed in Table 2.2. As mentioned previously, the SIB technique consists of applying a train of (ten) stimuli to the quadriceps when the participant reaches their peak torque during an MVIC. Providing a train of stimuli instead of a single stimulus or doublet is more uncomfortable for subjects.[380] When applying electrical stimulation over the quadriceps with SIB technique, longer stimulation durations are required to penetrate the muscle and evoke a greater summation of motor units. The reason why the ITT technique does not require a train of stimuli is because less electrical stimulation is required to activate the quadriceps via the femoral nerve (nerve stimulation) compared to activating the quadriceps via its intramuscular nerve branches (muscles stimulation).

Table 2.2. Superimposed Burst Technique Parameters

Parameter	**Common Range**
# of Stimuli	10
Train Duration	100 ms
Pulse Duration	0.2 - 0.6 ms
Pulse Frequency	100 Hz
Amperage	450 mA

Since a train of stimuli is more uncomfortable, researchers have explored the parameters (train duration, pulse duration, pulse frequency, voltage) used with the SIB technique to determine which parameters are the most comfortable for subjects without compromising the validity of quantifying voluntary quadriceps activation (CAR). Miller et al.[399] discovered that a 50 ms train duration was more comfortable for subjects compared to a 100 ms train duration, but the 100 ms train duration evoked greater superimposed torque during MVIC and was less

variable than the 50 ms train duration. However, previous studies have determined train durations greater than 100 ms do not evoke further increments in superimposed torque, and are therefore unnecessary to use with the SIB technique.[378,400,401] Pulse durations greater than 0.1 ms have also been found to not change superimposed torque increments,[399] which suggests that a pulse duration of 0.1 ms is sufficient for the SIB technique. Two of the more understudied SIB parameters are pulse frequency and stimulation intensity (voltage). A pulse frequency greater than 50 Hz has been shown to produce a similar quadriceps CAR to that of a 100 Hz pulse frequency, but 100 Hz is the preferred parameter to facilitate motor unit summation and the recruitment of all fiber types. Miller et al.[400] tested stimulation trains at 50 V, 100 V, and 200 V to determine which stimulation intensities evoke the largest superimposed torque increments during an MVIC. They reported a significant difference in the percentage of superimposed torque increments between the four voltages, with 150 V and 200 V evoking larger increments than 50 V and 100 V. However, there was no difference in evoked torque increments between 150 V and 200 V, implying that 150 V is a sufficient voltage for the SIB technique.

A point of concern with using either force-based technique to assess voluntary quadriceps activation is that the superimposed stimulus must be applied at the participant's peak MVIC in order to provide a valid measure of quadriceps activation. When force-based techniques were first introduced, the superimposed stimulus was manually triggered once the examiner observed a plateau in force on the oscilloscope. As you can imagine, this method is open to

much human error and negatively affects both the validity and reliability of force-based techniques. One method that has been used to standardize the delivery of the superimposed stimulus is a time-based triggering technique. This involves delivering the superimposed stimulus at a standard time point during the participant's MVIC. For example, the stimulus automatically triggered three seconds after the onset of the participant's MVIC. However, there is no way to insure that the all participants achieve or sustain their peak torque during the MVIC at three seconds, which again negatively affects the reliability and validity of the measure. The most promising method for standardizing the onset of stimulation is a torque-based triggering technique introduce by Krishnan et al.[402] With torque-based triggering, the superimposed stimulus is applied at a specific torque during the participant's MVIC. To insure that the superimposed stimulus is applied at the subject's peak torque during their MVIC, several MVIC trials are performed beforehand to determine the subject's peak torque value. The subject's peak torque value is then used to trigger the superimposed stimulus during their MVIC for the quadriceps activation trials. Torque-based triggering has improved both the validity and reliability of force-based triggering techniques, as well as limiting the number of times a participant is exposed to electrical stimulation.[402] However, torque-based triggering has only recently been adopted in studies assessing voluntary quadriceps activation. Torque-based triggering must become the gold standard with force-based assessments of voluntary quadriceps activation in order for results to be fairly compared across studies and generalizations to be legitimized.

Reliability

The reliability of both the ITT and SIB techniques have high test-retest reliability for the assessment of voluntary quadriceps activation in healthy individuals.[88,403-406] However, the majority of these studies assessed intrasession reliability; whereas intersession reliability is of more clinical significance because it demonstrates whether or not the force-based techniques are consistent longitudinally. The intersession intraclass correlation coefficient (ICC) for the ITT technique (using %ACT) has been reported to be high (ICC = 0.92 – 0.95), with a low standard error of measurement (SEM = 1.0 – 2.84%) and minimum detectable change (MDC = 2.8 – 6.6%).[403,406] There has only been on study to date that has assessed the intersession reliability of the SIB technique (using CAR).[404] The results demonstrated moderately-high reliability (ICC = 0.86), low SEM (2%), and a low MDC (5.5%). These results suggest that both force-based techniques have good reliability, and they can be used in longitudinal studies to assess voluntary quadriceps activation. It should be noted that none of these studies have assessed the reliability of either the SIB or ITT techniques in an ACLr patient population. Although this is not absolutely necessary, determining the ICC, SEM, and MDC of these techniques in an ACLr patient population would ensure their reliability in a clinical population.

2.3.2 Spinal-Reflexive Excitability

In 1910, Paul Hoffmann introduced a method to noninvasively assess the spinal stretch reflex,[280] which was later named as the Hoffman reflex (H-reflex).[275] The H-reflex serves as an electrical variant of the mechanically

induced stretch reflex, but contrary to the stretch reflex, the H-reflex bypasses the influence of the muscle spindles by directly activating their corresponding Ia afferents.[276] Therefore, the H-reflex is the preferred technique for assessing monosynaptic spinal-reflexive behavior in muscles of humans. More specifically, the H-reflex has been used extensively in orthopaedic research as a tool to assess presynaptic inhibition[279] and spinal-reflexive excitability[277] in the quadriceps of patients after ACLr,[34,51,84,97,273,281] or following a disinhibitory treatment.[407-409]

Within the past century, the methodology associated with the quadriceps H-reflex has evolved to improve the validity and reliability of the technique. The following review will discuss the most recent procedures that are associated with the quadriceps H-reflex technique used to assess spinal-reflexive excitability. This will include the recommended electrode placement, subject positioning, and parameters for the H-reflex technique. In addition, the reported reliability of the quadriceps H-reflex will be discussed. Please refer to Palmieri et al.[274] for a more in-depth review of H-reflex methodology.

Procedures

When assessing the quadriceps H-reflex, a percutaneous electrical stimulus is applied over the femoral nerve, and the evoked myoelectric response at the quadriceps is assessed through surface EMG. Since the stimulation is being applied to a mixed peripheral nerve, both afferent and efferent fibers have the potential to be depolarized.[276] The activation threshold of afferent fibers is lower than that of efferent fibers due to their larger diameter,[410] meaning that Ia

afferents are first to depolarize as the stimulation intensity is increased from baseline. The stimulation of Ia afferent fibers within the femoral nerve causes action potentials to be transmitted to the dorsal horn of the spinal cord, which results in the depolarization of aMNs and transmission of action potentials to the efferent fibers innervating the quadriceps. Once these action potentials reach the neuromuscular junctions and depolarize the sarcolemma, an EMG twitch response is observed at the quadriceps, defined as the H-reflex. Therefore, the electrically-induced H-reflex measures the efficacy of synaptic transmission as the stimulus travels from Ia afferents to the efferent fibers.[274,277]

As the intensity of the electrical stimulus is increased from baseline, the EMG amplitude of the H-reflex reaches a peak amplitude, termed as H_{max}, which is believed to represent an individual's spinal reflexive excitability. Continuing to increase the intensity causes the H-reflex to begin to diminish until it is no longer visible.[411] However, while the H-reflex diminishes, an earlier muscle response, called the M-wave, begins to appear on the EMG tracing, and its amplitude steadily increases with the stimulus intensity until it eventually reaches a plateau in amplitude, termed as M_{max} [265,274] M_{max} represents the maximum peripheral activation of an individual's motor units.[279] The behavior of the H-reflex and M-wave is depicted in Figure 2.2.

The lower threshold of Ia afferents compared to efferent fibers explains why the H-reflex is observed at lower stimulus intensities, and the M-wave only appears at higher stimulus intensities, but it does not explain why the H-reflex diminishes at higher stimulus intensities. As the stimulus intensity increases, the

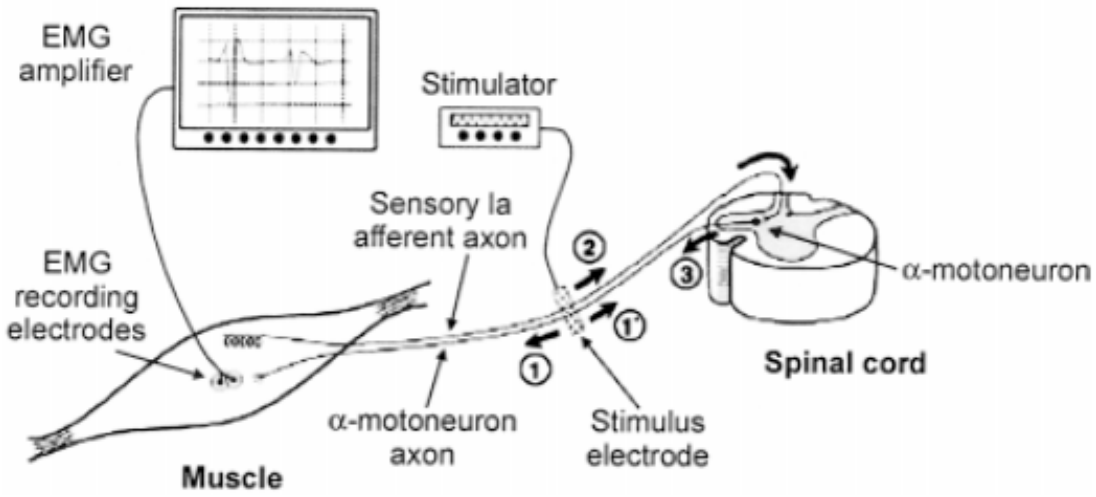

Figure 2.2. Hoffmann reflex (H-reflex) and muscle response (M-wave) pathways. When a short-duration, low-intensity electric stimulus is delivered to the tibial nerve, action potentials are elicited selectively in sensory Ia afferents due to their large axon diameter (response 2). These action potentials travel to the spinal cord, where they give rise to excitatory postsynaptic potentials, in turn eliciting action potentials, which travel down the alpha motor neuron (aMN) axons toward the muscle (response 3). Subsequently, the volley of efferent action potentials is recorded in the muscle as an H-reflex. Gradually increasing the stimulus intensity causes action potentials to occur in the thinner axons of the aMNs (response 1), traveling directly toward the muscle and recorded as the M-wave. At the same time, action potentials propagate antidromically (backward) in the aMN toward the spinal cord (response 1) to collide with action potentials of the evoked reflex response (response 3), thereby resulting in partial cancellation of the reflex response. At supramaximal stimulus intensities, orthodromic (toward the muscle) and antidromic (toward the spinal cord) action potentials occur in all MN axons; the former gives rise to a M_{max}, whereas the latter results in complete cancellation of the H-reflex. Taken from Palmieri RM, Ingersoll CD, Hoffman MA. The Hoffmann reflex: methodologic considerations and applications for use in sports medicine and athletic training research. J Athl Train. 2002;39(3):268-277.[412]

activation threshold for efferent fibers is met and signals are transmitted bidirectionally to both the muscle (orthodromic) and the spinal cord (antidromic).[255,274,278] The orthodromic signals are responsible for introducing the M-wave, whereas the antidromic signals collide with the efferent signals elicited via Ia afferent activation and ultimately “cancel out” the H-reflex; therefore, explaining why the H-reflex disappears at higher stimulation intensities. The

length of time it takes for the electrical stimulus to elicit an H-reflex and M-wave at a muscle (latency) is dependent on an individual's limb length.[413,414] For example, the more distal the muscle of interest is from the point of stimulation, the longer the H-reflex and M-wave latencies. Since the H-reflex travels both afferent and efferent pathways, and the M-wave only travels the efferent pathway, it is logical that the H-reflex latency is longer than that of the M-wave latency. The average H-reflex and M-wave latencies at the quadriceps has been reported to be approximately 17-22 milliseconds[265,415] and 11 seconds,[265] respectively. Refer to Figure 2.3 for further description of H-reflex pathways.

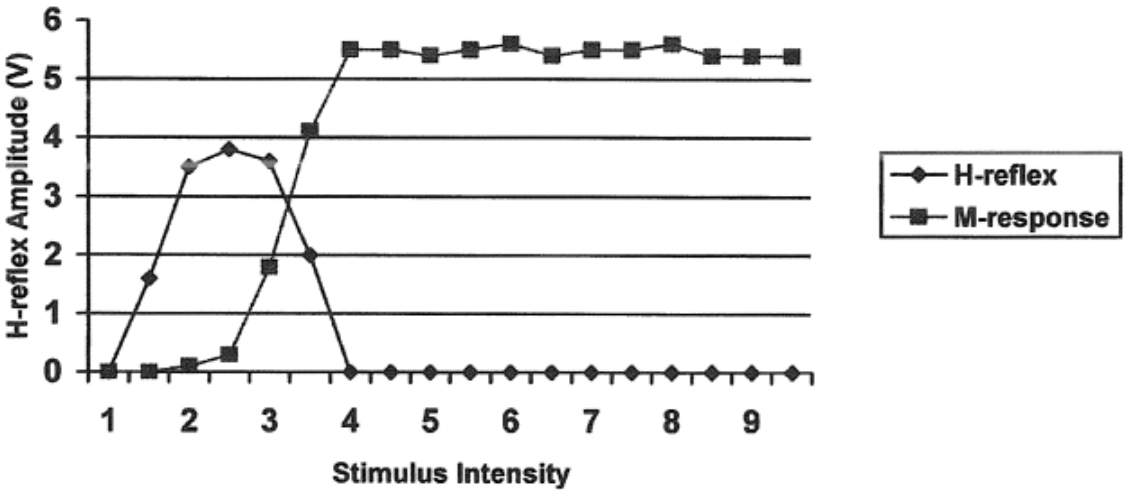

Figure 2.3. Recruitment curves of Hoffman reflex (H-reflex) and muscle response (M-wave). Taken from Hopkins JT, Ingersoll CD. Arthrogenic muscle inhibition: a limiting factor in joint rehabilitation. Sport Rehabil. 2000;9(2):135-159.[265]

H-reflex amplitudes are known to vary between subjects,[265,274] making it difficult for researchers to compare their results with others studies, and reducing the external validity of this measure. Therefore, it is highly recommended that researchers normalize H-reflex amplitudes when reporting their results, so to

allow for more valid comparisons between subjects and studies.[265,274] The H:M ratio is common method used to normalize H-reflex amplitudes,[265] and it is the preferred normalization method when H- reflex data is being collected longitudinally.[274] The H:M ratio of a given muscle is generated by dividing the H_{max} amplitude by the M_{max} amplitude. Since the M_{MAX} is thought to represent maximum muscle activation, the H:M ratio can be interpreted as the proportion of the aMN pool capable of being recruited via the monosynaptic pathway.[274] However, the H:M ratio is based on the assumption that M_{max} is a stable value. The number of aMNs in the spinal cord are thought to remain the same over time; thus, it is believed that the H:M ratio is a valid method for researchers to use when normalizing H-reflex data.[265]

Electrode Placement

Unipolar stimulation is recommended to observe the H-reflex in absence of the M-wave because it is thought to selectively activate Ia afferents at lower thresholds.[416,417] This involves placing the active electrode (cathode) directly over the nerve supplying innervation to the muscle on interest, and the dispersive electrode (anode) on the opposite side of the limb. It has been suggested that this electrode configuration is better than a longitudinal arrangement because the stimulus artifact is less, an anodal block is less likely to develop, and selective stimulation of the nerve trunk is easier.[417] However, if there are many nerves located adjacent to the nerve trunk being targeted, bipolar stimulation should be used to selectively activate the nerve trunk without stimulating any of the surrounding nerves.[416] With bipolar stimulation, both the anode and cathode are

contained in one electrode, which allows the stimulation to be more precise. For quadriceps H-reflex testing, the active electrode is placed at the superior-lateral corner of the femoral triangle, and the dispersive electrode is placed posteriorly at the gluteal fold. As mentioned previously, surface EMG is used to record the H-reflex and M-wave amplitudes after stimulation. Bipolar electrodes (2 cm inter-electrode distance) are adhered to the subject's skin, over the corresponding muscle belly and parallel with the muscle fibers.

Subject Positioning

Subject positioning is the most technical of the H-reflex testing procedures. Factors such as eye movement,[415] head position,[415,418] joint angles,[419-422] remote muscle contractions,[279,415,423] and muscle length[424,425] have been shown to affect H-reflex amplitude. As a result, H-reflex data can be highly variable between subjects and between studies based on differences in subject positioning.[426,427] Therefore, specific guidelines pertaining to the testing position of subjects have been promoted to control these factors and reduce H-reflex variability. Specifically, it is recommended that subjects be positioned in a semi-reclined, supine position with their head and arms supported and their hands being held at their side.[417] The knee on the involved limb should be supported at approximately 15° of flexion, and their heel should rest on a supportive foot rest.[428] The position of the extremities and angle of the joints should remain constant throughout H-reflex testing,[412,423,428] and the subjects should be instructed to keep their eyes open and stare at the ceiling prior to nerve stimulation.[417]

Parameters

As mentioned above, the fiber diameter of Ia afferents is larger than that of the efferents within a mixed nerve, making the rheobase (activation threshold) lower for Ia afferents.[429] Therefore, H-reflex of a given muscle can be provoked at lower stimulation intensities. In terms of the duration of stimulus used with H-reflex testing, longer stimulus durations have been previously shown to selectively activate Ia afferents;[430] whereas, shorter durations preferentially activate efferent fibers.[429] A stimulus duration of 1 millisecond is suggested to elicit an H-reflex.[417] Lastly, the rest-period between the deliverance of stimuli must be taken into consideration when testing the H-reflex in subjects. If stimuli are delivered too closely within each other, the H-reflex amplitude can be negatively affected. This is attributed to a neural phenomenon known as post-activation depression.[431] After a stimulus is delivered to a nerve, the Ia afferents become depolarized and neurotransmitters are released presynaptically to bind with spinal interneurons, which then excite aMNs and evoke a neuromuscular response (H-reflex). However, if a second stimulus is delivered before the neurotransmitters are replenished in the Ia afferent endplate, the H-reflex amplitude will be reduced. Therefore, as a method to avoid these effects of post-activation depression, stimuli should be delivered at an interval no less than 10 seconds apart.[416,431]

Reliability

Due to the variability that has been associated with H-reflex testing, it is important for researchers to determine the test-retest reliability of the H-reflex

amplitudes, especially when it is being used as a repeated measure in longitudinal studies. Ten to twenty measurements have been previously advocated as the standard for finding the mean H_{MAX},[417] but as little as 5 measurements has also been shown to produce sufficient reliability (ICC = 0.93).[432] The intrasession reliability of the quadriceps H-reflex has been reported to be very high (ICC = 0.96 – 0.97), with a low SEM (0.001) and MDC (0.002).[428] However, only moderate levels of intersession reliability have been reported, with the between-week reliability (4 weeks, ICC = 0.79 – 0.96)[428] being lower than that of the between-day reliability (5 days, ICC = 0.76).[428,433] Consequently, the SEM (0.01 – 0.06) and MDC (0.03 – 0.17) of the H-reflex are also higher when assessed between testing sessions.[428,433] It must be noted that quadriceps H-reflex reliability assessments (intrasession or intersession) have not been conducted in an ACLr patient population; thus it is unknown whether ACLr patients have more variable H-reflex amplitudes than that of healthy individuals.

2.3.3 Corticomotor Excitability

In 1980, Merton and Morton built a transcranial electrical stimulator (TES) that could invasively stimulate areas of the human brain through an intact scalp.[434] By delivering a high-voltage shock above the area of the brain represented by the primary motor cortex, a resulting muscle response, called a motor-evoked potential (MEP), could be observed. This invention was a scientific breakthrough in the field of neurology because it allowed scientists to assess the neural activity of the human brain without disrupting superficial tissues. However, the main problem with TES is that it is a painful for subjects due to its electrical

properties. Thus, five years later, Anthony Barker developed an alternative device that non-invasively stimulated areas of the brain, while providing little to no discomfort to subjects.[435] This invention is known as transcranial magnetic stimulation (TMS). Since its inception, TMS has largely replaced TES and is widely used to study both the neuroanatomy and neurophysiology of the human brain. With TMS, large electrical current flows through a coil placed on the scalp, generating a perpendicular magnetic field that penetrates through the scalp and skull, and induces an electrical current flowing parallel to the superficial layers of brain (see Figure 2.4).[286,436,437] Since the electric current of TMS penetrates through the scalp and skull, cutaneous pain receptors are not activated, resulting in a relatively painless experience for the subject.[438] This is contrary to TES whose electrical current passes through the scalp and skull, and subsequently activates pain receptors.[436,439] Due to the high electrical impedance of the skull, the current density required to successfully activate the cortical neurons using TES is much higher than that of TMS. The combination of these factors is what has made TMS the more popular tool of choice.

In addition, TMS and TES also activate the neurons within the cerebral cortex differently. Since the electrical current of TMS flows parallel to the surface of the brain, horizontally oriented neurons are preferentially activated, whereas the TES flows in all directions, directly activating neurons at the axon hillock.[436] Low-intensity TES causes a single descending volley, termed the D-wave (direct wave), which bypasses the synaptic network within the cortex. When higher

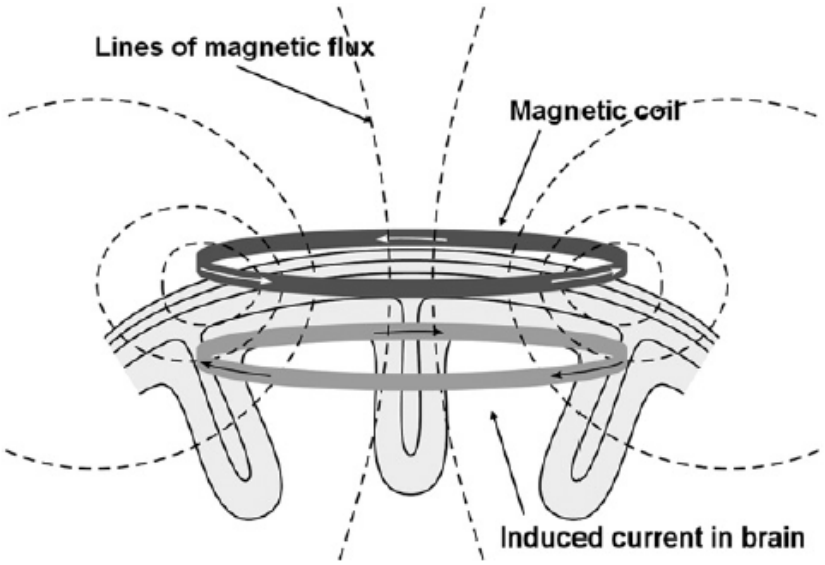

Figure 2.4. Illustration demonstrating the direction the electrical current flows in the magnetic coil, the generated magnetic field, and the induced electrical current in the brain. Taken from Hallett, M. Transcranial magnetic stimulation and the human brain. Nature. 2000;406:147–150.[437]

intensities of TES are used, greater electrical fields are produced and indirect trans-synaptic activation of pyramidal neurons occurs. This leads to a series of descending volleys that follow the D-wave termed I-waves (indirect waves). In contrast, the parallel nature of the TMS current commonly elicits I-waves due to preferentially activated trans-synaptic pyramidal neurons;[440] however, higher intensities of TMS tend to also elicit D-waves at the corticospinal tract. The summation of descending volleys travel to the anterior horn of the spinal cord and depolarize the alpha motor neurons. This progressive depolarization subsequently induces an action potential, resulting in a MEP within the targeted muscle group.[436]

Current TMS models are capable of inducing multiple types of pulses such as single-pulse, paired-pulse, or repetitive. Single-pulse TMS is especially useful for mapping cortical areas and assessing the integrity of the corticospinal tract.[94,441] and is generally used to assess corticomotor excitability via motor thresholds and MEP amplitudes. Single-pulse TMS involves the delivery of one monophasic magnetic stimulus to the brain and recording the resultant MEP. This stimulation involves currents that rapidly rise and then decay slowly, followed by a long duration low amplitude current of opposite polarity.[436,442]

Procedures

As TMS is delivered to an area of the motor cortex, the flow of ions introduced by the electrical field alters the electrical charge of the cell membrane, causing a depolarization and hyperpolarization of neurons.[439] The passive ion channels within the cell membrane make it permeable to these ions, which increases membrane conductance. Experiments have shown that the electrical field induced by TMS selectively activates neurons at lower threshold where the axons terminate (or bend sharply).[443,444] Hence, axons with larger diameters are expected to be activated at lower TMS intensities. These neuroanatomical and neurophysiological properties of TMS provide rationale for determining the area ("hotspot") of the motor cortex which elicits the highest MEP amplitudes for a given muscle group. This "hotspot" theoretically represents the area of the motor cortex under the stimulating coil where the electrical field is the strongest and acts on the axon terminate (i.e., synapse).

Motor threshold is defined as the lowest TMS output needed to elicit specific MEP amplitudes at a target muscle group when applying a single-pulse stimulus to the motor cortex.[445] This measure is believed to reflect membrane excitability and local density of a central core of corticospinal neurons (specifically pyramidal neurons) and interneurons.[285] Motor thresholds can be assessed with the subject's muscles in a relaxed or active state.[442] MEP amplitudes are typically larger in upper extremity muscles compared to lower extremity muscles. Therefore, when assessing motor thresholds at the lower extremity, subjects are commonly instructed to sustain a slight muscle contraction (5-15% of maximal voluntary force) so to enhance MEP amplitudes.[442] This is known as an active motor threshold technique. Conversely, a resting motor threshold technique (with the subject muscles relaxed) is often acceptable to use for upper extremity muscles. The recommended MEP amplitude for establishing resting motor thresholds is 50μv, and recommended MEP amplitude for active motor thresholds is 100 μv.[442]

There are several methods that have been used to measure motor threshold, but for the purpose of this review, the method used by the author will be discussed.[61,97,446] The first step is to identify the 'hotspot" on the scalp where the largest MEP amplitude is produced for the targeted muscle group using 50% of TMS output. Once the "hotspot" is identified and marked (on a swim cap), stimulus intensity should be increased or decreased in increments of 5% until the recommended MEP amplitude is reached (50 or 100 μv). Once MEP amplitude is reached, 5 out of 10 consecutive trials performed at that stimulus intensity

should elicit MEPs at or above the recommended amplitude, and 6 out of 10 trials should fall below the recommended amplitude when the stimulus intensity is decreased by 1% of TMS output. Multiple trials are performed to confirm the motor threshold level can be trusted due to the inherent variability of MEPs.

Another measure that is used to assess global corticomotor excitability is called a recruitment curve (or input-output curve). It represents gradually increasing TMS intensity and recording the resultant change in MEP amplitude. Increasing TMS output by increments of 10% motor threshold is one method that has been used.[288] MEP amplitudes are commonly expressed as a ratio between MEP and the maximal M-wave (using peripheral nerve electrical stimulation) of the targeted muscle. This stimulus-MEP relationship is then plotted to create a recruitment curve. Although this measure is less understood, it is thought to demonstrate the extent in which the alpha-motor neuron pool is activated with increasing TMS intensities.[287] Another hypothesis is that the progression of the curve reveals other neurons outside the core group of neurons that are activated as stimulation intensity is increases; thus, explaining the larger MEP amplitudes observed at high TMS intensities.[94,286]

The MEP amplitude elicited through single-pulse TMS is thought to reflect both the integrity and excitability of the corticospinal tract in relation to a targeted muscle group.[442,445] However, the absolute MEP amplitude consists of both upper and lower motor neuron activity; thus, making it difficult to assess neural activity at just the cortex. A solution to this problem was developed by Rossini et al.[442] who recommended correlating MEP amplitude evoked by TMS with the

amplitude of the compound muscle action potential (or M-wave) via peripheral electrical nerve stimulation. The equation involves dividing the MEP amplitude by the M-wave amplitude, and then multiplying the product by 100 to provide an MEP percentage (MEP%). This MEP% is said to estimate the portion of lower motor neurons in the anterior horn of the spinal cord that are activated by TMS. As the TMS intensity increases, MEP% of the targeted muscle group increases accordingly. Upper extremity muscles demonstrate a steep TMS-MEP% slope, while the MEP% in lower extremity muscles is more gradual as TMS intensity is increased.[447]

Since its inception 30 years ago, uses for single-pulsed TMS have continued to grow due to its noninvasive nature and clinical versatility. The following review will discuss the most recent procedures that are associated with single-pulsed TMS used to assess corticomotor excitability. This will include the recommended coil placement, subject positioning, and parameters for single-pulsed TMS. In addition, the reported reliability of the motor thresholds and MEP amplitudes will be discussed.

Coil Placement

MEP amplitude largely depends on the location of the TMS coil on the scalp and the direction of the induced electrical field.[448,449] With all TMS coil-types, the current within the coils (as viewed from above) should be in a clockwise orientation when stimulating the right hemisphere, and a counterclockwise orientation when stimulating the left hemisphere.[447] Therefore, the directions of the induced electrical fields are flipped and the motor cortices of

both hemispheres are being stimulated in a posterior-to-anterior fashion. This posterior-to-anterior stimulation is found to be optimal for eliciting MEPs at low thresholds over the motor cortex.[436]

When using figure-8 coil for focal TMS, the direction of the magnetic field is perpendicular to the long axis of the coil. Therefore, large difference in elicited MEP can be observed with different figure-8 coil orientations.[450] For example, when targeting the hand muscles in the motor cortex, the orientation of the magnetic field should be perpendicular to the central sulcus,[448] whereas the orientation should be perpendicular to the longitudinal fissure when targeting leg muscles.[450] Furthermore, since the stimulation pattern of the figure-8 coil is more focalized than the circular coil,[450] MEPs are more prone to variability if its coil placement is not standardized. This makes it important for examiners to find the "hotspot" on the scalp and mark it so that the reliability of the evoked MEPs can be improved.

Prior to performing assessments with TMS, the optimal site of cortical stimulation should be determined in relation to the muscle group that is being targeted. This "hotspot" corresponds to the location on the scalp that elicits the highest peak-to-peak MEP amplitude of the targeted muscle.[94,436,442] This location is often determined by having the subject wear a swim cap on their head that consists of two intersecting, perpendicular lines.[94,442] The sagittal line should run from the occiput to the tip of the nose, and the coronal line should run from one external ear canal to the other. This orientation allows the lines to intersect at the vertex of the skull. When targeting muscles of lower extremity (the

quadriceps specifically), the first MEP should be recorded with the center of the coil at the vertex (using 50% maximal stimulator output).[288] This is in accordance with the representation of the lower extremity in the primary motor cortex, as demonstrated by the motor homunculus. It is important to note that the direction of current flow in the coils (clockwise or counterclockwise) should be consistent throughout testing.[442] This is because the orientation of the induced electrical field within the motor cortex is opposite of the coil's current. Marking the current direction on the coil's frame helps to remind the examiner of the electrical field's orientation and the manner at which they are stimulating the motor cortex (i.e., posterior-to-anterior or anterior-to-posterior). After stimulating at the vertex, the coil should be repositioned anteriorly and posteriorly (in 0.5-1cm increments) until the highest peak-to-peak MEP amplitude is found.[288,296] The coil may also be repositioned lateral to the midline, on the cortical hemisphere contralateral to the targeted limb to search for larger MEP amplitudes. Once the hotspot has been located, a tracing of the coil should be drawn on the swim cap with a fine-point ink pen or marker.[94,436,442,451] This step allows for consistent coil placement throughout a given testing session.

EMG is commonly used to record and measure the MEP elicited through TMS. An output cable from a magnetic stimulator is connected to an EMG A/D board, which in turn is connected to a computer. EMG software is then used to monitor EMG activity of the targeted muscle/s, and record MEPs after TMS is delivered. The temporal latency from the onset of stimulation to an MEP is longer for lower extremity muscles (~100 ms) compared to upper extremity muscles

(~50 ms) due to the longer distance that is needed for the stimulus to travel.[442] Therefore, the recording window of the software's oscilloscope must be wide enough to capture MEPs in the lower extremity (>80 ms). To prevent an MEP from not being captured, an effective method is to use the TMS impulse to trigger the onset of the recording window on the oscilloscope. This ensures that MEPs are not recorded too early or too late, and allows both the stimulus and MEP to be observed on the oscilloscope. Surface electrodes are used more often than indwelling electrodes when recording MEPs. Bipolar surface electrodes should be applied on the subject's skin (shaved, abraded, and cleaned) overlying the target muscle with a 2 cm inter-electrode distance, identical to the procedures used when recording compound muscle action potentials or M-waves. Filtering should be relatively open, with a low-pass filter recommended to minimize stimulus artifacts caused by the TMS.[442] MEP amplitudes are measured from the highest to lowest peak of the MEP, and these values are commonly recorded in microvolts (μv).

Subject Positioning

Subjects should be positioned comfortably in either an upright, seated position or horizontal, prone position. The examiner must ensure that there is a sufficient amount of head space for the coil to be appropriately positioned.[436] The position of the subject's head and eyes should be constantly maintained, and the examiner should instruct them to relax their body throughout the testing session while still being alert. For those measurements that require a voluntary muscle contraction during the TMS, subjects should maintain a constant level of

contraction during stimulation trials, and be instructed to relax their muscle between trails.[446]

The size of the MEP amplitude not only depends on the strength and number of descending volleys induced through TMS, but also on the physical state of the subject's muscle. When a subject is in a relaxed state, higher stimulation intensities are needed to elicit an observable MEP because more descending volleys are needed for depolarization.[442] On the contrary, if the stimulus was delivered while a subject sustained a submaximal voluntary contraction of the targeted muscle, a lower intensity would be needed to produce an observable MEP due to the resting potential of the inactive motor neurons being closer to threshold.[442] In other words, when keeping stimulation intensity constant, TMS delivered during a voluntary muscle contraction elicits a larger MEP compared to that of a resting muscle because a portion of the muscle is already primed. Voluntary muscle contractions are often used as a method to both enhance MEP amplitudes and lower motor thresholds when assessing muscle groups less responsive to TMS.[442,452] Voluntary contractions have also been found to shorten the MEP latency by 2-3 ms compared to relaxed muscle. The reduced latency is suggestive of earlier lower motor neuron firing in response to earlier I-waves and D-waves during the contraction.[436] In addition, voluntary muscle contractions not only make MEP amplitudes easier to observe, but they have also been shown to improve the reliability of TMS measures by exhibiting more consistent MEP amplitudes across multiple trials.[453] Therefore, having subjects perform a background voluntary muscle contraction at a constant

submaximal level (5-10% of maximum contraction) while delivering TMS is recommended to improve MEP measurement quality.

Parameters

Magnetic stimulators commercially used for TMS produce magnetic fields from 1-2.5 Tesla that last 100 to 200 μs, and induce electrical fields in the cortex of up to 150 V/m,[439,442] and are be capable of reaching depths of 1.5-3 cm beneath the scalp based upon which coil type is used. Circular, Figure-8, and double-cone coils are the coil types routinely used for TMS. Circular (round) coils induce a circular current that is maximal at the diameter of the coil (8-12 cm).[436,442] As a result, no stimulation occurs at the center of the coil, making it suitable for broad stimulation of the brain. For more focal stimulation, Figure-8 coils consisting of two adjacent coils with opposite current directions are recommended. This flat coil configuration allows for a more pinpoint stimulation, but lacks the strength to penetrate deeper cortical areas.[436,442,454] The coil type that provides both strong and focal stimulation is the double-coned coil. The double-coned coil has the same configuration as the Figure-8 coil, except that the two adjacent coils are angulated at 95° instead of being flat (180°). This double-cone figuration increase the power at the intersection, while allowing the stimulus to be focused simultaneous.[286,442,455] While the circular and Figure-8 coils are suitable for eliciting MEPs in upper extremity muscles, the double-coned coil is recommended for targeting muscles of the lower extremity.[436]

The amplitudes of MEPs increase as the TMS output intensity is increased. This suggests that application of a stronger stimulus also recruits

more upper and lower motor neurons. However, compared to the amplitudes of M-waves elicited through peripheral electrical nerve stimulation, the MEP amplitudes evoked by TMS are smaller in size. In fact, this stimulus-response relationship for M-waves demonstrates a sigmoidal curve, while a gradual, linear relationship is observed for MEPs with increasing TMS intensities. The stimulus-response relationship has been found to vary considerably between subjects. When the TMS intensity is standardized to individual MEP motor thresholds (i.e., 120% motor threshold), significant differences between MEP amplitudes have been observed between subjects.[456] As a method to normalize MEP amplitudes across individuals, a ratio of the MEP amplitude to the M-wave of the targeted muscle group has been recommended.[442] However, this MEP ratio has also been shown to differ between subjects, [59,61] which may be due to the location of the peripheral stimulus.[59] Applying the electrical stimulation more proximally at the nerve (i.e., sciatic nerve) may account for the dispersion that occurs when applied more distally (i.e., peroneal nerve).[457,458]

Reliability

It is important to test the intersession reliability of corticomotor excitability TMS measures in healthy subjects to determine whether they are both stable and sensitive enough to detect changes over time in a pathological population or treatment group. The majority of the reliability studies for MEP amplitudes and motor thresholds have been performed in upper extremity muscles. Over a timespan of 3-14 days, these studies have reported very high intersession reliability for motor thresholds (ICC = 0.83 – 0.99),[451,459] whereas the reliability for

MEP amplitudes range from low to very high reliability (ICC = 0.5 – 0.99).[451,460-462] Recently, Livingston et al.[451] assessed the intra-rater reliability of corticomotor excitability measures in the hand muscles of 16 healthy subjects. Their subjects attended 6 sessions over the span of 15 days, and both MEP% and resting motor thresholds were assessed bilaterally during these sessions. They reported very high intra-rater reliability with resting motor thresholds (ICC = 0.83 – 0.93), while the reliability of MEP% was low to high (ICC = 0.28 – 0.72). Although both corticomotor excitability measures appear to demonstrate adequate reliability in the upper extremity, MEP amplitudes are more variable than motor thresholds, and should therefore be interpreted with caution.

The intersession reliability of corticomotor excitability measures in lower extremity muscles has been less explored compared to the upper extremity. Of the few studies that have examined the reliability of corticomotor excitability measures in lower extremity muscles, the intersession reliability for motor thresholds was high to very high (ICC = 0.78 – 0.98),[463,464] whereas the reliability for MEP amplitudes range from very low to very high (ICC = -0.14 – 0.99).[463-465] It is important to note that the time between sessions for these studies was 10-56 days, and some of these studies included both healthy subjects and patients (stroke and spinal cord injury).[464,465] The most recent study by Luc and colleagues[463] assessed the intersession reliability of active motor thresholds and MEP amplitudes in the vastus medialis oblique and peroneus longus (bilaterally). Twenty subjects attended a baseline testing session and returned for follow-up assessments at 2 and 4 weeks. MEP amplitudes were evaluated at multiple TMS

intensities relative to the percentage of active motor thresholds (95%, 100%, 105%, 110%, 120%, 130%, and 140%). These amplitudes were also normalized to the peripheral M-waves to obtain an MEP%. Both muscles demonstrated high to very high intersession reliability at both day 14 (ICC = 0.78 – 0.96) and day 28 (ICC = 0.92 – 0.95). However, the reliability of MEP% was highly variable across TMS intensities and between days (ICC = -0.14 – 0.99), demonstrating low to very high intersession reliability. These findings for the lower extremity are in agreement with what has been reported in upper extremity muscles. Motor thresholds are more reliable than MEP amplitudes, and they should be preferentially used when conducting longitudinal assessments of cortical excitability in subjects.

2.4 DISINHIBITORY INTERVENTIONS FOR NEURAL QUADRICEPS DYSFUNCTION

The influence quadriceps strength has on long-term health and function, combined with the limiting effect NQD has on a patient's ability regain quadriceps strength using traditional quadriceps strengthening exercises, has prompted the development and evaluation of interventions used to combat NQD exhibited in patients after knee-joint injury/surgery. These interventions, termed disinhibitory interventions, have grown in variety over the past decade, but not all of them have demonstrated efficacy. Disinhibitory interventions can be categorized into either sensory-based or motor-based modalities based on their treatment effects. Sensory-based modalities serve to disinhibit efferent pathways of the quadriceps

after knee-joint injury/surgery, by attenuating the influx of inhibitory afferent stimuli arising from the involved knee-joint and/or overriding it with excitatory afferent stimuli. Conversely, motor-based modalities serve to facilitate quadriceps activation after knee-joint injury/surgery, by activating the intramuscular nerves directly and/or targeting the supraspinal efferent pathways projecting to the inhibited motorneuron pool.

The final section of this review will discuss the various sensory and motor-based modalities that have been used disinhibitory interventions, and their effectiveness in mitigating NQD in patients with knee-joint pathology and/or surgery.

2.4.1 Sensory-Based Modalities

Cryotherapy

Cryotherapy involves the application of cooling modalities (i.e. ice bag, cold tub, etc.) to a site of musculoskeletal trauma. It is commonly applied after acute musculoskeletal injuries to decrease cell metabolism, limit edema formation, and control pain during the inflammatory phase.[466] However, cryotherapy has also been shown to possess disinhibitory capabilities.[407,408,467-471] Studies using artificial knee-joint effusion models were the first to demonstrate disinhibition of the quadriceps by applying cryotherapy at the knee,[408,470] but there have been several studies since then that have replicated these outcomes in patients with knee-joint pathology or surgery.[407,467-469] Pietrosimone et al.[469] assessed the disinhibitory effect of applying cryotherapy (crushed ice bags) to the knees of patients with tibiofemoral OA and quadriceps inhibition (CAR <

90%). Compared to the control group that did not undergo the cryotherapy, those in the cryotherapy group had a significantly higher percent change in quadriceps CAR after applying cryotherapy to their knees for as little as 20 minutes (5.75% ± 7.25 vs -3.5% ± 8.0, $P < 0.01$). Furthermore, a strong treatment effect size was demonstrated in the cryotherapy group (Cohen's D = 1.21, 95% CI = 0.28 – 2.05), implying that cryotherapy has both statistical and clinical significance as a disinhibitory modality for patients who exhibit NQD after knee injury/surgery.

However, the maximum treatment duration of cryotherapy is limited (20-30 minutes) to protect against peripheral neuropathy, but the residual disinhibitory effects of cryotherapy have been reported to last up to 30 minutes after the cold modality is removed (attributed to rewarming).[408,470,472] Therefore, the true potential of cryotherapy is thought to "open" the efferent pathways of the quadriceps at the beginning of a patient's rehabilitation, so that the available motoneurons can be "exploited" when they perform quadriceps strengthening exercises.[407] To test this hypothesis, Hart et al.[407] conducted a randomized clinical trial on patients with prior ACLr who presented with of quadriceps inhibition (CAR ≤ 90%). The patients were randomized into 2-week interventions consisting of either cryotherapy treatments, traditional quadriceps strengthening exercises, or a combination of cryotherapy and exercises. Those patients in the cryotherapy group applied ice bags to their involved knee-joints once a day (20 minutes/session) for two weeks, and the exercise group performed progressive open and closed kinetic chain exercises each of the 14 days (1 hour/session). Whereas, the cryotherapy+exercise group performed the same exercise protocol

as the exercise group, but they applied the same cryotherapy protocol as the cryotherapy group prior to exercising. The authors assessed peak isometric KET (at 90° of knee flexion), voluntary quadriceps activation (using the SIB technique and CAR), and spinal reflexive excitability (H:M ratio) in groups before and after their 2-week interventions. Interestingly, the cryotherapy+exercise group was the only group that demonstrated a statistically significant improvement in quadriceps function after two weeks, and this was specific to peak isometric KET (pre = 1.6 ± 0.4 Nm/kg, post = 2.2 ± 0.7 Nm/kg, p = .002). Although voluntary quadriceps activation did not achieve statistical significance in the cryotherapy+exercise group, clinical significance was observed with the strong treatment effect size (Cohen's D = 1.4, 95% CI = 0.42, 2.4). These results suggest that cryotherapy should be administered prior to exercise for patients who exhibit NQD, so that they may take advantage of the available motoneurons when exercising their quadriceps.

Transcutaneous Electrical Nerve Stimulation

Like cryotherapy, transcutaneous electrical nerve stimulation (TENS) is a sensory-based modality originally intended to control arthrogenic pain through principles of the gate control theory.[473] Non-painful, cutaneous receptors are innervated by large diameter, myelinated afferent fibers (type II/A-beta and III/A-delta); whereas, pain receptors are innervated by small diameter, unmyelinated afferent fibers (type IV/C). When both of these fiber types are activated together, the non-painful stimuli are preferentially interpreted by the central nervous

system, and the afferent signals arising from pain receptors become “gated” (via presynaptic inhibition).

Although cryotherapy and TENS both use these principles to control pain, they target different afferent structures. When cryotherapy is applied to a painful joint (i.e., ice bag application), cutaneous thermoreceptors detect the abrupt changes in skin temperature, causing type III (A-delta) fibers become activated. As a result, these signals are transmitted to the central nervous system, and the type IV (C) fibers become overridden.[474] Depending on how long the cryotherapy is applied, and the thickness of subcutaneous tissue superficial to the joint, cryotherapy may also work to control pain by decreasing conduction velocities of type IV fibers originating from nociceptors within the joint. On the other hand, TENS selectively activates larger diameter, type II (A-beta) fibers.[475,476] These fibers innervate cutaneous mechanoreceptors that respond to touch/pressure. Therefore, when TENS is applied to the skin surrounding a painful joint, the stimuli arising from the TENS is favored by the central nervous system, and pain is diminished due to the inhibition of type IV fibers.

Given their ability to control pain, it is intuitive to assume that cryotherapy and TENS can disinhibit the quadriceps in patients after knee injury/surgery because of the contribution knee-joint pain has with AMI (i.e., flexion reflex). However, the majority of inhibitory mechanisms at the core of AMI are not driven by arthrogenic pain, but by the disruption of joint mechanoreceptors instead. Therefore, the gate control theory of pain does not explain why cryotherapy and TENS have been shown to increase motor output of the quadriceps after artificial

knee-joint effusion. Although some joint discomfort is expected after artificial knee-joint effusion, the NQD that is observed in these subjects is primarily caused by the disruption of joint mechanoreceptors via capsular distention. Since cryotherapy and TENS have been shown to disinhibit the quadriceps after artificial knee-joint effusion, they must also have the ability to target the inhibitory mechanisms triggered by capsular distention (i.e. Ib inhibition, presynaptic inhibition, and post-synaptic inhibition).

Similar to pain control, cryotherapy and TENS are believed to disinhibit the quadriceps in different ways. Applying cryotherapy to a joint transmits excitatory stimuli to the central nervous system through activation large diameter afferent fibers, which in turn, facilitate the motorneuron pool projecting to the quadriceps. In addition, cryotherapy has been shown to slow the nerve conduction velocity of afferent fibers,[477] and is hypothesized to slow the discharge rate of joint mechanoreceptors if applied for a long enough duration.[408] Previous reports have demonstrated that intraarticular temperature can decrease during and after application of cryotherapy to a joint.[478,479] Oosterveld et al.[479] reported a decrease of 16.9°F in intra-articular temperature after a 30-minute cryotherapy treatment. Even after the ice was removed, intra-articular temperatures continued to decrease for up to 45 minutes. Therefore, by being able to reach the depth of the knee-joint, cryotherapy can slow the discharge rate of joint mechanoreceptors, which would attenuate the influx of afferent stimuli projecting to the central nervous system, and disengage the inhibitory mechanisms. Conversely, TENS has been reported to decrease presynaptic inhibition of Ia

afferents through stimulation of cutaneous afferent fibers.[339] It has also been hypothesized that the afferent stimuli from TENS may inhibit the Ib inhibitory interneuron, or excite the Ia excitatory interneuron, which would facilitate the motoneuron pool.[408] Furthermore, both cryotherapy and TENS have been thought to disinhibit the quadriceps by triggering supraspinal centers that inhibit Ib interneurons through descending pathways.[408] Supraspinal centers are known to regulate spinal reflexive activity to allow for controlled movement.[355,356] Therefore, the overload of excitatory and inhibitory stimuli arising from the knee-joint during TENS or cryotherapy treatments, may force supraspinal centers to intervene and control the efferent pathways projecting to the quadriceps.

The disinhibitory effect of TENS was first demonstrated during studies of the mid-1980s.[480,481] Arvidsson and Eriksson[481] assigned 15 knee-surgery patients (12 ACLr, 1 meniscectomy, 1 lateral release, 1 MCL repair) to groups that consisted of either TENS or placebo-TENS interventions. In both groups, the interventions were applied to the involved knee for 15-20 minutes post-surgery (at rest). Integrated EMG of the quadriceps was assessed in patients before and after the treatment sessions. Compared to baseline, integrated EMG significantly increased by 305% in the TENS group after treatment, whereas no significant changes were demonstrate in the placebo-TENS group. However, much like what was realized with cryotherapy, the true disinhibitory potential of TENS is maximized when used in conjunction with exercise.[467,482]

Pietrosimone et al.[482] randomized 36 patients, with tibiofemoral OA and quadriceps inhibition (CAR < 90%), into TENS+exercise, placebo-

TENS+exercise, and exercise-only groups. The groups were matched by voluntary quadriceps activation (CAR) and OA grade (Kellgren-Lawrence score). All three groups performed a 4-week exercise program (3 sessions/week) that consisted of progressive lower extremity range-of-motion and strengthening exercises. Additionally, the TENS and placebo-TENS groups applied treatments to their involved knees for eight hours per day when they were the most active. Peak isometric KET (at 70° of knee flexion) and voluntary quadriceps activation (using the SIB technique and CAR) were assessed in each group at baseline, and at weeks two and four of their intervention program. There were no group differences observed at baseline for both measures of quadriceps function. Voluntary quadriceps activation were significantly higher in the TENS+exercise group (CAR = 94%) than the exercise-only group at two weeks (CAR = 82%, $p = 0.02$), and significantly higher than the placebo-TENS+exercise group at four weeks (CAR = 94% vs. 81%, $p = 0.03$). Peak isometric KET was higher in the TENS+exercise group than the placebo-TENS+exercise group at both two (2.5 Nm/kg vs. 1.6 Nm/kg, $p < 0.01$) and four weeks (2.8 Nm/kg vs. 1.6 Nm/kg, $p < 0.01$), but not significantly higher compared to the exercise-only group ($p = 0.09$). Although these results imply that the placebo-TENS and exercise-only interventions possess disinhibitory effects, the clinical significance of the interventions was better conveyed by observing the treatment effect sizes (Cohen's D). The TENS+exercise group demonstrated strong effect sizes for peak isometric KET and voluntary quadriceps activation at weeks two (KET: 1.05, 95% CI = 0.16, 1.86; CAR: 1.93, 95% CI = 0.91, 2.83) and 4 (KET: 1.26,

95%, CI = 0.35, 2.09; CAR: 1.81, 95% CI = 0.80, 2.68), while the placebo-TENS+exercise group was the only other group to demonstrate at significant effect size (though moderate) for voluntary quadriceps activation (0.88, 95% CI = 0.02, 1.68). This observation in the placebo-TENS+exercise group may have truly been the result of the "placebo effect".

Perhaps the most surprising result of this study was the disinhibition of the quadriceps that was maintained in the TENS+exercise group following removal of the TENS treatment. Although previous studies have claimed that disinhibition of the quadriceps is negated after TENS is removed,[408] this was the first study to assess the disinhibitory effect of TENS when applied over a period of weeks. Thus, the greater exposure to TENS may have generated a lasting disinhibitory effect in their patients. The authors hypothesized that the greater exposure to TENS may have facilitated synaptic plasticity within the motorneuron pool,[483] which may allow a patient to access previously inhibited motoneurons after TENS is removed.[482] Hebbian theories suggest that postsynaptic neurons that continually depolarize in response to excitatory presynaptic potentials may allow for multiple postsynaptic neurons to depolarize together, even when the postsynaptic neurons are not directly depolarized by presynaptic potentials.[484] Therefore, after weeks of being able to access motor units of the quadriceps through TENS, synaptic plasticity may have ensued within the motoneuron pool, which allows them to depolarize simultaneously, regardless of the excitatory presynaptic potential.[482]

Previous reviews support TENS as not only the most effective sensory-based disinhibitory intervention, but the most effective disinhibitory intervention in general.[100,101] In one of my earlier publications, I developed a critically appraised topic to determine whether TENS or cryotherapy was the more effective disinhibitory modality for improving voluntary quadriceps activation (quantified via CAR) in patients with knee-joint pathologies.[100] I searched the literature to find all of the studies that used TENS and/or cryotherapy as a disinhibitory interventions for patients with knee-joint pathologies (i.e. osteoarthritis, ACL deficiency, patellofemoral pain, etc.). A total of three randomized clinical trials satisfied my eligibility criteria and were included in the review.[467,469,482] To compare the clinical effectiveness between TENS and cryotherapy, I extracted (or calculated) Cohen's D effect sizes (difference in mean CAR from baseline to posttest, divided by the pooled standard deviation of the two means) for CAR from the intervention groups of each study (see Figure 2.5). TENS consistently exhibited stronger effect sizes than cryotherapy, and unlike cryotherapy, maintained significant effect sizes at each post-treatment measurement time point. This suggests that TENS may be the more clinically effective disinhibitory modality. Furthermore, the clinical versatility of TENS is greater than cryotherapy. Unlike cryotherapy, there is no limit to treatment duration or dosage with TENS, and most all TENS units can be worn during exercise without obstructing movement. Therefore, the strong disinhibitory effect and clinical versatility of TENS, gives it an advantage over cryotherapy.

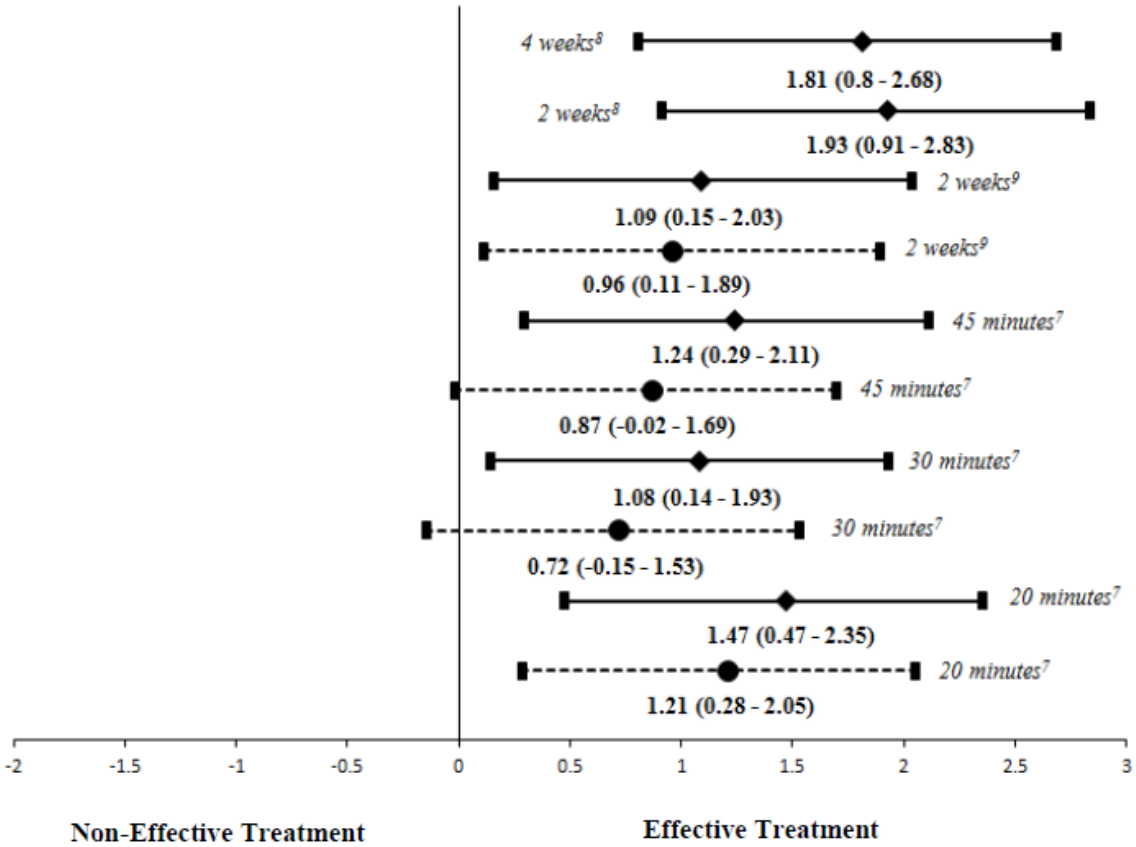

Figure 2.5. CAR effect sizes with 95% confidence intervals: Diamonds with solid error bars represent effect size point estimates for TENS interventions and 95% confidence intervals, whereas circles with broken lines represent effect size point estimates for cryotherapy and 95% confidence intervals. All point measures and confidence intervals on the right of the vertical solid line represents beneficial and statistically significant effects (confidence intervals do not cross 0), whereas the left of the line represents non-beneficial and statistically insignificant effects.

Muscle Vibration

Although cryotherapy and TENS are considered to be the most effective sensory-based disinhibitory interventions, muscle vibration is novel modality that has demonstrated early promise, and is beginning to receive more attention in the literature. Muscle vibration can be applied in two different modes: whole body vibration (WBV) or local muscle vibration (LMV). WBV involves having individuals stand on a vibratory platform, whilst performing stationary, closed kinetic chain

exercises (i.e. squats). LBV, as the name implies, involves a portable, vibratory device that is strapped to the muscle of interest while individuals perform lower extremity exercises. Although both modes of muscle vibration are equally effective at improving neuromuscular function,[485] LBV is more cost-effective and less restrictive to exercise type. Thus, LBV tends to be more clinically applicable compared to WBV.

The neuromuscular effects of muscle vibration is founded on principles of the tonic vibration reflex.[486] By applying repetitive vibratory stimuli to a muscle, the Ia afferents at the muscle spindles become highly excitable, which lead to a heightened motor output of the muscle. Pollock and colleagues[487] found that immediately after muscle vibration, the recruitment threshold was lowered for fast-twitch (type II) motor units and elevated for slow-twitch motor units. This suggests that muscle vibration enhances neuromuscular function by specific targeting motoneurons projecting to fast-twitch motor units. However, other reports have shown that the neural effects of muscle vibration are not confined to just motoneurons within spinal cord, but at the motor cortex as well.[488,489] Mileva et al.[489] used TMS to assess the MEP amplitudes at the tibialis anterior muscle, while their participants simultaneously underwent a WBV protocol (330 second isometric squat). They reported MEP facilitation in all participants during the WBV protocol. These results indicate that muscle vibration may improve neuromuscular function by increasing corticomotor excitability.

Since muscle vibration has been shown to facilitate quadriceps activation in healthy individuals,[490-495] it seems logical that it would produce disinhibitory

effects in patients after knee-joint injury/surgery. However, most of the current literature involves determining the effects muscle vibration on quadriceps strength,[496,497] lower extremity function,[498,499] and postural stability[497,499,500] in patients with knee-joint pathologies. Although these measures are important to understanding the complete benefits muscle vibration, they do not provide information in regard to its disinhibitory effect. Blackburn and colleagues[485] recently sought to determine the disinhibitory effect of muscle vibration using an artificial knee-joint effusion model. To induce AMI in the quadriceps, they injected the knee-joints of 45 healthy individuals with 60 mL of saline. The individuals were then randomized into WBV, LBV, or control groups. Each group performed an isometric squat (40° of knee flexion), but the WBV and LBV (at the quadriceps tendon) groups received simultaneous muscle vibration (30 Hz, 2g). Voluntary quadriceps activation (via SIB technique and CAR) and peak isometric KET (60° of knee flexion) were assessed in all groups at post-effusion and immediately post-intervention. Artificial knee-joint effusion decreased voluntary activation (CAR > 90%) and peak KET in all groups, and there were no significant differences between the groups at post-effusion ($p > 0.05$). Significant improvements in voluntary activation were only observed in the WBV (+11.4%, $p = 0.21$), and LBV (+7.3%, $p < 0.001$) groups immediately post-effusion, but not in the control group (+1.3%, $p = 0.18$). Compared to the control group (1.2%, $p > 0.05$), peak KET was also improved to a greater extent in the WBV (16.5%, $p = 0.02$) and LBV (23%) groups immediately post-intervention, but the LBV group did not achieve statistical significance ($p < 0.08$). The immediate disinhibitory

effects of muscle vibration that were observed in this study provide further support for this sensory-based modality as a disinhibitory intervention. However, muscle vibration has yet to be investigated as a disinhibitory intervention for patients with knee-joint pathology/surgery. Studying muscle vibration in a patient-based population will provide evidence-based justification for its use as a disinhibitory intervention.

Lastly, heightened neuromuscular function has been reported to remain in individuals up to 30 minutes after muscle vibration in healthy individuals.[491] Cryotherapy and TENS are considered to be superior disinhibitory interventions largely because of their residual effect on patients. Therefore, if the same residual effects can be demonstrated in patients after muscle vibration, it will not only promote its legitimacy as a disinhibitory intervention, but it will receive the same respect as the above-mentioned sensory-based modalities

2.4.2 Motor-Based Modalities

Neuromuscular Electrical Stimulation

Neuromuscular electrical stimulation (NMES) is a motor-based modality which applies a series of external stimuli to skeletal muscles through surface electrodes at the skin. NMES is commonly prescribed for patients who exhibit muscle dysfunction or weakness, as a method to reeducate muscle contraction and/or augment muscle force. Unlike the physiology of a voluntary muscle contraction, NMES elicits muscle contractions by directly activating the intramuscular nerve branches.[103] In addition, the temporal recruitment order of motor units observed during NMES is believed to differ from that of the biological

recruitment pattern. The biological recruitment pattern of motor units is asynchronous, and based on the Henneman size principle,[501] with smaller motor units (type I) being recruited prior to larger motor units (type II). With NMES, this recruitment is fairly synchronous,[502] but larger motor units tend to be preferentially recruited before smaller motor units due to their larger surface area.[115,503,504]

NMES has been well established in the literature as an effective modality for restoring quadriceps strength in patients after ACLr.[70,104-110] Although these strength improvements are easily attributed to the muscle hypertrophy that develops during NMES interventions,[111-115] it is believed that neural adaptations elicited by NMES are partly responsible for the increases in muscle strength.[111-113,116,117] Initial increases in muscle strength during strength training have been attributed to neural adaptations within the central nervous system;[505-507] thus, it is reasonable that the same effects would be observed during the early phase of an NMES regimen. Studies assessing the therapeutic effect of NMES interventions on healthy individuals, have demonstrated progressive increases in muscle strength throughout the intervention period, with muscle hypertrophy only being evident during the late phase of the intervention.[111-114] Gondin and colleagues[113] reported that after applying four weeks of NMES treatments to the quadriceps of healthy individuals, significances increases in quadriceps strength (+11%, $p < 0.001$), EMG (+42-44%, $p < 0.05$), and voluntary activation (+5%, $p < 0.05$; via ITT) were observed, but there were no significant changes in quadriceps CSA (+2%, $p > 0.05$). Between weeks four and eight, further improvements in

quadriceps strength (+11%, $p < 0.001$) were accompanied by changes in quadriceps CSA (+4%, $p < 0.001$). Therefore, quadriceps strength improvements with NMES can be attributed to neural adaptions within the central nervous system during the early phase of intervention, and muscle hypertrophy during the later phase.

Perhaps the most compelling evidence supporting the neural adaptive effect of NMES, is the presence of cross-education in skeletal muscles of the extremities.[111,138,139,508] Although cross-education has been observed with voluntary exercise,[509-512] there is evidence to suggest that NMES may induce greater cross-education effects than voluntary exercise.[138,139] Hortobagyi et al.[138] randomized 32 healthy women to a NMES and control groups, and asked them to perform 840 eccentric contractions (control = voluntary, NMES = stimulated) over six weeks. Each group was tested before and after six weeks to assess for changes in eccentric quadriceps strength. Improvements in quadriceps strength of the trained limb were observed in both groups, but the untrained limb of the NMES group demonstrated a 60% increase in quadriceps strength, which was greater than that of the control group. Since the untrained limb did not received the NMES and was unexercised, the bilateral improvement in quadriceps strength after a unilateral NMES intervention could only be explained by a neural adaptation within the central nervous system. This cross-education effect observed after NMES or exercise has been attributed to both spinal and supraspinal mechanisms.[116,513-516]

The exact neural mechanism underlying the neural adaptations observed with NMES have yet to be fully comprehended. Based on limited evidence, NMES does not seem to influence spinal reflexive excitability.[117,517] Instead, the neural adaptations observed with NMES are believed to involve alterations at the supraspinal level.[116,136,137] In a study by Blickenstorfer et al.,[136] a single session of electrical stimulation was applied to wrist extensor and flexor muscles of healthy individuals, while cerebral activation patterns were being captured with fMRI. During electrical stimulation, there was significant activation noted in the contralateral primary motor cortex, primary somatosensory cortex and premotor cortex, the ipsilateral cerebellum, bilateral secondary somatosensory cortex, the supplementary motor area, and anterior cingulate cortex. Although, longitudinal studies are necessary to determine whether neuroplasticity occurs in these supraspinal centers after NMES interventions, the current cross-sectional evidence demonstrates that they are at least influenced by NMES.

Hortobagyi and Maffuiletti[116] proposed an alternative model in which heightened afferent input elicited by NMES may explain the neural adaptations observed with NMES. Since NMES cannot bypass the afferent fibers located within both the skin and muscle, it is thought to elicit a barrage of afferent input to the sensory system. As was discussed with TENS, this discharge of sensory information is thought to trigger supraspinal centers to allow for descending control motoneurons, which elicits a facilitation of motor output to the involved muscle. Although this theory has merit, it must be supported by research before it

can be considered as a legitimate mechanism of the neural adaptations demonstrated with NMES.

Due to the neural adaptations it elicits in healthy individuals, it is expected that NMES would be considered as an effective disinhibitory intervention for the quadriceps in patients after knee injury/surgery. Furthermore, the preferential recruitment of type II motor units that has been associated with NMES, make it an attractive modality for patients with ACL injury/surgery, since type II muscle fibers tend to be most affected in their quadriceps. However, there is conflicting evidence concerning the disinhibitory effects of NMES on restoring quadriceps function in a patient population. Several studies have reported improvements in the voluntary quadriceps activation of patients with NMES interventions.[116,118-122] In a case series by Stevens et al.,[118] patients were assigned to one of two interventions, four weeks after receiving bilateral, total knee arthroplasty. Three patients participated in a 6-week (3 sessions/week), bilateral exercise program consisting of range-of-motion exercises, lower extremity strengthening exercises, and functional activities. Five other patients participated in the same exercise program, while also receiving NMES on the weaker quadriceps. Voluntary quadriceps activation (via SIB and CAR) was assessed in all patients at baseline, mid-intervention (3 weeks), post-intervention (6 weeks), and at three and six months. Due to the small sample size, the authors did not perform a statistical analysis. However, a recent systematic review calculated the treatment effect sizes (Cohen's D) for each group to compare the disinhibitory effect of NMES to exercise.[101] Strong effect sizes were observed at the 3-week (1.66, 95% CI =

0.10, 2.90), 6-week (1.65, 95% CI = 0.09, 2.89) 3-month (1.71, 95% CI = 0.13, 2.96) and 6-month (1.87; 95% CI = 0.24, 3.13) time points in the NMES group. Conversely, the effect sizes of the exercise group were weak (-0.08 – 0.-48) and insignificant (95% CI crossed 0). Thus, it would seem that NMES is an effect motor-based modality for improving voluntary quadriceps activation in patients.

However, an equal amount of studies have negated the effect NMES has on improving voluntary quadriceps activation in patients.[123-128] Palmieri-Smith et al.[125] randomly assigned 30 patients with radiographic knee OA to NMES (4 weeks; 3 sessions/week) and control groups. The NMES group received NMES to their quadriceps three times per week, for a total of four week. Whereas, the control group served as the standard-of-care, and did not receive any treatment. Voluntary quadriceps activation (via SIB and CAR) was assessed in all patients at baseline, and one and 16 weeks post-intervention. Compared to the control group, there were no significant differences in MVIC or CAR changes at 5 weeks (1 week post-treatment) or 16 weeks (12 weeks post-treatment). The authors elected to report treatment effect sizes for each group to compare disinhibitory effects between groups. Unfortunately, weak and insignificant effect sizes were observed in both the NMES and control groups at five (0.2, 95% CI = -0.53, 0.91 vs. 0.0, 95% CI = -0.78, 0.78) and 15 weeks (0.42, 95% CI = -0.36, 1.18 vs. 0.33, 95% CI = -1.15, 0.51). Therefore, the authors concluded that there was no additional benefit from NMES for improving voluntary quadriceps activation in patients with knee OA.

The conflicting results between these studies may have been due to different patient populations, but the limitations that are associated with NMES are most likely to blame. The two main limitations of NMES are the discomfort experienced with high intensities of surface stimulation,[518,519] and the limited spatial recruitment of motor units.[518,520] Coincidentally, stimulation intensity is believed to directly affect spatial recruitment.[518,520,521] NMES applied at a constant intensity, activates the motor units closest in proximity to the stimulating electrodes.[518] Deeper motor units are targeted by increasing the inter-electrode distance,[520] but this can also be achieved by increasing the stimulation intensity.[521] Thus, it is recommended that NMES intensity be progressed to prevent against fixed, superficial recruitment.[518] However, a new alternative to conventional NMES, known as multipath NMES, has recently been shown to elicit better improvements in quadriceps strength due to its advanced spatial recruitment properties.[130] While a single current pathway is applied between an electrode pair during conventional NMES, multipath NMES distributes its current to multiple pairs of electrodes within single channels. Furthermore, multipath NMES has been shown to elicit greater evoked KET from the quadriceps when compared to conventional NMES.[522] These effects are mainly attributed the higher stimulation intensity that is tolerated with multipath NMES, and the wider current distribution between multiple pairs of electrodes.

When applying NMES, the stimulation intensity is typically based on the patient's tolerance. However, the neuromuscular improvements observed with lower levels of stimulation intensity are not as large when compared to higher

levels of stimulation intensity.[104,523] Previous reports suggest that the stimulation intensity of NMES needs to evoke 50 to 60% of an individual's MVIC in order to elicit hypertrophy,[524,525] and intensities up to 80% MVIC are needed to produce strength gains.[526] Thus, similar principles may apply for voluntary quadriceps activation. Adams et al.[502] developed a formula to predict the activated muscle cross-sectional area as a function of NMES training intensity. By applying this formula, it can be found that at the normal ranges of NMES intensity (40–60% MVC), only 29–43% of the total muscle is being targeted. Therefore, patients should be familiarized with NMES and encouraged to progress the stimulation intensity in order to maximize the neuromuscular benefits of NMES.

Further research is needed to determine whether NMES is an effective disinhibitory intervention, especially in patients who exhibit NQD following ACLr. In addition, studies need to determine which stimulation parameters elicit the greatest disinhibitory effects, and whether these effects are greater when NMES is applied during voluntary relaxation or contraction. The superimposition of NMES on voluntary muscle contractions has been hypothesized to facilitate neuromuscular outcomes.[130,527-529] Since neural adaptions are found to occur during the early phase of NMES programs, NMES may be most appropriate during the early stages of rehabilitation, when patients are immobile and/or grossly inhibited. Studies are needed to determine whether NMES should be prescribed to patients based upon neuromuscular status. Lastly, portable NMES units have demonstrated promising results in regard to restoring neuromuscular function.[129-131] The higher volume of NMES combined with the convenience of

home-based NMES, make these units attractive modality for postsurgical patients. Therefore, research is need to determine whether home-based NMES offers a greater disinhibitory benefit for patients after ACL injury and reconstruction.

Electromyographic Biofeedback

Electromyographic biofeedback (EMGBF) is another motor-based modality that is used to re-educate and strengthen muscle. Like NMES, has been shown to enhance quadriceps strength and activation in both healthy individuals[530-533] and in patients with knee-joint pathology/surgery.[127,533-547] However, EMGBF is believed to have a greater effect on patients since they tend to exhibit large deficits in quadriceps strength and activation.[533] Interestingly, there is evidence to suggest the EMGBF improves quadriceps function more than NMES in patients after knee-joint surgery.[127,538] Biofeedback is used in rehabilitation to reveal internal, physiological events to patients through external modalities.[548] In other words, EMGBF provides information on the myoelectric activity of their muscles (internal) through concurrent, external feedback, so that it may be interpreted on a conscious level.

The methodology behind EMGBF involves surface EMG electrodes which are applied to the muscle belly of interest. The active electrodes monitor the myoelectric activity within the muscle, while a reference electrode is used filter irrelevant stimuli (noise). The EMG signals are transmitted through channels and transformed into either auditory or visual cues, which provide a quantifiable representation of the underlying myoelectric activity to the patient.[549] These

external cues are used facilitate neuromuscular control of a muscle by teaching patients how to modulate their motor output in real-time. EMGBF is hypothesized to enhance quadriceps strength and activation by improving volitional recruitment of motor units (temporal and spatial) through corticomotor excitablity.[531,550-552] It has been discovered that when muscular force is produced, there is increased neuronal activity in the motor cortex of the brain.[552] Furthermore, when visual feedback is provided during a movement task, neuronal activity in the motor cortex and production of muscular force are symmetrically enhanced.[550] Pietrosimone et al.[551] discovered that corticomotor excitability is enhanced when EMGBF is used during an MVIC task. Peak isometric KET (at 90° of knee flexion) and MEP amplitudes (normalized to M-waves) were assessed in healthy individuals before and after MVIC tasks, between two conditions: with (experimental) and without (control) EMGBF being simultaneously applied to the quadriceps. Compared to the control condition, the EMGBF elicited greater improvements in both MEP amplitudes and KET, suggesting that EMGBF enhances quadriceps strength by increasing descending output from the motor cortex.

The positive neuromuscular effects associated with EMGBF may be explained by motor learning theories of motor control and development. Specifically, the rapid neuromuscular facilitation observed with EMGBF is believed to be based upon the principles of focused feedback. Feedback can be focused in one of two ways during a motor task: internally or externally. Internally focused feedback focuses an individual's attention on their actions used during a

task (knowledge of performance), whereas externally focused feedback focuses an individual's attention on the outcome of their actions used during a task (knowledge of results).[553-555] In other words, internally focused feedback aims to improve performance by having individuals focus on intrinsic movement patterns, while externally focused feedback aims to improve performance by having individuals focus on extrinsic goals related to movement. Evidence has shown that externally focused feedback is superior to internally focused feedback in regard to the performance and retention of motor skills.[553-557] Therefore, EMGBF employs an externally focused feedback approach to enhancing neuromuscular performance, by having patients focus on the external cue of myoelectric activity from their quadriceps instead of relying on internal cues of a quadriceps contraction (i.e. muscle tone).

EMGBF was originally introduced in the early 1960s as a therapeutic modality for neuromuscular dysfunction, after discovering that individuals could learn to voluntarily control individual motor units by modulating their motor output.[558] Since then, it has been widely used in rehabilitation as a method to improve neuromuscular control and strength in patients with neuromuscular dysfunction. As would be expected, EMGBF is regularly used early on in the rehabilitation of patients following ACLr. The severe quadriceps AMI that is present in patients acutely after ACLr, often impedes the ability of patients to observe a visible contraction of their quadriceps. Administering EMGBF allows these patients to better gauge the contractile behavior of their quadriceps. Secondly, EMGBF can be used to facilitate motor unit recruitment, by motivating

patients to maximize their motor output during quadriceps-specific exercises. Therefore, it is logical to assume that EMGBF may have a disinhibitory effect on patients who exhibit NQD following ACLr.

Although sensory-based modalities, such as cryotherapy and TENS, are believed to disinhibit the quadriceps by targeting inhibitory mechanisms originating at the spinal cord, it is believed that EMGBF is a motor-based modality that may be able target the supraspinal inhibitory mechanisms associated with neural NQD. Not only could EMGBF be used disinhibit the quadriceps of patients after ACLr by reversing the reported decreases in corticomotor excitability, but it could also do so by overriding the spinal inhibitory mechanisms with greater control over the descending pathways projecting to the quadriceps.

Unfortunately, there have been no studies that have assessed whether EMGBF can increase corticomotor or spinal-reflexive excitability in patients who exhibit NQD. Although there is evidence demonstrating that EMGBF enhances quadriceps activation in these patients, [127,534,539-541,545,547,559,560] only one of these studies[540] used a force-based measure of voluntary quadriceps activation (ITT), whereas the other used EMG measures. Krebs[534] was the first to demonstrate a disinhibitory effect in the quadriceps of a patient population through the use of EMGBF. A total of 26 patients were randomized to EMGBF and/or exercise interventions following meniscectomy (20 min/day, 3 days). Both groups performed 20 minutes of isometric quadriceps exercises a day for three consecutive days, while the EMGBF group also applied EMGBF to their

quadriceps while exercising. Peak EMG amplitudes were assessed before and after the 3-day intervention period. When comparing the results between the two groups, peak EMG amplitude was found to increase 2.5 μV/day in the exercise only group, whereas it improved 25 μV per day in the EMGBF group ($p<0.001$). Furthermore, a multiple regression analysis revealed that group membership was a significant predictor of the variance in peak EMG changes ($\beta = 0.68$, $p < 0.01$), with the EMGBF intervention significantly explaining the improvements in peak EMG.

The lone study that used a force-based measure of voluntary quadriceps activation was that of Maitland et al.[540] Although the results were only derived from one patient, making it difficult to generalize to a population, they were quite astounding. A 34 year old patient who was eight months removed from ACLr, and experiencing knee-joint instability, underwent 12 weeks of isometric quadriceps exercises (seated and standing at 20° of knee flexion) and leg press exercises (3 x 10 repetitions) using EMGBF (24 sessions, 2 hours/session). Peak isometric KET (at 90° knee flexion) and voluntary quadriceps activation (via ITT) were measured on the patient before and after the 12-week intervention period. After 12 weeks, left knee MVIC increased by 209%, and quadriceps activation decreased by 22%.

These results offer a glimpse of the disinhibitory potential EMGBF may have on patients after ACLr, but more studies using the recommended techniques to assess NQD (i.e. TMS, H-reflex, ITT, SIB, etc.) are needed to determine its full potential as a disinhibitory intervention. Furthermore, a greater

retention of disinhibitory effects in the quadriceps of patients may be elicited through EMGBF if a “fading-schedule” is administered during rehabilitation. A fading-schedule involves applying more EMGBF early in a patient’s rehabilitation, and then tapering it later on when you have observed discernible improvements in quadriceps function. Winstein and Schmidt[561] used a fading-schedule on individuals for a skill acquisition task (feedback on half of the trials), and compared their performance to that of a group who received constant feedback (every trial). At the end of the intervention, no differences performance were observed between the groups, but the group who received feedback on a fading-schedule had better performance scores on a delayed-retention test. They hypothesized that the differences in retention between groups were because the fading-schedule forced individuals to rely on other cognitive processes to achieve the same outcome, whereas constant feedback may have produced a dependency in individuals, where their performance could not be sustained without feedback. Therefore, it may be beneficial for patients to perform quadriceps-specific exercise without EMGBF immediately after each rehabilitation session to foster retention of neuromuscular facilitation. Furthermore, the neural and motor learning characteristics of EMGBF indicate that neuroplasticity within the CNS may be induced to account for retained disinhibitory effects.[562]

Eccentric Exercise

Traditional rehabilitation programs consisting of isometric or concentric modes of exercise to enhance quadriceps strength in patients after ACLr have

been largely ineffective.[98,99] The lack of quadriceps strength gains that is observed in these patients after rehabilitation can be at least partially attributed to the limiting effects of concurrent NQD. The inability to fully activate a muscle during exercise, it prevents the neuromuscular components from being sufficiently overloaded, and the resulting strength improvements are minimal due to a lack of neural adaptations and hypertrophy. However, eccentric exercise is an alternative mode of exercise that has been shown to be more effective than either concentric or isometric exercise for restoring both quadriceps strength and hypertrophy in patients after ACLr.[290,563-570]

A muscle is eccentrically exercised either when an external force exceeds the internal force of a contracted muscle, or when the external force is decelerated by the internal force of a contracted muscle; thus, causing the contracted muscle to lengthen (also referred to as negative work). Eccentric muscle contractions have been shown to produce two to three times greater force than either isometric or concentric muscle contraction.[571,572] Therefore, it is suggested that the large quadriceps strength gains observed in patients after eccentric exercise is due to its ability to overload the peripheral components of a muscle to a greater extent. However, applying eccentric exercise to the surgical limbs of patients during the early phases ACLr rehabilitation was once contraindicated in the practice of sports medicine, because clinicians believed that it may overstress the graft or damage muscle fibers. Recent evidence has demonstrated the early eccentric exercise is a safe and effective mode of quadriceps strengthening in patients after ACLr, when the external forces are

gradually progressed,[566,567] and exercises are performed in the closed kinetic chain.[563]

Interestingly, eccentric exercise has been shown to facilitate voluntary quadriceps activation in patients after ACLr,[290,570] thus demonstrating its potential as a disinhibitory intervention. In a study by Brasileiro et al.,[570] nine patients, 9 to 10 months removed from ACLr, were prescribed 12 weeks (2 sessions/week) of eccentric quadriceps training. The EMG activity of the vastus lateralis and vastus medialis were assessed at baseline, mid-training (6 weeks), and post-training (12 weeks). The EMG activity of the vastus lateralis and vastus medialis increased at mid-training (213±107 to 289±81 μV, p=0.04 and from 207±65 to 229±69 μV, p=0.04, respectively), and these activity levels were maintained at post-training. More recently, Lepley and colleagues[290] aimed to compare the disinhibitory effects between eccentric exercise and NMES. The assigned 36 patients to either NMES, Eccentric, NMES+Eccentric, or control groups following ACLr. All groups received standard ACL rehabilitation. The NMES group began their 6-week NMES intervention immediately after their first post-operative rehabilitation visit, the Eccentric group began their 6-week eccentric exercises six weeks post-ACLr, and the NMES+Eccentric groups received both interventions (6 weeks of NMES, followed by 6 weeks of eccentric exercise), beginning at the same time as the NMES group. The control group served as a standard-of-care comparison. Voluntary quadriceps activation (via SIB and ITT) was assessed in all patients at pre-ACLr, 12 weeks post-ACLR, and at the time they returned to play (RTP). No significant group differences were present at pre-ACLr (p = 0.61) or between pre-

ACLR to 12 weeks post-ACLr time points (p = 0.21). From pre-ACLr to RTP, the Eccentric group (2.6 ± 4.1) demonstrated greater improvements in voluntary quadriceps activation than both the NMES (-3.4 ± 7.3%, p < 0.05) and control groups (-3.2 ± 5.0%, p < 0.05). No differences were observed between the Eccentric and NMES+Eccentric (+1.6 ± 3.9%) groups (p = 0.63), but the NMES+Eccentric only demonstrated greater quadriceps activation improvements than the control group (p = 0.04). Although there were no group differences observed during the first 12 weeks, the differences at RTP suggest that eccentric exercise is more effective at restoring voluntary quadriceps activation in patients after ACLr compared to NMES, and that the neural function of the quadriceps is in a better condition when eccentric exercise is administered in rehabilitation.

The neural mechanisms involved with the quadriceps activation improvements observed in patients following ACLr have yet to be understood. It has been hypothesized that quadriceps activation is enhanced with eccentric exercise due to the preferential effect it has been shown to have on Type II muscle fibers.[290,573] Given that high threshold (type II) motor units are thought to be selectively inhibited in patients after ACL reconstruction (via gamma loop dysfunction), it is plausible to believe that eccentric exercise may serve to disinhibit these patients' quadriceps by facilitating the activation of type II motor units. Secondly, unilateral eccentric exercise interventions have been shown to produce bilateral improvements in quadriceps strength and activation.[510,511,574] The cross-education effect of eccentric exercise is pertinent to clinicians when treating patients with acute, unilateral knee-joint injuries, or patients who have

recently undergone unilateral knee-joint surgery. Most of these patients are not permitted to perform eccentric exercise on their involved limbs, but they are have gross AMI of their quadriceps that needs to be addressed. Until these patients are cleared to perform eccentric exercise on their involved limbs, the cross-education effect of eccentric exercise allows them to perform eccentric exercise on their uninvolved limbs to facilitate quadriceps activation on their involved limbs. Given that cross-education seems to be a characteristic of most of the disinhibitory interventions discussed in this review, it provides further support for eccentric exercise as a disinhibitory intervention. However, the evidence of cross-education with eccentric exercise has only been from a healthy population. More research is needed determine if eccentric exercise can induce cross-education of quadriceps function in patients after knee-joint injury/surgery. Furthermore, additional studies are needed to support the early evidence of eccentric exercise as a disinhibitory intervention for patients following ACLr.

CHAPTER 3: METHODOLOGY

3.1 RESEARCH DESIGN

This study was a single-blind (orthopaedic surgeon) randomized clinical trial (1:1 sample ratio) that was conducted at the University of Kentucky. Patients were recruited from the UK Healthcare Sports Medicine Clinic located in Lexington, Kentucky. All assessments were conducted on the University of Kentucky's campus, in the Musculoskeletal Laboratory of the Charles T. Wethington building. This randomized clinical trial was registered on clinicaltrials.gov (NCT02058862).

3.2 PARTICIPANTS

Patients between the ages of 14-40 years who sought care for a primary ACL injury (diagnosed via magnetic resonance imaging) and were scheduled to undergo unilateral ACL reconstruction were recruited for this study. Potential participants were identified by their treating physician and/or physician's assistant during their clinical visit. To have been eligible to participate in this study, patients must have sustained their initial ACL injury within the previous six months leading up to their clinical visit with an orthopaedic surgeon. Patients who had a previous surgery to either their involved or contralateral hip, knee, or ankle were excluded from the study. Furthermore, patients were excluded if they had an injury to their involved or contralateral hip, knee, or ankle within the past six months. Patients who were currently being treated for low back pain were also be excluded from

the study. This was included in the exclusion criteria because of recent evidence showing that low back pain alters volitional quadriceps activation.[575,576] For safety reasons, patients who had heart condition/pacemaker, were planning to get pregnant within the next six months (females), or had a history and/or family history of seizures/epilepsy were deemed ineligible to participate in the study. Those with vestibular or other balance disorders that might affect their test performance during a single leg standing task were also excluded. There were no exclusions based on sex, race, or other demographic characteristics.

Potential participants were prospectively identified during their initial clinical visit by three orthopaedic surgeons at the UK Healthcare Sports Medicine Clinic, Darren Johnson, MD, Christian Lattermann, MD, and Mary Lloyd Ireland, MD. Patients that meet the eligibility criteria were then approached by study personnel and invited to participate in the study. Informed consent and HIPPA authorization was provided to eligible patients after they reviewed the study objectives, procedures, and potential risks of participation. Informed written consent was obtained from those patients who agreed to participate in the study. For those participants who were minors (< 18 years of age), informed written consent was obtained from a legal parent/guardian, and informed written assent was obtained from the minor. Approval for this study was granted by Institutional Review Board at the University of Kentucky (IRB #13-0776-F2L).

3.2.1 Randomization

Participants were allocated to either the treatment (home-based NMES) group or control (standard-of-care) group via block randomization using a

computer-generated randomization program. Randomization was further stratified by the time-from-injury (TFI) to baseline testing, and the autograft type used to reconstruct the ACL. Each of the stratification factors had two levels (TFI: ≤ 4 weeks vs. > 4 weeks, and autograft: bone-patellar tendon-bone vs. semitendinosus-gracilis tendon). These stratification factors were chosen because they have both previously been shown to influence quadriceps function in patients after ACLr.[577,578]

3.2.2 Power Analysis

An a priori power analysis (using nQuery software program) was completed for voluntary quadriceps activation levels to determine the sample size with an alpha level of $\alpha = 0.05$. At the time of this study, there were no studies that investigated the effect of NMES on improving voluntary quadriceps activation in patients after ACLr. Therefore, the parameters used for the power analysis were taken from observational data on patients before and after. Based on the literature,[32] the participants' CARs were expected to be approximately 0.75 (± 0.12 SD) prior to ACLr. The participants in the treatment group were hypothesized to improve their CAR to approximately 0.90 (± 0.12) 12 weeks post-surgery, and the control group was hypothesized to improve to approximately 0.85 (± 0.12) 12 weeks post-surgery. To achieve a power level of at least 0.80, the sample size of at least 40 participants (20 per group) were needed based upon a 2-sided power analysis using the above parameters. This would allow for a 5% chance of committing a type I error, and a 20% chance of committing a type II error.

3.3 PROTOCOL

3.3.1 Timeline

After informed written consent was received and the participant was enrolled in the study, baseline measures were assessed by the primary investigator before their scheduled ACLr. These assessments included isometric quadriceps strength, voluntary quadriceps activation, and corticomotor excitability (see section 3.4 for detailed a description of the outcome measures). After baseline testing, each participant was randomly allocated to either the treatment group or control group. After ACLr, each group was advised to attend physical therapy visits as recommended by their orthopaedic surgeon, and to perform their assigned home-based programs (NMES or standard-of-care) in addition to their standardized postoperative rehabilitation protocol. The groups were not to begin their assigned home-based programs until the third day after ACLr, and were told to continue their assigned programs for 12 weeks. At the completion of their home-based programs (3 months post-ACLr), the outcome measures were reassessed by the primary investigator. The participants were then asked to return at six months following their ACLr for a final assessment of the outcome measures, with the addition of lower extremity postural control and self-reported knee function. Each participant was provided the option to review his/her data at the completion of the study. See Figure 3.1 for a flowchart of the protocol timeline.

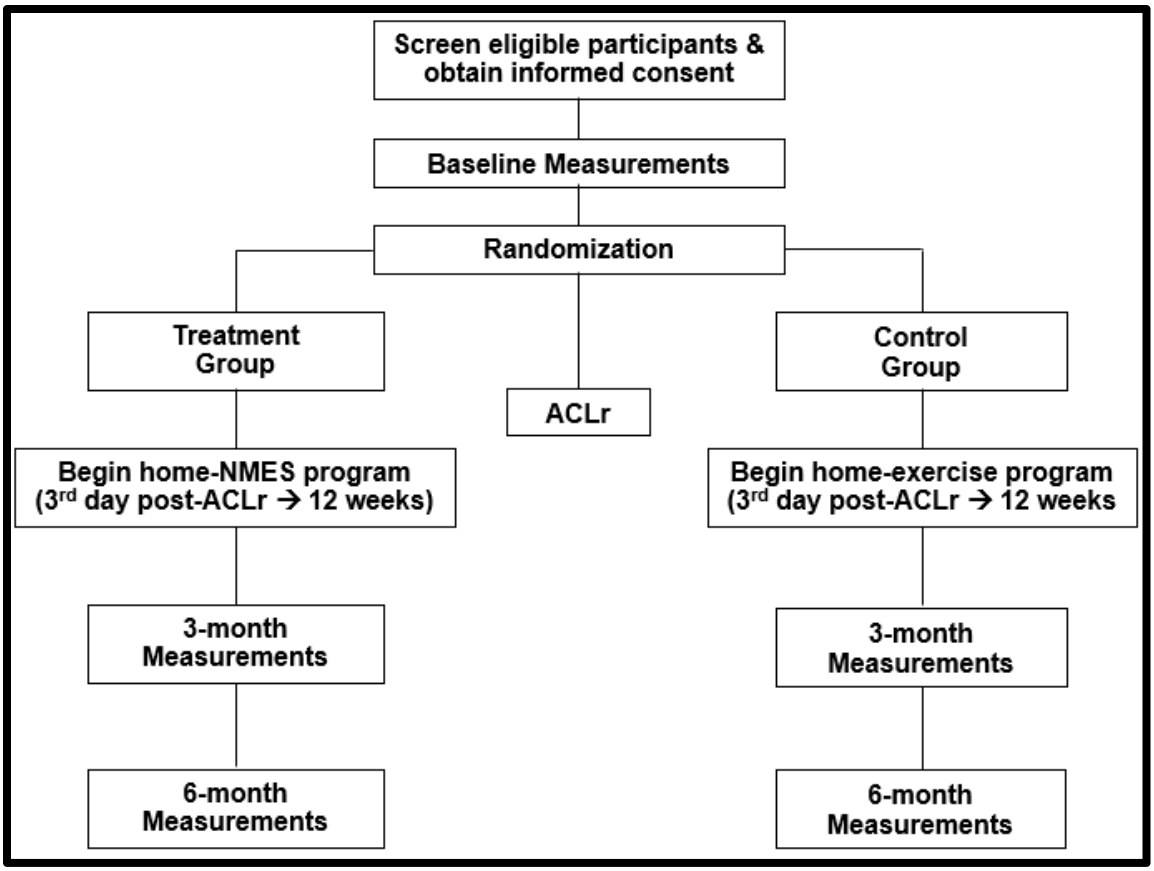

Figure 3.1. Flowchart of the protocol timeline.

3.3.2 Interventions

The participants in the treatment (Home-NMES) group received a thigh sleeve that has a NMES unit (EMPI Phoenix, DJO Global, Vista, CA) embedded into the garment that they controlled during the home-NMES program (see Figure 3.2).[131,579,580] Superimposed electrical stimuli were delivered percutaneously to artificially contract the quadriceps of the treatment group.[107,123,131,580] Participants were instructed to maintain maximal knee extension during the home-NMES treatment. The first two minutes of the Home-NMES treatment was a warm-up period to get the participants accustomed to the

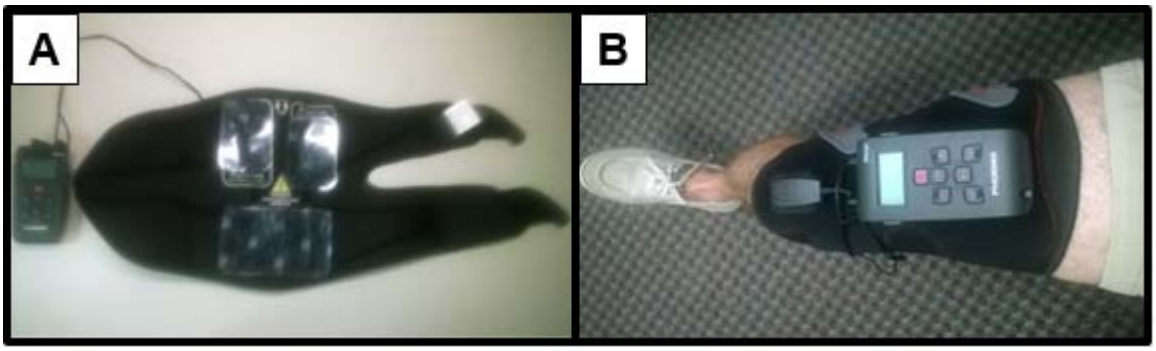

Figure 3.2. Portable neuromuscular electrical stimulation (NMES) sleeve given to the intervention group. (A) NMES thigh sleeve displaying the controller and electrode pads, and (B) NMES thigh sleeve assembled and secured to the right quadriceps.

stimulation. After the warm-up period, a 15-minute exercise period followed. During the exercise period, the stimulation was delivered to the rectus femoris, vastus lateralis, and vastus medialis muscles at a frequency of 75Hz (300 μs pulse duration) with a duty cycle of four seconds on and 10 seconds off. The treatment group was instructed to perform an isometric quadriceps contraction throughout each 4-second stimulation period, and relax their muscles during the 10-second rest period.[130] Beginning on the third day post-operatively, the treatment group was instructed to perform their assigned Home-NMES program three sessions a day for 15 minutes, and five days a week for 12 weeks.[130] Participants in the treatment group were encouraged to progressively increase the intensity of NMES to maximal toleration (max intensity = 100 mA) throughout the 12-week Home-NMES program in order to appropriately overload the muscle. The participants in the Home-NMES group were blinded to an internal monitor within the Home-based NMES unit, which was used to assess total dosage (in minutes) at the completion of the study.

The control group was treated according to the current standard-of-care, performing a home-based treatment of volitional isometric quadriceps contractions without the addition of NMES beginning on the third day post-operatively. Participants performed 15 minutes of quadriceps contractions holding each contraction for four seconds followed by a rest time of 10 seconds between each contraction. Like the treatment group, the control group were instructed to perform their home-exercise program three sessions a day for 15 minutes, and five days a week for 12 weeks. This was intended to make the exercise volume of the control group comparable to that of the Home-NMES group.

3.4 OUTCOME MEASURES

3.4.1 Isometric Quadriceps Strength

Isometric quadriceps strength was assessed on both legs of each participant. An isokinetic dynamometer (Cybex Norm, Humac 2014 System, Computer Sports Medicine Inc., Stoughton, MA) was used to measure isometric KET. The participants were seated and secured into a stationary chair with their hips fixed at 85° flexion and knee fixed at 90° flexion. The knee being tested was aligned with the axis of the dynamometer and a resistance pad attached to the lever arm was fastened to the front of the lower third of their shin (~ two inches superior to the medial malleolus). Participants performed three maximal voluntary isometric contraction (MVIC) trials of their quadriceps by pushing their lower leg against the resistance pad. The highest isometric KET observed from the first

three MVICs was recorded and used as the target torque level during the voluntary quadriceps activation testing. To account for the relationship between muscle mass and strength, peak KET was normalized to each participant's body weight (Nm/kg). A 60-second rest period was provided to the participants after each MVIC trial and before performing voluntary quadriceps activation testing.

3.4.2 Voluntary Quadriceps Activation

Voluntary quadriceps activation was measured on both legs of each participant. The same dynamometer used to assess isometric quadriceps strength was used for voluntary quadriceps activation testing, and participants were seated and secured into the dynamometer chair in the same position as described above. Volitional quadriceps activation was assessed on participants using a superimposed burst (SIB) technique. The SIB technique involves superimposing a brief train of percutaneous electrical stimulation during an MVIC of a muscle. A square wave stimulator (Grass S48, Natus Neurology, W. Warwick, RI) and stimulation isolation unit (SIU8T, W. Warwick, RI) with a 100 ms train of 10 stimuli delivered at 100 pulses per second, a pulse duration of 0.6 ms with a 0.01 ms pulse delay, and a stimulation intensity of 650 mA delivered at 150 V was used to create the SIB.[381] Two, 7x13 cm self-adherent surface electrodes (Dura-Stick Plus Chattanooga, DJO Global, Vista, CA) positioned on the proximal vastus lateralis and distal vastus medialis were used to deliver the electrical stimulus to the quadriceps. Figure 3.3 depicts the participant positioning and electrode placement for voluntary quadriceps activation testing. The SIB was then used to calculate the central activation ratio (CAR), which compares the

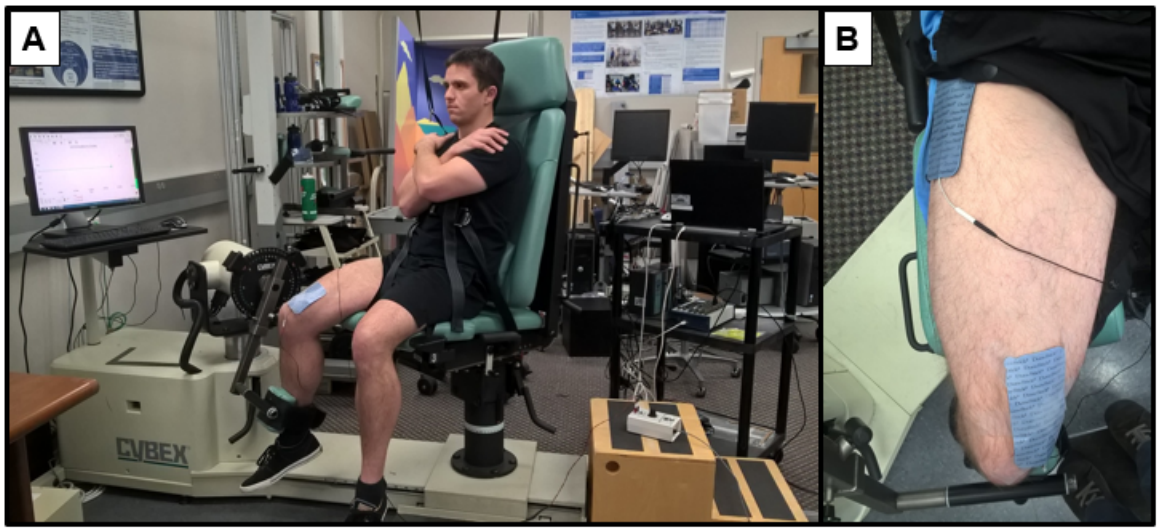

Figure 3.3. Participant positioning (A) and electrode placement (B) for superimposed burst (SIB) testing (proximal = vastus lateralis, distal = vastus medialis).

amount of superimposed torque produced from the SIB to that of the MVIC torque measured just prior to the SIB (CAR = MVIC/superimposed MVIC). To familiarize the participants with the stimulation, a graded stimulation warm-up was provided prior to the voluntary quadriceps activation test. Participants were instructed to perform three submaximal isometric contractions at approximately 25%, 50%, and 75% of their perceived MVIC. During each of these submaximal contractions, a corresponding submaximal electrical stimulus (25%, 50%, and 75% of 150 V, respectively) was delivered to the quadriceps in attempt to acclimate the participants to the stimulation. For the SIB test, participants performed one MVIC of their quadriceps and a brief automated stimulus (150 V) was triggered once the participants reached their peak knee extension torque (derived from their isometric quadriceps strength trials). To provide participants with visual feedback of their torque output, a monitor was placed in front of the participants during the SIB test with a target torque level set at 120% of their

peak MVIC. This target torque level was used to further motivate the participants and ensure that they were providing maximal effort. Refer to Figure 3.4 for description of SIB protocol and CAR calculation.

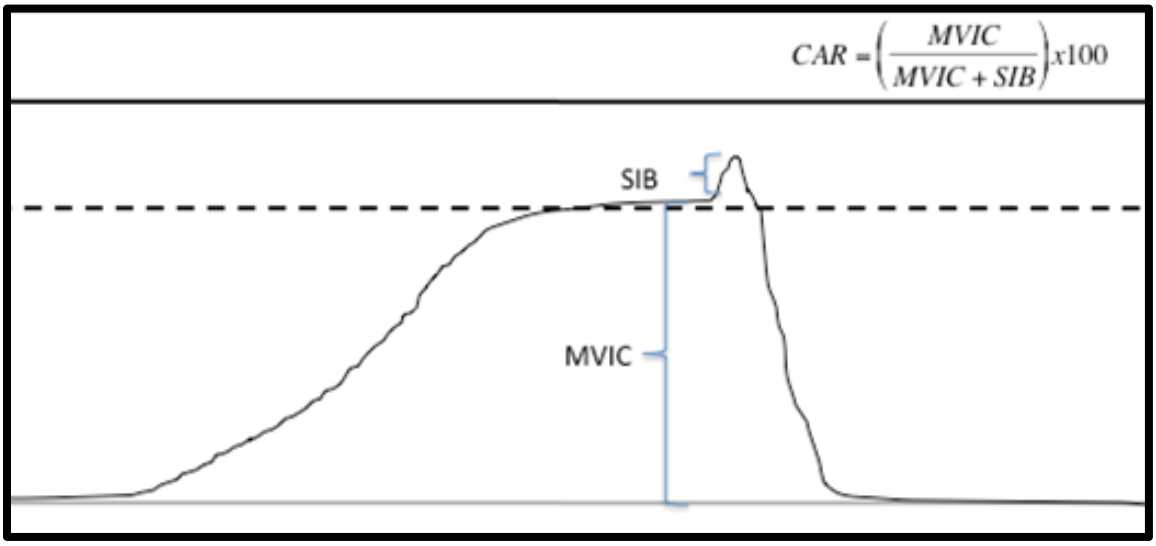

Figure 3.4. Depiction of torque graph from the superimposed burst (SIB) test. The dashed line was set on the screen and represents the peak MVIC produced during the quadriceps strength testing. The top, solid black line represents 120% of the peak maximal voluntary isometric contraction (MVIC) and serves as the target torque level. Participants are instructed to attempt to reach the solid black line to ensure maximal effort. An automated stimulus was delivered once the torque output reached the dotted line. If the participant was unable to reach the dotted line during the trial, the stimulus was never delivered and more rest was provided between trials. MVIC values and superimposed burst torque values were used to calculate a central activation ratio (CAR) as seen by the equation in the figure.

3.4.3 Corticomotor Excitability

For cortical excitability testing, the participants were seated in the same position on the dynamometer as the strength and activation tests. All participants were fitted with a swim cap so the investigator could mark (with a semi-permanent marker) specific anatomical landmarks to determine the ideal placement of the magnetic coil for eliciting an MEP of the quadriceps. Quarter-sized areas on the skin over the vastus medialis and the medial malleolus of the

ankle were gently abraded with fine-grade sandpaper and cleaned with an isopropyl alcohol pad. This step was necessary to remove any oils, lotions, and dry skin that may impede the recording of myoelectrical potentials. Surface EMG electrodes were then placed over the cleaned areas of the distal quadriceps to record MEPs and a ground electrode was placed on the medial malleolus. The vastus medialis electrodes were placed approximately 4 cm superior and 3 cm medial to the superomedial border of the patella and oriented 55° to the vertical.[581] These electrodes were secured in place using self-adhesive tape (see Figure 3.5).

Figure 3.5. Placement of surface electromyography (EMG) electrodes for corticomotor excitability testing. The red and white wires correspond to the active and reference electrodes at the vastus medialis (respectively), and the black wire corresponds to the ground electrode at the medial malleolus.

Transcranial magnetic stimulation (TMS) was delivered using the MagStim200^2 unit synchronized with the Myopac system for amplification and filtering. A double-cone coil connected to the MagStim200^2 was used to deliver a single electromagnetic impulse to the primary motor cortex of the cerebral hemisphere contralateral to the limb being used to record MEPs. To find the ideal placement of the double-coned coil for each participant, the coil was moved anterior to posterior over the vertex (1 cm increments) of the skull while the primary investigator applied an electromagnetic impulse (50% of maximal TMS output) until the largest MEP is elicited in the quadriceps. This area ("hot spot") was indicated on each participant's swim cap with a marker for every testing session. The coil was held in place during testing by the primary investigator (see Figure 3.6).

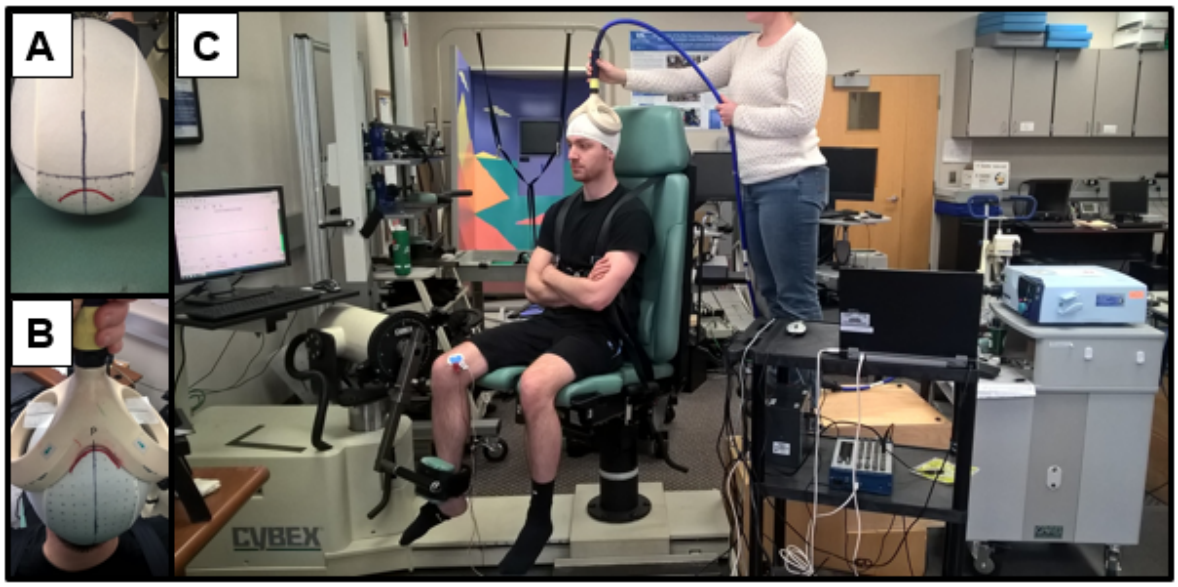

Figure 3.6. Depiction of the equipment and participant setup employed during corticomotor excitability testing. (A) The "hot spot" was marked with marker (red) on a swim cap, and the posterior border of the double-coned coil overlaid the marked spot (B) to elicit motor evoked potentials (MEP) at the vastus medialis and determine the active motor threshold (AMT).

To find the active motor threshold (AMT) of the quadriceps, participants performed an isometric knee extension at a normalized intensity of 5% of their MVIC observed during isometric quadriceps strength testing. A monitor was placed in front of the participants to provide visual feedback of their torque output. TMS was first delivered at 50% of the maximum stimulator output (110 – 120 V)[61,296,451] with the stimulating coil placed over the primary motor cortex area of the cerebral hemisphere contralateral to the limb being used to record the MEPs. The active motor threshold was defined as the minimum stimulus intensity at which an electrical response of at least 100 μV is achieved. Active motor threshold was obtained by first decreasing the magnetic stimulus by 5% until six out of 10 trials had an MEP amplitude of <100 μV.

The percentage of stimulator intensity was then gradually increased until five out of 10 consecutive stimuli produced an MEP of equal to or greater than 100 μV (see Figure 3.7). The stimulator intensity (% TMS output) used to achieve this value was recorded as the active motor threshold for each participant.[442]

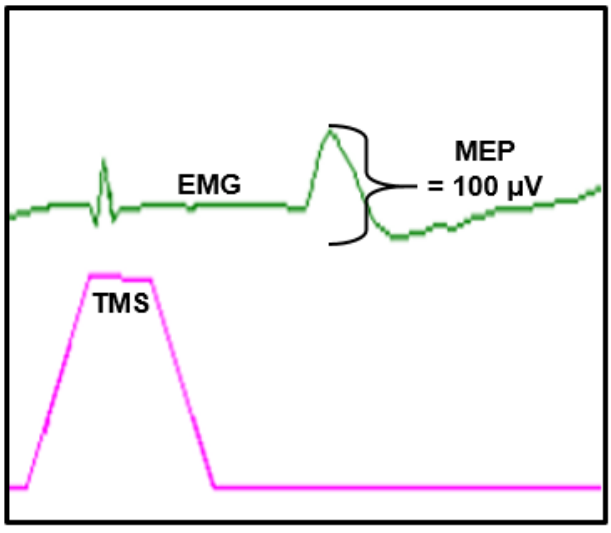

Figure 3.7. Representation of transcranial magnetic stimulation (TMS) impulse and resultant motor evoked potential (MEP) recorded via surface electromyography (EMG) from the vastus medialis muscle. The TMS intensity (% TMS output) needed to achieve an MEP equal to 100 μV represents a participant's active motor threshold.

3.4.4 Lower Extremity Postural Control

The Y-balance test™ (YBT; FunctionalMovement.com, Danville, VA) was used to assess the patients' lower extremity postural control at 6 months post-ACLr. The YBT is the commercialized version of the Star Excursion Balance Test (SEBT) that was developed to improve its reliability.[582] Both the YBT and the SEBT assess an individual's ability to move from a position of bilateral stance to a position of unilateral stance whereby the contralateral limb is used to reach maximally in three different directions (anterior, posterolateral, and posteromedial) without compromising their balance. Although some evidence suggests the YBT and SEBT require different kinematic strategies to achieve maximal reach distances,[583,584] the two tests continue to be strongly correlated. Furthermore, anterior reach distance has been shown to predict lower extremity injuries in athletes,[585,586] and the integrated EMG activity of the quadriceps is the highest with the anterior reach.[587] Therefore, the anterior reach direction was preferentially assessed in participants of this study.

The anterior reach distance on the YBT (YBT-A) was measured on both limbs of each participant. Participants were instructed to stand unilaterally on the center platform of the Y-balance device, and to place their hands on their hips. While balancing on the stance limb, the participants were encouraged to slide the anterior block with their contralateral limb as far away from the center platform as possible while maintaining their balance (see Figure 3.8). Once they achieved their maximal reach distance, they returned their contralateral limb to the starting position and were allowed to step off of the platform. If the anterior block was

Figure 3.8. Representation of the Y-balance test for anterior reach (YBT-A) procedure used to assess lower extremity postural control.

kicked, the stance foot moved, a hand was removed from the hip, or the participant lost balance during any point of the trial, the trial was discarded and another was allotted until a total of three clean trials were recorded for both limbs. Participants were given three practice trials before the recorded trials in attempt to neutralize a learning effect. The average reach distance for the three recorded trials were normalized to each participant's respective leg length measured from the anterior superior iliac spine to the medial malleolus (anterior reach distance/leg length).

3.4.5 Self-Reported Knee Function

The Knee Injury and Osteoarthritis Outcome Score (KOOS) was used to assess the self-reported knee function of the participants at six months post-

ACLr (see Appendix). The KOOS is a questionnaire intended to assess both the short-term and long-term consequences of knee injury or surgery.[193] It has demonstrated excellent validity and reliability in patients after ACLr.[190-193] Compared to other patient-reported knee questionnaires, the KOOS is meant for younger, and more physically active patients who have sustained a knee injury or have undergone knee surgery.[588] The KOOS consists of 42 questions that are separated and scored into five domains [Symptoms, Pain, Activities of Daily Living (ADLs), Quality of life (QOL), and Function in Sports/Recreational Activities (Sports/Rec)]. Each question includes a Likert scale answer format scored from 0 (No Problems) to 4 (Extreme Problems). It takes patients approximately 5-10 minutes to complete the entire KOOS questionnaire. Once completed, the sum of the item scores for each domain were calculated and transformed on a 0-100 scale (0 = lowest function, 100 = highest function).

Of the five domains, the QOL and Sports/Rec domains have demonstrated the most unidimensionality,[589] and are the most sensitive to changes over time in patients after ACLr.[193] Therefore, the QOL and Sports/Rec domains were preferentially assessed in the participants of this study.

3.5 STATISTICAL ANALYSES

Statistical analyses were performed using SAS software (version 9.3, SAS Institute, Inc., Cary, NC) Shapiro-Wilk tests were performed on all demographics and outcome measures to confirm the normality of baseline data (pre-ACLr). All of the variables were deemed to possess normal distribution, except for

quadriceps CAR. Therefore, quadriceps CAR was transformed (arcsin√[CAR/100]) to achieve normal distribution during statistical analyses, but it was untransformed to the original units (%) when reporting it in the results (sin[transformed CAR^2]*100).

3.5.1 Group Characteristics

Independent (Student's) t-tests were performed on age, height (cm), weight (kg), number of concomitant knee injuries, TFI (days), and time from surgery (TFS) to 3-month and 6-month testing (months) to assess for demographic differences between the treatment and control groups. Fisher's Exact tests were used to assess for demographic differences in sex and autograft type between groups. Independent t-tests were also used to detect for differences in the outcome measures between groups at baseline. Means and standard deviations were reported to represent central tendency and variability of the continuous variables. Alpha level was set *a priori* at $P \leq 0.05$.

3.5.2 Specific Aim 1

A 2x3 (limb x time) mixed model, analyses of variance (ANOVA) with repeated measures was performed in the control group to assess differences between the involved limb and the uninvolved limb in isometric quadriceps strength (peak KET), and voluntary quadriceps activation (CAR) from baseline to three months post-ACLr, baseline to six months post-ACLr, and three months post-ACLr to six months post-ACLr. A one-way mixed model, ANOVA with repeated measures was performed in the control group to assess differences in corticomotor excitability (AMT) over time (baseline, 3 months post-ACLr, and 6

months post-ACLr). Post-hoc comparisons with simulated P-value adjustments were performed when appropriate.[590] Model estimates and 95% confidence intervals were reported to represent the results. Alpha level was set *a priori* at $P \leq 0.05$.

3.5.3 Specific Aim 2

Means and standard deviations were calculated for the lower extremity functional outcome measures of the control group at six months post-ACLr. Separate, mixed model, linear regression analyses were performed in the control group (involved limb) to determine the effect that isometric quadriceps strength (normalized peak KET), voluntary quadriceps activation (CAR), and corticomotor excitability (AMT) measures assessed at baseline and three months post-ACLr, had on lower extremity postural control (YBT-A) and self-reported knee function (KOOS-QOL and KOOS-Sports/Rec) assessed at six months post-ACLr. Beta estimates and 95% confidence intervals were reported for each baseline and 3-month post-ACLr neuromuscular variable, corresponding with each 6-month lower extremity functional outcome measure. Alpha level was set *a priori* at $P \leq 0.05$.

3.5.4 Specific Aim 3

A 2x2x3 (group x limb x time) mixed model, ANOVA with repeated measures was performed to assess group differences between the involved limb and the uninvolved limb in isometric quadriceps strength (peak KET), and voluntary quadriceps activation (CAR) from baseline to three months post-ACLr, baseline to six months post-ACLr, and 3 months post-ACLr to six months post-

ACLr. A 2x3 (group x time) mixed model, ANOVA with repeated measures was performed to assess group differences in corticomotor excitability (AMT) over time (baseline, 3 months post-ACLr, and 6 months post-ACLr). Post-hoc comparisons with simulated P-value adjustments were performed when appropriate.[590] Model estimates and 95% confidence intervals were reported to represent the results. Alpha level was set *a priori* at $P \leq 0.05$.

CHAPTER 4: RESULTS

4.1 GROUP CHARACTERISTICS

4.1.1 Demographics

A total of 50 patients with ACL injuries volunteered to participate in this study (25 Home-NMES group, 25 control group). Baseline group demographic data can be found in Table 4.1. There were no statistically significant demographic differences between the groups at baseline ($p > 0.05$).

Table 4.1. Baseline Group Demographics (Means ± SD)

Demographic	Home-NMES Group (n = 25)	Control Group (n = 25)	P-value
Sex (Males/Females)	6/19	11/14	0.23
Age (years)	18.9 ± 5.4	19.4 ± 4.5	0.71
Height (cm)	170.8 ± 9.7	171.1 ± 11.5	0.90
Weight (kg)	74.6 ± 18.5	70.7 ± 11.9	0.40
Time from injury to baseline testing (days)	28.0 ± 20.0	24.9 ± 18.5	0.56
Time from ACLr to 3-month testing (months)	3.7 ± 0.3	3.4 ± 0.4	0.06
Time from ACLr to 6-month testing (months)	6.5 ± 0.7	6.3 ± 0.5	0.18
Graft Choice (BPTB/STG)	18/7	19/6	1.00

Home-NMES, home-based neuromuscular electrical stimulation program; ACLr, anterior cruciate ligament reconstruction; BPTB, bone-patellar tendon-bone autograft; STG, semitendinosus-gracilis autograft.

4.1.2 Outcome Measures

All 50 patients reported for baseline testing. Baseline outcome group measures can be found in Table 4.2. There were no group differences between baseline outcome measures ($p > 0.05$), except for normalized peak KET in the

uninvolved limb (p = 0.02). Thirty nine patients (78%) were available for 3-month postoperative testing (20 Home-NMES group, 19 control group), and 42 patients (84%) were available for 6-month post-operative testing (23 Home-NMES group, 19 control group).

Table 4.2. Baseline Group Outcome Measures (Means ± SD)

Outcome Measure	Home-NMES Group (n = 25)	Control Group (n = 25)	P-value
Normalized Peak KET (Nm/kg) - Involved	2.6 ± 0.7	2.9 ± 0.9	0.19
Normalized Peak KET (Nm/kg) - Uninvolved	2.9 ± 0.6	3.3 ± 0.7	0.02*
CAR (%) - Involved	94.6 ± 5.5	91.3 ± 8.3	0.12
CAR (%) - Uninvolved	89.5 ± 8.4	87.7 ± 9.7	0.51
AMT (%) - Involved	33.9 ± 7.2	39.1 ± 10.2	0.06

Home-NMES, home-based neuromuscular electrical stimulation program; KET, knee extension torque; CAR, central activation ratio; AMT, active motor threshold; YBT-A, Y-balance test-anterior reach (reach distance/leg length); KOOS, Knee Injury and Osteoarthritis Outcome Score; Sports/Rec, sports and recreation; QOL, quality of life.
*Significant difference between groups (P ≤ 0.05)

4.2 SPECIFIC AIM 1

4.2.1 Descriptive Statistics

Model estimates and 95% confidence intervals for the temporal neuromuscular quadriceps outcome measures in patients before and after ACLr (control group) can be found in table 4.3.

4.2.2 Isometric Quadriceps Strength

A significant limb by time interaction was discovered for normalized peak KET ($F_{2,18.6}$ = 29.7, P < 0.001) in patients. Patients demonstrated lower normalized peak KET on their involved limbs compared to their uninvolved limbs

Table 4.3. Model estimates (95% CI) of temporal neuromuscular outcome measures between limbs (control group).

Measure	Time Point	Involved limb	Uninvolved limb
Normalized Peak KET (Nm/kg)	Baseline (pre-ACLr)	2.87 (2.52, 3.22)*	3.36 (3.07, 3.65)
	3-month (post-ACLr)	1.67 (1.31, 2.03)*†	3.23 (2.94, 3.51)
	6-month (post-ACLr)	1.97 (1.58, 2.36)*†‡	3.06 (2.71, 3.40)†
CAR (%)**	Baseline (pre-ACLr)	93.4 (90.2, 96.0)	91.0 (87.8, 93.8)
	3-month (post-ACLr)	94.1 (91.1, 96.5)	91.8 (88.1, 94.9)
	6-month (post-ACLr)	92.7 (88.1, 96.2)	90.1 (84.4, 94.6)
AMT (%)	Baseline (pre-ACLr)	39.1 (34.5, 43.8)	N/A
	3-month (post-ACLr)	39.2 (34.3, 44.1)	N/A
	6-month (post-ACLr)	39.7 (35.6, 43.7)	N/A

95% CI, 95% confidence interval (lower bound, upper bound); Home-NMES, home-based neuromuscular electrical stimulation program; KET, knee extension torque; CAR, central activation ratio; AMT, active motor threshold; TMS, transcranial magnetic stimulation; ACLr, anterior cruciate ligament reconstruction
*Significant difference compared to the uninvolved limb ($p \leq 0.05$)
†Significant difference compared to baseline (pre-ACLr) time point ($p \leq 0.05$)
‡Significant difference compared to 3-month (post-ACLr) time point ($p \leq 0.05$)
**Significant main effect for limb ($p \leq 0.05$)

at baseline (-0.49 Nm/kg, $p = 0.015$), three months post-ACLr (-1.56 Nm/kg, $p < 0.001$), and six months post-ACLr (-1.09 Nm/kg, $p < 0.001$). Normalized peak KET progressively decreased in the involved limbs of patients from baseline to 3 months post-ACLr (-1.20 Nm/kg, $p < 0.001$), baseline to six months post-ACLr (-0.90 Nm/kg, $p = 0.002$), and increased from three months to six months post-ACLr (0.30 Nm/kg, $p = 0.016$). Normalized peak KET was also decreased in the uninvolved limbs of patients from baseline to six months post-ACLr (-0.30 Nm/kg,

p = 0.016). No other time-based differences were detected in the uninvolved limb (p > 0.05). Refer to Figure 4.1 for visual representation of normalized peak KET model estimates.

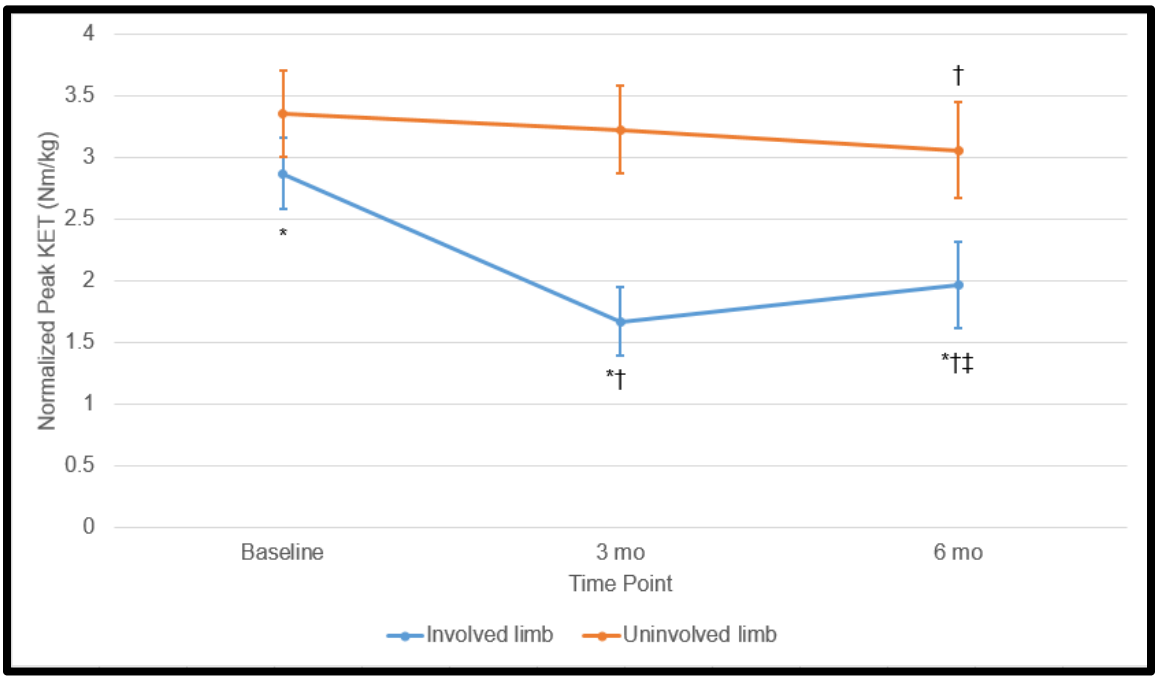

Figure 4.1. Model estimates and 95% confidence intervals of normalized peak KET (Nm/kg) for the involved and uninvolved limbs at baseline, 3 months post-ACLr, and 6 months post-ACLr.
*Significant difference compared to the uninvolved limb (p ≤ 0.05)
†Significant difference compared to baseline (pre-ACLr) time point (p ≤ 0.05)
‡Significant difference compared to 3-month (post-ACLr) time point (p ≤ 0.05)

4.2.3 Voluntary Quadriceps Activation

There was a significant main effect for limb observed with quadriceps CAR ($F_{1,24}$ = 4.68, p = 0.04) in patients, but there was no main effect for time ($F_{2,17.1}$ = 0.57, p = 0.58) or limb by time interaction. Irrespective of when it was assessed, quadriceps CAR was approximately 2.4% higher (on average) in the involved

limbs of patients compared to their uninvolved limbs (p = 0.04). Refer to Figure 4.2 for visual representation of quadriceps CAR model estimates.

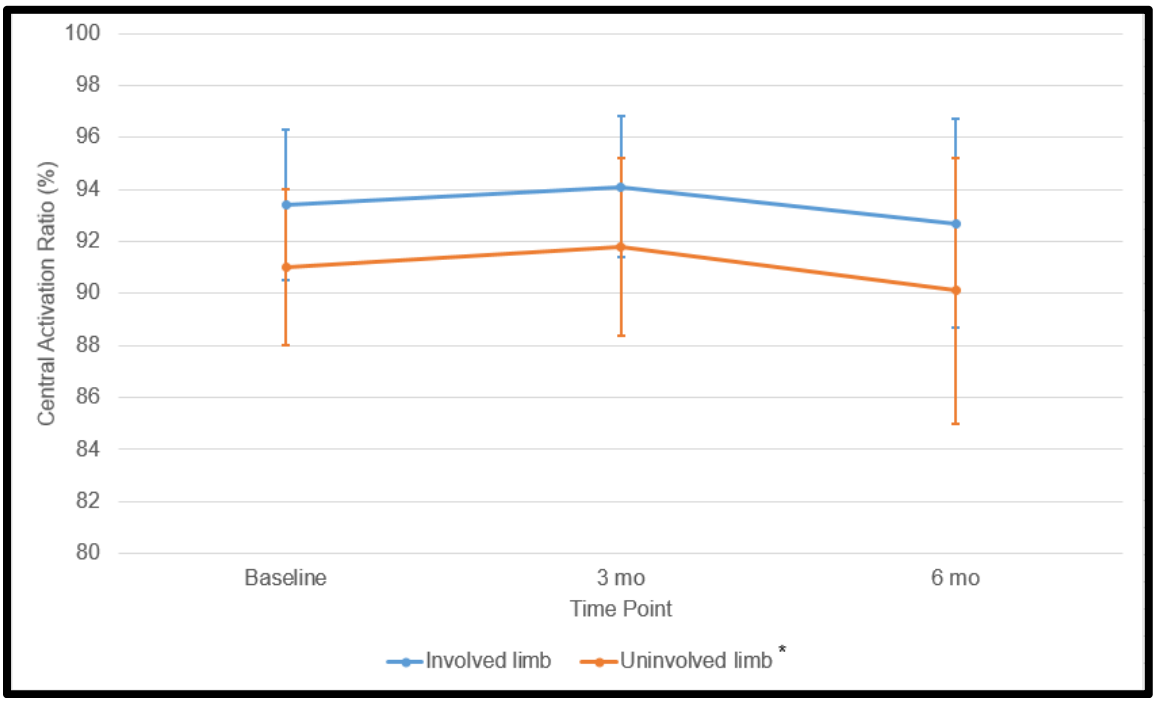

Figure 4.2. Model estimates and 95% confidence intervals of quadriceps CAR (%) for the involved and uninvolved limbs at baseline, 3 months post-ACLr, and 6 months post-ACLr.
*Significant main effect for limb ($p \leq 0.05$)

4.2.4 Corticomotor Excitability

There was no main effect for time ($F_{2,16.1} = 0.08$, $p = 0.93$) observed for quadriceps AMT in the involved limbs of patients ($p > 0.05$).

4.3 SPECIFIC AIM 2

4.3.1 Descriptive Statistics

Means and standard deviations for the lower extremity functional outcome

measures of patients at six months after ACLr (control group) can be found in table 4.4. The beta estimates and 95% confidence intervals from the linear regression analyses for each baseline and 3-month post-ACLr neuromuscular variable, corresponding with each 6-month lower extremity functional outcome measure, can be found in table 4.5.

Table 4.4. Means (± SD) of lower extremity functional outcome measures in patients six months after ACLr (control group).

Measure	6-month Outcome
YBT-A (%) - Involved	62.6 ± 8.0
KOOS-Sports/Rec (/100)	77.7 ± 17.5
KOOS-QOL (/100)	63.5 ± 18.7

YBT-A, Y-balance test-anterior reach; KOOS, Knee Injury and Osteoarthritis Outcome Score; Sports/Rec, sports and recreation; QOL, quality of life.

4.3.2 Effect of Early Neuromuscular Quadriceps Outcome Measures on 6-month Lower Extremity Functional Outcome Measures

The normalized peak KET of patients at three months post-ACLr had a significant positive effect on their 6-month YBT-A performance ($t_{16} = 12.29$, $p = 0.04$) and KOOS-QOL score ($t_{17} = 2.14$, $p = 0.047$). For every 1 Nm/kg increase in normalized peak KET at three months post-ACLr, an estimated 5.1% increase in YBT-A reach distance was expected at six months post-ACLr. Likewise, for every 1 Nm/kg increase in normalized peak KET at three months post-ACLr, an estimated 8.9 point increase in KOOS-QOL score was expected at 6-months post-ACLr. Normalized peak KET at three months post-ACLr did not have an

Table 4.5. Regression analyses to determine effect of baseline and 3-month post-ACLr neuromuscular variable on lower extremity functional outcomes at six months post-ACLr (control group).

6-month Outcome	Variable	Time Point	Beta Estimate (95% CI)	P-value
YBT-A - Involved (%)	Normalized Peak KET	Baseline	1.9 (-2.9, 6.7)	0.42
		3-month	5.1 (0.4, 9.8)*	0.04
	CAR	Baseline	-13.5 (-39.5, 12.6)	0.29
		3-month	10.7 (-8.0, 29.4)	0.24
	AMT	Baseline	0.2 (-0.3, 0.6)	0.40
		3-month	0.2 (-0.3, 0.6)	0.38
KOOS-Sports/Rec (/100)	Normalized Peak KET	Baseline	1.7 (-8.1, 11.5)	0.72
		3-month	5.3 (-3.5, 14.1)	0.22
	CAR	Baseline	1.2 (-5.2, 7.6)	0.70
		3-month	-2.4 (-6.1, 1.3)	0.18
	AMT	Baseline	0.1 (-0.7, 1.0)	0.74
		3-month	0.3 (-0.6, 1.2)	0.50
KOOS-QOL (/100)	Normalized Peak KET	Baseline	0.8 (-9.7, 11.3)	0.88
		3-month	8.9 (0.1, 17.7)*	0.047
	CAR	Baseline	-0.4 (-7.3, 6.4)	0.90
		3-month	0.6 (-3.5, 4.7)	0.76
	AMT	Baseline	-0.5 (-1.3, 0.4)	0.24
		3-month	-0.6 (-1.5, 0.3)	0.19

ACLr, anterior cruciate ligament reconstruction; 95% CI, 95% confidence interval (lower bound, upper bound); YBT-A, Y-balance test (anterior reach); KOOS, Knee Injury and Osteoarthritis Outcome Score; Sports/Rec, sports and recreation; QOL, quality of life; KET, knee extension torque; CAR, central activation ratio; AMT, active motor threshold

*Significant association with 6-month outcome ($p \leq 0.05$)

effect on 6-month KOOS-Sport/Rec score ($p > 0.05$). Neither quadriceps CAR or AMT (at baseline or 3-month post-ACLr) had a significant effect on any of the 6-month lower extremity function outcome measures ($p > 0.05$).

4.4 SPECIFIC AIM 3

4.4.1 Descriptive Statistics

Model estimates and 95% confidence intervals for the temporal neuromuscular quadriceps outcome measures in both the Home-NMES group and control group can be found in table 4.6.

4.4.2 Isometric Quadriceps Strength

There was a significant main effect for group observed with normalized peak KET ($F_{1,46.4} = 4.5$, $p = 0.04$) in the control group. Irrespective of limb or when it was assessed, normalized peak KET was 0.36 Nm/kg higher (on average) in the control group compared to the Home-NMES group ($p = 0.04$). A significant limb by time interaction was discovered for normalized peak KET ($F_{2,40.3} = 52.17$, $P < 0.001$), regardless of group assignment. Both groups demonstrated lower normalized peak KET on their involved limbs compared to their uninvolved limbs at baseline (-0.32 Nm/kg, $p < 0.001$), three months post-ACLr (-1.35 Nm/kg, $p < 0.001$), and six months post-ACLr (-0.95 Nm/kg, $p < 0.001$). Normalized peak KET progressively decreased in the involved limbs of both groups from baseline to three months post-ACLr (-1.07 Nm/kg, $p < 0.001$) and baseline to six months post-ACLr (-0.75 Nm/kg, $p < 0.001$), and increased

Table 4.6. Model estimates (95% CI) of temporal neuromuscular outcome measures between groups and limbs

Measure	Time Point	Home-NMES involved limb	Home-NMES uninvolved limb	Control involved limb	Control uninvolved limb
Normalized Peak KET (Nm/kg)**	Baseline (pre-ACLr)	2.55 (2.27, 2.82)*	2.94 (2.70, 3.19)	2.91 (2.63, 3.18)*	3.30 (3.06, 3.55)
	3-month (post-ACLr)	1.48 (1.21, 1.74)*†	2.83 (2.59, 3.07)	1.84 (1.57, 2.11)*†	3.19 (2.95, 3.44)
	6-month (post-ACLr)	1.80 (1.51, 2.08)*†‡	2.75 (2.49, 3.01)	2.16 (1.87, 2.45)*†‡	3.11 (2.84, 3.38)
CAR (%)	Baseline (pre-ACLr)	95.5 (93.1, 97.5)*	91.7 (88.5, 94.4)	93.4 (90.6, 95.7)*	88.9 (85.3, 92.0)
	3-month (post-ACLr)	95.0 (91.6, 97.6)	92.5 (89.4, 95.1)	92.7 (88.8, 95.9)	89.8 (86.2, 92.9)
	6-month (post-ACLr)	92.5 (88.7, 95.5)	92.2 (88.7, 95.0)	89.8 (85.5, 93.4)	89.4 (85.5, 92.8)
AMT (%)	Baseline (pre-ACLr)	34.6 (30.8, 38.3)	N/A	38.5 (34.8, 42.1)	N/A
	3-month (post-ACLr)	35.8 (31.8, 39.8)	N/A	39.8 (35.8, 43.7)	N/A
	6-month (post-ACLr)	36.2 (32.5, 39.9)	N/A	40.2 (36.5, 43.8)	N/A

95% CI, 95% confidence interval (lower bound, upper bound); Home-NMES, home-based neuromuscular electrical stimulation program; KET, knee extension torque; CAR, central activation ratio; AMT, active motor threshold; TMS, transcranial magnetic stimulation; ACLr, anterior cruciate ligament reconstruction

*Significant difference compared to the uninvolved limb ($p \leq 0.05$)

†Significant difference compared to baseline (pre-ACLr) time point ($p \leq 0.05$)

‡Significant difference compared to 3-month (post-ACLr) time point ($p \leq 0.05$)

**Significant main effect for group ($p \leq 0.05$)

from three months to six months post- ACLr (0.32 Nm/kg, $p < 0.001$). Normalized peak KET was also decreased in the uninvolved limbs of both groups from baseline to six months post-ACLr (-0.19, $p = 0.02$ unadjusted), but this decrease did not achieve statistical significance after the simulated adjustment ($p = 0.13$). No other time-based differences were detected in the uninvolved limb for either group ($p > 0.05$). Refer to figure 4.3 for visual representation for normalized peak KET model estimates.

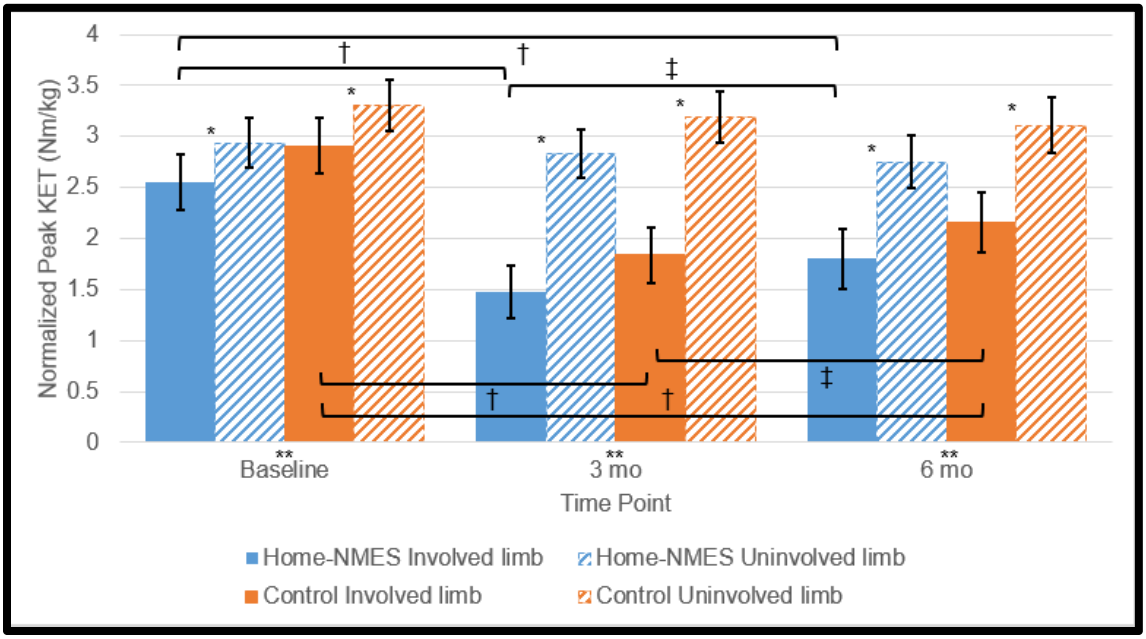

Figure 4.3. Model estimates and 95% confidence intervals of normalized peak KET (Nm/kg) for the involved and uninvolved limbs of both the Home-NMES and control groups at baseline, 3 months post-ACLr, and 6 months post-ACLr.
*Significant difference compared to the uninvolved limb ($p \leq 0.05$)
†Significant difference compared to baseline (pre-ACLr) time point ($p \leq 0.05$)
‡Significant difference compared to 3-month (post-ACLr) time point ($p \leq 0.05$)
**Significant main effect for group ($p \leq 0.05$)

4.4.3 Voluntary Quadriceps Activation

There was no main effect observed for group with quadriceps CAR ($F_{1,48.3}$ = 1.83, p = 0.18). Regardless of group assignment, there was a significant limb by time interaction ($F_{1,32.6}$ = 4.52, p = 0.02). At baseline, quadriceps CAR was approximately 4.2% higher (on average) in the involved limbs of both groups compared to their uninvolved limbs (p = 0.003). No other limb differences were observed in either group at three or six months post-ACLr (p > 0.05). Quadriceps CAR decreased in the involved limbs of both groups from baseline to six months post-ACLr (3.3%, p = 0.02 unadjusted), but this decrease did not achieve statistical significance after the simulated adjustment (p = 0.11). No other time-based differences were detected in the involved limb or uninvolved limb for either group (p > 0.05). Refer to Figure 4.4 for visual representation of quadriceps CAR model estimates.

4.4.4 Corticomotor Excitability

There were no main effects for group ($F_{1,40.2}$ = 2.25, p = 0.14) or time ($F_{2,33}$ = 1.45, p = 0.25) observed with quadriceps AMT in the involved limbs of either group (p > 0.05).

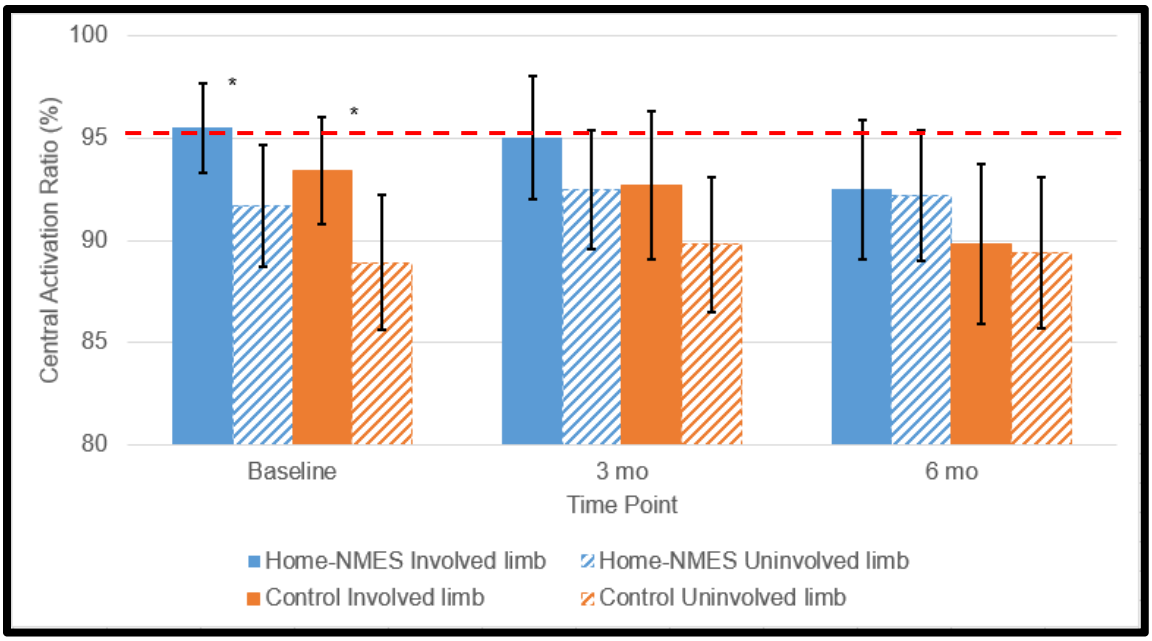

Figure 4.4. Model estimates and 95% confidence intervals of quadriceps CAR (%) for the involved and uninvolved limbs of both the Home-NMES and control groups at baseline, 3 months post-ACLr, and 6 months post-ACLr. The dashed red line corresponds to the healthy normative quadriceps CAR (95%) reported by Park and Hopkins, 2013, International Journal of Neuroscience, 123 (1), 55-59.[404]

*Significant difference compared to the uninvolved limb ($p \leq 0.05$)

CHAPTER 5: DISCUSSION

5.1 SPECIFIC AIM 1

5.1.1 Modifications in Quadriceps Strength

Involved Limb

As was hypothesized, the group of patients who received the standard-of-care after ACLr (control group) demonstrated significantly lower quadriceps strength on their involved limbs compared to their uninvolved limbs at baseline (pre-ACLr), three months post ACLr, and six months post-ACLr. Secondly, the magnitude of this side-to-side difference was different depending on when quadriceps strength was assessed in these patients. The largest side-to-side difference in normalized peak KET was observed at three months post-ACLr (-1.56 Nm/kg); with the 6-month post-ACLr time point having the second largest difference (-1.09 Nm/kg), and the baseline having the least difference (-0.49 Nm/kg). A criterion that is regularly used by clinicians when determining whether a patient is ready to return to activity/sport after ACLr, is if their quadriceps strength LSI is equal to or greater than 90%.[8,28,68,180,181] If our limb model estimates reported for normalized peak KET at baseline, three months post-ACLr, and six months post-ACLr were converted into quadriceps strength LSI, they would correspond to 85%, 51%, and 64%, respectively. Although the 6-month quadriceps strength LSI of the ACLr patients in our study looks to be lower than what has been reported in the ACLr literature,[98,132] there are several studies that have reported asymmetries of 30% or more in patients at six months post-ACLr.[50,143,146,154,156,160,162,173,174,177]

The variability of 6-month quadriceps strength LSI that has been reported in patients at six months post-ACLr is most likely attributed to methodological differences in measurement and surgical techniques between studies. Quadriceps strength can be assessed isometrically or isokinetically (concentric or eccentric), and at different knee-joint angles or velocities, respectively. Several studies have reported insufficient quadriceps strength LSI (≤90%) in patients after ACLr when isokinetically testing (concentrically) at an angular velocity of 60°/s, but when angular velocities of 120°/s or faster were used, these same patients meet the criterion (LSI ≥90%).[30,31,57,132,133,142,168,178,179] Hsiao et al.[31] recently assessed quadriceps strength LSI in patients after ACLr using a variety of angular velocities (isokinetic) as well as knee-joint angles (isometric). When compared to the pre-ACLr values, significant decreases in quadriceps strength LSI were only observed at the slower angular velocities (concentric at 50°/s and 100°/s) and the larger knee flexion angles (70° and 90°). Current evidence suggests that quadriceps strength should be tested isometrically at 70-90° of knee flexion,[31] or isokinetically at an angular velocity of 60°/s (concentric) in order to detect asymmetries in patients following ACLr.[98,132] Quadriceps strength of the patients in our study was assessed isometrically at 90° of knee flexion. Secondly, studies use different units to assess quadriceps strength LSI, which can alter the LSI value that is reported. Quadriceps strength can be recorded as force (i.e., Newtons, pounds, etc.) or torque (i.e., Nm, ft·lbs, etc.), or normalized to a patient's bodyweight (i.e., Nm/kg, ft·lbs/lb, %bodyweight, etc.). If quadriceps strength is recorded as force, it assumes that the force is applied in a linear

direction. However, since quadriceps force is applied across a joint (knee), it produces an angular force (torque). Therefore, recording quadriceps strength as KET is more valid than force. Furthermore, individuals who are heavier in weight are generally able to produce more KET due to higher quadriceps muscle mass. Therefore, it is recommended that a patient's peak KET be normalized to their bodyweight, such as what was done in this study. Lastly, the type of autograft used to reconstruct a patient's ACL has been shown to effect postoperative quadriceps strength.[132,591] A recent systematic review and meta-analysis assessed quadriceps strength differences between patients after ACLr, based on the type of autograft they received.[591] At 12 months post-ACLr, the quadriceps strength of patients who received hamstring tendon autografts was an average of 9% higher than those patients who received bone-patellar tendon-bone autografts. As a result, patients who receive hamstring tendon autografts for ACLr may have higher quadriceps strength LSI than those who receive bone-patellar tendon-bone autografts. In our study, the majority of patients (78%) in the control group received bone-patellar tendon-bone autografts, which may explain the large side-to-side quadriceps strength difference observed at six months post-ACLr. However, there were not enough patients who received hamstring tendon autografts in our study to determine whether autograft type had an effect on normalized peak KET outcomes. Methodological differences in quadriceps strength assessments between studies must be considered when comparing the results of quadriceps strength LSI in patients following ACLr.

The temporal pattern of side-to-side quadriceps strength differences can be easily attributed to the unilateral quadriceps strength changes observed over time in the involved limb of the patients. We originally hypothesized that quadriceps strength would decrease in the involved limbs of patients at three months post-ACLr compared to baseline, and then return to baseline values at six months post-ACLr. Compared to baseline, quadriceps strength decreased in patients at three months post-ACLr (-1.20 Nm/kg), and then increased at six months post-ACLr (+0.30 Nm/kg), but this increase did not reach baseline value (-0.90 Nm/kg); thus, rejecting our hypothesis. These changes can all be described as true change that occurred beyond measurement error (MDC_{95} = 0.30 Nm/kg).[592] In other words, we are 95% confident that true clinical changes occurred with quadriceps strength in the involved limb after ACLr. The V-shaped pattern (see Figure 4.1) of quadriceps strength changes observed in our study is consistent with what has been reported in a previous study that longitudinally assessed quadriceps strength in the involved limb of patients before and after ACLr. Zech and colleagues[24] assessed the (isometric) quadriceps strength of patients before ACLr, and at multiple time points after ACLr, up until 48 weeks post-ACLr. At 12 weeks (3 – 4 months) post-ACLr, the patients' peak KET values were 12% (± 14) lower than their pre-ACLr values. However, there were no differences between preoperative and postoperative peak KET values observed in patients after 24 weeks (5 – 6 months) post-ACLr. Several longitudinal studies have supported these authors' findings of quadriceps strength being restored to (or surpassing) preoperative values in the involved limb of patients at

approximately six months post-ACLr.[149,158,186] Conversely, there are other studies that have reported similar results to our study,[27,28] with the involved limb having less quadriceps strength at six months compared to baseline (pre-ACLr). In a recent study by Lepley et al.,[27] they reported significantly lower normalized (isometric) peak KET in the involved limb of patients at seven months post-ACLr (2.2 Nm/kg ± 0.6) compared to their preoperative values (2.5 Nm/kg ± 0.7). Even with their post-ACLr time point being a month longer than our study (7.2 months vs. 6.3 months), a pre-to-post-ACLr deficit in quadriceps strength was still present in the involved limb of patients.

As stated previously, the contrasting results observed between studies concerning time-based differences in ipsilateral quadriceps strength of patients after ACLr may be due to methodological variances in measurement and surgical techniques. However, the combination of limb asymmetry and persistent weakness observed in the involved limb of patients at six months post-ACLr, warrants a more conservative approach when clearing patients to return to competitive or recreational sport activities. The current timeframe for a patient to expect to return to sport is between six and 12 months following their ACLr,[593,594] but if quadriceps strength deficits are still present in the involved limbs of patients at six or seven months, this timeframe may need to be extended closer to 12 months post-ACLr. In our study, the control group consisted of high school athletes (15), college athletes (2), and recreational athletes (8). Only one (recreational athlete) of the 25 patients was cleared by a physician to return to unrestricted sport activity at the 6-month assessment time point. Therefore, this

information may help physicians be better informed and possibly employ a more conservative approach when deciding when to return patients to unrestricted sport activities after ACLr, and providing more time for patients to recover their quadriceps strength.

Although the rate of recovery after ACLr is unique to each patient, and other outcomes (i.e., SLH tests, step-down tests, YBT/SEBT, KOOS/IKDC, psychological readiness to return to sport, etc.) are necessary when making the clinical decision to clear a patient to return to sport, quadriceps strength is an important factor to asses from both a performance and health standpoint. Restoring quadriceps strength in patients after ACLr is not only beneficial to their performance during sport activities, but it can reduce risk of patients developing early knee OA. Individuals who have a history of ACL injury and/or ACLr are reported to be at a higher risk of developing early knee OA than healthy individuals.[195,196] Furthermore, evidence has shown that although ACLr is a successful treatment for restoring knee-joint stability in these patients, patients who undergo ACLr are found to have a 29% higher odds of developing knee OA compared to those who are ACL-deficient.[23] Within the first decade after ACLr, it has been reported that over one third of patients develop knee OA, and this prevalence approaches 50% by the second decade.[23] Interestingly, there is growing evidence demonstrating that quadriceps weakness contributes to the onset and progression of knee OA in patients.[73-75,197] During normal gait, three to four times the bodyweight of a healthy individual is transmitted through their knee-joint.[73] To limit excessive joint loading, the quadriceps serve as the primary

shock absorber for the knee-joint. During ground contact (weight acceptance), the quadriceps contract eccentrically to absorb the majority of external forces at the knee.[73-75] As a result, the forces transmitted through the knee-joint become dissipated, and minimal stress is placed on articular cartilage.[76,77] Therefore, quadriceps weakness is thought to allow higher loads to be transmitted at the knee-joint, and expose the articular cartilage to more contact forces.

Within the past decade, there have been a handful of longitudinal studies that have been able to demonstrate that quadriceps weakness is a significant contributor to the onset of knee OA in patients.[78-82] Tourville and colleagues[79] assessed tibiofemoral joint space narrowing and isokinetic KET (concentric at 60 deg/s) in 38 patients prior to ACLr (baseline) and 4 years postoperatively. After follow-up testing, the authors separated patients into narrow and normal joint space groups based upon their 4-year radiographs. They also compared the ACLr patients' quadriceps strength to that of 32 healthy controls of similar age, body mass index, and physical activity level. At baseline, the quadriceps strength in both ACLr groups was lower than that of healthy controls ($p < 0.001$). However, the quadriceps strength of the narrow ACLr group's peak KET was also significantly lower than that of the normal ACLr group. Four years after ACLr, the quadriceps strength of the normal ACLr group (95 ± 10.3% LSI) improved and was not significantly different compared to healthy controls (99 ± 11.6% LSI, $p > 0.05$), while the narrow ACLr group's quadriceps strength (83 ± 23.1% LSI) remained lower than both the normal ACLr group ($p = 0.04$) and healthy controls ($p = 0.01$). A more recent systematic review and meta-analysis

by Oiestad et al.[78] reported that early quadriceps weakness increased the odds of patients developing knee OA (radiographic and/or symptomatic) by 65% (OR = 1.65, CI = 1.23-2.21). Therefore, the quadriceps weakness that was observed at six months post-ACLr in the patients of our study may place them at risk for developing knee OA if these strength deficits continue to persist. This is especially true for those patients who plan to return to sport activity, because their knee will be exposed to higher ground reaction forces during sports compared to activities of daily living. Furthermore, these patients may develop knee OA at a very young age, with the average age of patients in the control group being 19.4 (± 4.5) years. Since one third of patients are predicted to develop knee OA within the first decade after ACLr, at least eight of the 25 patients can be expected to develop knee OA. However if patients also demonstrate persistent quadriceps weakness after ACLr, it may expedite the onset of knee OA and/or exacerbate the severity of cartilage degradation. The potential for this unfortunate sequence of events supports the significance of restoring quadriceps strength in patients during post-ACLr rehabilitation as a strategy better protect the knee-joint cartilage from further damage.

Uninvolved Limb

Perhaps the most significant findings from our study were the neuromuscular quadriceps changes that occurred in the uninvolved limb of patients after unilateral ACLr. We hypothesized that the quadriceps strength in the uninvolved limb would gradually decrease up until six months after ACLr. Our results confirmed this hypothesis, revealing that quadriceps strength was

significantly decreased in the uninvolved limb of patients at six month post-ACLr when compared to their baseline values. As observed in Figure 4.1, quadriceps strength in the uninvolved limb does not follow the same V-shaped temporal pattern as the involved limb. The temporal pattern of quadriceps strength in the uninvolved limbs tended to have a more gradual decline than that of the involved limb. However, instead of improving between three and six months post-ACLr like what was observed in the involved limb, quadriceps strength continued to decrease. This decrease in quadriceps strength from baseline to six months post-ACLr (-0.30 Nm/kg) can be described as true change beyond measurement error;[592] thus, we are 95% confident that a clinical decrease in quadriceps strength occurred in the uninvolved limb of patients at six months post-ACLr.

Although the quadriceps strength deficits observed in the uninvolved limb of patients were not as large as those observed in the involved limb, this finding still holds significant clinical value. Based on our knowledge of current literature, this would be the first study to report time-based quadriceps strength deficits in the uninvolved limb of patients after unilateral ACLr. However, there have been several studies that have reported cross-sectional strength deficits in the uninvolved limb of patients before and after ACLr when compared to healthy-matched controls.[32,42,45,51,52] Chung and colleagues[45] recently assessed the longitudinal changes in bilateral isokinetic (concentric) quadriceps strength of 75 patients at three, six, 12, and 24 months after unilateral ACLr. In addition to comparing strength values between limbs, they also compared the peak KET values of the ACLr patients to 75 healthy controls who were of equal age, sex,

height, weight, and pre-injury physical activity level. In the ACLr group, the uninvolved limb's peak KET was significantly higher than that of the involved limb at three months (266.1 ± 43.7 Nm vs. 178.8 ± 51.2 Nm), six months (276.4 ± 42.7 Nm vs. 224.2 ± 58.5 Nm), 12 months (276.7 ±44.9 Nm vs. 235.4 ± 56.9 Nm), and 24 months (276.6 ± 42.8 Nm vs. 242.8 ± 55.5 Nm) after ACLr. Interestingly, when these values were compared to that of the healthy control group (290.9 ± 40.1 Nm), both the involved and uninvolved limbs of ACLr group demonstrated significantly lower peak KET at each follow-up time point. Although more research is needed to understand the manifestation of contralateral quadriceps weakness in patients after unilateral ACLr, the results of our study combined with prior evidence is enough to deserve clinical consideration.

This evidence suggests that using the uninvolved limb as the reference when assessing quadriceps strength in patients after unilateral ACLr may underestimate the magnitude of quadriceps strength deficits. Therefore, using quadriceps strength LSI as an indicator of recovery should not be heavily relied upon by physicians when making the decision of returning a patient to sport activity after ACLr. Quadriceps strength LSI could mask residual quadriceps weakness in the involved limb and deceive clinicians when making the decision to return patients to their pre-injury activity after ACLr. For example, a patient may demonstrate greater than 90% quadriceps strength LSI, but if the quadriceps strength of their uninvolved limb has also declined since the initial ACL injury, then the recovery of quadriceps strength on the involved limb may have been overestimated by the LSI. Clearing a patient to return to their pre-

injury activity prior to restoring bilateral quadriceps strength may place both of their limbs at risk for subsequent knee-joint injury, and expose the knee to increased contact forces due to the decreased force absorption capabilities from the quadriceps.

To unmask the quadriceps strength deficits in the involved limbs of patients, we recommend that clinicians should not depend on a LSI when assessing the recovery of quadriceps strength in patients after unilateral ACLr. Alternatively, it is recommended that clinicians compare the quadriceps strength of their ACLr patients to those of healthy individuals who are of similar age and stature (preferably normalized to bodyweight). If data from healthy individuals is not available to clinicians, the second best alternative is to compare the postoperative quadriceps strength of the involved limb to the patient's preoperative quadriceps strength of their uninvolved limb recorded prior to ACLr. If we use model estimates in our study (see Table 4.3) as an example, the 6-month quadriceps strength LSI is 64%. However, if the 6-month peak KET of the involved limb is compared to the baseline value of the uninvolved limb, the LSI equates to 59%. Although acute ACL injury is known to elicit deficits in ipsilateral quadriceps strength, there is no evidence to suggest that acute ACL injury affects quadriceps strength in the contralateral limb. However, we encourage clinicians to assess the quadriceps strength on the uninvolved limb of patients as soon as possible after ACL injury to account for the possibility of a crossover effect from developing in the uninvolved limb later on. Using these alternative comparison

strategies provides clinicians with a clearer representation of quadriceps strength recovery in the involved limbs of patients after ACLr

We believe that it is also important for clinicians to account for the potential quadriceps strength deficits that are present in uninvolved limb of patients after unilateral ACLr. We agree that in order to improve a patient's function and prevent them from sustaining a subsequent injury upon return to sport activity, improving quadriceps strength in involved limb of patients is one of the most important goals during post-ACLr rehabilitation. However, neglecting potential quadriceps strength deficits in the uninvolved limb could also put patients at risk upon return to sport activity. In a study by Schmitt et al.,[67] they reported that external biomechanical forces during a drop-jump task were distributed differently between the limbs of patients at the time of return to sport activity after unilateral ACLr. The authors divided patients into high and low quadriceps strength groups, and compared biomechanical data to that of age-matched, healthy participants. Compared to the patients with high quadriceps strength and healthy participants, the patients with low quadriceps strength demonstrated greater asymmetry in peak external knee flexion moments, peak vertical ground reaction forces, and peak loading rates. Specifically, all three biomechanical measures were significantly lower in the involved limbs and higher in the uninvolved limbs of patients with low quadriceps strength. Whereas, there were no significant differences between those patients with high quadriceps strength and the healthy participants in regard to biomechanical limb symmetries. The asymmetrical distribution of external forces between limbs of patients who

exhibit quadriceps weakness after ACLr has been theorized to place both knee-joints at risk for subsequent knee-joint injury.[67,194] While the quadriceps weakness exhibited in the involved limb of patients after unilateral ACLr may decrease their ability to absorb shock at the surgical knee-joint, their increased reliance on the uninvolved limb combined with a potential quadriceps strength deficit may also overload the nonsurgical knee-joint. Therefore, we believe that clinicians should begin to incorporate a bilateral approach when treating quadriceps strength deficits in patients after unilateral ACLr.

There is compelling evidence supporting the effectiveness of cross-exercise on improving neuromuscular quadriceps function.[111,138,139,509-512,574] Cross-exercise is the practice of training unilaterally to achieve bilateral improvements based on a neural phenomenon known as cross-education.[116,513-516] Cross-education through cross-exercise has been observed with both exercise[509-512,574] and NMES interventions.[111,138,139] However, only one study to date has investigated the effect of cross-exercise on the bilateral quadriceps strength of patients after ACLr.[509] A total of 42 patients were randomized to the standard-of-care (control) or cross-exercise group after ACLr. The patients in the cross-exercise group performed eccentric exercises (3-5 days/week) on the uninvolved limb for eight weeks. Quadriceps strength (isometric) was assessed in patients before surgery and nine weeks post-ACLr. Compared to the control group, post-ACLr quadriceps strength was 4-8% higher in the uninvolved (trained) limb of patients who performed cross-exercise. Quadriceps strength in the involved limb still decreased in all patients post-ACLr, but this decrease was

21-31% greater in control group. Clinicians should be encouraged to incorporate a cross-exercise rehabilitation protocol such as this when treating patients who have recently undergone unilateral ACLr. During the first couple months after surgery, most patients are not permitted to perform high-intensity quadriceps exercises on their involved limbs to protect the graft; yet these patients have gross atrophy and inhibition of their quadriceps that needs to be addressed to preserve and restore quadriceps strength. Therefore, until patients are cleared to perform high-intensity quadriceps exercises on their involved limb, cross-exercise can be performed on their uninvolved limb to facilitate quadriceps strength in the uninvolved limb, and mitigate strength deficits in the involved limb. Even afterwards, clinicians should continue to incorporate bilateral quadriceps strength training during rehabilitation as a way to maximize neuromuscular outcomes and improve the protection of both joints.

5.1.2 Modifications in Neural Quadriceps Dysfunction

Voluntary Quadriceps Activation

An unexpected outcome of this study was the lack the neural quadriceps dysfunction in the involved limb of patients after ACLr. We hypothesized that voluntary quadriceps activation in the involved limb of patients would follow the same V-shaped temporal pattern as what was observed with quadriceps strength. However, voluntary quadriceps activation in the involved limb remained unchanged in patients after ACLr. Secondly, the degree of quadriceps inhibition present in the involved limb before and after ACLr was quite unremarkable. Although the quadriceps CAR in the involved limb of patients ranged from 60% to

100%, the model estimates at baseline, three and six months, were 93.4%, 94.1% and 92.7%, respectively. Unfortunately, we are unable to discuss whether these estimates are lower than the patients' quadriceps CAR values of when they were healthy, prior to ACL injury. Therefore, we can only compare our results on voluntary quadriceps activation to what has been established in the literature. Park and Hopkins[88] assessed voluntary quadriceps activation levels of 91 healthy individuals without a history of knee injury or surgery, and reported an average quadriceps CAR value of 95%. Therefore, a quadriceps CAR value of greater than or equal to 95% has been generally accepted as the threshold for determining whether or not a patient has neural inhibition of their quadriceps after ACLr.[89,90] In our study, each of the quadriceps CAR estimates fell below this threshold (< 95%), but the only time point where the quadriceps could be defined as being inhibited beyond measurement error (SEM = 2%),[404] was at six months post-ACLr (CAR = 92.7%). However, the 95% confidence interval of this 6-month estimate (88.1, 96.2) crosses the voluntary quadriceps activation threshold of 95%, and true change beyond measurement error was not reached (MDC = 2.8%); thus, we cannot be confident that true quadriceps inhibition was present at this time point.

Based upon the last 20 years of research in this area, the average voluntary quadriceps activation in the involved limb of patients, both before and after ACLr, has been reported to be as low as 75% to 77%,[32,145,289] and as high as 99%.[24] However, these studies assessed voluntary quadriceps activation in patients using different measurement techniques (ITT and %ACT) compared to

our study (SIB and CAR), which have been known to provide different results.[385,395,595-597] Therefore, we felt that it was necessary to only compare our results to studies that assessed voluntary quadriceps activation in patients using the same measurement techniques. The majority of studies have reported average quadriceps CAR values that were at 95% in the involved limb of patients before ACLr (90 – 95%).[27,89,172,232,290] Lepley et al.[51] is the only study that has reported a quadriceps CAR value in the involved limb that was below 90% (83.1 ± 8.1%) before ACLr. Conversely, the average quadriceps CAR values that have been reported in the involved limb of patients after ACLr vary anywhere between 75-92%.[27,34,48,51,55,91,97,290-293] Interestingly, the lowest quadriceps CAR value (75.2 ± 13.4%) was reported in a study whose patients were four years removed from ACLr,[292] and the highest quadriceps CAR values (91.7 ± 6.4% and 91.8 ± 4.6%) were reported in a study whose patients were three and seven months post-ACLr (respectively).[292] The results from the later study are similar to those of our study, with high quadriceps CAR estimates (>92%) being observed in patients at both three and six months post-ACLr. It can be expected that a high degree of quadriceps inhibition is present in patients immediately after ACLr based on the principles of AMI. During this acute stage after ACLr, the effusion, pain, and inflammation present within the knee-joint is sufficient to inhibit the involved limb's quadriceps. However, force-based measures of voluntary quadriceps activation are typically contraindicated in the involved limb of patients within the first two months after ACLr due to increased pain, inadequate range-of-motion, and/or postoperative guidelines that are enforced to protect the graft

from being stressed prematurely. After this acute stage, AMI may begin to resolve in the quadriceps of patients during the first few months after ACLr, with voluntary quadriceps activation approaching normal levels up until one year post-ACLr. However, a decline in voluntary quadriceps activation may be apparent in patients who are years removed from ACLr. Quadriceps inhibition that persists in patients years after ACLr may be defined as QAF. Alternatively, a relapse of quadriceps inhibition years later may be a reoccurrence of quadriceps AMI that is due to the insidious onset of a subsequent knee-joint pathology, such as knee OA. Similar patients after ACL injury or reconstruction, patient with knee OA have been reported to exhibit deficits in voluntary quadriceps activation.[295] However, further research is need to explore this theory, and to determine whether deficits in voluntary quadriceps activation after ACLr are truly time-dependent.

The most significant finding observed with the voluntary quadriceps activation of patients after ACLr was not in that of the involved limb, but in that of the uninvolved limb. We originally hypothesized that voluntary quadriceps activation would be lower in the involved limb compared to the uninvolved limb at each time point; however, the exact opposite was observed in our results. There was a significant main effect for limb observed with quadriceps CAR in patients. Regardless of when it was assessed, quadriceps CAR estimate was approximately 2.4% lower (on average) in the uninvolved limbs of patients compared to their involved limbs. A bilateral voluntary quadriceps activation deficits after ACL injury and subsequent ACLr has been consistently reported in the literature, and is now considered to be a regular phenomenon in

patients.[34,51,84,85,91] Furthermore, the amount of neural inhibition present within the quadriceps of the contralateral limb is equivalent to that of the ipsilateral (involved) limb following unilateral ACLr. In a recent study by Thomas et al.,[91] voluntary quadriceps activation was assessed bilaterally in the limbs of patients who were seven months removed from ACLr. The mean quadriceps CAR value of the patients' involved limbs was 87%, while the uninvolved limbs demonstrated a quadriceps CAR value of 85% (see Table 4.3). However, our findings were unique because the voluntary quadriceps activation in the uninvolved limb of patients was actually lower than that of their involved limb. Although we can conclude that this difference was beyond measurement error (SEM = 2%), but we cannot confidently say that this difference was true due to the confidence intervals of our estimates and the MDC (2.8 – 5.5%) for quadriceps CAR.[404]

Compared to baseline, no temporal changes were observed with voluntary quadriceps activation in the uninvolved limb of patients after ACLr. This finding was similar to what was observed in the involved limb of patients after ACLr. However, true quadriceps inhibition was more apparent in the uninvolved limb of patients before and after ACLr compared to the involved limb. The quadriceps CAR estimates at baseline (91%), three months (91.8%), and six months (90.1%) post-ACLr were all below the 95% threshold value for determining whether a patient has quadriceps inhibition.[89,90] These estimates were not only below the measurement error for quadriceps CAR (SEM = 2%),[404] but their 95% confidence intervals did not cross the 95% threshold. Furthermore, true quadriceps inhibition can be assumed with more confidence at the 6-month post-ACLr time point

(MDC_{90} = 4.65%) compared to baseline and the 3-month post-ACLr time point (MDC = 2.83%).[404] However, we are unable to determine whether the pre-injury voluntary quadriceps activation levels of our patients would have met the 95% threshold that has been previously reported in healthy individuals;[88] we can only assume that the quadriceps CAR estimates reported in the uninvolved limb of our patients reflected quadriceps inhibition, based on the 95% threshold criterion.

The joint trauma present within the surgically reconstructed knee-joint of patients after ACL injury and/or reconstruction seems to be modulating the voluntary quadriceps activation of their uninvolved limb. Scientists have yet to fully understand the reason for the bilateral quadriceps inhibition that is observed in patients after unilateral ACLr. The most popular explanation is that of a neural crossover effect that occurs in the central nervous system due to altered afferent information being transmitted from the involved knee-joint.[42,145,272] Due to this bilateral deficit, clinicians are cautioned when using a patient's uninvolved limb as a comparison when assessing the recovery of neuromuscular quadriceps function in the involved limb and making return-to-activity decisions after ACLr. Consequently, clinicians should be advised to consider a healthy-matched control as a comparison, and clinicians should place further attention on the uninvolved limb during the rehabilitation of patients following ACLr.

Corticomotor Excitability

Like voluntary quadriceps activation, temporal changes in corticomotor excitability at the quadriceps were not observed in the involved limb of patients after ACLr. As a reminder, a lower quadriceps AMT value (%TMS output)

corresponds to higher corticomotor excitability at the quadriceps. The only study that has assessed quadriceps AMT in the involved limb of patients prior to ACLr was that of Lepley et al.[51] They assessed quadriceps AMT in their patients at an average of 35 days after ACL injury, and reported an average AMT of 39.9%. This value is very similar to the quadriceps AMT estimate that we reported in our patients (39.7%) who were assessed an average of 25 days after ACL injury. However, the postoperative quadriceps AMT estimates in our study were relatively low compared to what has been previously reported in patients after ACLr.[34,51,61,84,97] The quadriceps AMT estimates of our patients were 39.1% and 39.2% at three and six months post-ACLr, respectively (see Table 4.3). The majority of studies have reported average quadriceps AMT values that fall between 44% and 62% in patients after ACLr.[34,51,84,97] It must be noted that most of these studies assessed quadriceps AMT in patients who were more than two years removed from ACLr.[34,84,97] However, Lepley et al.[51] assessed quadriceps AMT in patients at a time point similar to our study (6 months post-ACLr), but their AMT value was higher (46.1% vs. 39.2%). There has been one study that has reported low quadriceps AMT values (33.2%) in patients after ACLr,[61] but their assessment was performed at a time point (33.2 months post-ACLr) much later than our study.

It is not clear why the quadriceps AMT estimates of our patients were different than when they were healthy (prior to ACL injury). Therefore, we can only compare our results to what has been reported for healthy individuals. Of the aforementioned studies that assessed corticomotor excitability in patients

before and/or after ACLr, most of them assessed quadriceps AMT in a group of healthy individuals as comparison. The majority of these studies reported quadriceps AMT values between 36% and 38% in healthy controls.[34,51,97] However, Kuenze et al. reported quadriceps AMT values in healthy controls that were greater than 60%. Although the inconsistent results between studies may be due to methodological variances, more studies are needed to determine the normative values of quadriceps AMT that can be expected in healthy individuals. Secondly, due to the limited evidence of corticomotor excitability changes in patients before and after ACLr, more longitudinal studies are needed to confirm whether corticomotor excitability at the quadriceps is altered in patients after ACL injury and reconstruction, and to what extent these alterations exist. Furthermore, other supraspinal areas (i.e., sensory cortex, cerebellum, brainstem, etc.) should be explored to determine the systemic effect that ACL injury and reconstruction have on the neural function of CNS.

5.2 SPECIFIC AIM 2

5.2.1 Early Neuromuscular Effects on Lower Extremity Function Outcomes

Lower Extremity Postural Control

We originally hypothesized that the patients' quadriceps strength assessed at baseline and three months post-ACLr would be associated with their lower extremity postural control at six months post-ACLr. The YBT-A was used to assess lower extremity postural control in patients at six months post-ACLr. We

chose the anterior reach direction of the YBT, because quadriceps EMG activity has been reported to be the highest in that direction.[587] The normalized peak KET of patients at three months post-ACLr was the only variable that demonstrated a significant positive association with 6-month YBT-A reach distance (see Table 4.5). For every 1 Nm/kg increase in normalized peak KET at three months post-ACLr, an estimated 5.1% increase in normalized YBT-A reach distance could have been expected at six months post-ACLr. If we use the results from Specific Aim 1 as an example (Table 4.3), the model estimate for normalized peak KET of patients at three months post-ACLr was 1.67 Nm/kg. Therefore, if the patients increased their normalized peak KET to 2.67 Nm/kg between three and six months post-ACLr, they would see a 5.1% increase in their normalized YBT-A reach distance at six months post-ACLr, which would signify an improvement in their postural control. However, we are only able to conclude that this 5.1% increase is statistically significant, and not beyond measurement error or a true increase in lower extremity postural control, because no study has determined the MDC of the normalized YBT-A reach distance.

Our results were similar to those reported by Kline and colleagues.[72] They found that the 3-month postoperative isometric quadriceps strength of ACLr patients was significantly correlated their knee flexion excursion and internal knee extension moment observed with running at six months post-ACLr. Knee flexion excursion and internal knee extension moments are biomechanical measures that are believed to be controlled by the activity of quadriceps,[68] and

they have previously been found to be correlated with quadriceps strength in patients at the time of return-to-sport after ACLr.[63] However, the problem is that most studies choose to assess these correlations in patients cross-sectionally after they have returned to sport activity, and are unable to determine whether earlier quadriceps strength deficits can explain the reduced function and/or poor biomechanics that are observed in patients around the time that they have returned to sport activity. The results of our study combined with those of Kline et al.,[72] have begun to fill this void by demonstrating that quadriceps strength of patients at three months post-ACLr have a direct influence on their lower extremity function and biomechanics at six months post-ACLr. Therefore, these results demonstrate the importance for clinicians to focus on quadriceps strengthening during the early stages of ACLr rehabilitation in order to provide patients the opportunity for better outcomes around the time that they are cleared to return to sport activity.

Other studies have also reported significant associations between quadriceps strength and lower extremity functional performance in patients after ACLr.[3,4,7-9,28,39,53-59] Keays and colleagues[28] sought to determine whether quadriceps strength was correlated with SLH performance before and after ACLr. They assessed the isokinetic (concentric) peak KET, single hop for distance, and triple hop for distance of 31 patients before unilateral ACLr and at their 6-month postoperative follow-up. Prior to surgery, significant correlations were observed between isokinetic quadriceps strength and performance on the SLH tests (r = 0.53 – 0.59). However, stronger correlations were observed at six months post-

ACLr between quadriceps strength and the SLH (r = 0.62 – 0.74). The results of our study not only demonstrated a significant association between postoperative quadriceps strength and lower extremity postural control, but that the amount of quadriceps strength a patient has earlier after ACLr has a direct effect on the degree of postural control they will have months later.

The anterior reach component of the YBT has been shown to predict lower extremity injuries in athletes.[585] A recent study by Smith et al.[585] assessed the bilateral YBT-A reach distance of 184 Division-1 collegiate athletes during their pre-participation physical examinations. These athletes were then followed throughout their respective sport seasons, and the number of lower extremity non-contact injuries were recorded. A total of 81 athletes sustained a lower extremity non-contact injury during their sport season. The authors found that greater limb asymmetry with the pre-participation YBT-A significantly increased the odds of athletes sustaining a lower extremity non-contact injury during their sport season (OR = 2.33; 95% CI = 1.15 – 4.76). Therefore, the results of our study carry great clinical significance from an injury prevention standpoint. More focus should be made to enhancing quadriceps strength in patients during the early months after ACLr as a proactive attempt to improve their lower extremity postural control and reduce the odds of them sustaining a subsequent lower extremity injury upon return to sport activity. However, more research is needed to explore the effect that early postoperative quadriceps strength has on other measures of lower extremity functional performance, and whether these measures can predict subsequent knee-joint injuries.

Self-Reported Knee Function

We also hypothesized that the patients' quadriceps strength assessed at baseline and three months post-ACLr would be associated with self-reported knee function at six months post-ACLr. The Sport/Rec and QOL domains of the KOOS were used to assess self-reported knee function in patients at six months post-ACLr. The normalized peak KET of patients at three months post-ACLr was not found to be associated to their 6-month postoperative KOOS-Sport/Rec score. Similar to what was reported with 6-month YBT-A outcomes, the normalized peak KET of patients at three months post-ACLr was the only variable that demonstrated a significant positive association with any of the 6-month KOOS domains (see Table 4.5). The 6-month postoperative KOOS-QOL score of patients was the only domain that was influenced by their 3-month postoperative quadriceps strength. For every 1 Nm/kg increase in normalized peak KET at three months post-ACLr, an estimated 8.9 point increase in KOOS-QOL score could have been expected at 6-months post-ACLr. This 8.9 point increase in KOOS-QOL score would be defined as true change beyond measurement error because it surpasses the MDC associated with that KOOS domain (MDC_{95} = 7.2 pts).[192]

The fact that 3-month postoperative quadriceps strength effected 6-month postoperative KOOS-QOL scores, but not KOOS-Sport/Rec scores may be explained by the different aspects of knee function that are addressed by the two domains. For the KOOS-Sport/Rec domain, there are five questions that pertain to five different activities/movements (squatting, running, jumping,

twisting/pivoting, and kneeling). Patients are asked to think of the degree of difficulty that they experience (within the past week) with their knee for each question. Difficulty is graded on a 5-point Likert scale, ranging from no difficulty to extreme difficulty. Conversely, for the KOOS-QOL domain, there are four questions that pertain knee function from a broader level of QOL instead of activities/movements. Rather than asking patients the degree of difficulty that they have with their knee, patients are asked to think of the frequency and degree of difficulty that they experience with their knee. Again, the answers are graded on a 5-point Likert scale, ranging from either never-to-constantly, or from none/not at all-to-extreme/totally. As stated earlier, only one of the 25 patients in our study was cleared by a physician to return to unrestricted sport activity at the 6-month assessment time point. Therefore, the KOOS-Sport/Rec score that was observed in patients at six months post-ACLr may not have been accurate, because the majority of them were not exposed to sport activities at that time point; thus, they did not have a valid reference to relate to when answering questions form that domain. Unlike our study, Ithburn et al.[63] reported that the KOOS Sport/Rec scores observed in patients after ACLr (~ 8 months post-ACLr) were different depending on their levels of isometric quadriceps strength. Compared to patients with high quadriceps strength (LSI ≥ 90%), patients with low quadriceps strength (LSI < 85%) also demonstrated lower KOOS-Sport/Rec scores (89.5 ± 11.7 pts vs. 79.6 ± 15.5 pts). The primary difference between our study and theirs, is that their patients completed the KOOS-Sport/Rec after they were cleared to return to sport activity (~ 7 months post-ACLr), whereas the

majority of our patients had not returned to sport activity prior to completing the 6-month KOOS-Sport/Rec. Although hypothetical, if our patients were exposed to sport activity prior to completing the KOOS-Sport/Rec domain at six months post-ACLr, more accurate scores may have been evidenced, and significant associations may have resulted with 3-month postoperative quadriceps strength. Since the KOOS-QOL domain does not pertain to sport activities, but rather a broader construct of knee function, it may explain why a significant association was observed with that self-reported functional outcome measure.

In addition to the KOOS, several studies have demonstrated significant associations between IKDC scores and the quadriceps strength of patients following ACLr.[8,55,60-62] Perhaps the most impressive study that demonstrated this association was that of Pietrosimone and colleagues.[61] They assessed isometric peak KET and IKDC scores in 15 patients who were an average of 54 months removed from ACLr, and performed a linear regression analysis to determine the amount of variability in self-reported knee function that could be explained by their quadriceps strength. Remarkably, they discovered that isometric quadriceps strength predicted over 60% ($r^2 = 0.61$) of the variance in the IKDC scores of patients who have a history of ACLr; thus, demonstrating that the majority of IKDC scores can be explained by a patient's quadriceps strength after ACLr, and that quadriceps weakness can severely limit their self-perceived function. We may have observed more and/or greater associations between early postoperative quadriceps and 6-month self-reported knee function if we used the IKDC, however, the KOOS-Sport/Rec and KOOS-QOL were intentionally chosen

to represent the self-reported knee function in our sample of patients. Compared to other self-reported outcome measures, the KOOS is meant for younger, and more physically active patients who have sustained a knee injury or have undergone knee surgery.[588] Furthermore, of the five domains in the KOOS, the QOL and Sports/Rec domains have demonstrated the most unidimensionality,[589] and are the most sensitive to changes over time in patients after ACLr,[193] thus, justifying our rationale for choosing to preferentially assess those two domains in our study. That being said, further investigations should performed to determine whether early postoperative quadriceps strength has an effect on other self-reported outcome measures (i.e., IKDC, Cincinnati Knee Score, Knee Outcome Survey, etc.) at the time of return to sport activity.

Lack of Associations with Neural Measures

Neither quadriceps CAR or AMT (at baseline or 3-months post-ACLr) had a significant effect on any of the 6-month lower extremity function outcome measures. Based on our original hypotheses, we expected that corticomotor excitability would not have a significant influence on the patients' lower extremity function, because quadriceps AMT has been previously shown to be minimally correlated with the quadriceps strength of patients after ACLr,[61,97] and as evidenced in our study, quadriceps strength has been consistently reported to influence lower extremity function in patients after ACLr. Therefore, since voluntary quadriceps activation has been reported to explain nearly 40% of quadriceps strength in patients after ACLr ($r^2 = 0.37$),[97] we hypothesized that it

would influence the lower extremity function of our patients at six months post-ACLr, yet this not supported in our results.

Although we hoped to observe an association between voluntary quadriceps activation and lower extremity function in patients after ACLr, the absence of this finding is not surprising. To date, only one study has reported on the association between voluntary quadriceps activation and lower extremity function in patients following ACLr.[48] Kuenze and colleagues[48] used receiver-operator-characteristic (ROC) curves as a method to establish clinical thresholds for voluntary quadriceps activation (CAR) associated with self-reported knee function (KOOS) in patients who were at least six months removed from unilateral ACLr. They found that quadriceps CAR LSI greater than 99.2% (area under curve = 0.67) was the most effective in identifying a patient with a total KOOS score similar to that of healthy individuals (96 pts). However, there are several limitations associated with this study, which questions the clinical significance of its findings. To begin, quadriceps CAR LSI is not commonly assessed, and as was mentioned earlier, LSI may underestimate the amount quadriceps dysfunction present in patients after ACLr. Secondly, reporting the total KOOS score, which is the sum of the scores for each domain is not advised. This is because the intention of the KOOS is to allow clinicians to analyze and interpret each domain separately. This is one advantage the KOOS has over other self-reported knee outcome measures.

The correlation between voluntary quadriceps activation and lower extremity function may be too low to reach statistical significance. However,

voluntary quadriceps activation may serve to moderate the relationship between quadriceps strength and lower extremity function in patients with knee OA.[134] Fitzgerald et al.[134] assessed quadriceps activation and strength, and lower extremity function (Western Ontario and McMaster Universities Osteoarthritis Index combined with Get Up and Go test) in 105 patients with radiographic knee OA. After performing regression analysis, the authors found that adding the quadriceps activation by strength interaction to the regression model resulted in the highest explanation of variance for lower extremity function ($r^2 = 0.22$); thus, quadriceps inhibition was believed to serve as a moderator between quadriceps strength and function. For example, patients who exhibited higher levels of quadriceps weakness and quadriceps inhibition, had lower levels of function than those with comparable strength and less inhibition. Conversely, patients who exhibited lower levels of quadriceps weakness and higher levels of quadriceps inhibition, had higher levels of function compared to those of comparable strength and less inhibition. Although the authors could not explain why stronger patients with more quadriceps inhibition had higher levels of function, they hypothesized that if a patient has good quadriceps strength, the presence or absence of quadriceps inhibition may not play an important role in affecting their function.[134] If a patient has enough strength to function well, they may not need to fully activate their quadriceps. In contrast, if a patient has significant quadriceps weakness and quadriceps inhibition, the combination of the two may be sufficient enough to affect their function. Regardless, the effect that voluntary

quadriceps activation has on quadriceps strength alone, makes it an important outcome for clinicians to consider when treating patients after ACLr.

5.3 SPECIFIC AIM 3

5.3.1 Group Patterns

Isometric Quadriceps Strength

We hypothesized that those patients who were randomly allocated to the Home-NMES group would demonstrate greater bilateral improvements in quadriceps strength, voluntary activation, and corticomotor excitability at both three and six months post-ACLr compared to patients in the control group. However, the only significant group difference that was observed in our randomized clinical trial was with the isometric quadriceps strength outcome measure (see Table 4.6). A main effect for group was reported with isometric quadriceps strength, with the control group having an average of 0.36 Nm/kg higher normalized peak KET than that of the Home-NMES group (irrespective of limb and time). However, this group difference was not because the Home-NMES group had a negative treatment effect from the home-based NMES program, but because group differences in normalized peak KET were present at baseline. Although the only statistically significant group difference that was present at baseline was with normalized peak KET on the uninvolved limb being higher in the control group (see Table 4.2), a trend was also observed in the involved limb, with the control group again being higher than the Home-NMES group. The mixed model analyses may have accounted for this trend, causing

the model estimates for normalized peak KET to be significantly higher in the control group at baseline, regardless of limb. Even if normalized peak KET was the same bilaterally between groups at baseline, we do not foresee that the Home-NMES group would have demonstrated a greater bilateral improvement in isometric quadriceps strength than the control group at either three or six months post-ACLr, due to the differences in model estimates for limb and time being identical between both groups. Therefore, the isometric quadriceps strength deficits observed in Home-NMES group followed the same pattern as the control group after ACLr, but they happened to begin with weaker quadriceps at baseline.

Regardless of group allocation, significant limb by time interaction that was demonstrated in the results of Specific Aim 3. Similar to the results of Specific Aim 1, there was a side-to-side difference in isometric quadriceps strength between limbs at each time-point. For both groups, the normalized peak KET of the involved limb was significantly lower than that of the uninvolved limb at baseline, three months, and six months post-ACLr. Again, the largest difference between limbs was observed at three months post-ACLr (-1.35 Nm/kg), with the next largest difference occurring at six months post-ACLr (-0.95 Nm/kg), and the smallest difference between limbs was observed at baseline (-0.32 Nm/kg). Furthermore, if we convert the 6-month model estimates for normalized peak KET (see Table 4.6) into quadriceps strength LSIs, they fall below the 90% LSI return-to-sport criterion in both groups (Home-NMES = 65.5%; control = 69.5%) post-ACLr. Thankfully, only one patient in both the

Home-NMES group (high-school athlete) and control group (recreational athlete) was cleared by a physician to return to sports activity before the 6-month post-ACLr time point; thus, the majority of the patients in this clinical trial were not exposing their surgical knees to the increased external forces associated with sport activities, prior to achieving an acceptable limb symmetry in quadriceps strength. However, as stated earlier in this chapter, when interpreting a patient's quadriceps strength LSI after unilateral ACLr, it is important to consider the possibility of bilateral deficits in quadriceps strength. When available, we recommended that clinicians compare the quadriceps strength of their ACLr patients to those of healthy individuals, and if healthy data is not available, the second best alternative is to compare the postoperative quadriceps strength of the involved limb to the patient's preoperative quadriceps strength of their uninvolved limb recorded as soon as possible after ACL injury. These alternative comparison strategies to LSI will provide clinicians with a more accurate representation of the recovery of quadriceps strength in patients after ACLr.

Like the results of Specific Aim 1, a V-shaped curve was observed with quadriceps strength changes for both groups. Compared to baseline, quadriceps strength decreased in patients at three months post-ACLr (-1.07 Nm/kg), and then increased at six months post-ACLr (+0.32 Nm/kg), but this increase did not reach baseline value (-0.75 Nm/kg); thus, rejecting one component of our hypothesis. These changes can all be described as true change that occurred beyond measurement error (MDC_{95} = 0.30 Nm/kg),[592] making us 95% confident that true clinical changes in quadriceps strength occurred in the involved limb of

both groups after ACLr. Unlike the results of Specific Aim 1, there were no statistically significant changes with quadriceps strength in the uninvolved limb for either group. However, this was most likely due to larger mixed model analysis used for Specific Aim 2. Before post-hoc adjustments, normalized peak KET was significantly decreased from baseline to six months post-ACLr an average of 0.19 Nm/kg in the uninvolved limbs of both groups (unadjusted p = 0.02), but after adjusting for multiple comparison, this decrease in peak KET on the uninvolved limb did not achieve statistical significance (adjusted p = 0.13). In addition, the 95% confidence intervals of the 6-month peak KET estimates crossed the baseline estimates in both groups, and only 65% confidence can be had that true change occurred in quadriceps strength from baseline to six months post-ACLr (MDC = 0.16 Nm/kg).[592] The inclusion of the group variable adjusted the model estimates for normalized peak KET observed in the uninvolved limb of the control group (see Tables 4.3 and 4.6). Since the normalized peak KET estimate of the uninvolved limb was lower in the Home-NMES group than the control group at baseline, it may have decreased the likelihood of observing a statistically significant postoperative decrease in the uninvolved limb. Greater responsiveness to change after ACLr can be expected with higher normalized peak KET estimates, but since the Home-NMES started with lower normalized peak KET, the likelihood of a statistically significant decrease after ACLr is reduced; thus, explaining why no temporal changes were observed in the uninvolved limb of the control group. Regardless, we still believe that clinicians should account for potential bilateral deficits in the quadriceps strength of

patients after unilateral ACLr, by incorporating bilateral quadriceps strengthening interventions during rehabilitation.

Voluntary Quadriceps Activation

As observed with Specific Aim 1, there was a significant difference in voluntary activation observed between limbs at baseline. Regardless of group membership, the baseline quadriceps CAR estimate in the uninvolved limb of patients was on average 4.2% lower than that of the involved limb. However, a limb difference in quadriceps CAR was not significant in either group at three or six months post-ACLr. The lack of statistically significant limb differences in quadriceps CAR of the control group at three and six months post-ACLr are likely do to the larger mixed model analysis used for Specific Aim 3 compared to Specific Aim 1. The estimated 4.2% difference in quadriceps CAR between limbs (involved limb > uninvolved limb) at baseline was greater than what was reported in Specific Aim 1 (2.4%). Furthermore, this difference was beyond measurement error (SEM = 2%), and can be considered as true change with 68% confidence (MDC = 2.8%). As discussed earlier, a bilateral deficit in voluntary quadriceps activation of patients after unilateral ACLr has been previously demonstrated in the literature,[34,51,84,85,91] which is likely the result of a neural crossover effect.[42,145,272] This bilateral deficit further rejects the practice of relying on LSI measurements when assessing the recovery of neuromuscular quadriceps function in the involved limb and making return-to-activity decisions for patients after ACLr, and supports the inclusion of bilateral interventions during the rehabilitation of patients following unilateral ACLr.

Although there were no other statistically significant findings observed in this clinical trial concerning voluntary quadriceps activation, a case can be made that quadriceps inhibition was present in both groups of patients (see Table 4.6). Since quadriceps CAR was not assessed in the groups prior to ACL injury, we are unable to determine whether the injury and/or ACLr elicited decreases in voluntary quadriceps activation. By using the 95% voluntary quadriceps activation threshold established in the literature to determine the presence of quadriceps inhibition,[88-90] we can see that several quadriceps CAR estimates in both groups fall below this 95% threshold. In the involved limb, quadriceps inhibition was present beyond measurement error at three and six months post-ACLr in the control group, and at six months post-ACLr in the Home-NMES group (SEM = 2%).[404] However a true difference (with 90% confidence) to the 95% threshold was only observed with quadriceps CAR estimate at six months post-ACLr (89.8%) in the control group (MDC_{90} = 4.6%).[404] In the uninvolved limb, quadriceps inhibition was present beyond measurement error at each time point in both groups, but unlike the control group, true difference to the 95% threshold could only be seen at baseline (91.7%) and six months (92.2%) post-ACLr in the Home-NMES group. Furthermore, only 68% confidence can be given to the quadriceps inhibition (quadriceps CAR < 95%) that was present in the Home-NMES group at baseline and six months post-ACLr (MDC = 2.8%); whereas, 90% confidence (MDC_{90} = 4.6%) can be given to the quadriceps inhibition that was present in the control group at three months (quadriceps CAR = 89.8%) post-ACLr, and 95% confidence (MDC_{95} = 5.5%) to the quadriceps

inhibition present at baseline (quadriceps CAR = 88.9%) and six months (quadriceps CAR = 89.4%) post-ACLr.

Perhaps this point can be made clearer by observing the 95% confidence intervals (error bars) associated with the quadriceps CAR estimate (columns) for each group. Figure 4.4. The dashed red line in Figure 4.4 corresponds to the healthy normative quadriceps CAR (95%) reported by Park and Hopkins,[404] which is also used as the threshold for determining the presence of quadriceps inhibition. In the Home-NMES group, the only confidence interval that did not cross the 95% CAR threshold was seen with uninvolved limb at baseline (95% CI = 88.5%, 94.4%). Conversely, in the control group, the confidence intervals for all time points in the uninvolved limb were below the 95% CAR threshold, and even the confidence intervals for the 6-month quadriceps CAR estimate in the involved limb fell below this threshold (95% CI = 85.5%, 93.4%). Regardless of the observation that less inhibition was observed in the Home-NMES group than the control group, we cannot conclude that the home-based NMES treatment was effective at improving voluntary quadriceps activation in patients after ACLr. This observed difference between groups can be explained by the greater quadriceps inhibition observed in the control group at baseline, since no significant changes in quadriceps CAR were observed in either group over time. However, the main observation of this clinical trial was the presence of quadriceps inhibition in the uninvolved limb of patients before and after ACLr. This finding suggests that disinhibitory interventions may need to be applied bilaterally in patients after

unilateral ACLr as an attempt to maintain quadriceps activation and foster quadriceps strength gains during rehabilitation.

Corticomotor Excitability

In agreement with Specific Aim 1, no temporal changes in corticomotor excitability were observed in either group after ACLr, and no differences were found between groups at either time point. Since the quadriceps AMT estimates of both groups did not change postoperatively, and are similar to the quadriceps AMT values that have been reported in healthy individuals,[34,51,97] we believe that ACLr may not effect corticomotor excitability as much as what has been reported in earlier studies. Due to the limited evidence of corticomotor excitability changes in patients after ACLr, more studies are needed to determine the extent that these alterations exist. In addition, other supraspinal areas should be explored to determine the systemic effect that ACLr has on the CNS.

5.3.2 Explaining the Lack of Treatment Effect in the Home-NMES Group

Quadriceps Strength

The most disappointing finding of this randomized clinical trial was the lack of a treatment effect observed with the home-based NMES for any of the outcome measures pertaining to neuromuscular quadriceps function. Based on the time points in which quadriceps strength was assessed in our study, we expected that both groups would demonstrate a V-shaped pattern with temporal quadriceps strength changes. However, we hypothesized that the decreases in quadriceps strength at three and six months post-ACLr would be less extreme in

the Home-NMES group compared to the control, due to the superior treatment effects that have been reported with NMES. NMES has been well established in the literature as an effective modality for restoring quadriceps strength in patients after ACLr.[70,104-110,598] In a systematic review conducted in 2010, Kim et al.[105] assessed the effect sizes of six randomized clinical trials that compared the effect of NMES interventions on improving quadriceps strength in patients after ACLr, to that of other strengthening interventions (i.e., exercise, EMGBF, etc.). Of the seven clinical trials, six of them had effect sizes which favored the NMES interventions, and half of those demonstrated significant effect sizes (95% confidence intervals did not cross 0). From a physiological standpoint, NMES is effective at improving quadriceps strength in patients ACLr because it preferentially recruits type II (fast-twitch) muscle fibers,[115,503,504] which are thought be more effected in the quadriceps of patients after ACLr.[56,65,86,241-243] Therefore, since type II muscle fibers are responsible for high muscle force production, it is logical that NMES would be an effective modality for improving quadriceps strength.

Furthermore, NMES has demonstrated cross-education capabilities after unilateral application.[111,138,139,508] Although cross-education has been typically reported with exercise,[509-512] there is evidence to suggest that NMES may induce an even greater cross-education effect.[138,139] Hortobagyi et al.[138] randomized 32 healthy women to a NMES and control groups, and asked them to perform 840 eccentric contractions (control = voluntary, NMES = stimulated) over six weeks. Each group was tested before and after six weeks to assess for changes in

eccentric quadriceps strength. Improvements in quadriceps strength of the trained limb were observed in both groups, but the untrained limb of the NMES group demonstrated a 60% increase in quadriceps strength, which was greater than that of the control group. Since the untrained limb did not received the NMES and was unexercised, the bilateral improvement in quadriceps strength after a unilateral NMES intervention could only be explained by a neural crossover effect within the central nervous system.[116,513-516]

Lastly, there have been a handful of recent studies that have also demonstrated significant outcomes in patients with the use of home-based NMES devices.[129-131] The main benefit of home-based NMES is that a larger dosage of NMES can be provided to patients after ACLr. Although the control group in this study received NMES treatments on their quadriceps at physical therapy during the 12-week intervention period (average of 2-3 visits/week), the Home-NMES group was allowed more exposure to NMES within the same time window. Because of the convenience and higher NMES dosage that is associated with home-based NMES devices, we hypothesized that the Home-NMES group would demonstrate better quadriceps strength outcomes.

The reason why we did not observe a treatment effect in the Home-NMES group with quadriceps strength may have been due to the different treatment procedures used in our study, compared to those studies that have reported significant quadriceps strength improvements with NMES.[70,104,107,110] In our study, we had the Home-NMES group perform their NMES treatments with their knees in full/maximal extension. However, the most effective NMES protocols used for

improving quadriceps strength require patients to position their knees at 60° to 90° of flexion when applying NMES to achieve a quadriceps contraction that is at least 50% of their MVIC.[70,98,104,107,110] Although, there have also been studies have demonstrated positive quadriceps strength outcomes in patients when applying NMES in full knee extension.[108,130] Secondly, even though a greater training intensity can be provided by applying NMES in knee flexion, it tends to be more uncomfortable for patients, and difficult to attain during home-based NMES treatments.

Another reason as to why we did not observe superior quadriceps strength outcomes in the Home-NMES group may have been due to the length of our intervention. Our study consisted of a 12-week intervention period, which is longer compared to most studies that have shown positive quadriceps strength outcomes with NMES.[105] In the aforementioned systematic review, [105] the three randomized clinical trials that demonstrated significant effects sizes in favor of NMES for improving quadriceps strength, also had the shortest intervention periods (mean = 4.3 weeks).[70,110,598] Thus, the authors concluded that longer NMES interventions after ACLr may not be as effective in patients. However, their conclusion is interesting since quadriceps strength increases observed within the first few weeks of an NMES intervention have been attributed to neural adaptations, while those observed in the later weeks have been attributed to muscle hypertrophy. [111-114] Therefore, NMES interventions may be more effective at increasing quadriceps strength via neural adaptations instead of muscle hypertrophy. In our study, the soonest our physicians allowed us to assess

postoperative quadriceps strength in patients was at 12 weeks post-ACLr; therefore, even if a shorter NMES intervention period was used in the Home-NMES group, we would have been unable to determine whether neural adaptations moderated quadriceps strength deficits in patients within the first few weeks after ACLr.

To date, there have been a total of two studies which have assessed the effectiveness of home-based NMES for improving quadriceps strength in patients following ACLr.[104,130] Most recently, Feil et al.[130] assessed the effectiveness of three home-based interventions at restoring quadriceps strength in patients after ACLr by conducting a randomized clinical trial. A total of 131 patients were randomly allocated into one of three groups after ACLr: control group, Polystim group, or Kneehab group. The Polystim and Kneehab interventions were both home-based NMES interventions with identical stimulation parameters (50 Hz, 0 – 70 mA), but the Polystim intervention was a traditional two-channel NMES device with a single current pathway that is applied between an electrode pair, whereas the Kneehab intervention is a multipath NMES device that distributes its current to multiple pairs of electrodes within single channels. Both NMES groups began their interventions three days post-ACLr, and continued them for a total of 12 weeks (20 min/day, 5 days/week). The control group received the standard-of-care, but similar to our study, they performed isometric quadriceps contractions of the same duration and frequency as the home-based NMES groups, as a method to equalize the exercise volume. Isokinetic (concentric) quadriceps strength was assessed prior to ACLr, and every six weeks after ACLr, up to 24

weeks. The authors reported that the Kneehab group demonstrated significant increases from baseline to 24 weeks post-ACLr that were greater than both the Polystim and control groups. However, there were no significant differences observed between the Polystim and control groups in regard to quadriceps strength outcomes. The authors concluded the Kneehab group demonstrated better improvements in quadriceps strength because multipath NMES allowed for more spatial recruitment than the traditional NMES that was used in the Polystim group.[130]

Multipath NMES has been shown to elicit greater evoked KET from the quadriceps when compared to traditional NMES.[522] Maffiuletti et al.[522] attributed these effects to both the higher stimulation intensity that is tolerated with multipath NMES, and the wider current distribution between multiple pairs of electrodes. Compared to the study by Feil et al.,[130] the home-based NMES device used in our randomized clinical trial was more similar to the Polystim group than it was to the Kneehab group. Like the Polystim group, our traditional, home-based NMES device consisted of a two channel, single current pathway that was applied between a pair of electrodes. Therefore, the lack of quadriceps strength improvements observed in the Home-NMES group of our study may have been due to the limitation of traditional NMES.

However, traditional, home-based NMES has also been shown to be less effective at restoring quadriceps strength in patients after ACLr than traditional, clinic-based NMES.[104] In an earlier randomized clinical trial, Synder-Mackler and colleagues[104] randomly allocated 52 patients to either a clinic-based NMES

group or a home-based NMES group following ACLr. The patients in the clinic-based NMES group received traditional NMES treatments to their quadriceps during their physical therapy visits (3 days/week); whereas the patients in the home-based NMES group administered traditional NMES treatments to their quadriceps using a portable device (15 mins/treatment, 4 treatments/day, 5 days/week). Both groups began their respective interventions two weeks post-ACLr, and continued them for the following four weeks. The stimulation parameters were the same for clinic-based and home-based NMES (75 Hz, 300 μs, 50 – 100 mA), and each group was encouraged to increase the NMES intensity to maximal toleration. The contraction intensity was monitored weekly by assessing the evoked KET (%MVIC) on the uninvolved limb with each patients' maximally tolerated NMES intensity. After four weeks, isometric quadriceps strength was assessed in both groups. The clinic-based NMES group was reported to train with higher contraction intensities, and had greater quadriceps strength recovery than the home-based NMES group. Furthermore, there was a significant correlation observed between contraction intensity and quadriceps strength recovery in the clinic-based NMES group, but not in the home-based NMES group. Interestingly, the home-based NMES group in their study trained at a higher average NMES intensity (83 mA) than the clinic-based NMES group (55 mA). However, the traditional, clinic-based NMES was able to elicit greater contraction intensities in patients after ACLr. This observation is odd, because the evoked KET from NMES is known to be linearly related with spatial recruitment of the quadriceps, and NMES intensity is believed to directly

affect the evoked force of the quadriceps.[518,520,521] Therefore, the higher NMES intensity used by the home-based NMES group in this study should have produced a high contraction intensity, resulting in greater quadriceps strength recovery than what was reported.

The absence of this observation suggests that traditional NMES my only be effective with clinic-based devices, due to a limitation associated with portable NMES devices. With portable NMES devices, the electrodes are usually housed in a garment that is wrapped around the thigh, like the one used in our Home-NMES group. However, the distances between electrodes are confined to the surface area of the garment, which may restrict the degree of spatial recruitment NMES has within the quadriceps. Although spatial recruitment can be improved by increasing NMES intensity,[521] deeper motor units can also be targeted by increasing the inter-electrode distance.[520] Conversely, clinic-based NMES devices are not restricted to a specific inter-electrode distance. Therefore, the lower evoked KET observed in the home-based NMES group of the above study,[104] may be due to the limited inter-electrode distance of portable NMES devices.

However, this potential limitation of portable NMES devices may be corrected if multipath NMES is used instead of traditional NMES. As stated above, multipath NMES is believed to allow for more spatial recruitment with the quadriceps compared to traditional NMES.[130] Furthermore, patients have also reported experiencing less discomfort with multipath NMES compared to traditional NMES. Since three randomized clinical trials have now failed to

demonstrate significant quadriceps strength recovery with traditional, home-based NMES, multipath NMES seems to be the more attractive home-based modality for restoring quadriceps strength in patients after ACLr. Regardless, more studies are needed to determine whether multipath, home-based NMES is as effective as clinic-based NMES for restoring quadriceps strength in patients after ACLr.

Irrespective of the potential limitations associated with the home-based NMES device used in our study, we believe that the main reason why quadriceps strength improvements were not observed in the Home-NMES group, was because of their poor treatment compliance. Compliance has previously been shown to be strongly associated with improved functional outcomes and an increased likelihood of returning to sport in athletes after ACLr.[599] We recommended the Home-NMES group to administer the portable NMES device to their quadriceps three times a day, five days a week, for 12 weeks following ACLr, with each treatment session lasting 15 minutes. Therefore, the targeted treatment duration for the Home-NMES group totaled to 45 hours over the 12-week intervention. However, after extracting the logged minutes from the portable NMES devices, only one of the 25 patients randomized to the Home-NMES group meet the targeted treatment duration (48 hours, 10 minutes), and the average treatment duration of the entire group was just below 11 hours. Based on this average, the treatment compliance of the Home-NMES group was 24%. This observation was discouraging, based upon the treatment compliance that has been reported with other home-based NMES studies.[104,130] Of the two

previous studies that assessed the effectiveness of home-based NMES on restoring quadriceps strength in patients after ACLr,[104,130] both demonstrated far better treatment compliance than the Home-NMES group of our study. In the study by Feil et al.,[130] the targeted treatment duration for the Polystim and Kneehab groups was a total of 60 hours over 12 weeks. Although the Polystim group registered less total hours (mean = 39 hours, 18 minutes) than the Knee group (mean = 45 hours, 20 minutes), they had nearly three times the treatment compliance of our Home-NMES group (65% and 75%, respectively). Likewise, the targeted treatment duration for the home-based NMES group in the study by Synder-Mackler et al.,[104] was a total of 20 hours over four weeks. They registered an average treatment duration of 18 hours and 41 minutes, which equates to over 93% treatment compliance.

Except for minor differences in the prescribed treatment duration and frequency, these studies mentioned no other factors that may have explained the higher treatment compliance compared to our study. Like Snyder-Mackler et al.,[104] patients in the Home-NMES group were contacted on several occasions during the intervention period to insure that they were performing the prescribed home-based NMES treatments. Although we did not expect the Home-NMES group to achieve 100% compliance, we hoped that they would be similar to previous home-based NMES studies. We believe that the age of our patients may explain why our patients had lower treatment compliance compared to the other two home-based NMES studies. The average age of patients in our Home-NMES group was 19 years, with the majority of them being high school-aged.

Conversely, the average age of patients in the two previous studies ranged from 25 to 35 years.[104,130] Due to these age differences, it is likely that immaturity contributed to the low treatment compliance observed in our Home-NMES group. If this group consisted of patients whose ages were similar to those of the other two studies, we may have observed higher treatment compliance, which would have allowed us to better determine the effectiveness of our home-based NMES intervention on restoring quadriceps strength in patients following ACLr. In conclusion, because of the low treatment compliance observed in this randomized clinical trial, we were unable to reject or support the effectiveness of our home-based NMES intervention.

Voluntary Quadriceps Activation

We hypothesized that voluntary quadriceps activation would be more improved in the Home-NMES group after ACLr, based on the neural adaptions that are associated with NMES. Although improvements in muscle strength are easily attributed to the muscle hypertrophy that develops during NMES interventions,[111-115] neural adaptations elicited by NMES are also responsible for these increases in muscle strength.[111-113,116,117] Gondin and colleagues[113] reported that after 4-weeks of NMES treatments to the quadriceps of healthy individuals, significances increases in quadriceps strength (+11%,, EMG (+42-44), and voluntary activation (+5%) were observed, but there were no significant changes in quadriceps CSA. However, between weeks four and eight, further improvements in quadriceps strength (+11%) were accompanied by changes in quadriceps CSA (+4%). The neural adaptations demonstrated in this study

supports NMES as a potentially effective disinhibitory intervention for the quadriceps of patients following ACLr.

However, there is conflicting evidence concerning the disinhibitory effects of NMES on restoring quadriceps function in a patient population. Several studies have reported improvements in the voluntary quadriceps activation of patients with NMES interventions.[116,118-122] In a case series by Stevens et al.,[118] patients were assigned to one of two interventions, four weeks after receiving bilateral, total knee arthroplasty. Three patients participated in a 6-week (3 sessions/week), bilateral exercise program consisting of range-of-motion exercises, lower extremity strengthening exercises, and functional activities. Five other patients participated in the same exercise program, while also receiving NMES on the weaker quadriceps. Voluntary quadriceps activation was assessed in all patients at baseline, mid-intervention (3 weeks), post-intervention (6 weeks), and at three and six months. Due to the small sample size of patients, the authors chose to not report statistics, but a recent systematic review calculated the treatment effect sizes for each group to compare the disinhibitory effect of NMES to exercise.[101] Strong effect sizes were observed at the 3-week (1.66, 95% CI = 0.10, 2.90), 6-week (1.65, 95% CI = 0.09, 2.89) 3-month (1.71, 95% CI = 0.13, 2.96) and 6-months (1.87; 95% CI = 0.24, 3.13) time points in the NMES group. Conversely, the effect sizes of the exercise group were weak (-0.08 – 0.-48) and insignificant (95% CI crossed 0). Thus, it would seem that NMES is an effective motor-based modality for improving voluntary quadriceps activation in patients.

Conversely, there have been an equal number of studies which report less favorable effects of NMES for improving voluntary quadriceps activation in patients.[123-128] Palmieri-Smith et al.[125] randomly assigned 30 patients with radiographic knee OA to NMES (4 weeks; 3 sessions/week) and a control group. The NMES group received NMES to their quadriceps three times per week, for a total of four weeks. Whereas, the control group served as the standard-of-care, and did not receive any treatment. Voluntary quadriceps activation was assessed in all patients at baseline, one week, and 16 weeks post-intervention. Compared to the control group, there were no significant differences in quadriceps CAR changes at either post-intervention time point. The authors reported treatment effect sizes for each group to compare disinhibitory effects between groups. Unfortunately, weak and insignificant effect sizes were observed in both the NMES and control groups at five (0.2, 95% CI = -0.53, 0.91 vs. 0.0, 95% CI = -0.78, 0.78) and 15 weeks (0.42, 95% CI = -0.36, 1.18 vs. 0.33, 95% CI = -1.15, 0.51). Therefore, they concluded that there was no additional benefit from NMES for improving voluntary quadriceps activation in patients with knee OA.

In addition to the mixed evidence pertaining to the effectiveness of NMES as a disinhibitory intervention for the quadriceps of patients, the potential limitations of the home-based NMES device used in our study, combined with the poor treatment compliance of the Home-NMES group (discussed above), may have contributed to the lack of voluntary quadriceps activation improvements of observed in patients after the 12-week home-based NMES intervention. Furthermore, minimal quadriceps inhibition was observed in the limbs of patients

in the Home-NMES both before and after ACLr. Therefore, a potential ceiling effect with voluntary quadriceps activation may have prevented us from observing a disinhibitory effect with home-based NMES. However, this is the first known study that has investigated the disinhibitory effectiveness of NMES for the quadriceps of patients following ACLr.

Corticomotor Excitability

We believed that changes in corticomotor excitability would be demonstrated in the patients randomized to the Home-NMES group, because the neuromuscular improvements that have been previously reported with NMES are believed to involve alterations at the supraspinal level.[116,136,137] In a study by Blickenstorfer et al.,[136] a single session of electrical stimulation was applied to wrist extensor and flexor muscles of healthy individuals, while cerebral activation patterns were being captured with fMRI. During electrical stimulation, there was significant activation noted in the contralateral primary motor cortex, primary somatosensory cortex and premotor cortex, the ipsilateral cerebellum, bilateral secondary somatosensory cortex, the supplementary motor area, and anterior cingulate cortex. Additionally, Hortobagyi and Maffuiletti[116] proposed an alternative model in which heightened afferent input elicited by NMES may explain the neural adaptations observed with NMES. Since NMES cannot bypass the afferent fibers located within both the skin and muscle, this barrage of afferent impulses may be transmitted to the sensory system. This sensory discharge is thought to trigger supraspinal centers to allow for descending control of motoneurons, which elicits a facilitation of motor output to the involved muscle.

Therefore, the home-based NMES intervention used in our study was thought to elicit corticomotor excitability changes in the Home-NMES group through the above mechanisms.

The fact that no changes in corticomotor excitability were observed in the Home-NMES group after the home-based NMES intervention was not particularly surprising. The quadriceps AMT of the Home-NMES group was similar to that which has been reported in healthy individuals, and there were no changes observed at any of the postoperative time points. Therefore, a floor-effect with quadriceps AMT may have prevented a treatment effect from being observed in the Home-NMES group. Furthermore, to our knowledge, this is the first study to investigate whether an NMES intervention can elicit changes in the corticomotor excitability measured via quadriceps AMT. Since there was no previous evidence to compare to, our hypothesis was generated through inductive reasoning.

5.4 LIMITATIONS AND DELIMITATIONS

5.4.1 Limitations

There were several limitations in this study that were beyond the control of the investigators. The *a priori* power analysis was performed for voluntary quadriceps activation. Since there has been no study that has investigated the effect of NMES on improving voluntary quadriceps activation in patients after ACLr, we had to base our power analysis on observational data from patients before and after ACLr.[32] This procedure may have incorrectly estimated the sample size needed to achieve statistical power. Secondly, the poor treatment

compliance of the Home-NMES group was disappointing, and it may have prevented us from observing a treatment effect with any of the neuromuscular outcome measures.

5.4.2 Delimitations

There were also several delimitations in this study that were within the investigators' control. A healthy-matched control group was not included in this study; thus, we were forced to compare the results of Specific Aims 1 and 3 to that of previously reported data on healthy individuals. The group differences in peak KET at baseline was an observation of this study that could have been prevented by using a different randomization protocol. In addition to stratifying patients by autograft type and TFI, we could have included baseline peak KET as a stratification factor. Alternatively, we could have performed our statistical analyses by using the baseline outcome measures of the groups as a covariate. However, the similar limb and time patterns that were observed with peak KET between groups after ACLr suggests that this limitation did not confound our results substantially. Secondly, the lack of a healthy-matched control group prevented us from comparing our patient outcome measures to healthy individuals who were assessed using the same equipment and procedures. Although inter-rater reliability was established with the majority of outcome measures used in this study, we cannot not be fully confident that our techniques were exactly the same as those of other investigators. Therefore, comparing our results to those of data on healthy individuals collected from other investigators was not ideal. Thirdly, unlike other neuromuscular outcome measures, we did not

assess the corticomotor excitability in the uninvolved limb of patients. We chose not to assess quadriceps AMT in both limbs of patients because this measure requires the most, and with several other outcome measures being collected, we wanted limit the duration of the testing session for our patients. Lastly, we did not monitor the contraction intensity used with the home-based NMES device for those patients randomized to the Home-NMES group. This delimitation is important, because the contraction intensity elicited by NMES is known to be linearly related with spatial recruitment and the recovery of quadriceps strength in patients after ACLr.[104,518] Monitoring the contraction intensity in the Home-NMES group would have allowed us to determine the exercise load that was being applied to the quadriceps via the home-based NMES device, and whether this load was high enough to expect neuromuscular improvements in quadriceps function. Contraction intensity could have been determined by assessing the KET output of each patient's selected NMES intensity on a weekly basis.

CHAPTER 6: CONCLUSION

Our purpose was to determine the temporal neuromuscular quadriceps deficits that develop in patients after ACLr, the effect that early deficits have on the lower extremity function of patients at six months post-ACLr, and whether a home-based NMES intervention could be used to reduce the extent of these deficits in patients following ACLr. Our results from Specific Aim 1 indicate that although quadriceps weakness is more apparent in the involved limb of patients after ACLr, the quadriceps strength of their uninvolved limb is also affected, demonstrating reductions at six months post-ACLr. Due to this observation, clinicians are encouraged to not rely on quadriceps strength LSI when making return-sport-decisions for their patients after recovering from ACLr. In addition, the quadriceps inhibition in the involved limb of patients was not as significant as what has been previously reported in patients after ACL injury and reconstruction. However, the quadriceps in the uninvolved limb of patients demonstrated more inhibition, which may explain the quadriceps strength deficits observed in the uninvolved limb of patients following ACLr. To reduce the risk of subsequent injury upon return-to-sport and protect against the development of knee OA, we recommend that clinicians incorporate bilateral interventions aimed at restoring quadriceps strength and disinhibiting the quadriceps.

Our results from Specific Aim 2 indicate that the early postoperative quadriceps strength of patients around three months after ACLr are associated with the lower extremity function of these patients at six months post-ACLr. More specifically 3-month quadriceps strength was associated with 6-month lower

extremity postural control and self-reported quality of life. These findings demonstrate the importance of intensive quadriceps strengthening in the early stages of ACLr rehabilitation, so that both lower extremity postural control and knee-related quality of life of patients can be improved later on. Although the neural measures of quadriceps function in patients did not demonstrate significant associations with postoperative lower extremity function, the effect that NQD has on quadriceps strength is sufficient for it to be considered during the rehabilitation of these patients following ACLr.

Lastly, we are unable to prove or disprove the effectiveness of home-based NMES as a modality for restoring quadriceps strength and activation in patients after ACLr based on the results from Specific Aim 3. Although the lack of treatment effect observed with home-based NMES may be contributed to limitations that are associated with portable NMES devices, we believe that poor treatment compliance was the main contributor to the lack of treatment effect observed in this study. Home-based NMES provides patients with the ability to receive higher doses of NMES to the quadriceps. However, before portable NMES devices can be prescribed to patients after ACLr, it must be determined whether these devices can elicit similar contraction intensities to that of clinic-based NMES, and if treatment compliance in patients can be enhanced. Furthermore, more randomized clinical trials are needed to determine whether NMES and other motor-based modalities have disinhibitory effects in the involved limb of patients who exhibit quadriceps inhibition after ACLr, and if these

modalities possess the capabilities to elicit a crossover effect in the uninvolved limb of patients.

APPENDIX: KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE

KOOS KNEE SURVEY

Today's date: _____/_____/_____ Date of birth: _____/_____/_____

Name: _____

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms

These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S3. Does your knee catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S4. Can you straighten your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

S5. Can you bend your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

Stiffness

The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

P1. How often do you experience knee pain?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of knee pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P3. Straightening knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P4. Bending knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P5. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P6. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P7. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P8. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P9. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A2. Ascending stairs

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A3. Rising from sitting

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A4. Standing

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A5. Bending to floor/pick up an object

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A6. Walking on flat surface

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A7. Getting in/out of car

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A8. Going shopping

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A9. Putting on socks/stockings

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A10. Rising from bed

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A11. Taking off socks/stockings

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

A12. Lying in bed (turning over, maintaining knee position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A14. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Jumping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Twisting/pivoting on your injured knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP5. Kneeling

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of Life

Q1. How often are you aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your knee?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Thank you very much for completing all the questions in this questionnaire.

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VITA

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EDUCATIONAL BACKGROUND

DOCTOR OF PHILOSOPHY
University of Kentucky, Lexington, KY
Rehabilitation Sciences
College of Health Sciences
Advisor: Carl Mattacola, PhD, AT, FNATA
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MASTER OF SCIENCE
Ohio University, Athens, OH
Athletic Training
Advisor: Chad Starkey, PhD, AT, FNATA
Conferred: June 2012

BACHELOR OF SCIENCE
University of Wisconsin at Eau Claire, Eau Claire, WI
Athletic Training
Advisor: Robert Stow, PhD, AT
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PROFESSIONAL BACKGROUND

CLINICAL EXPERIENCE

Athletic Trainer: UK HealthCare Sports Medicine Clinic: Lexington, KY
August 2012 – Present
Responsibilities: Measure and fit braces/prophylactics on patients for DonJoy Orthopedics; prepare patients for injections/aspirations and post-operative wound care; assist with clinical coverage for Fayette County high school athletic events

Graduate Assistant: Ohio University: Head Athletic Trainer: Wellston High School, Wellston, OH
July 2010 – June 2012
Responsibilities: Provided daily care, prevention, and rehabilitation of injuries; properly evaluated and documented all injuries; provided game coverage for all high school sports; supervised undergraduate athletic training students

EDITORIAL EXPERIENCE

Editorial Assistant: The Journal of Sport Rehabilitation, Human Kinetics, Champaign, IL
January 2014-Present

Responsibilities: Oversee electronic management of submitted and revised manuscripts; assign reviewers to manuscripts that have the potential to be published; assist the editor with strategic development to improve the journal

TEACHING BACKGROUND

UNIVERSITY OF KENTUCKY

Teaching Apprentice: Division of Athletic Training – University of Kentucky
Course/s:
AT 740: Musculoskeletal Anatomical Dissection (Summer 2013-2015)

Guest Lecturer: College of Health Sciences – University of Kentucky
Course/s:
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AT 672: Sports Inquiry in Athletic Training III (Fall 2015)
KHP 720: Sports Medicine Seminar (Fall 2015)
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OHIO UNIVERSITY

Teaching Assistant: Division of Athletic Training – Ohio University
Course/s:
AT 180C: Practical Applications in Athletic Training (Spring 2012)
AT 418A: Cadaver Anatomy (Fall 2011)

PUBLICATIONS

ACCEPTED MANUSCRIPTS

1. **Gabler CM**, Lepley AS, Uhl TL, Mattacola CG. Comparison of transcutaneous electrical nerve stimulation and cryotherapy for increasing quadriceps activation in patients with knee pathologies. *J Sport Rehabil*. Epub Ahead of Print. DOI: http://dx.doi.org/10.1123/jsr.2014-0292

2. **Gabler CM,** Jacobs CA, Howard JS, Mattacola CG, Johnson DL. Comparison of Graft Failure Rate between Autografts Placed via an Anatomic Anterior Cruciate Ligament Reconstruction Technique: A Systematic Review, Meta-analysis, and Meta-regression. *American Journal of Sports Medicine.* 2016;44(4):1069-1079.

3. **Gabler CM**, Kitzman PH, Mattacola CG. Targeting quadriceps inhibition with electromyographic biofeedback: a neuroplastic approach. *Critical Reviews in Biomedical Engineering.* 2013;41(2):125-135.

4. **Gabler CM**, David DS, Howe CA, White J, Ragan BG. (2012) Effectiveness of neuromuscular training on modifiable anterior cruciate ligament injury risk factors. Published Thesis – Ohio University.

5. Bowers K, Brinza L, **Gabler CM**, Vick LE. The effects of mouthguards on agility performance in athletic and non-athletic populations. *Journal of Undergraduate Kinesiology Research.* 2010;5(2):28-35.

SUBMITTED MANUSCRIPTS

1. McCullough MM, **Gabler CM**, Howard JS, Medina McKeon JM. Risk factors of anterior cruciate ligament injury: A meta-analysis. Submitted to Journal of Athletic Training.

PRESENTATIONS

1. **Gabler CM,** Pietrosimone BG, Johnson DL, Mattacola CG. Temporal Quadriceps Dysfunction occurs Bilaterally in Patients following Unilateral Anterior Cruciate Ligament Reconstruction. Doctoral Oral Student Award Finalist presentation at the *67th Annual National Athletic Trainers' Association Clinical Symposia & AT Expo.* Baltimore, Maryland, June 23, 2016.

2. **Gabler CM,** Jacobs CA, Butterfield TA, Pietrosimone BG, Mattacola CG, Johnson DL. Knee Extension Torque Deficits Exist Bilaterally in Patients Following Unilateral Anterior Cruciate Ligament Reconstruction. Accepted presentation at the *63rd American College of Sports Medicine Annual Meeting.* Boston, MA, June 3, 2016.

3. **Gabler CM,** Mattacola CG. Unlocking the Quadriceps after Knee Surgery: An Evidence-Based Approach to Treatment. An evidence-based practice module/webcast on *CE Central, Sponsored by UKHealthcare Orthopaedic Surgery and Sports Medicine.* November 5, 2015.

4. **Gabler CM,** Mattacola CG, Johnson DL, Lattermann C. Preoperative Patient Factors Associated with Neuromuscular Quadriceps Function Prior to Anterior Cruciate Ligament Reconstruction. A thematic poster presentation at the *66th Annual National Athletic Trainers' Association Clinical Symposia & AT Expo.* St. Louis, Missouri, June 25, 2015.

5. **Gabler CM,** Mattacola CG. Determining the Temporal Changes in Neural Quadriceps Function after Anterior Cruciate Ligament Reconstruction. An Oral Presentation at the *3rd Annual Athletic Trainers' Osteoarthritis Consortium Meeting.* St. Louis, MO, June 23, 2015.

6. **Gabler CM,** Mattacola CG, Johnson DL, Lattermann C. Preoperative Patient Factors Associated with Neuromuscular Quadriceps Function Prior

to Anterior Cruciate Ligament Reconstruction. An oral presentation at the *10th Annual Center for Clinical and Translational Science Spring Conference.* Lexington, KY, March 25, 2015.

7. **Gabler CM,** Mattacola CG. Unlocking the Quadriceps after Knee Surgery: An Evidence-Based Approach to Treatment. An evidence-based practice presentation at the *40th Annual Southeastern Athletic Trainers' Association Clinical Symposium & Members Meeting*. Atlanta, GA, March 13, 2015.

8. McCullough MM, **Gabler CM**, Howard JS, Medina McKeon JM. Risk factors of anterior cruciate ligament injury: A meta-analysis. A poster presentation at the *65th Annual National Athletic Trainers' Association Clinical Symposia & AT Expo.* Indianapolis, Indiana, June 26, 2014.

9. **Gabler CM,** Dwyer MK, Butterfield TA. Temporal myoelectric and architectural adaptions in distal hindlimbs of rats following experimentally-induced proximal muscle weakness: Preliminary findings. A poster presentation at the *1st Annual College of Health Sciences Research Day.* Lexington, KY, March 27, 2014.

10. **Gabler CM,** David SD, Howe CA, White J, Ragan BG. Effectiveness of neuromuscular training on modifiable anterior cruciate ligament injury risk factors. A poster presentation at the *63rd Annual National Athletic Trainers' Association Clinical Symposia & AT Expo.* St. Louis, Missouri, June 28, 2012.

FUNDING ACTIVITIES

EXTERNAL GRANTS FUNDED

Title: Effect of a Superimposed Electrical Stimulation Knee Garment on Strength, Function, and Patient Reported Outcomes after Knee Surgery
Funding Agency: DonJoy Orthopedic Research Grant. DJO Global, Vista, CA.
Amount: $41,400
Date: 1/2014 – 1/2016
Description: The goal of this study was to evaluate the effect of home-based neuromuscular electrical stimulation applied via a knee sleeve on strength, function, inhibition, and patient reported outcomes.
Role: Co-Investigator
Title: Effectiveness of Neuromuscular Training on Modifiable Anterior Cruciate Ligament Injury Risk Factors
Funding Agency: National Athletic Trainers' Association Research & Education Foundation
Amount: $1,000
Date: 6/2011 – 6/2012
Description: The goal of this study was to compare the effectiveness of a commercialized neuromuscular training program to a standard strength

training program of equal exercise volume for modifying frontal plane kinematics during a drop-jump that are risk factors for anterior cruciate ligament injury.
Role: Principal Investigator

INTERNAL GRANTS FUNDED

Title: Effectiveness of home-based electrical stimulation on restoring neuromuscular quadriceps function in patients after anterior cruciate ligament reconstruction
Funding Agency: National Center for Advancing Translational Sciences & National Institutes of Health
Amount: $4,000
Date: 11/2014 – 11/2015
Description: The goal of this study was to compare the effectiveness of a home-neuromuscular electrical stimulation program on improving quadriceps activation and strength in patients after ACL reconstruction compared to a standard home-exercise program.
Role: Principal Investigator

MENTORING

MASTER'S THESIS COMMITTEES

1. Baez S. Using the Response-Shift Theory to Explain Differences between Functional Scores and Patients Reported Outcomes in Patients with Knee Pathologies at Return to Physical Activity. Committee Co-Chair.
2. Webb J. Comparison of Knee Extension Rate of Torque Development in Patients after Unilateral Anterior Cruciate Ligament Reconstruction and Healthy Individuals. Expected to graduate May 2016. Committee Co-Chair.
3. McCullough M. Risk factors of anterior cruciate ligament injury: A meta-analysis. May 2014. Committee Co-Chair.

PROFESSIONAL AFFILIATIONS/CERTIFICATIONS

CERTIFICATIONS

1. Licensed Athletic Trainer – Kentucky #AT.1012 (2012-Present)
2. Certified Athletic Trainer; Board of Certification, Inc. #2000003722 (2010-Present)
3. American Heart Association BLS Healthcare Provider CPR/AED (2010-Present)
4. Sportsmetrics™ Certified Instructor (2010-Present)
5. Licensed Athletic Trainer – Ohio #AT.003405 (2010-2012)
6. American Red Cross Emergency First Responder (2008-2011)

MEMBERSHIPS

1. National Athletic Trainers' Association (2007-Present)
2. Kentucky Athletic Trainers' Society (2012-Present)
3. Southeastern Athletic Trainers' Association (2012-Present)

4. Ohio Athletic Trainers' Association (2010-2012)
5. Great Lakes Athletic Trainers' Association (2007-2012)
6. Wisconsin Athletic Trainers' Association (2007-2010)

PROFESSION SERVICE ACTIVITIES

EDITORIAL BOARDS

1. Journal of Sport Rehabilitation – Editorial Assistant (2014-Present)

MANUSCRIPT REVIEWER

1. Journal of Athletic Training (2015-Present)
2. European Journal of Physical and Rehabilitation Medicine (2015-Present)
3. Journal of Sport Rehabilitation (2013-Present)