TARGETING QUADRICEPS WEAKNESS FOLLOWING ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

By

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ACL	anterior cruciate ligament
ANOVA	analysis of variance
CAR	central activation ratio
CI	confidence interval
CKC	closed kinetic chain
deg/sec	degrees per second
E-only	eccentric-only intervention group
m	meter
mA	milliamperage
ms	milliseconds
MVIC	maximal voluntary isometric contraction
N	Newton
N-only	NMES-only intervention group
N&E	NMES and eccentric intervention group
NMES	neuromuscular electrical stimulation
kg	kilogram
OA	osteoarthritis
OKC	open kinetic chain
QI	quadriceps index

QAF	quadriceps activation failure
RM ANOVA	repeated measures analysis of variance
RTP	return-to-play
sec	seconds
SD	standard deviation
SIB	superimposed burst
STND	standard of care intervention group
TENS	trancutaneous electrical nerve stimulation
TMS	transcranial magnetic stimulation

ABSTRACT

This dissertation represents a series of clinical investigations that provide critical insight into the development of rehabilitation approaches to combat the ubiquitous quadriceps weakness that occurs following anterior cruciate ligament injury. As quadriceps weakness accelerates joint degeneration and leads to a lower quality of life, identifying therapies capable of restoring strength is essential to preserving long-term health. With the above in mind, aim one examined if eccentric cross-education, whereby the uninvolved limb is exercised, is capable of improving quadriceps function in the unexercised limb. It was found that exercising with eccentric contractions resulted in mode and velocity specific strength gains in the unexercised limb, as well as a trend toward improvement in quadriceps neural activity. As a reduction in neural activity of the quadriceps (i.e. quadriceps activation failure [QAF]) is thought to be a primary cause of weakness, rehabilitation programs may be able to utilize this type of therapy to enhance neural activity and quadriceps strength. Examining the role of QAF further, aim two investigated the relationship between pre-operative QAF and post-operative QAF and strength. It was found that pre-operative QAF was positively related to the recovery of post-operative QAF, but not strength. Hence, therapies that target pre-operative QAF should help to improve the recovery of neural activity post-reconstruction. Further, clinicians should continue to focus on maximizing strength before surgery. Lastly, aim three was conducted to determine the effectiveness of a combined neuromuscular electrical stimulation (NMES) and eccentric exercise intervention to improve the recovery of quadriceps strength and knee mechanics post-reconstruction. It was found that eccentric exercise was capable of restoring levels of quadriceps activation and strength that were similar to those of healthy adults and better than

NMES alone. Whereas individuals that received the combined NMES and eccentrics intervention demonstrated the best recovery of knee mechanics. Taken together, these results indicate that eccentric exercise is an effective therapy to improve quadriceps neural activity and strength, though a longer intervention may be needed to positively influence movement. Additionally, interventions that are capable of minimizing pre-operative QAF should be employed to improve the recovery of post-operative quadriceps function.

Chapter 1. Introduction & Specific Aims

1.1 Statement of the problem

Rupture of the anterior cruciate ligament (ACL) is common and costly. Approximately 250,000 ACL injuries occur in the United States annually (Griffin et al., 2006) at an average cost of $25,000 per reconstruction (Hootman and Albohm, 2012). Though ACL reconstruction restores static knee stability and rehabilitation improves functionality, patients often return back to activity with diminished quadriceps strength (Anderson et al., 2002; Hiemstra et al., 2000; Nakamura et al., 2002; Nyland et al., 2003; Snyder-Mackler et al., 1994a; Urbach et al., 2001). Quadriceps weakness is related to reduced functional performance (Keays et al., 2003; Schmitt et al., 2012), the potential for re-injury (Hurley et al., 1992; Schmitt et al., 2012), and is linked to the development of post-traumatic osteoarthritis (OA) (Tourville et al., 2014) that occurs in more than 50% of ACL reconstructed limbs (Roos, 2005). As the peak age for ACL rupture is 16 (Shea et al., 2004), it is likely that a significant number of 20 to 30 year old adults will suffer from the debilitating symptoms associated with OA. Given the importance of the quadriceps muscle to knee joint health, it is critical that rehabilitative approaches capable of improving the recovery of quadriceps strength are developed.

1.2 Justification of research

Though the precise mechanism(s) of quadriceps weakness associated with ACL injury and reconstruction are unknown, there is evidence to suggest that quadriceps activation failure (QAF) and possibly quadriceps muscle atrophy are primarily responsible for strength deficits (Palmieri-Smith et al., 2008; Williams et al., 2005a). QAF is the inability to completely

volitionally contract the muscle due to alterations in neural signaling (Hopkins and Ingersoll, 2000) and is common following ACL reconstruction (Hart et al., 2010; Ingersoll et al., 2008). Whereas muscle atrophy that occurs following ACL reconstruction is thought to manifest due to alterations in selective fiber atrophy (Lorentzon et al., 1989; Snyder-Mackler et al., 1993), muscle architecture (Kawakami et al., 2000; Narici and Cerretelli, 1998), or even as a consequence of QAF (Palmieri-Smith et al., 2008). Taken together, these factors explain more than half of the variance in quadriceps strength deficits post-ACL injury (Williams et al., 2005a). Consequently, QAF and muscle atrophy are attractive factors to target to improve the recovery of quadriceps strength.

With the above in mind, this dissertation will explore therapies aimed at improving the recovery of quadriceps strength by utilizing interventions that have been theorized, and shown to, improve QAF and minimize muscle atrophy. Further, this research will explore the impact of pre-operative QAF on post-operative outcomes to aid in the design of future pre-operative rehabilitative protocols. Ultimately, the purpose of this dissertation is to develop and test novel therapeutic approaches that are capable of markedly improving quadriceps strength and to determine whether quadriceps activation is a mechanism that leads towards improvements in strength.

1.3 Specific Aims

The Specific Aims of this dissertation research comprised the following:

AIM 1: To determine the effect of eccentric cross-education on quadriceps activation and strength in the unexercised knee.

Hypothesis 1A: Exercising with eccentric contractions will lead to improved quadriceps *activation* in the unexercised limb of eccentric exercise participants.

Hypothesis 1B: Exercising with eccentric contractions will lead to improved quadriceps *strength* in the unexercised limb of eccentric exercise participants.

Significance of Aim 1: Eccentric cross-education, whereby the uninvolved limb is eccentrically exercised, is an alternative therapeutic approach to early eccentric strengthening of the injured limb that may improve quadriceps activation and strength. Protocols utilizing cross-education have been shown to successfully improve quadriceps strength in healthy (Hortobagyi et al., 1997; Komi et al., 1978; Seger et al., 1998) and pathological populations (Papandreou et al., 2013). The strength gains that are produced in the unexercised limb are thought to result from alterations in neural activity (Carr et al., 1994; Zhou, 2000). As deficits in quadriceps strength following ACL injury are hypothesized to occur, in part, because of alterations in quadriceps activation (Hopkins and Ingersoll, 2000), identifying if eccentric cross-education can improve quadriceps activation can help researchers to develop novel targeted interventions for populations with quadriceps strength deficits following knee injury and surgery.

AIM 2: To determine the effect of pre-operative quadriceps activation and strength on post-operative quadriceps activation and strength.

Hypothesis 2A: Greater pre-operative quadriceps *activation* will be positively associated with greater post-operative quadriceps *activation*.

Hypothesis 2B: Greater pre-operative quadriceps *activation* will be positiviely associated with greater post-operative quadriceps *strength*.

Hypothesis 2C: Greater pre-operative quadriceps *strength* will be positively associated with greater post-operative quadriceps *strength*.

Significance of Aim 2: Pre-operative rehabilitation may help to minimize post-operative quadriceps strength deficits. There is evidence to suggest that greater pre-operative quadriceps strength leads to a better recovery of strength following ACL reconstruction (de Jong et al., 2007; Eitzen et al., 2009; Shelbourne and Johnson, 2004). Yet the impact of pre-operative quadriceps activation on post-operative quadriceps activation and strength is less understood. As quadriceps activation is a major component of quadriceps strength (Stackhouse et al., 2000), it is likely that better pre-operative activation is related to an improved recovery of quadriceps function post-reconstruction. Understanding how pre-operative quadriceps activation contributes to post-operative strength is important when directing care and should help clinicians design more effective pre-operative interventions.

AIM 3: To determine the effectiveness of a combined neuromuscular electrical stimulation and eccentric exercise intervention to improve quadriceps function and knee mechanics post-ACL reconstruction.

Hypothesis 3A: Participants allocated into the combined neuromuscular electrical stimulation (NMES) and eccentric exercise group will demonstrate significantly greater gains in quadriceps activation and strength at 12 weeks post-ACL reconstruction and at return-to-play when compared to participants in the NMES-only, eccentric-only and standard of care groups (Chapter 5).

Hypothesis 3B: Greater gains in quadriceps activation will be positively associated with greater quadriceps strength (Chapter 5).

Hypothesis 3C: The combined NMES and eccentric exercise group will demonstrate greater sagittal plane limb symmetry, wherein these patients would demonstrate knee flexion angles and moments that more closely resemble their contralateral non-injured limb during dynamic activity at return-to-play (Chapter 6).

Hypothesis 3D: Greater gains in quadriceps strength will be positively associated with greater knee mechanic limb symmetry (Chapter 6).

Significance of Aim 3: Although data exist documenting the separate effectiveness of NMES (Delitto et al., 1988; Fitzgerald et al., 2003; Snyder-Mackler et al., 1991; Wigerstad-Lossing et al., 1988) and eccentric exercise (Brasileiro et al.; Gerber et al., 2007a, b) post-ACL reconstruction, there is no data in the published literature regarding the combined effectiveness of NMES and eccentric exercise to improve quadriceps function. Data generated from this study has the potential to improve ACL rehabilitation techniques by establishing if deficits in quadriceps function can be best restored by using a combination of therapies that have been shown to improve quadriceps activation and minimize muscle atrophy. Further, as QAF has been implicated as an important underlying factor that contributes to quadriceps weakness (Palmieri-Smith et al., 2008; Williams et al., 2005a), this study will focus on

determining whether improvements in activation result in strength gains. Additionally, in order to translate this research into clinical practice, it is necessary to identify if gains in quadriceps strength are capable of improving movement. This data will provide clinicians and researchers with practical information related to how this intervention can influence functional performance and knee mechanics post-ACL reconstruction.

1.4 Organization of Dissertation

This dissertation was structured such that the main body (**Chapters 3-6**) details three separate aims conducted over a period of four years (2010-2014) at the University of Michigan. Manuscripts for each aim have been either accepted or submitted for publication in peer-reviewed journals.

The literature review (**Chapter 2**) provides the background and motivation for this dissertation. **Chapters 3-6** were conducted to test novel therapeutic approaches aimed at markedly improving quadriceps strength and to determine whether quadriceps activation was a mechanism that led towards improvements in quadriceps strength. With this purpose in mind, **Chapter 3** examined the effect of eccentric cross-education on quadriceps activation and strength in the unexercised limb. To examine this, healthy subjects were randomized into one of two groups, an eccentric exercise group and a control group. Participants allocated to the eccentric exercise group exercised their dominant limb with an isokinetic dynamometer in eccentric mode three times a week for eight weeks. Quadriceps strength and activation measures were collected at pre-, mid- and post-intervention in the unexercised limb to determine the effect of eccentric cross-education. **Chapter 4** examined the effect of pre-operative QAF on post-operative quadriceps activation and strength in ACL reconstructed patients. To accomplish this, patients were tested on two separate occasions: post-injury but prior to ACL reconstruction, and post-ACL reconstruction once patients had been cleared by their physician to return to activity. Lastly, **Chapters 5 and 6** detail a clinical intervention that was divided into two parts to examine the effectiveness of a combined NMES and eccentric exercise intervention to improve quadriceps function (Part I, Chapter 5) and movement during a single-legged landing task post-ACL reconstruction (Part II, Chapter 6). To test this, patients scheduled for ACL reconstruction were placed into one of four groups; NMES and eccentric exercise group, NMES-only group, eccentric-only group, and a standard of care group. Patients then attended three testing sessions (pre-operative, 12 weeks and return-to-play) where quadriceps strength and activation were assessed (Chapter 5, Part I). At a time when patients were returned-to-play, motion capture testing was collected to assess knee mechanics (Chapter

6, Part II). **Chapter 7** highlights the key outcomes from Chapters 3-6, discusses the limitations of these aims and proposes future directions for work related to this research.

Chapter 2. Literature Review

The purpose of this review of literature is to detail 1) the anatomy and function of the ACL, 2) ACL injury, 3) ACL reconstruction, 4) mechanisms and clinical implications of quadriceps weakness and 5) current rehabilitation strategies aimed at restoring quadriceps strength.

2.1 Anterior Cruciate Ligament

The ACL plays an essential role in maintaining knee joint stability and is the most commonly injured knee ligament during sport and work related activities (Beaty, 1999). ACL reconstruction is performed with the aim of maximizing knee stability and functional capacity, thereby facilitating a return to sport and promoting long-term knee joint health. However, despite the best efforts of clinicians and researchers, nearly two-thirds of ACL reconstructed patients do not return back to activity at 12 months post-reconstruction (Ardern et al., 2010) and more than 50% of ACL reconstructed knees have radiographic signs of OA 5-14 years after injury (Roos, 2005). With these facts in mind, identifying rehabilitation approaches that are capable of reducing the short and long-term consequences of ACL injury are imperative.

2.1.1 Anatomy

The ACL is a band-like structure of dense connective tissue that runs anteriorly, medially and distally through a large portion of the intercondylar notch of the femur (Duthon et al., 2006) and serves as both a passive stabilizer of the knee (Berns et al., 1992; Markolf et al., 1995) and provides neural information to the central nervous system (Kennedy et al., 1982; Schutte et al., 1987). Proximally, the ACL attaches on the posterior aspect of the medial surface of the lateral

femoral condyle (Girgis et al., 1975) and distally, the ligament inserts on a fossa located anterior and lateral to the medial intercondylar eminence (Duthon et al., 2006). The distal tibial attachment of the ACL is wider and stronger than the femoral attachment (Girgis et al., 1975). In addition to the direct attachment sites on the femur and tibia, some fibers of the ACL also insert on the anterior and posterior horns of the lateral meniscus (Dodds and Arnoczky, 1994). The blood supply of the ACL is provided by the middle genicular artery, with a greater number of blood vessels located in the proximal femoral attachment than the distal attachment (Duthon et al., 2006).

The ACL is composed of three bundles including the anteromedial, posterolateral and intermediate (Duthon et al., 2006; Girgis et al., 1975; Zantop et al., 2006). Bundle names are based on tibial attachments and these three bundles are generally grouped into two functional bundles including the anteromedial and posterolateral (Girgis et al., 1975). The ACL bundles are composed of a variety of collagen fibers that form fascicles that are oriented in a complex, multi-hierarchical fashion (Clark and Sidles, 2005). The collagen matrix is primarily composed of Type I fibrils, which are longitudinally oriented to provide the greatest tensile strength (Amiel et al., 2005; Neurath and Stofft, 1992). In addition to the Type I fibrils, the ligament also contains Type III (Amiel et al., 2005), IV and VI fibrils. (Neurath and Stofft, 1992) The remaining ligament structure is composed of water, ground substance and elastic fibers, which help distribute stress during motion (Duthon et al., 2006).

2.1.2 Mechanical function

The ACL is the primary restraint to anterior tibial displacement (Berns et al., 1992; Markolf et al., 1990). The greatest stress on the ACL occurs when the knee is near extension, and decreases when the knee moves into flexion (Beynnon et al., 1992a; Woo et al., 1991). In situ studies have shown that the functional bundles of the ACL resist anterior translation differently, where the anteromedial bundle limits anterior translation during knee flexion and the posterolateral bundle limits anterior translation during knee extension (Gabriel et al., 2004; Sakane et al., 1997).

The bundles of the ACL are formed by fibrils that combine to form fascicles which are organized to resist excessive ligament elongation (Duthon et al., 2006). Fascicles that are centrally located form a linear wave pattern that combines with the surrounding peripheral fascicles in a nonlinear, helical pattern that creates an accordion-like crimp (Duthon et al., 2006; Smith et al., 1993). When movement occurs, small loads first tighten the crimp before larger loads elongate the fascicles. Thus, as loads increase, a greater number of fascicles provide tension, which leads to a gradual increase in ligament stiffness (Duthon et al., 2006).

Evidence suggests that in addition to providing sagittal plane stability, the ACL may also provide some secondary function to forces in the frontal and transverse planes. Specifically it is thought that the ACL restricts internal rotation, especially when the knee is near full extension (Duthon et al., 2006) and that the ACL may also function to resist external rotation and valgus and varus movements in weight bearing positions (Beynnon et al., 1992b; Duthon et al., 2006; Matsumoto et al., 2001).

2.1.3 Somatosensory function

The ACL has an extensive neural network that receives information from articular nerves, mechanoreceptors and free nerve endings (Kennedy et al., 1982; Schutte et al., 1987; Zimny et al., 1986). Due to the dense population of neural receptors that are located in the ACL (Schutte et al., 1987), the ACL is believed to act not only as a mechanical restraint, but also as a source of afferent signals that contributes to muscle activity about the knee joint (Beard et al., 1993; Dhaher et al., 2003; Johansson et al., 1991; Solomonow et al., 1987).

The ACL primarily receives neural input from the posterior articular nerve (Duthon et al., 2006; Kennedy et al., 1982), which is a branch of the posterior tibial nerve that arises near the popliteal fossa. In addition to innervating the ACL, the posterior articular nerve also supplies the posterior capsule, the collateral ligaments, the posterior cruciate ligament and the fat pads of the knee (Kennedy et al., 1982).

Mechanoreceptors function as transducers that convert mechanical pressure into nervous signals (Zimny et al., 1986). In the knee, mechanoreceptors are stimulated by tension that is developed in the collagenous fibers in response to joint acceleration and deceleration, direction of motion and knee joint positions (Zimny et al., 1986). The three classifications of mechanoreceptors that have been identified in the ACL are the 1) Ruffini endings, 2) Pacinian corpuscles, 3) and Golgi tendon organs (Kennedy et al., 1982; Schutte et al., 1987; Zimny et al., 1986). Specifically, Ruffini endings are small, low threshold slowly adapting mechanoreceptors that respond to changes in intra-articular pressure (Spencer et al., 1984), static joint position, direction amplitude and velocity of the joint (Schutte et al., 1987). Pacinian corpuscles are also low threshold mechanoreceptors and respond rapidly to detect vibration (Zimny, 1988). Golgi tendon organs are large, high threshold, slowly adapting mechanoreceptors that respond to changes in tension at the extreme ends of joint range of motion (Umphred and McCormack, 1985).

Free nerve endings function to transmit pain signals to the central nervous system (Biedert et al., 1992; Freeman and Wyke, 1967). In the ACL, free nerve endings are primarily located in the insertions sites on the femur and tibia (Kennedy et al., 1982). Free nerve endings have also been identified in the joint capsule, the posterior cruciate ligament and in the medial meniscus (Freeman and Wyke, 1967; Heppelmann et al., 1990).

2.1.4 Prevalence

ACL injuries are common. Approximately 250,000 ACL injuries occur annually in the United States (Griffin et al., 2006) at a rate of 1 in 3,000 in the general population (Daniel and Fritschy, 1994). The vast majority of these injuries occur between the ages of 18-45 when individuals are participating in sporting activities (Bjordal et al., 1997; Daniel and Fritschy, 1994; Zelisko et al., 1982). Although males sustain more ACL injuries than females due to higher sport participation levels, females have been reported to be two to eight times more likely to tear their ACL when compared to their male counterparts participating in similar high-risk sports (Arendt et al.,

1999; Bjordal et al., 1997; Daniel and Fritschy, 1994; Harmon and Ireland, 2000; Malone et al., 1993).

2.1.5 Short and long-term consequences

ACL injury results in both short and long-term disability. In the short-term there is pain, loss time from work, school, sports and even reduced academic performance (Freedman et al., 1998; Hewett et al., 2006). Long-term ACL injury leads to the early onset of OA (Roos, 2005) and reduced quality of life (Lohmander et al., 2004). What's more, it has been reported that the average length of time between ACL reconstruction to total knee arthroplasty is approximately 19 years (Hoxie et al., 2008). Given that the peak age of ACL injury is 16 (Shea et al., 2004), it is likely that a significant number of young adults will encounter substantial knee joint degeneration. Thus, developing therapeutic approaches that can successfully counter the consequences of ACL injury is imperative.

2.1.6 Mechanisms of non-contact ACL injury

Non-contact ACL injuries account for nearly 70% of all ACL injuries (Griffin et al., 2000) and occur when a person, him or herself, generates the forces and/or moments at the knee that leads to excessive loading of the ACL (Yu and Garrett, 2007). Although the non-contact ACL injury mechanism has been investigated using a variety of research models (prospective, retrospective, observational, in vivo and in vitro) a direct determination of how injury occurs remains elusive.

In general, data gathered from many studies (Boden et al., 2000; Cochrane et al., 2007; Hewett et al., 2005; McNair et al., 1990) have reported that a common characteristic among non-contact ACL injuries is the dynamic knee valgus positioning following a sudden deceleration and/or jump landing. Of note, one prospective investigation has reported that increased knee valgus during a jump landing task is predictive of ACL injury with a coefficient of determination of 0.88 (Hewett et al., 2005). Knee flexion angle at the time of injuries also appears to be an important characteristic, with knee flexion of 20 degrees or less leading to injury (Boden et al.,

2000; McNair et al., 1990). In addition, excessive multi-plane loading has been shown to more than double the tensile forces on the ACL (Markolf et al., 1990). Further, the ACL appears to be at the greatest risk for injury when the knee is near full extension and there is a combination of excessive knee valgus loads with internal rotation of the tibia (Durselen et al., 1995; Gabriel et al., 2004; Kanamori et al., 2002).

The supporting musculature of the knee may also contribute to ACL injury. In particular, in vitro studies have found that excessive quadriceps force between 200-400 N (Shimokochi and Shultz, 2008) is hazardous to the ACL, and ACL strain can reach 200 N of tensile force during isolated quadriceps contractions when the knee is in less than 40 degrees of knee flexion (Draganich and Vahey, 1990; Durselen et al., 1995; Markolf et al., 1990; Markolf et al., 2004). Less than 100 N of hamstring force and a lack of coordination between the quadriceps and hamstring also seem to contribute to ACL strain (Draganich and Vahey, 1990; Li et al., 2004; Markolf et al., 2004).

In summary, the risk of non-contact ACL injury appears to be the greatest when the ACL is excessively loaded by the quadriceps muscle in combination with insufficient hamstring coordination with frontal and/or transverse-plane loading when the knee is near extension (Shimokochi and Shultz, 2008).

2.1.7 ACL reconstruction

While the collateral ligaments generally respond well to conservative treatment (Jones et al., 1986; Reider et al., 1994) and exhibit strong healing potential (Sandberg et al., 1987), the ACL has poor intrinsic healing capability, due in part to its poor vascular supply (Nau et al., 2002). As a result, surgical reconstruction of the ACL is the most frequent mode of treatment following injury (Dye et al., 1998). In fact, in the United States nearly 100,000 ACL reconstructions are performed yearly (Garrett Jr, 2004), which ranks ACL reconstruction third among the most common surgeries performed by general surgeons (CDC, 1996).

Once an individual decides to undergo ACL reconstruction they are confronted with several different graft choices. Over the years many different grafts have been tested, including synthetic ligaments, allografts, autografts and extraarticular reconstruction (Corry et al., 1999). Today, autografts of the patellar tendon and hamstring tendon are the most commonly used grafts by orthopedic surgeons (Beynnon et al., 2005). Several investigations have compared patellar tendon grafts to hamstring grafts to determine which graft type is superior (Beynnon et al., 2002; Carter and Edinger, 1999; Ejerhed et al., 2003; Freedman et al., 2003; Jansson et al., 2003; Lephart et al., 1993; Shaieb et al., 2002), and at this point it appears that both graph types produce similar re-injury rates (Aglietti et al., 2004), functional results (Gobbi et al., 2004; Mohtadi et al., 2011) and activity levels (Corry et al., 1999; Mohtadi et al., 2011). Despite the fact that both graft types produce similar functional results, some clear advantages of each graft type have been reported in the literature. In particular, one advantage of the patellar tendon graft is the bone-tendon-bone fixation. Because of the bony fixation the patellar tendon graft is stronger than the hamstring graft (West and Harner, 2005), and has been reported to have a mean tensile strength of 168% of the ACL (Noyes et al., 1984). In contrast, the hamstring graft produces a mean strength of 70% of the ACL (Noyes et al., 1984). Another advantage of the patellar tendon graft is that the bony ends of the graft are reported to heal within six weeks after surgery (West and Harner, 2005), while the soft tissue ends of the hamstring graft heal between 8-12 weeks post-reconstruction (Rodeo et al., 1993; West and Harner, 2005). The primary advantage of the hamstring graft relates to less long-term anterior knee joint pain (Aune et al., 2001; Freedman et al., 2003; Jansson et al., 2003), a common report among individuals that have patellar tendon grafts (Jansson et al., 2003; O'Brien et al., 1991). In addition, some authors report that because the quadriceps extensor mechanism is not violated there is less initial quadriceps atrophy following a hamstring graft, allowing for a quicker return of quadriceps strength (Huegel and Indelicato, 1988; Sachs et al., 1989). In contrast, more recent work by Lephart et al.(Lephart et al., 1993) reported that there is no difference in quadriceps strength between hamstring and patellar tendon graft types at one and two years post-ACL reconstruction. In summary, ACL reconstruction is common following injury and there is no consistent data that indicates that one graft type is superior to the other.

2.2 Quadriceps weakness

The quadriceps muscle group plays a pivotal role in the dynamic stabilization of the knee joint. Consequently, following ACL injury, the restoration of quadriceps strength is often a primary goal of rehabilitation. Although ACL reconstruction successfully restores static knee stability and rehabilitation improves functionality, patients often return back to activity with diminished quadriceps muscle function (Anderson et al., 2002; Hiemstra et al., 2000; Nakamura et al., 2002; Nyland et al., 2003; Snyder-Mackler et al., 1994a; Urbach et al., 2001).

Quadriceps strength deficits lead to a reduction in force production and improper force attenuation throughout the knee and lower extremity (Hurwitz et al., 1997; Lewek et al., 2002). Although the severity of quadriceps weakness appears to lessen with time, the literature consistently indicates that strength deficits can persist for years following ACL reconstruction (Hart et al., 2010; Palmieri-Smith et al., 2008). In addition, persistent quadriceps weakness is clinically important because it reduces physical function (Keays et al., 2003) and quality of life (Lohmander et al., 2004), increases the risk of re-injury (Hurley et al., 1992; Schmitt et al., 2012) and contributes to the development and progression of post-traumatic OA following ACL injury (Keays et al., 2010; Tourville et al., 2014).

Two primary causes of quadriceps strength deficits are thought to be quadriceps activation failure and muscle atrophy (Keays et al., 2003; Krishnan and Williams, 2011; Snyder-Mackler et al., 1994a; Snyder-Mackler et al., 1995; Urbach et al., 2001; Williams et al., 2005a; Williams et al., 2005b). Quadriceps activation failure is the inability to completely volitionally contract the muscle due to alterations in neural signaling, and is universal following ACL reconstruction (Hart et al., 2010; Ingersoll et al., 2008). Quadriceps activation failure is a barrier to successful rehabilitation because it only allows portions of the quadriceps muscle to be volitionally utilized during exercise (Hopkins and Ingersoll, 2000). During the first few months after injury or surgery, quadriceps activation failure can be so extensive that rehabilitation protocols are rendered largely ineffective (Hurley et al., 1994; Keays et al., 2000; Rice and McNair, 2010; Rossi et al., 2002). Importantly, quadriceps activation failure does not fully account for strength

deficits associated with ACL injury and reconstruction (Snyder-Mackler et al., 1993), which has led some researches to suggest that quadriceps muscle atrophy is also responsible for strength deficits (Krishnan and Williams, 2011; Williams et al., 2005a). Quadriceps atrophy that occurs following ACL injury and reconstruction is thought to result from disuse of the muscle and/or immobilization of the knee joint (Appel, 1990; Edgerton et al., 2002). Although most research has established a weak relationship between quadriceps muscle atrophy and strength deficits, a recent study conducted by Williams et al. (Williams et al., 2005a) has shown that when quadriceps atrophy is combined with activation failure they account for more than 60% of variance in quadriceps weakness post-ACL injury. As a result, quadriceps muscle atrophy may play a role in reducing quadriceps strength.

In summary, despite the reinstitution of static stability achieved through ACL reconstruction, quadriceps weakness is often persistent long after rehabilitation concludes. The recovery of quadriceps strength is crucial to normal knee joint function, thus restoring strength is often an essential component of rehabilitation. Collectively, it appears that quadriceps activation failure and muscle atrophy are both underlying mechanisms that may contribute to quadriceps weakness.

2.3 Quadriceps activation failure

Quadriceps activation failure is hypothesized to result from reflex activity in which altered afferents arising from an injured joint lead to diminished efferent motor drive to the supporting musculature (Hopkins and Ingersoll, 2000). The diminished ability to volitionally contract the quadriceps muscle following ACL injury hinders rehabilitation by preventing strength gains (Hurley, 1997; Hurley et al., 1994; Hurley et al., 1992), influences alterations in knee loading patterns (Torry et al., 2000), impairs functional performance (Hurley et al., 1992), and potentially contributes to the early onset of OA (Hopkins and Ingersoll, 2000; Suter and Herzog, 2000).

Ultimately, a reduction in alpha motoneuron output is responsible for quadriceps activation failure, although the precise mechanism(s) involved in reducing the excitability of the

quadriceps alpha motoneuron pool is unknown (Hopkins and Ingersoll, 2000). Currently several mechanisms of quadriceps activation failure are proposed to contribute to quadriceps strength deficits following ACL injury and reconstruction. The following section will discuss peripheral and central mechanisms of quadriceps activation failure that have been implicated in the literature.

2.4 Peripheral contributors to QAF

Following ACL injury and reconstruction, a number of factors such as swelling, pain, and loss of output from damaged joint receptors may alter afferent discharge from the joint that contribute to quadriceps activation failure.

2.4.1 Swelling

Swelling has been shown to cause significant quadriceps activation failure. In fact, as little as 10mL of fluid has been shown to cause notable quadriceps inhibition (de Andrade et al., 1965; Torry et al., 2000; Young et al., 1987). This is particularly troubling in an ACL population, where knee effusion can persist for up to three months post-injury and up to 12 months post-reconstruction (Frobell et al., 2009). The effects of swelling have been well documented in knee effusion models where reductions in quadriceps electromyographic (EMG) activity (de Andrade et al., 1965; Hopkins, 2006; Palmieri-Smith et al., 2007; Torry et al., 2005; Torry et al., 2000), Hoffman reflex (Hopkins, 2001; Hopkins et al., 2002; Iles et al., 1990; Spencer et al., 1984), and force output (Jensen and Graf, 1993; McNair et al., 1996; Wood et al., 1988) are commonly reported. It is thought that fluid in swollen knee joints causes a rise in intra-articular pressure and the discharge of group II articular afferents from the knee, which in turn causes a strong inhibitory effect on the quadriceps muscle (Rice and McNair, 2010). Alternatively, in an ACL injured population, Lynch et al. (Lynch et al., 2012) has recently shown that knee effusion does not play a role in quadriceps activation failure. The discrepancy between the results of this study and others may have occurred due to the amount of time between effusion to testing. Specifically, the effects of experimentally induced effusions are often tested within minutes to hours after the event, whereas patients enrolled in the Lynch et al. (Lynch et al., 2012) study

were tested on an average of 27 days post-ACL injury. Lynch and colleagues suggest that the nervous system may have had time to adapt the effusion, diminishing the muscle inhibition observed in their investigation (Lynch et al., 2012). Future work is warranted to determine the effects of chronic swelling on quadriceps activation post-ACL reconstruction.

2.4.2 Pain

Pain can also result in quadriceps activation failure and is thought to occur as a protective mechanism in an effort to immobilize the joint following injury (Eriksson, 1981). Specifically, an increase in the afferent discharge of free nerve endings, which increases pain signaling to the central nervous system, is thought to cause an inhibitory effect on the quadriceps muscle (Schaible and Grubb, 1993). It has been shown that intra-articular injections of local anesthetics can improve quadriceps activation after open meniscectomy (Stokes and Young, 1984) and can improve both quadriceps activation (de Andrade et al., 1965) and isokinetic torque (Baxendale et al., 1985) following experimental knee effusions. However, it should be noted, that the relationship between pain and quadriceps activation failure is inconsistent in the literature. Although some authors have reported that pain contributes to quadriceps activation failure (Doxey and Eisenman, 1987; Eriksson, 1981), other investigations have reported that pain is not associated with quadriceps inhibition (Davies et al., 1984; Stokes and Young, 1984; Young, 1993; Young et al., 1987). Knee effusion models provide the best evidence that quadriceps activation failure can occur in the absence of pain (de Andrade et al., 1965; Hopkins, 2001; Hopkins, 2006; Hopkins et al., 2002; Iles et al., 1990; Palmieri-Smith et al., 2007; Spencer et al., 1984; Torry et al., 2005; Torry et al., 2000). Future work needs to be done to elucidate the relationship between pain and quadriceps activation failure.

2.4.3 Damaged joint receptors

Ultimately, when the ACL is injured, the sensory receptors that innervate the ACL are disrupted and the loss and/or change in sensory output from the ACL may contribute to quadriceps activation failure (Young, 1993). Sensory receptor regeneration following ACL injury remains controversial, with some authors suggesting that regeneration does not occur (Shimizu et al.,

1999), whereas others suggest that regeneration may occur to a limited degree (Georgoulis et al., 2001; Ochi et al., 1999). Although the ability of the receptors to regenerate post-ACL injury remains unclear, the somatosensory function of the ACL is thought to be diminished following injury (Ochi et al., 2002; Ochi et al., 1999). The reduced sensory capacity of joint receptors has been linked to a disruption in the afferent signaling to the quadriceps muscle that leads to activation failure (de Andrade et al., 1965).

2.5 Central Mechanisms of QAF

The central nervous system functions to modulate the afferent input arising from the periphery. Following ACL injury, the central nervous system is thought to contribute to quadriceps activation failure by reducing the excitability of the quadriceps alpha motorneuron pool that leads to decreased quadriceps force production. The following section will discuss possible central mechanisms leading to quadriceps activation failure.

2.5.1 Pre-synaptic inhibition

Pre-synaptic inhibition may cause quadriceps activation failure by preventing a release of neurotransmitters that are necessary for muscle contractions (Gardner, 1948). Specifically, inhibitory interneurons cause a release of gamma-aminobutyric acid (GABA) neurotransmitters, which cause primary afferent depolarization and an influx of chlorine that reduces the amplitude of the pre-synaptic action potential (Redman, 1998). A reduction in the amplitude of the pre-synaptic action potential results in a reduction of the calcium influx into the pre-synaptic terminal, leading to a reduction of neurotransmitter release into the synaptic cleft that causes an inhibitory effect on the muscle (Redman, 1998).

In investigations involving the knee, researchers have established the presence of pre-synaptic inhibition in effusion models (Iles et al., 1990; Jones et al., 1987; Palmieri et al., 2005; Spencer et al., 1984). Although the precise mechanism of pre-synaptic inhibition is not known, it has been suggested that increased afferent signaling, caused by joint effusion, is gated by GABA-ergic interneurons that ultimately cause a reduction in the efferent signaling to the quadriceps

(Palmieri et al., 2005). More work is needed to establish the effect of pre-synaptic inhibition post-ACL injury on quadriceps activation.

2.5.2 Reciprocal inhibition

Reciprocal inhibition is a process where Ia inhibitory interneurons receive excitatory input from the Ia afferents arising from the homonymous muscle spindle that simultaneously cause the agonist muscle to contract and inhibits the antagonist muscle (Tanaka, 1974).

The mechanism(s) of reciprocal inhibition within the quadriceps muscle is currently unknown. Some investigators postulate that a change in afferent information arising from the injured knee may activate the Ia inhibitory interneuron of the quadriceps muscle, possibly contributing to activation failure (Palmieri et al., 2003). Although no direct evidence of reciprocal inhibition exists following knee injury, evidence of reciprocal inhibition has been found in individuals suffering from chronic ankle instability (Sedory et al., 2007). Specifically, Sedory et al. (Sedory et al., 2007) have indicated that hamstring inhibition leads to quadriceps facilitation. More work is needed to identify the presence and extent of reciprocal inhibition in the quadriceps muscle post-ACL injury.

2.5.3 Recurrent inhibition

Recurrent inhibition is another inhibitory process that may also play a role in quadriceps activation failure. Recurrent inhibition is mediated by Renshaw cells. These cells regulate alpha motorneuron activity by innervating and inhibiting the same alpha motoneuron that caused it to fire. In addition, Renshaw cells can also synapse with gamma motoneurons (Ellaway, 1971; Ellaway and Murphy, 1981; Noth, 1983) and with Ia inhibitory interneurons (Gustafsson and Lindstrom, 1973; Hultborn et al., 1976; Hultborn et al., 1968, 1971; Hultborn et al., 1979; Lindstrom, 1973), allowing simultaneous inhibitory stimuli to be projected to synergistic muscles (Renshaw, 1941).

Experimental knee effusion models have provided evidence of recurrent inhibition in the quadriceps muscle (Iles et al., 1990; Palmieri et al., 2004; Spencer et al., 1984). Investigators

suggest that recurrent inhibition of the quadriceps occurs through Renshaw cells that alter the firing rate and amount of efferent drive to alpha motoneurons that innervate the quadriceps muscle (Windhorst, 1996).

2.5.4 Non-Reciprocal inhibition

Non-reciprocal inhibition is a neural process wherein Ib interneurons receive excitatory input from Ib afferents originating from Golgi tendon organs. The Ib afferent fiber arising from the homonymous muscle bifurcates in the spinal cord where one branch prevents the homonymous muscle from contracting, and the other branch innervates an excitatory interneuron that synapses on the antagonist muscle. Thus, the homonymous muscle is inhibited and the antagonist is able to contract allowing the opposing muscle groups to work together (Rice and McNair, 2010).

Iles et al. (Iles et al., 1990) have found evidence of non-reciprocal inhibition in knee effusion models. In their work, the presence of knee effusion depressed the neural activity of the quadriceps muscle during rest and volitional muscle contractions. Based on these data, Iles et al. (Iles et al., 1990) concluded that quadriceps inhibition, was at least in part, caused by non-reciprocal inhibition because this spinal pathway was still active during volitional contractions. However, it should be noted that the reduction in quadriceps neural excitability demonstrated in this experiment (Iles et al., 1990) may have also been due to alterations in the discharge of afferent signaling caused by joint effusion (Harrison and Jankowska, 1985; Lundberg et al., 1978a).

2.5.5 Flexion reflex

The flexion reflex is a polysynaptic pathway that generally results in flexor facilitation and extensor inhibition (Lundberg et al., 1978b). Thus, some researchers have suggested that an enhanced flexion reflex following knee injury may also partially contribute to quadriceps activation failure (Engelhardt et al., 2001; Young, 1993). Although the precise interneuron responsible for the flexion reflex has yet to be identified, evidence from animal studies suggest that a large range of interneurons likely play a role in modulating the flexion reflex (You et al.,

2008; You et al., 2003). In particular, it is thought that the interneurons responsible for the flexor reflex are primarily located in the lamina V of the dorsal horn, and likely receive input from articular receptors (Millan, 1999; Schomburg, 1990). Following knee injury, it has been hypothesized that a greater discharge of afferent signaling may cause alterations in interneuron activity (Neugebauer and Schaible, 1990).

Investigators have found that a reduction in the flexion reflex threshold in individuals with anterior knee pain results in concomitant inhibition of the quadriceps muscles during activity (Leroux et al., 1995). Evidence of a lower flexion reflex threshold has also been documented in patients with knee OA when compared to age and gender-matched controls (Courtney et al., 2009). More evidence is needed to document the relationship between quadriceps activation failure and the flexor reflex following ACL injury.

2.5.6 Gamma loop-dysfunction

The gamma-loop is a spinal reflex formed by the innervation of the gamma motoneurons with the primary muscle spindles. Gamma motorneurons function to regulate the function of the primary muscle spindle that sets the baseline of activity for alpha motoneurons and helps to regulate muscle length and tone. Thus, normal function of the gamma motoneuron is necessary to achieve full muscle activation during voluntary movement. Currently, the precise mechanism of gamma loop dysfunction in quadriceps activation failure is unknown.

Researchers have proposed that a potential neural mechanism of gamma loop dysfunction following ACL injury is the result of a loss of excitatory feedback from ACL mechanoreceptors to quadriceps gamma motoneurons (Konishi et al., 2002). Studies in support of this potential mechanism by Konishi et al. (Konishi et al., 2002; Konishi et al., 2003) have shown that injecting healthy knee joints with local anesthetic can reduced maximal quadriceps isometric torque and integrated EMG. In comparison, injection of the same local anesthetic into knee joints with an isolated ACL tear had no effect of quadriceps torque or EMG. Based on these data Konishi et al. (Konishi et al., 2002; Konishi et al., 2003) concluded that excitatory output from ACL sensory receptors play a critical role in the maintenance of gamma-loop function.

2.5.7 Descending cortical inhibition

Descending cortical pathways exert tonic inhibitory control over spinal neurons involved in a wide variety of functions by regulating the afferent information arising from the periphery into the central nervous system (Cervero et al., 1991; Millan, 1999). Descending cortical inhibition has been shown to contribute to bilateral muscle inhibition following joint injury (Young, 1993). However, more recent evidence (Heroux and Tremblay, 2006) has suggested that changes in the primary motor cortex occur on the side projecting to the ACL-injured limb only. Specifically, a lower resting motor threshold has been found on the ACL-injured limb as compared to the uninjured side. Thus, it appears that excitability may be increased in the primary motor cortex in the presence of knee joint pathology and could potentially have bilateral or unilateral effects (Heroux and Tremblay, 2006; Young, 1993). It is thought that this enhanced cortical excitability may allow the central nervous system to increase the corticospinal drive to counteract the reduced alpha motoneuron activity that occurs following injury (Pietrosimone et al., 2012; Rice and McNair, 2010).

2.6 Quadriceps atrophy

The second major mechanism thought to contribute to quadriceps weakness is quadriceps muscle atrophy (Palmieri-Smith et al., 2008), a decrease in the size of the muscle, which is thought to occur following disuse and immobilization of the knee joint (Appel, 1990). Quadriceps atrophy is often apparent following ACL reconstruction and has been suggested to contribute to strength deficits (Konishi et al., 2007; Snyder-Mackler et al., 1993). Although muscle atrophy has been suggested to contribute to strength deficits following ACL injury, the literature supporting this notion is inconclusive. Recent data published by Konishi et al. (Konishi et al., 2007) demonstrated that quadriceps muscle volume and strength per unit of muscle volume was significantly lower in the ACL reconstructed leg than that of healthy controls, supporting the idea that muscle atrophy negatively affects strength following injury. Further, it has been proposed that chronic strength deficits following ACL reconstruction are primarily related to peripheral changes in quadriceps muscle size and structure (Krishnan and Williams, 2011). Despite these reports, the effect of quadriceps atrophy on strength is inconsistent in the

literature, with many studies demonstrating a weak relationship between atrophy and strength deficits post-ACL injury (Elmqvist et al., 1988; Lorentzon et al., 1989).

Although neither quadriceps atrophy nor quadriceps activation failure can fully account for strength deficits independently (Stokes and Young, 1984), recent work suggests that when quadriceps muscle atrophy is combined with quadriceps activation failure it can account for approximately 60-85% of the variance in quadriceps strength (Mizner et al., 2005; Williams et al., 2005a). Interestingly, quadriceps activation accounted for nearly twice that of muscle atrophy in the regression equation used to predict quadriceps strength in patients post-total knee arthroplasty (Mizner et al., 2005), which supports additional literature regarding the ankle joint (Stevens et al., 2006). The independent contribution of quadriceps activation and atrophy to the model was not reported in the study with individuals post-ACL injury by Williams et al. (Williams et al., 2005a).

Although it appears that quadriceps activation deficits have a greater impact on quadriceps strength loss (Lorentzon et al., 1989; Mizner et al., 2005), quadriceps atrophy is an important factor that likely contributes to quadriceps weakness, however more work is needed to better understand the impact of quadriceps atrophy on strength deficits post-ACL injury. Ultimately, a reduction in muscle size is responsible for quadriceps atrophy, although like quadriceps activation, the precise mechanism(s) is unknown. Several mechanisms of quadriceps atrophy are proposed to contribute to quadriceps strength deficits following ACL injury and reconstruction.

2.6.1 Alterations in muscle architecture

Following periods of disuse, a decrease in muscle size has been found to be associated with alterations in muscle fascicle length and pennation angle (Kawakami et al., 2000; Narici and Cerretelli, 1998). Reductions in muscle fascicle length and pennation angle are thought to occur as a result of a loss of muscle sarcomeres (de Boer et al., 2008), which are the basic unit of muscle tissue. Therefore, this loss of muscle fascicle length implies that there is reduced shortening of sarcomeres in series (de Boer et al., 2008). This shortening of the sarcomeres is

believed to interrupt the length-tension relationship of the muscle fascicle, which ultimately results in reduced muscle force production (Gordon et al., 1966). The reduction in the pennation angle of muscle is thought to occur from a loss of sarcomeres in parallel (Gans and Bock, 1965). Thus, alterations in muscle fascicle length and pennation angle that occur as a result of muscle atrophy collectively contribute to strength deficits. Although alterations in muscle architecture, such as pennation angle and fascicle length, have been shown to have an effect on muscle strength (Gordon et al., 1966), there is currently no published literature aimed at identifying a relationship between alterations in muscle architecture and ACL injury. Future research should look to identify if, and how, muscle architecture is affected following ACL injury and surgery, and to what extent these changes have on muscle strength.

2.6.2 Selective muscle fiber atrophy

Selective fiber type atrophy of the quadriceps muscle may also contribute to strength deficits and have been reported in the literature following ACL injury and reconstruction (Edstrom, 1970; Lopresti et al., 1988; Lorentzon et al., 1989). Although the results in the literature are inconsistent, there is evidence to suggest that both Type I and Type II atrophy may occur. Researchers (Edstrom, 1970) have found predominantly Type I atrophy of the vastus lateralis following ACL rupture, while others (Lopresti et al., 1988) have found predominantly Type II atrophy following ACL reconstruction, whereas others have found no consistent morphological changes (Lorentzon et al., 1989; Nakamura et al., 1986). Previous authors (Snyder-Mackler et al., 1993) has suggested that selective Type IIb fiber atrophy may occur following ACL reconstruction, although alterations in muscle morphology were not directly measured in this investigation. Future studies are warranted to determine the effect of selective fiber type atrophy associated with quadriceps strength deficits following ACL injury.

2.6.3 Reduced neural input

Another potential contributing factor to quadriceps atrophy following ACL injury is the reduction in the neural input to the muscle (Palmieri-Smith et al., 2008). As quadriceps activation failure prevents the full volitional activation of the muscle, the presence of activation

failure can result in muscle fiber disuse, which can ultimately lead to atrophy of the affected tissue. The mechanisms leading to muscle activation failure, as described in the previous section, can therefore contribute to muscle atrophy as well. Also as stated previously, other investigations have found that following injury, muscle activation deficits explain a greater amount of the variance seen in muscle weakness when compared to muscle atrophy (Mizner et al., 2005; Stevens et al., 2006). Thus, it seems plausible, that muscle activation failure, which contributes to strength deficits, may also contribute to muscle atrophy.

2.7 Clinical implications of quadriceps weakness

2.7.1 Biomechanical consequences

Lingering quadriceps weakness has been linked to altered movement patterns following ACL reconstruction (Bulgheroni et al., 1997; DeVita et al., 1998a; Lewek et al., 2002; Snyder-Mackler et al., 1991; Timoney et al., 1993). Specifically, quadriceps weakness has been correlated with altered knee movements in the sagittal plane during walking and jogging activities (Lewek et al., 2002; Snyder-Mackler et al., 1991). Previous authors (Snyder-Mackler et al., 1991) has found that knee motion during walking was directly and significantly correlated with quadriceps strength following ACL reconstruction. Moreover, these investigators (Snyder-Mackler et al., 1991) have found that patients with stronger quadriceps walked with more normal sagittal plane knee joint excursions than those that had less quadriceps strength. Work by others (Lewek et al., 2002) has further illustrated this relationship reporting that knee flexion angles and moments of a strong-ACL reconstructed group to be indistinguishable from a non-injured group, while a weak-ACL reconstructed group displayed smaller knee flexion angles and reduced knee flexion moments during walking and jogging activities. Furthermore, quadriceps strength and self-report function accounted for approximately 60% of the variance in ACL reconstructed subjects' knee moments at peak knee flexion during activity (Lewek et al., 2002). Collectively these studies (Lewek et al., 2002; Snyder-Mackler et al., 1991) support the contention that quadriceps strength deficits are associated with alterations in movement.

2.7.2 Functional performance

Quadriceps weakness is associated with lower performance-based measures, even after the contributions of graft type, meniscal injury, knee pain and knee symptoms are taken into consideration (Schmitt et al., 2012). The current literature indicates that quadriceps strength deficits are associated with reduced hopping ability (Hopper et al., 2008; Mattacola et al., 2002; Noyes et al., 1991), agility (Schmitt et al., 2012; Wilk et al., 1994) and side stepping tasks (Keays et al., 2003). Quadriceps strength has also been shown to account for up to 40% of alterations in functional performance following ACL reconstruction (Schmitt et al., 2012).

2.8 Therapeutic approaches to combat quadriceps weakness

To successfully restore quadriceps strength and promote long-term knee joint health, several rehabilitation objectives have been identified following ACL reconstruction. Although the progression of each ACL rehabilitation protocol depends on surgical procedures and concomitant injuries, clinicians can universally agree that the following items are essential components of ACL rehabilitation; 1) control of post-operative pain and swelling, 2) protection of healing graft, 3) restoration of full range of motion, 4) strengthening of lower extremity muscles that stabilize the knee, 5) improve neuromuscular control and 6) progression to functional activities (Myer et al., 2006; Shelbourne and Wilckens, 1990). Advances in ACL reconstruction and rehabilitation have allowed clinicians to achieve most of the above-mentioned goals, as most individuals have successfully controlled post-operative pain (Reuben et al., 1998; Shelbourne et al., 1994; Williams et al., 2006; Williams et al., 2004; Williams et al., 2003) and swelling (Ohkoshi et al., 1999; Shelbourne et al., 1994), restored knee range of motion (Biggs et al., 2009; Shelbourne and Klotz, 2006) and are capable of performing functional activities (Chmielewski et al., 2008; Keays et al., 2007; Myer et al., 2006). Despite these successes, an optimal rehabilitation protocol that is capable of restoring pre-injury quadriceps strength has not been identified.

Quadriceps activation failure has been called a limiting factor in joint rehabilitation (Hopkins and Ingersoll, 2000), which has led researchers to suggest that this is an important underlying

factor that contributes to strength deficits and that alterations in neural activity should be addressed before engaging in exercise (Hopkins and Ingersoll, 2000; Hopkins et al., 2002; Palmieri-Smith et al., 2008). It is important to note that traditional rehabilitation has not focused on improving quadriceps activation before muscle strengthening (Hurley et al., 1994). It has been suggested that clinicians should first restore quadriceps activation. Once volitional activation is improved, a more optimal neural environment should allow strength gains to be realized (Hopkins and Ingersoll, 2000; Palmieri-Smith et al., 2008).

The following section will discuss current therapies aimed at removing quadriceps activation failure and then will focus on strengthening approaches aimed at minimizing quadriceps atrophy.

2.9 Therapies targeting QAF

2.9.1 Knee aspiration

In patients with knee effusions, aspiration of fluid from the knee appears to be an effective treatment to improve quadriceps activation (Fahrer et al., 1988; Stokes and Young, 1984). Following meniscectomy, an aspiration of fluid from the knee three to five days post-surgery has been found to reduce quadriceps activation failure (Stokes and Young, 1984). The aspiration of fluid in individuals with chronic knee inflammation has also been reported to improve quadriceps EMG and strength (Fahrer et al., 1988). Thus, aspirating post-operative knee effusions appears to be a good method of improving quadriceps activation and strength. Importantly, no current data exists documenting the effectiveness of knee aspiration post-ACL reconstruction to improve quadriceps function.

2.9.2 Anesthetics

Local anesthetics have been used to reduce the afferent impulses arising from the knee joint in an attempt to improve activation by means of reducing pain in patients with knee OA (Fahrer et al., 1988; Hassan et al., 2002), meniscectomy (Shakespeare, 1985), and following ACL reconstruction (Arvidsson et al., 1986). The injection of lidocane directly into the knee joint has

been shown to improve quadriceps strength in patients with knee OA (Hassan et al., 2002) and has been found to improve quadriceps EMG activity when lidocane is administered through epidural following ACL reconstruction (Arvidsson et al., 1986). However, in clinical practice the therapeutic benefit of this treatment needs to be weighed as local anesthetics produce a short therapeutic effect and are invasive. Hence, the application of topical analgesics may be a better alternative to local anesthetics, though the effectiveness of topical anesthetics on quadriceps activation has not been established.

2.9.3 Cryotherapy

In addition to reducing pain and inflammation, cryotherapy may also temporarily improve quadriceps activation. The application of cold to the knee is thought to reduce quadriceps inhibition by slowing the rate of afferent information arising to the central nervous system (Hopkins and Ingersoll, 2000). The benefits of cryotherapy have been investigated by Hart and colleagues (2012) where ACL deficient individuals were randomly allocated into three groups: 1) exercise with trancutaneous electrical nerve stimulation (TENS), 2) 20 minutes of cryotherapy pre-exercise and 3) exercise alone. Although quadriceps strength and activation improved after two weeks of exercise, there was no significant difference found between the three treatment groups, which suggest that cryotherapy and TENS did not influence changes in quadriceps activation and strength post-ACL injury (Hart et al., 2012). In contrast, Pietrosimone et al. (2009) have reported in patients with tibiofemoral OA that a 20-minute application of ice applied to the knee joint improved quadriceps activation.

Evidence in support of cryotherapy has also been revealed by Hopkins (2002) where the application of ice to the knee joint was capable of reversing a decline in quadriceps alpha motoneuron excitability observed following an experimental joint effusion. This investigator also reported that 30 minutes of cryotherapy was capable of negating reductions in quadriceps peak torque, power and EMG that were caused by the knee joint effusion, and that these effects lasted up to 60 minutes after the ice was removed (Hopkins et al., 2002). In a separate study, Hopkins (2006) noted that cryotherapy is also capable of negating alterations in

movement observed after knee joint effusion. Collectively, these studies suggest that cryotherapy may be a good method of improving quadriceps activation and may also help to minimize functional deficits. However, it should be noted that the results derived from the Hopkins studies (2006; 2002) were observed in knee effusion models. Thus, it remains unknown how these results apply to actual injury, where in addition to knee effusion, pain and inflammation are also present.

2.9.4 Trancutaneous electrical nerve stimulation

Trancutaneous electrical nerve stimulation (TENS) is a therapeutic modality that works by stimulating cutaneous nerves that send excitatory afferent stimuli to the spinal cord (Pietrosimone et al., 2008). These afferent stimuli are thought to override the inhibitory signals that arise from an injured or distended joint (Hart et al., 2012; Hopkins et al., 2002). Researchers have suggested that TENS may work through several different mechanisms to improve quadriceps activation (Hopkins et al., 2002). More specifically, it has been suggested that TENS may cause an inhibition of the Ib inhibitory interneurons (Hopkins et al., 2002), which are responsible for mediating the activity of the homologous muscle motoneuron pool, and may also reduce pre-synaptic inhibition (Iles, 1996). As such, TENS may be a helpful modality used post-ACL reconstruction.

The effectiveness of TENS has been investigated in patients that are ACL deficient (Hart et al., 2012), ACL reconstructed (Arvidsson and Eriksson, 1986), and in patients with tibiofemoral OA (Pietrosimone et al., 2009; Pietrosimone et al., 2006). In ACL reconstructed individuals, small to marginal improvements in quadriceps muscle activity were found after the administration of high-intensity TENS (Arvidsson and Eriksson, 1986). Similarly, in patients with tibiofemoral OA, Pietrosimone et al. (2009) found that a single 45-minute treatment of TENS significantly improved quadriceps activation. Despite these noted improvements, Hart et al. (2012) found that TENS did not significantly improve quadriceps activation and strength better than exercise or application of cryotherapy post-ACL injury. Further, earlier work by Pietrosimone and colleagues (2006) found that TENS and quadriceps strengthening did not alter sagittal plane

knee mechanics during gait in participants with tibiofemoral OA. Future investigations are needed to clarify the therapeutic effectiveness of TENS following ACL reconstruction.

The effects of TENS have also been studied by Hopkins (2002) using knee effusion models. The investigator reported that during the 30-minute treatment of TENS post-effusion, quadriceps alpha motoneuron excitability returned to baseline levels. When the TENS was removed, quadriceps inhibition returned . Interestingly, in the same experiment, cryotherapy was found to be a more effective disinhibitory modality than TENS at all times points post-knee effusion (Hopkins et al., 2002).

2.9.5 Neuromuscular Electrical Stimulation

In contrast to the therapies that are aimed at improving alterations in spinal reflexive pathways, neuromuscular electrical stimulation (NMES) is a clinical modality that "overrides" muscle activation failure by directly stimulating the inhibited alpha motorneurons, resulting in an involuntary contraction of the inhibited muscle. Because NMES exogenously stimulates the muscle, large diameter, Type II muscle fibers are thought to be selectively recruited (Lake, 1992). This results in a greater potential for muscle force production, as Type II muscle fibers are utilized to produce higher force (Binder-Macleod et al., 1995; Trimble and Enoka, 1991). In addition, NMES has been thought to limit muscle atrophy (Stevens et al., 2004).

In ACL reconstructed individuals, NMES has been found to be more effective than exercise alone at improving quadriceps activation (Kim et al., 2010; Palmieri-Smith et al., 2008). Specifically, Snyder-Mackler and colleagues (1991) reported that four weeks of exercise (initiated during the third postoperative week) combined with NMES treatments delivered at the patient's maximal tolerance level resulted in quadriceps strength that averaged 70% of the uninvolved side as compared to 47% in the group treated with volitional exercise-only. Consistent with these findings, Delitto et al. (1988) Wigerstad-Lossing et al. (1988) and Fitzgerald et al. (2003) have all reported that NMES in combination with exercise results in greater quadriceps strength than exercise alone at approximately six to 12 weeks post-ACL reconstruction.

Conversely, beneficial results following NMES treatments are not homogenous in the literature. Sisk et al. (1987) Draper et al. (1991) and Paternostro-Sluga et al. (1999) have reported that NMES does not provide any additional benefit to quadriceps strength than traditional exercise. However, these articles self-report methodological flaws, such as high pre-operative strength in the treatment groups and variability in NMES parameters utilized across trials (Paternostro-Sluga et al., 1999). Although there is contradicting evidence in the literature regarding the benefits of NMES, the majority of published data, as well as recent systematic reviews (Bax et al., 2005; Kim et al., 2010; Wright et al., 2008) recommend NMES in conjunction with exercise as an intervention to successfully target strength deficits following ACL reconstruction.

Despite the fact that NMES appears to positively influence quadriceps function immediately following ACL reconstruction, the lasting effectiveness of NMES is not known. In patients following total knee arthroplasty, Stevens et al. (2004) demonstrated that high-intensity NMES is capable of immediately improving quadriceps strength and activation, and that these strength and activation gains lasted for up to six months post-surgery. Hence, in order to determine the lasting effectiveness of NMES, more work is needed that tracks ACL reconstructed patients longitudinally, similar to the data gathered by Stevens and colleagues (2004).

In addition to improving quadriceps strength and activation, NMES can also positively influence movement (Fitzgerald et al., 2003; Snyder-Mackler et al., 1991) and patient self-reported function (Fitzgerald et al., 2003). Snyder-Mackler and colleagues (1991) have reported that patients that received high-intensity NMES displayed more normal knee flexion-excursions during walking, and walked with a faster cadence and more velocity as compared to an exercise-only group. Similarly, Fitzgerald and colleagues (2003) found that a greater proportion of patients that received NMES in conjunction with exercise were capable of progressing to agility training at 16 weeks post-reconstruction than the exercise-alone group and had higher self-reported function. The results from these studies (Fitzgerald et al., 2003; Snyder-Mackler et al., 1991) suggest that in addition to improving quadriceps strength and activation, NMES may

also be capable of improving movement and self-reported function following ACL reconstruction.

A recent systematic review of NMES on quadriceps strength has identified the most successful NMES treatment parameters following ACL reconstruction (Kim et al., 2010). Based on the data gathered from eight randomized controlled trials, authors concluded that NMES delivered at the patient's maximal tolerance level with phase durations between 300-400 microseconds is the most beneficial. Further, duty cycles with the longest 'off' times (between 10-15 seconds on, 50 seconds off) demonstrated the strongest effect sizes, despite the fact that these interventions where the shortest in treatment duration (4-6 weeks, total of 12-15 NMES treatment sessions).(Kim et al., 2010) Additionally, NMES delivered with the knee in mid-range flexion (near 60° of flexion) is more effective than NMES delivered with the knee in full extension (Fitzgerald et al., 2003; Snyder-Mackler et al., 1994b; Snyder-Mackler et al., 1991). One of the shortcomings of current NMES protocols is that the majority of studies utilize stimulus intensity reported as "maximal tolerable intensity". Data gathered by Snyder-Mackler et al. (1994b) suggests that at minimum to achieve benefits in quadriceps function, the threshold for treatment intensity needs to be set at 10% of the patient's contralateral quadriceps strength. The intensity of NMES treatments that produce the most beneficial outcomes remains unknown.

In summary, NMES appears to be a promising intervention to improve quadriceps function post-ACL reconstruction. Additionally, improvements achieved via NMES also appear to translate into improved movement and functional outcomes.

2.9.6 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a therapy capable of stimulating areas on the primary motor cortex that cause an excitatory contraction in the periphery (Rossini, 1994). Specifically, TMS uses a powerful handheld magnet that is capable of creating magnetic fields that depolarize superficial neurons, which in turn, create electrical current in the brain (George et al., 2003). In patients approximately two weeks post-total knee arthroplasty, Urbach and

colleagues (2005) have found that TMS improves quadriceps activation when it is applied during a maximal voluntary isometric contraction. These investigators have also noted that a trend towards improvements in quadriceps activation and peak torque persisted up to 60 minutes following the delivery of three single pulses of TMS (Urbach et al., 2005). Based on these results, some authors have recommend that TMS may help to reduce quadriceps dysfunction in patients suffering from knee joint injury (Pietrosimone et al., 2012). Importantly, the therapeutic effects of TMS have not been investigated in an ACL population.

2.9.7 Biofeedback

Biofeedback is a clinical modality that works by providing the patient with a sensory or motor stimuli while they are performing volitional muscle contractions in an attempt to help encourage a greater awareness of volitional muscle control (Levitt et al., 1995; Yilmaz et al., 2010). Researchers hypothesize that biofeedback can improve volitional muscle control by enhancing motor unit recruitment (Croce, 1986) as well as optimizing firing rates of cortically generated mechanisms (Levitt et al., 1995; Lucca and Recchiuti, 1983).

In terms of knee rehabilitation, EMG biofeedback is the most common (Draper, 1990; Draper and Ballard, 1991; Dursun et al., 2001; Levitt et al., 1995). Other forms of biofeedback include verbal, pressure and positional feedback (Thompson et al., 1999; Wannstedt and Craik, 1978). In patients post-ACL reconstruction, Draper et al. (1990) found that individuals that used EMG biofeedback demonstrated greater quadriceps torque at 12 weeks post-reconstruction as compared to ACL reconstructed patients that did not exercise with biofeedback. In a separate study conducted by Draper and colleagues (1991), EMG biofeedback was reported to be more effective at restoring quadriceps strength at six weeks post-ACL reconstruction than electrical stimulation therapy. However, it should be noted that the maximal intensity of the electrical stimulation delivered to the quadriceps muscle in this study was relatively low (50mA) (Draper and Ballard, 1991), thus the training intensity of the electrical stimulation may not have been high enough to induce quadriceps strength gains (Snyder-Mackler et al., 1994b). In addition to these findings, a recent system review reports that EMG biofeedback improves quadriceps

strength better than exercise alone in patients with anterior knee pain and OA (Lepley et al., 2012). Hence, the application of EMG biofeedback may be an effective therapy to improve quadriceps strength post-ACL reconstruction.

2.9.8 Cross-Education

Cross-education is the ability for exercise of one limb to cause an increase in strength of the contralateral unexercised limb (Scripture, 1900) and may be an alternative approach to early eccentric exercise of the involved limb to improve quadriceps activation. Protocols utilizing cross-education have been shown to successfully improve quadriceps strength in the limbs of healthy uninjured subjects (Hortobagyi et al., 1997; Komi et al., 1978; Seger et al., 1998) and in individuals post-ACL reconstruction (Papandreou et al., 2013). Though the exact mechanism of cross-education has yet to be identified, the strength gains that are produced in the unexercised limb are thought to occur as a result of alterations in neural activity (Carr et al., 1994; Zhou, 2000). As alterations in neural activity are believed to contribute to deficits in quadriceps strength following injury, determining whether cross-education causes gains in quadriceps strength by improving volitional muscle activation could help researchers to continue to develop targeted interventions for populations with quadriceps dysfunction.

At present, there is limited evidence to show that gains in quadriceps strength in the unexercised limbs of healthy individuals can be improved through an eccentric exercise protocol (Hortobagyi et al., 1997; Seger et al., 1998) and there is no peer reviewed literature documenting the effectiveness of eccentric exercise on volitional quadriceps muscle activation in the unexercised leg. Though recent evidence has shown that eccentric exercise improves quadriceps muscle activity (Brasileiro et al., 2011) and strength (Papandreou et al., 2013) in the ACL reconstructed limb and contralateral limb, respectively, the mechanism(s) leading to these gains are not well understood. Based on the current literature, it seems plausible that eccentric cross-education may cause neuromuscular improvements in the unexercised knee that led to strength gains. Understanding if greater quadriceps strength can be achieved through improvements in activation with an eccentric cross-education protocol, can help to identify

alterative rehabilitation protocols for populations where eccentric exercise with the injured limb is contraindicated (e.g. meniscal injury/repair, acute quadriceps injury, ACL, total knee arthroplasty).

2.10 Therapies targeting muscle atrophy

2.10.1 Open Kinetic Chain versus Closed Kinetic Chain Exercise

The primary concern following ACL reconstruction is to protect the healing graft while inducing progressive strength gains. Given that the ACL is the primary restraint to anterior tibial translation, exercises that induce anterior shear forces can be harmful to the healing graft. For this reason it has been suggested that closed kinetic chain (CKC [i.e. weight-bearing]) exercises are safer than open kinetic chain (OKC [i.e. non-weight bearing]) exercises, because CKC exercises are thought to decrease the likelihood of harmful stresses being placed on the reconstructed knee. Specifically, OKC exercises have been proposed to increase the anterior shear forces at the knee to a greater extent than CKC exercises (Bynum et al., 1995; Henning et al., 1985). Due to the potential for injury, clinicians often wait to incorporate OKC exercises until the late phases of ACL rehabilitation (~3 to 4 months post-reconstruction). While the clinical rationale for waiting to incorporate OKC is reasonable, OKC may help to strengthening the weak quadriceps muscle beyond that of CKC exercises. Studies have shown that the incorporation of OKC quadriceps exercises can led to significantly greater quadriceps strength when combined with CKC exercises in ACL reconstructed individuals (Mikkelsen et al., 2000) and when compared to strengthening with CKC exercises-only in ACL deficient individuals (Tagesson et al., 2008). Further, Perry and colleagues (2005) have shown that the initiation of OKC chain exercise at eight weeks post-ACL reconstruction did not induce greater knee laxity. Moreover, Beynnon et al. (1997) found that ACL strain measured via a differential variable reluctance transducer in patients post-arthroscopic surgery was similar during active OKC and CKC exercises. In addition, a recent review of the literature reports that although non-invasive biomechanical measures indicate that OKC and CKC produce different strains on the ACL, they are likely not clinically significant (Fleming et al., 2005). In spite of these findings, other

investigators have found that OKC exercises do increase anterior knee laxity (Bynum et al., 1995), and that there is no clinical difference in quadriceps strength gains achieved with OKC as compared to CKC exercises (Lobb et al., 2012).

Due to the inconsistency in the literature, the incorporation of OKC exercises into clinical practice should be utilized with caution until more evidence on the safety and effectiveness of OKC exercise becomes available.

2.10.2 Eccentric Exercise versus Concentric Exercise

A muscle's force producing capacity is most optimal when an external force exceeds that of the muscle while the muscle lengthens (LaStayo et al., 2003). As such, the potential to improve muscle strength by overloading the tissue is greater with eccentric strengthening than with concentric strengthening (Enoka, 1996; LaStayo et al., 2003). Traditionally the application of early post-operative high-intensity eccentric resistance training to the ACL reconstructed limb has been contraindicated, as there is potential for injury to the ACL graft, articular cartilage, or surrounding soft tissue structures (Wilk et al., 2003). However, recent evidence suggests that the application of early progressive, high-force eccentric resistance exercises to the involved limb can be used to safely increase muscle volume (Brasileiro et al., 2011; Gerber et al., 2007a, 2009), strength (Gerber et al., 2007b, 2009), muscle activity (Brasileiro et al., 2011), and functional performance (Coury et al., 2006; Gerber et al., 2007a) in ACL reconstructed individuals. As a result, eccentric strengthening may be an attractive alternative to traditional concentric strengthening to improve quadriceps strength post-ACL reconstruction (Lepley and Palmieri-Smith, 2013).

Gerber and colleagues (2007b, 2009) have directly compared the effects of early post-operative eccentric strength training on quadriceps strength to concentric strength training. Their studies have shown that eccentric strength training produces greater quadriceps strength immediately following ACL reconstruction (Gerber et al., 2007b), and up to one-year post surgery (Gerber et al., 2009). Eccentric strengthening programs initiated approximately nine months post-reconstruction also seem to positively influence quadriceps strength (Brasileiro et al., 2011;

Coury et al., 2006). Brasilerio and colleagues (2011) have reported that significant improvements in quadriceps strength can occur following six weeks of eccentric exercise while Coury et al. (2006) have found significant improvements in quadriceps strength after 12 weeks of eccentric exercises.

In addition to positively influencing quadriceps strength, eccentric exercise has been found to increase quadriceps muscle volume (Brasileiro et al., 2011; Gerber et al., 2007a, 2009), quadriceps muscle activity (Brasileiro et al., 2011) and functional performance (Coury et al., 2006; Gerber et al., 2007a). Gerber and colleagues have reported that eccentric exercise results in a 23% increase in quadriceps muscle volume following a 12-week intervention (2007a) and is capable of increasing quadriceps muscle volume by more than 50% at one year post-ACL reconstruction (2009). Similarly, Brasileiro et al. (2011) found significant improvements in quadriceps muscle volume after only six weeks of eccentric exercise. These investigators also noted a strong correlation existed between improvements in quadriceps muscle volume and gains in quadriceps strength and EMG activity (Brasileiro et al., 2011). In addition, improvements in quadriceps strength achieved via eccentric exercise also appear to positively influence knee function. Coury et al. (2006) found a significant increase in knee flexion angles during walking following an eccentric intervention, where knee flexion angles improved from 51° at baseline to 58° post-intervention. Further, Gerber et al. (2007a) have shown that hop distance was significantly better in the eccentric exercise group as compared to the control group. Collectively, these results suggest that in addition to positively influence quadriceps muscle strength, eccentric exercise is also capable of improving quadriceps muscle mass, activity and functional performance.

The devices utilized to deliver the eccentric interventions, the time interval between ACL reconstruction to initiation of eccentric exercise, and the intensity of training are all important protocol considerations that vary across the literature. Interventions that have utilized an isokinetic dynamometer have initiated treatment approximately nine months post-ACL reconstruction (Brasileiro et al., 2011; Coury et al., 2006), likely due to the OKC nature of the device. In contrast, interventions that have utilized an eccentric ergometer have initiated

treatment just three weeks post-ACL reconstruction (Gerber et al., 2007a, b, 2009). Further, there is a lack of consensus regarding the intensity of the eccentric strengthening necessary to elicit strength gains. Gerber and colleagues have utilized the Borg Rating of Perceived Exertion Scale to grade intensity (Noble et al., 1983), where subjects were allowed to gradually progress to a "hard" intensity over the course of a 12 week intervention (2007a, b, 2009). Other studies have utilized an isokinetic dynamometer where participants used maximal effort while performing three sets of ten eccentric contractions at 30°/second twice a week for 12 weeks (Brasileiro et al., 2011; Coury et al., 2006). Future investigations will need to consider tracking the dose-response of eccentric exercise on quadriceps strength to allow for more discrete clinical recommendations.

2.11 Summary of literature review

Quadriceps strength deficits are common following ACL injury and reconstruction and affect knee mechanics. Quadriceps activation failure is a mechanism of quadriceps weakness that may be dictated by spinal reflexive or cortical pathways that ultimately results in muscle inhibition that negatively impairs the recovery of quadriceps strength. Quadriceps weakness may also be the result of muscle atrophy, which may be caused alterations in muscle architecture and possibly reduce neural input following injury. Traditional ACL rehabilitation approaches do not adequately improve quadriceps muscle strength. Inability to restore pre-injury quadriceps strength affects short-term goals such as a safe return to sport, and may also contribute to the high incidence of post-traumatic OA following ACL injury and reconstruction. As such, the best approach to optimizing quadriceps strength may be to combine interventions that have been shown to improve quadriceps activation failure as well as those that minimize muscle atrophy.

Chapter 3. Effect of Eccentric Exercise on Cross-Education Strength and Activation

A manuscript based on the research presented in this chapter has been accepted for publication:

Lepley LK, Palmieri-Smith RM (In press). Journal of Athletic Training

3.1 Abstract

Context: Following injury, eccentric exercise of the injured limb is often contraindicated. Cross-education training, whereby the uninvolved limb is exercised, is an alternative that may improve quadriceps strength and activation in the unexercised limb. **Objective:** Determine the effect of eccentric exercise on quadriceps strength and activation gains in the unexercised limb. **Patients or Other Participants:** Eighteen healthy individuals were randomly assigned to an eccentric training (EX) or a control (CNTRL) group. **Intervention(s):** Quadriceps strength and activation measures were collected at pre-, mid- and post-intervention. EX participants exercised their dominant limb with a dynamometer in eccentric mode at 60°/sec, three times per week for eight weeks. **Main Outcome Measure(s):** Quadriceps strength was quantified at 30 and 60°/sec in concentric and eccentric modes. Quadriceps activation was assessed using the burst superimposition technique and quantified via the central activation ratio. 2x3 repeated measures ANOVA was used to detect the effects of group and testing session on quadriceps strength and activation. Where appropriate, *post hoc* Bonferroni multiple comparison procedures were used. **Results:** Greater eccentric strength was found in the unexercised limbs of EX participants between pre-to-mid and pre-to-post intervention (Pre-to-

Mid: 30°/sec P=0.05; Pre-to-Post: 30°/sec P=0.02; 60°/sec P=0.02). No differences were noted in concentric strength (P>0.05). An overall trend towards greater quadriceps activation in the unexercised knee was detected between pre-to-post intervention (P=0.063) with the EX group demonstrating a strong effect (Cohen's *d*= 0.83). CNTRL strength did not change (P>0.05). **Conclusions:** Exercising with eccentric actions resulted in mode and velocity specific gains in quadriceps strength in the unexercised limb. A trend towards greater quadriceps activation in the unexercised knee was detected suggesting that strength gains may have occurred due to enhanced neural activity. Rehabilitation programs may be able to utilize this type of therapy to improve quadriceps strength. **Key words:** cross-education training, knee, quadriceps, rehabilitation

3.2 Introduction

The quadriceps muscle group plays a pivotal role in dynamic stabilization of the knee joint. Consequently, following injury, the restoration of quadriceps function is often central to any knee rehabilitation protocol. However, despite the best efforts of clinicians and researchers to improve rehabilitative techniques quadriceps weakness often persists long after rehabilitation concludes (McLeod et al., 2012; Meier et al., 2008; Palmieri-Smith et al., 2008). Given the importance of the quadriceps muscle to knee joint health, it is critical that rehabilitation approaches that are capable of maximizing post-operative quadriceps function are identified.

It has been well established that the potential to improve muscle strength by overloading the tissue is greater with eccentric strengthening than with concentric strengthening (Enoka, 1996; LaStayo et al., 2003). Yet, the application of early eccentric resistance to the injured and/or surgical limb is often contraindicated, as there is potential for injury to the graft, articular cartilage or surrounding soft tissue structures (Wilk et al., 2003). Although there is some evidence that has recently shown that early eccentric exercise can be employed safely post-anterior cruciate ligament (ACL) reconstruction (Gerber et al., 2007b) the long-term safety and effectiveness of this intervention are unknown. As a result, there is still a clear need to identify a rehabilitative protocol that can be utilized to safely overload the quadriceps muscle early to induce strength.

Cross-education training of the uninvolved limb is an alternative to early eccentric exercise of the involved limb that could potentially improve quadriceps function post-knee injury. Cross-education is the ability for exercise of one limb to cause an increase in strength of the contralateral unexercised limb (Scripture, 1900). Protocols utilizing cross-education have been shown to successfully improve quadriceps strength in the limbs of healthy uninjured subjects (Hortobagyi et al., 1997; Komi et al., 1978; Seger et al., 1998). Although the exact mechanism of cross education has yet to be identified, the strength gains that are produced in the unexercised limb are thought to occur as a result of alterations in neural activity (Carr et al., 1994; Zhou, 2000). Because deficits in quadriceps strength following injury are hypothesized to occur, in part, because of alterations in quadriceps activation (Hopkins and Ingersoll, 2000) identifying if cross-education training can improve quadriceps activation could help researchers to develop targeted interventions for populations with volitional muscle activation failure.

To date, there is limited evidence to show that gains in quadriceps strength in the unexercised limb of healthy individuals can be improved through an eccentric exercise protocol (Hortobagyi et al., 1997; Seger et al., 1998) and we are unaware of any evidence that documents the effectiveness of a single-legged eccentric exercise protocol on volitional quadriceps muscle activation in the unexercised leg. Recent evidence has shown that eccentric exercise in the ACL limb at nine months post-reconstruction improves quadriceps muscle activity (Brasileiro et al., 2011) warranting further questioning as to whether or not eccentric training results in neuromuscular gains of the unexercised limb following cross-education training. Further, if greater quadriceps strength and muscle activation can be achieved with an eccentric training protocol in the unexercised limb of healthy individuals, future investigations may be able to incorporate this training protocol to populations where eccentric exercise may be contraindicated in the injured limb (e.g. meniscal injury/repair, acute quadriceps injury, ACL, total knee arthroplasty). Therefore, the primary purpose of this study was to determine the cross-education benefits of a single-legged eccentric exercise program on quadriceps muscle strength and activation of the unexercised limb in a healthy population. A secondary objective was to determine the dose of eccentric exercise necessary to elicit quadriceps strength and activation gains in the unexercised knee quadriceps.

3.3 Methods

Pilot Data

To ensure exposure to the equipment and testing protocol did not cause a learning-effect, three subjects that met study inclusion and exclusion criteria underwent pilot testing on the non-dominant limb. Pilot subjects participated in eight testing sessions in which quadriceps strength and activation was assessed in the non-dominant limb. No change in quadriceps strength or activation was detected ($P>0.05$, Appendix A). This pilot data ensured that if a change in quadriceps strength and activation occurred during the experiment, it would be due to the effects of cross-education and not a learning effect.

Subjects

Eighteen healthy individuals were randomly assigned into one of two groups, an eccentric training group (EX) and a control (CNTRL) group. No significant differences in subject demographics and activity levels existed between groups prior to enrollment (Table 3.1). Potential subjects were excluded if they: had a previous history of knee surgery, suffered a lower extremity injury within the past six months, were currently suffering from knee pain or had a known heart condition. Pregnant females were also excluded. Written informed consent was obtained for all subjects prior to testing.

Table 3.1 Participant Demographics (mean±SD)

Group	Participants	Sex	Age (yrs)	Height (m)	Mass (kg)	Pre-intervention Activity Level	
						Tegner	Marx
EX	N=9	4F/5M	23.3±2.4	1.73±0.1	70.6±14.3	5.67±1.1	8.89±3.9
CNTRL	N=9	6F/3M	22.6±3.6	1.72±0.1	66.9±10.0	6.11±1.1	7.67±3.4

Abbreviations: CNTRL, control group; EX, eccentric group

Testing protocol

All participants were required to report for testing on three occasions over the duration of the eight-week intervention (pre-intervention, mid-intervention, post-intervention). At each testing session, measurements of quadriceps strength and activation were recorded in the dominant and non-dominant limb. The dominant limb was determined to be the leg that would be used to kick a soccer ball (Jacobs et al., 2005). Participants in the EX group also had quadriceps strength and activation measured in the non-dominant/unexercised limb once a week, following the last training session of that week.

Training protocol

Subjects that were randomized into the EX group were required to report for three training sessions per week, for a total of 24 training sessions. Participants began each training session by performing a warm-up series of ten concentric isokinetic knee actions in an isokinetic dynamometer (HUMAC NORM, Computer Sports Medicine, Inc., Stoughton, MA, USA) with the dominant limb at 60 deg/sec. Following the warm-up trial, all EX subjects performed four sets of ten maximal eccentric isokinetic actions of the dominant limb at 60 deg/sec. Repetitions were continuous and sets were separated by a rest of two minutes. Participants performed all actions through approximately 90° of knee flexion. The other, non-dominant/unexercised limb, hung freely during training.

Quadriceps Strength Measurements

In order to assess quadriceps strength, participants were positioned with their hips flexed to 90°, their back supported, and their testing leg and torso strapped securely in an isokinetic dynamometer. Participants were asked to perform three concentric knee actions at a speed of 30 deg/sec to serve as a warm-up and to familiarize participants with the testing procedure. Following the warm-up, each participant performed three maximal concentric and eccentric trials at 30 and 60 deg/sec with two-minutes of rest between each trial. The order in which limbs were tested was counterbalanced. The average torque across the three trials was normalized to body weight (Nm/kg) and used for statistical analysis.

Quadriceps Activation Measurements

Quadriceps activation was quantified using the central activation ratio assessed via the superimposed burst (SIB) technique (Snyder-Mackler et al., 1994a). SIB testing was initiated by asking subjects to perform maximal voluntary isometric knee extension contractions (MVICs), while their hip and testing knee were flexed to 90° and with two minutes of rest between each trial. There was no limit to the number of MVIC trials a subject could perform, but contractions were ceased when an improvement in torque was no longer evident. This procedure helped to ensure that each participant's maximum voluntary contraction was achieved and has been used by others (Palmieri-Smith et al., 2010). Verbal encouragement and visual feedback of the real-time torque output were provided to help facilitate maximal effort. Once the maximal knee extension torque output was achieved, subjects were asked to perform an additional MVIC and maintain this contraction for approximately five seconds. A custom written LabVIEW (LabVIEW version 8.5, National Instruments, Austin, TX, USA) program was set to deliver a supramaximal electrical stimulus to the quadriceps (100 pulses per second, 600 microsecond pulse duration, 100 millisecond train duration, and 130 volts) (Palmieri-Smith et al., 2010; Snyder-Mackler et al., 1994a) once the maximal knee extension torque was reached and then subsequently dropped by 1 Nm. The automatic delivery of the stimulus was chosen instead of doing it manually because it has been shown to reduce measurement error by improving stimulus timing (Krishnan et al., 2009). The electrical stimulus provided to participants during the superimposed burst technique was delivered through two self-adhesive stimulating electrodes

(Dura-Stick II [7 x 13cm] Chattanooga Group, Hixson, TN, USA) applied over the vastus lateralis muscle proximally and the vastus medialis distally using a Grass S88 Dual Output Square Pulse Stimulator (S88, Grass Technologies, West Warick, RI, USA) with an SIU8T Transformer Stimulus Isolation Unit (SIU8T, Grass Technologies, West Warick, RI, USA) attached. Volitional activation of the quadriceps was determined using the central activation ratio (CAR) formula (Equation 3.1). Wherein, the subject's peak torque generated immediately prior to the delivery of the stimulus was divided by the peak torque generated as a result of the electrical stimulus (SIB). A CAR of 1.00 was used to represent complete quadriceps activation (Kent-Braun and Le Blanc, 1996). The average CAR across three trials was used for statistical analysis.

Equation 3.1 Central Activation Ratio

$$\text{Central Activation Ratio} = \left(\frac{\text{MVIC}}{\text{MVIC} + \text{superimposed burst torque}} \right)$$

Scales to Asses Activity Level

All subjects were encouraged to maintain their normal activity level during study participation. To monitor this, and to ensure activity level did not change over the course of the intervention, subjects in both groups were required to complete the Marx (2001) and Tegner (1985) scales weekly. Subjects that were allocated to the EX group completed the scales during the last training session of each week. Subjects allocated to the CNTRL group were contacted by email weekly and provided an electronic copy of the scales to complete and return to the primary investigator. The Marx (2001) activity scale was selected because it takes into account the frequency of participation and the intensity of the activity. Four separate activities are rated: running, cutting, decelerating and pivoting. Frequency of participation is then classified for each activity, "none," "one time a month," "one time per week," "two to three times per week," and "four or more times per week." The Tegner (1985) activity level scale was selected because it is capable of quantifying activity levels in both sport and work activities into an 10-level gradient. Wherein levels 10-8 account for competitive sport, recreational and competitive sport account for level 7, level 6 represents "other recreational sports", and levels 5-1 combine work and

sport together. All participants rated their level prior to study enrollment and their current level at the end of each week.

Statistical Analysis

To ensure group randomization was successful, participant demographics (sex, age, height and mass) and pre-intervention activity levels were compared between groups using a student's t-test. To determine the magnitude of change in each limb associated with eccentric training, the unexercised/non-dominant knee was compared with the exercised/dominant knee using a 2x2x3 (limb x group x time) repeated measures analysis of variance (ANOVA). To determine the cross-education benefits of a single-legged eccentric exercise program in the unexercised knee, a 2x3 repeated measures ANOVA was utilized to detect the main effects of group and testing session on quadriceps strength and activation measurements. Activity levels were also monitored within the 2x3 repeated measures ANOVA to ensure participant's activity did not change over the course of the intervention. To detect the dose of eccentric exercise necessary to elicit sustained gains in quadriceps strength and activation in the unexercised knee, paired t-tests were utilized within the EX group. Where appropriate, *post hoc* Bonferroni multiple comparison procedures were used. Standardized effect sizes (Cohen's *d* = (pre-intervention – post-intervention)/pooled standard deviation)) and 95 % confident intervals were calculated to assess gains in quadriceps strength and activation in the unexercised and exercised limbs. Effect sizes were interpreted using the guidelines describe by Cohen (1977) with values less than 0.5 interpreted as *weak*; values ranging from 0.5 to 0.79 interpreted as *moderate* and values greater than 0.8 interpreted as *strong*. The α-level was set *a priori* at $P \leq 0.05$. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 19.0 (SPSS, Inc., Chicago, IL, USA).

3.4 Results

Demographics

No significant differences in subject sex (t_{16}=0.918, P=0.372); age (t_{16}=-0.535, P=0.600); height (t_{16}=-0.277, P=0.786); mass (t_{16}=-0.634, P=0.535); or pre-intervention activity levels (Tegner:

t_{16}=0.977, P=0.343; Marx: t_{16}=-0.704, P=0.491) were noted between groups suggesting successful randomization (Table 3.1).

Eccentric Training Compliance

EX subjects were required to participate in a minimum of 90% of the scheduled training session (21 out of 24 scheduled sessions). All EX subjects met the required number of training sessions with the average number of training sessions attended being (mean ± standard deviation) 23.4±0.73.

Activity Levels

All participants were able to maintain their pre-intervention activity level over the course of the intervention (Tegner: $F_{2,32}$=2.118, P=0.137; Marx: $F_{2,32}$=0.130, P=0.879).

Magnitude of Cross-over Effect Quadriceps Strength and Activation

A significant three-way interaction was found for eccentric quadriceps strength at 30 deg/sec ($F_{2,32}$=3.417, P=0.045), wherein the EX group demonstrated greater strength in the exercised limb as compared to the unexercised limb at the mid- ($F_{1,8}$=30.211, P=0.001) and post-intervention time point ($F_{1,8}$=16.186, P=0.004, Table 3.2). No difference in eccentric quadriceps strength at 30 deg/sec was found in the CNTRL group (P>0.05). Additionally, no other significant three-way interactions were identified for eccentric quadriceps strength at 60 deg/sec, concentric strength at 30 and 60 deg/sec or for quadriceps activation (P>0.05).

Quadriceps Strength and Dose Response Unexercised Limb

Benefits of cross-education training were found in the unexercised limb of the EX participants between the pre-to-mid-intervention and pre-to-post-intervention time points. Greater eccentric strength was found within the unexercised limb at 30 deg/sec between the pre-to-mid intervention time point ($F_{1,8}$=5.374, P=0.049, Table 3.2) and at 30 and 60 deg/sec between the pre-to-post intervention testing session (30 deg/sec: $F_{1,8}$=8.218, P=0.021; 60 deg/sec: $F_{1,8}$=8.212, P=0.021, Table 3.2). Gains in eccentric strength at 30 and 60 deg/sec were associated with large effect sizes and confidence intervals that did not cross zero (Table 3.5). No

significant differences were noted in the EX group between the mid-to-post-intervention time point or for concentric strength over the course of the intervention (P>0.05). EX subjects were found to have consistently stronger eccentric quadriceps strength in the unexercised limb, compared to pre-intervention strength, at week five through the end of the eight-week intervention (P=0.029, Table 3.3).

Quadriceps Strength Exercised Limb

Training was found to have a positive effect on eccentric quadriceps strength in the exercised limb for participants in the EX group between the pre-to-mid-intervention and pre-to-post-intervention time points. Specifically, EX subjects demonstrated greater eccentric strength in the exercised limb at 30 and 60 deg/sec (Pre-to-Mid: 30 deg/sec: $F_{1,8}$=13.379, P=0.006; 60 deg/sec: $F_{1,8}$=25.090, P=0.001; Pre-to-Post: 30 deg/sec: $F_{1,8}$=17.230, P=0.003; 60 deg/sec: $F_{1,8}$=19.452, P=0.002, Table 3.2). Large effect sizes and confidence intervals that did not cross zero were associated with gains in eccentric strength at 30 and 60 deg/sec (Table 3.5). No change in quadriceps strength was observed in the CNTRL group (P>0.05, Table 3.2). Additionally, no significant differences were noted in the EX group for concentric strength over the course of the intervention or between the mid-to-post-intervention time points in the exercised limb (P>0.05, Table 3.2).

Quadriceps Activation

An overall trend towards greater quadriceps activation was found in the unexercised limb ($F_{2,32}$=3.022, P=0.063). No difference was detected in the exercised limb ($F_{2,32}$=0.466, P=0.632, Table 3.4).

Table 3.2 Average Isokinetic Torque (Nm/kg) (mean±SD)

Group	Velocity (deg/sec)	Exercised/Dominant Limb			Unexercised/Non-dominant Limb		
		Pre-intervention	Mid-intervention	Post-intervention	Pre-intervention	Mid-intervention	Post-intervention
EX	E 30	2.23±0.5	3.48±1.3[ac]	3.85±1.4[ac]	2.17±0.7	2.82±1.1[a]	3.27±1.3[a]
	C 30	2.08±0.5	2.48±0.7	2.66±0.9	1.85±0.6	2.22±0.8	2.45±0.8
	E 60	2.15±0.6	3.58±1.1[b]	3.86±1.3[a]	2.26±0.7	3.00±1.3	3.31±1.3[a]
	C 60	1.58±0.5	2.18±0.7	2.22±0.9	1.51±0.6	1.93±0.8	2.26±0.8
CNTRL	E 30	2.72±0.7	2.80±0.7	2.98±0.6	2.76±0.6	2.77±0.5	2.58±0.5
	C 30	2.33±0.5	2.39±0.4	2.51±0.5	2.25±0.4	2.22±0.5	2.35±0.5
	E 60	2.76±0.7	2.91±0.6	3.02±0.7	2.91±0.6	2.88±0.5	2.84±0.5
	C 60	1.70±0.4	1.85±0.4	2.10±0.5	1.87±0.5	1.85±0.5	2.06±0.7

Abbreviations: C, concentric; CNTRL, control group; E, eccentric; EX, eccentric group

[a]$P<0.05$, [b]$P\leq0.001$ as compared to pre-intervention

[c]$P<0.05$ as compared to the unexercised limb

Table 3.3 Dose Response- Quadriceps Strength (Nm/kg) Unexercised Limb (mean±SD)

Eccentric Mode	Pre-intervention (Wk0)	Wk1	Wk2	Wk3	Mid-intervention (Wk4)	Wk5	Wk6	Wk7	Post-intervention (Wk8)
30 deg/sec	2.17±0.7	2.28±0.7	2.43±0.8	2.84±1.1	2.82±1.1	3.17±1.2*	3.33±1.4*	3.36±1.2**	3.27±1.3*
60 deg/sec	2.26±0.7	2.55±0.8	2.74±0.7	2.77±0.9	3.00±1.3	3.30±1.3*	3.45±1.4*	3.36±1.2*	3.31±1.3*

*P<0.05, ** P≤0.01

Table 3.4 Quadriceps Activation: Central Activation Ratio (mean±SD)

Group	Exercised/Dominant Limb			Unexercised/Non-dominant Limb		
	Pre-intervention	Mid-intervention	Post-intervention	Pre-intervention	Mid-intervention	Post-intervention
EX	0.91±0.04	0.93±0.05	0.93±0.07	0.92±0.05	0.95±0.01	0.95±0.01
CNTRL	0.95±0.02	0.94±0.03	0.95±0.02	0.93±0.04	0.95±0.02	0.92±0.04

Abbreviations: CNTRL, control group; EX, eccentric group

Table 3.5 Standardized Effect Size Interpretations (Effect Size [95% Confidence Interval])

Group	Exercised Limb					Unexercised Limb				
	Quadriceps Strength (Velocity [deg/sec])				Quadriceps Activation	Quadriceps Strength (Velocity [deg/sec])				Quadriceps Activation
	E 30	C 30	E 60	C 60	CAR	E 30	C 30	E 60	C 60	CAR
EX	1.54 (0.49, 2.59) *strong*	0.80 (-0.16, 1.76) *strong*	1.69 (0.61, 2.77) *strong*	0.88 (-0.09, 1.85) *strong*	0.35 (-0.58, 1.28) *weak*	1.05 (0.07, 2.04) *strong*	0.85 (-0.12, 1.81) *strong*	1.01 (0.03, 1.99) *strong*	1.15 (0.15, 2.15) *strong*	0.83 (-0.13, 1.80) *strong*
CNTRL	0.40 (-0.53, 1.33) *weak*	0.36 (-0.57, 1.29) *weak*	0.37 (-0.56, 1.30) *weak*	0.88 (-0.08, 1.85) *strong*	0.00 (-0.92, 0.92) *weak*	-0.33 (-1.26, 0.60) *weak*	0.22 (-0.71, 1.15) *weak*	-0.13 (-1.05, 0.80) *weak*	0.31 (-0.62, 1.24) *weak*	-0.25 (-1.18, 0.68) *weak*

Abbreviations: CAR, central activation ratio; CNTRL, control group; EX, eccentric group

3.5 Discussion

The primary purpose of this study was to determine if a single-legged eccentric exercise protocol was capable of producing quadriceps strength and activation gains in the unexercised limbs of healthy participants. The greater clinical intent of this research was to determine if this eccentric training regimen could be used in populations with quadriceps strength and activation deficits immediately post-injury (i.e. ACL injury), whereby eccentric exercise with the involved limb would be contraindicated. Our findings indicate that eccentric training leads to gains in eccentric quadriceps strength in the exercised and unexercised limbs of healthy participants. Further, we noted a trend toward greater quadriceps muscle activation in the unexercised limb.

Quadriceps Activation Unexercised Limb

Our results indicate that a single-legged eccentric exercise protocol will improve eccentric quadriceps strength in the unexercised limb, and may also lead to gains in quadriceps activation. Given that the underlying mechanism of cross-education is hypothesized to occur because of alterations in neural activity (Carr et al., 1994; Zhou, 2000), we had anticipated that tracking the CAR of EX participants would provide evidence of a change in neural activity. Although we did not find a statistically significant change in quadriceps activation, an overall trend towards greater quadriceps activation was found (P=0.063; Cohen's *d* = 0.83; 95% CI=-0.13, 1.80, Table 3.5), with the EX group demonstrating higher quadriceps activation in the unexercised limb at the post-intervention time point as compared to pre-intervention and the CNTRL group (Table 3.4). Though the p value is close to p<.05 and the effect size is large it is important to note that the confidence interval around the effect size crosses zero suggesting that the effect or result may not be clinically meaningful. Utilizing electromyographic (EMG) measures as a way to detect changes in neural activity may have provided additional insight, as previous authors have shown an increase in vastus lateralis activity in the unexercised limbs of healthy participants following an eccentric exercise protocol (Hortobagyi et al., 1997). Further, the effects of eccentric training may be larger in patients that are experiencing quadriceps activation failure, such as those who have undergone an ACL reconstruction.

Quadriceps Strength Unexercised Limb

Exercising with eccentric actions resulted in specific eccentric gains in quadriceps strength in the unexercised limb. Previous authors (Hortobagyi et al., 1997; Seger et al., 1998) have found mode-specific gains in quadriceps strength in the unexercised limbs of healthy participants following a single-legged exercise protocol. The transfer of quadriceps strength with concentric and isometric muscle contractions has been well established. More recently, Hortobagyi et al. (1997) and Seger et al. (1998) have demonstrated that greater mode-specific cross-education training benefits occur with eccentric exercise rather than concentric. Hortobagyi et al. (1997) reported eccentric quadriceps strength gains as high as 77% versus 30% with concentric actions at 60 deg/sec. While Seger et al. (1998) found eccentric quadriceps strength gains of 15% versus 10% with concentric actions at 90 deg/sec. Our data showed a similar trend at 30 deg/sec, where EX participants had eccentric quadriceps strength gains of 51% versus 32% with concentric strength. Interestingly at 60 deg/sec, our EX participants demonstrated a greater change in quadriceps strength with concentric actions at a percent increase of 49% versus 46% gain in eccentric strength. However, the overall increase in concentric quadriceps strength at 60 deg/sec over time was not found to be statistically significant (P=0.071) with the mean difference between the pre-to-post-intervention time points demonstrating that there was a small increase in concentric quadriceps strength (mean difference at 60 deg/sec: concentric= 0.75 Nm/kg; eccentric=1.05 Nm/kg). A few important points can be made based on these strength outcomes. First, our data is in agreement with the current literature (Hortobagyi et al., 1997; Seger et al., 1998), with our EX participants demonstrating mode specific eccentric gains in quadriceps strength at both 30 and 60 deg/sec. Second, a trend towards greater concentric quadriceps strength at 60 deg/sec appeared to emerge in our EX group. Given that our EX participants trained at 60 deg/sec, it is possible that velocity-specific gains in quadriceps strength occurred in the unexercised limb. Evidence of cross-education training producing velocity specific gains in quadriceps strength has previously been reported (Hortobagyi et al., 1997; Seger et al., 1998).

Dose-Response Unexercised Limb

In order to provide clinicians with recommendations for the dose of eccentric exercise necessary to elicit gains in quadriceps strength in the unexercised knee, we measured the non-exercised limb at the end of each week. Our results indicate that EX subjects produced consistently stronger eccentric actions, compared to their pre-intervention strength, at week five through the end of the eight-week intervention. Based on these results, we recommend that clinicians implementing a cross-exercise eccentric protocol have participants train three times per week for at least five weeks (Table 3.3). To our knowledge this is the first study to examine the length of eccentric training required to induce strength gains using cross-education exercise. This finding is critical, as understanding the number of training sessions that elicit improvements in the unexercised limb is necessary to appropriately delivering this type of therapy.

Quadriceps Strength Exercised Limb

Similar to the unexercised limb, a mode and speed-specific response to eccentric strength training was also found in the exercised leg of EX participants. The increase in quadriceps torque production in the exercised limb during eccentric actions is similar to the magnitude that has been previously reported in studies with comparable training intensities (3-6 sets of 10-12 repetitions), velocities (60-90 deg/sec) and durations (10-12 weeks) (Higbie et al., 1996; Hortobagyi et al., 1997; Seger et al., 1998). At a velocity of 30 deg/sec, the average torque produce by EX participants increased by approximately 60% with eccentric actions versus 27% with concentric actions. Similar results were also produced at speeds of 60 deg/sec, where EX participants increased their eccentric torque by 80% versus 40% with concentric actions. EX participants produced the greatest strength gains at the training velocity (60 deg/sec), which indicates that quadriceps strength gains in the exercised limb where not only mode, but were also velocity specific, just as we saw with the unexercised limb (Hortobagyi et al., 1997; Seger et al., 1998).

Quadriceps Activation Exercised Limb

No change in quadriceps activation was found in the exercised limb of EX participants. Again, the most reasonable explanation for this is that the lack of detection in neural changes was due

to an inadequate measurement technique (CAR) in a healthy population, with no deficits in voluntary activation at pre-intervention. However, it should be noted that limb differences in the CAR appeared to change over time with little to no change in the exercised limb (P=0.632) versus marginal improvements in the unexercised limb (P=0.063, Table 3.4). Because that relationship between the CAR and strength is curvilinear (Stackhouse et al., 2000), and the greatest strength gains were achieved in the exercised limb, we had expected that improvements in the CAR would be greatest in the exercised limb. It is possible that improvements in the exercised limb CAR were not found because the CAR measurement is taken during an isometric contraction. Due to the fact that the greatest quadriceps strength gains achieved in our EX participants were mode and velocity specific, it is possible that these strength gains did not transfer to the isometric contraction. Hence, EMG may have been a more appropriate measurement technique, as this has previously been shown to detect improvements in quadriceps muscle activity following an eccentric exercise protocol (Hortobagyi et al., 1997).

Magnitude of Cross-over Effect: Quadriceps Strength and Activation

Our results indicate that exercising with eccentric contractions will lead to greater quadriceps strength in the exercised limb as compared to the unexercised limb at 30 deg/sec. Given that muscle adapts when it is stressed, this result in the exercised limb is not surprising. In contrast, no difference in quadriceps strength was detected between the exercised and unexercised limb at 60 deg/sec in eccentric mode. We suspect the lack of difference at 60 deg/sec can be attributed to inadequate statistical power to detect a three-way interaction (1-β=0.325), rather than revealing equivalent strength gains between limbs. When examining our results we noted an 80% change from baseline in the exercised limb as compared with only a 46% change in the unexercised limb, suggesting that the exercise limb may indeed see greater gains at 60 deg/sec. Future work may be necessary to provide additional insight into the magnitude of strength gains that results for each limb following cross-education training.

Limitations

Our study is not without limitations. First, because we didn't measure muscle morphology, we could not detect if changes in quadriceps strength were related to gains in muscle mass. Knowing if quadriceps muscle volume increased following eccentric exercise could have helped to explain if different mechanisms were at work in the exercised versus the unexercised limbs. It seems reasonable to suggest that gains in quadriceps strength in the exercised limb could have been the result of greater muscle mass, while improvements in the unexercised limb's strength where more likely due to neural adaptations. Future investigations, with magnetic resonance imaging capability should consider using this measure. Second, our participants exercised using only isokinetics, which resulted in specific mode and velocity strength gains. It is unclear if isotonic exercise, which requires only basic resistance equipment, is capable of producing the same results. We can only speculate that if our subjects had used isotonic exercise, rather than isokinetic, strength gains would not have been velocity specific. Further, because isokinetic exercise is capable of maximally loading the muscle through the entire range of motion, this type of exercise has been shown to result in greater strength gains than isotonic exercise (Pipes and Wilmore, 1975). Hence, it is possible that smaller strength gains would be achieved with isotonic cross-education training. Thus, our results cannot be generalized to isotonic exercise protocols. Third, calculation of the effect size and confidence interval for the quadriceps activation measure in the unexercised limbs of EX participants revealed a strong effect size with a wide confidence interval that crossed zero. We interpret this to mean that beyond utilizing other measurement techniques such as EMG, a larger sample size may have been able to detect a change in quadriceps activation. It is important to note that our sample size was similar to other investigations examining cross-education training in healthy participants (Hortobagyi et al., 1997; Komi et al., 1978; Seger et al., 1998). Lastly, although this study was not powered to consider sex as an independent variable, it is possible that neural changes could have been influenced by gender. Thus, future work may want to examine if males and females respond differently to a cross-education eccentric training protocol. Future investigations should take all these limitations into consideration.

Clinical Implications

Identifying interventions aimed at safely overloading the quadriceps muscle early after injury is essential to reducing the consequence of persistent quadriceps weakness. Because the long-term safety and effectiveness of early eccentric exercise on the involved limb are unknown, alternative rehabilitative techniques that are capable of improving quadriceps strength are needed. Our results indicate that a five-week single-legged eccentric exercise protocol is capable of successfully improving quadriceps strength in the unexercised limb of healthy individuals and may also produce some modest improvements in quadriceps activation. Based on this investigation, we suggest that populations with quadriceps activation and strength deficits may benefit from cross-education training. Furthermore, it appears indicated to exercise the uninvolved limb three times per week (4 sets of 10 repetitions) for five weeks to realize quadriceps strength gains in the unexercised limb. It is important to note that these exercise recommendations are based on data extrapolated from healthy individuals and future studies will need to be performed with participants post-injury to make recommendations for specific clinical populations.

3.6 Conclusion

This investigation is the first to provide insight into the neuromuscular response of the unexercised quadriceps muscle to eccentric cross-education training using volitional muscle activation testing. In addition, this study is unique because it is the first to determine the dosage of eccentric cross-education training necessary to elicit changes in quadriceps strength of the unexercised limb. Based on the results of our study, we concluded that training with eccentric actions resulted in both mode and speed specific gains in quadriceps strength in the exercised and unexercised limbs of healthy participants. We also found that five-weeks of eccentric cross-exercise lead to consistently stronger eccentric quadriceps strength in the unexercised limb. A trend towards greater volitional quadriceps activation in the unexercised limb was also detected, suggesting that strength gains may have occurred due to enhanced neural activity.

Chapter 4. The Effect of Pre-operative Quadriceps Activation Failure on Post-operative Quadriceps Function

A manuscript based on the research presented in this chapter has been submitted for publication:

> Lepley LK, Palmieri-Smith RM (In review). Scandinavian Journal of Medicine & Science in Sports

4.1 Abstract

Quadriceps activation failure (QAF) is considered to contribute to the weakness that lingers following anterior cruciate ligament (ACL) reconstruction. Importantly, the impact of pre-operative QAF on post-operative quadriceps function is unknown. Accordingly, the purpose of this study was to investigate the relationship between pre-operative QAF and post-operative quadriceps strength and activation. To accomplish this, fifty-four individuals post-ACL injury reported for testing on two occasions: prior-to-surgery and post-surgery once they returned to activity. All participants underwent reconstruction with a patellar-tendon graft, however some experienced concomitant meniscal repair (n=14) or meniscectomy (n=7). Quadriceps activation was assessed using the burst superimposition technique and quantified using the central activation ratio. Quadriceps strength was assessed using the peak knee extension torque produced during isokinetic testing. Multiple linear regressions were utilized to detect the relationships between pre-operative activation and post-operative strength and activation. Concomitant meniscal injury was entered as a covariate in each model. Pre-operative

quadriceps activation was associated with post-operative activation (R^2=0.383,P<0.001), not strength (R^2=0.008,P=0.805). Concomitant meniscus surgery did not affect these relationships (P>0.05). Individuals with better pre-operative quadriceps activation demonstrated greater post-operative activation. Pre-operative QAF was not a predictor of post-operative strength. Pre-operative QAF may be mediated by different factors than post-operative QAF. **Key Terms.** central activation ratio, isokinetic strength, ACL, reconstruction, rehabilitation

4.2 Introduction

The restoration of quadriceps strength following anterior cruciate ligament (ACL) reconstruction is an essential component of rehabilitation. Although clinicians and researchers continue to make strides towards improving ACL rehabilitation protocols, patients often return to activity with diminished quadriceps strength (Palmieri-Smith et al., 2008). Lingering quadriceps weakness is linked to reduced physical function (Lewek et al., 2002; Schmitt et al., 2012) and quality of life (Lohmander et al., 2004), increases the risk of re-injury (Paterno et al., 2010; Schmitt et al., 2012) and contributes to the development and progression of post-traumatic osteoarthritis (Tourville et al., 2014). Given that the failure to restore quadriceps strength has deleterious consequences to the knee, it is critical to develop rehabilitative approaches capable of maximizing quadriceps strength deficits following ACL reconstruction.

Quadriceps activation failure (QAF), the inability to completely contract the quadriceps muscle due to altered neural signaling (Hart et al., 2010; Hopkins and Ingersoll, 2000), has been identified as a mechanism contributing to the lingering strength deficits following ACL reconstruction (Palmieri-Smith and Thomas, 2009). The changes in neural signaling associated with QAF reduce alpha motoneuron recruitment and/or firing rate, allowing only portions of the quadriceps to be volitionally utilized during exercise (Hopkins and Ingersoll, 2000). Clinically, rehabilitation professionals see QAF manifest as quadriceps weakness (Hart et al., 2010). Although QAF is believed to be a protective mechanism following knee injury (Hopkins and Ingersoll, 2000), the inability to achieve complete muscle activation during strength training creates a barrier to successful rehabilitation (Hurley et al., 1994; Rice and McNair, 2010).

Prior investigations have found a link between pre- and post-operative quadriceps strength and function, demonstrating greater isokinetic strength and function pre-operatively leads to better outcomes post-operatively (de Jong et al., 2007; Eitzen et al., 2009; Logerstedt et al., 2013; Shelbourne and Johnson, 2004). Given that QAF is a component of strength (Stackhouse et al., 2000), it seems plausible that better pre-operative quadriceps activation may also contribute to a better recovery of quadriceps strength and function following ACL reconstruction. Understanding the factors that contribute to the best recovery of post-operative quadriceps function can help clinicians and researchers design more effective rehabilitation interventions. Thus, in order to direct care and improve rehabilitative techniques, the primary purpose of this investigation was to determine if pre-operative quadriceps activation is related to post-operative quadriceps activation and strength following ACL reconstruction.

4.3 Materials and Methods

Participants

Fifty-four individuals scheduled for ACL reconstruction with a bone-patellar-tendon-bone graft were invited to participate in this study (Table 4.1). Potential participants were excluded if they: had a previous history of surgery to either knee, suffered a previous ACL injury, or had a known heart condition. Pregnant females were also excluded. Surgical reports were obtained to report any concomitant meniscal damage that required surgical intervention (Table 4.1). Informed consent was obtained from all participants and approved by the University's Institutional Review Board prior to testing.

Table 4.1 Participant Demographics (mean±SD)

Participants	Sex	Age (yrs)	Height (m)	Mass (kg)	Time to Test (months) Pre-operative	Post-operative	Meniscal Surgery
N=54	F=23 M=33	19.9±5.1 (range:14-38)	1.70±0.3	75.9±16.5	2.23±2.1 (range:0.5-10.4)	7.24±1.1 (range:5.2-11.7)	ACL-only=33 Meniscal Repair=14 Meniscectomy=7

Abbreviations: F, female; M, Male

The details of the post-operative rehabilitation protocol can be found in Appendix B. All participants completed standard post-operative rehabilitation at one orthopedic outpatient clinic. The rehabilitation protocol consisted of two to three physical therapy appointments per week beginning during the first post-operative week and concluding approximately six months post-surgery. The program emphasized full knee extension range of motion immediately and knee flexion as tolerated, progression of functional exercises, quadriceps re-education and muscle strengthening. Variation between rehabilitation protocols existed based on concomitant meniscal surgery, age and individual's response to treatment.

Overview of Testing Scheme

All participants were tested on two separate occasions: post-ACL injury but prior to ACL-reconstruction, and post-ACL reconstruction once patients had been cleared by their orthopedic surgeon to return back to activity (Table 4.1). To be cleared for activity all participants were required to complete a basic three-week agility program (Appendix C) and a leg press test. To pass the leg press test, the clinical protocols requires that patients need to complete at least 15 repetitions at 100% of body weight with the involved limb from a resting neutral position to a depth of 90° of knee flexion. If a patient was unable to successfully pass the leg press test or did not complete the agility program their clearance for participation was delayed until both of these criteria were met. At each testing session, QAF was assessed in the ACL injured/reconstructed limb. Measurements of quadriceps strength were also collected in the ACL injured/reconstructed limb and the healthy/uninvolved limb at each testing session.

QAF Measurement

QAF was quantified using the central activation ratio (CAR) assessed via the superimposed burst (SIB) technique (Park and Hopkins, 2013; Snyder-Mackler et al., 1994a). To record the joint torque produced during SIB testing, patients were positioned in an isokinetic dynamometer (Biodex System 3, Biodex Medical Systems, Shirley, NY, USA) with their hips flexed to 90°, their back supported, and their ACL limb and torso strapped securely into the dynamometer. SIB testing was initiated by asking participants to perform a minimum of three maximal voluntary isometric contractions (MVICs), while their ACL limb was flexed to 90° and with two minutes

rest between each trial. There was no limit to the number of MVIC trials a participant could perform, but contractions were ceased when an improvement in torque was no longer evident. This procedure helped to ensure that each participant's MVIC was achieved and has been used by others (Palmieri-Smith et al., 2010). Verbal encouragement and visual feedback of the real-time torque output were also provided to help facilitate maximal effort. Once maximal knee extension torque was achieved, participants were asked to perform an additional MVIC and maintain this contraction for approximately five seconds. A custom written LabVIEW (LabVIEW version 8.5, National Instruments, Austin, TX, USA) program was set to deliver a supramaximal electrical stimulus (100 pulses per second, 600 microsecond pulse duration, 100 millisecond phase duration, and 130 volts) to the quadriceps via a Grass S88 Dual Output Square Pulse Stimulator (S88, Grass Technologies, West Warrick, RI, USA) with an SIU8T Transformer Stimulus Isolation Unit (SIU8T, Grass Technologies, West Warrick, RI, USA) attached. The stimuli were delivered through two self-adhesive electrodes (Dura-Stick II [7x13 cm] Chattanooga Group, Hixson, TN, USA) applied proximally over the vastus lateralis and distally over the vastus medialis once the MVIC was reached and subsequently dropped by one Newton meter (Snyder-Mackler et al., 1994a). Automated stimulus delivery was utilized because it has been shown to improve stimulus timing and thus reduce measurement error (Krishnan et al., 2009). QAF was determined using the CAR formula (Equation 4.1). The participant's peak torque generated immediately prior to the delivery of the electrical stimulus was divided by the peak torque generated as a result of the electrical stimulus (SIB). A CAR of 100 was used to represent complete quadriceps activation or no QAF (Kent-Braun and Le Blanc, 1996). The maximal CAR measurement (i.e. trial that displayed the least amount of QAF) that was collected across three SIB trials was used for statistical analysis.

Equation 4.1 Central Activation Ratio

$$\text{Central Activation Ratio} = \left(\frac{\text{MVIC}}{\text{MVIC} + \text{superimposed burst torque}} \right) * 100$$

Quadriceps Strength Measurements

To assess quadriceps strength, participants were positioned in the isokinetic dynamometer using the same methods described above. To collect isokinetic strength, participants were asked to perform three maximal knee extension actions in concentric mode at a speed of 60°/second. Quadriceps isometric strength was also assessed in the ACL injured/reconstructed limb utilizing the MVIC measurement, which was collected prior to the deliver of the electrical stimulus during SIB testing. The peak torque that was generated during the three-isokinetic and isometric trials was normalized to body mass and used for statistical analysis. Importantly, participants were allocated sufficient rest time between contractions and measures to ensure an accurate assessment of torque.

Statistical Analysis

Sample size was estimated using an a priori power analysis based on previous work examining the ability of pre-operative quadriceps strength to predict post-operative quadriceps strength (McHugh et al., 2002). In order to detect associations with a α-level of 0.05 and the 1-β 0.80, it was determined that 37 participants would be needed for this investigation.

Multiple linear regressions were utilized to asses the relationships between 1&2) pre-operative activation and post-operative isokinetic and isometric strength, 3) pre-operative activation and post-operative activation, 4) pre-operative and post-operative isokinetic strength. Due to inclusion of participants with concomitant meniscus injury and subsequent repair, meniscal surgery was entered as a covariate in each of the regression models to detect if additional surgical procedures had an affect on these relationships. To measure the recovery of quadriceps strength in the ACL limb, the quadriceps index (Lephart et al., 1993) (Equation 4.2) was utilized to quantify isokinetic strength deficits at the pre-and post-operative time point in the ACL limb as compared to the contralateral limb. Paired t-tests were then utilized to detect the difference between pre-and post-operative quadriceps activation, strength and the quadriceps index. The α-level was set a priori at $P \leq 0.05$. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 21.0 (IBM Corp., Armonk, NY, USA).

Equation 4.2 Quadriceps Index

$$\text{Quadriceps Index}=\left(\frac{\text{ACL limb}}{\text{contralateral limb}}\right)*100$$

4.4 Results

Pre-operative Quadriceps Activation and Post-operative Quadriceps Strength

Quadriceps activation prior to ACL reconstruction was not related to post-operative quadriceps isokinetic or isometric strength (Isokinetic: R^2=0.008, P=0.805 [b_{QAF}=0.077, P_{QAF}=0.582, $b_{Meniscus}$=0.051, $P_{Meniscus}$=0.715], Figure 4.1; Isometric: R^2=0.064, P=0.186 [b_{QAF}=0.230, P_{QAF}=0.096, $b_{Meniscus}$=0.110, $P_{Meniscus}$=0.420]).

Pre-operative Quadriceps Activation and Post-operative Quadriceps Activation

Quadriceps activation prior to ACL reconstruction was positively associated with post-operative activation (R^2=0.383, P<0.001 [b_{QAF}=0.612, $P_{QAF}\leq$0.001], Figure 4.2). Concomitant meniscal surgery did not affect this relationship ($b_{Meniscus}$=0.102, $P_{Meniscus}$=0.357). Further, it was found that participants demonstrated greater QAF (smaller CARs) after ACL reconstruction compared to the pre-operative time point (t_{53}=5.283, P≤0.001, Table 4.2).

Pre-operative Quadriceps Strength and Post-operative Quadriceps Strength

Quadriceps strength prior to ACL reconstruction was positively related to post-operative strength (R^2=0.114, P=0.046 [$b_{Strength}$=0.334, $P_{Strength}$=0.014], Figure 4.3). Concomitant meniscal surgery did not affect this relationship ($b_{Meniscus}$=0.056, $P_{Meniscus}$=0.671). It was also found that quadriceps strength and the quadriceps index did not differ between the pre-and post-operative time points (Quadriceps Strength: t_{53}=1.755, P=0.085; Quadriceps Index: t_{53}=-0.131, P=0.896, Table 4.2).

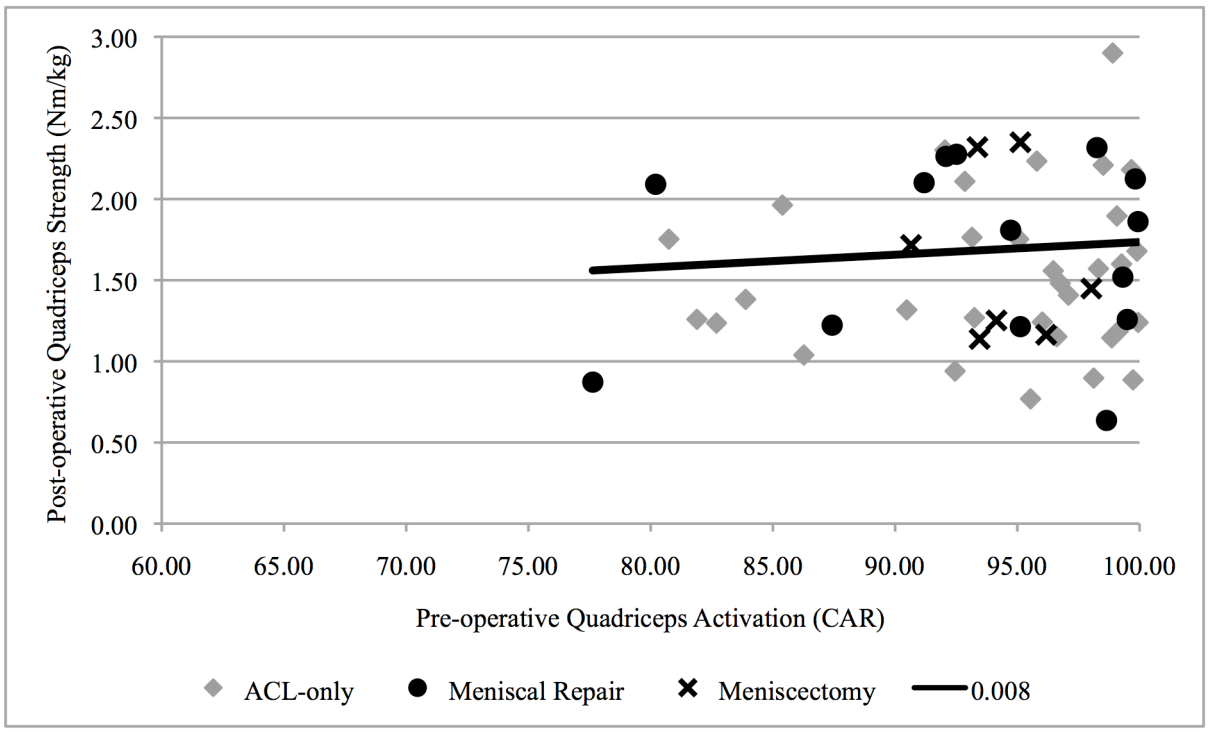


Figure 4.1 Pre-operative quadriceps activation plotted against post-operative isokinetic strength (P=0.805).

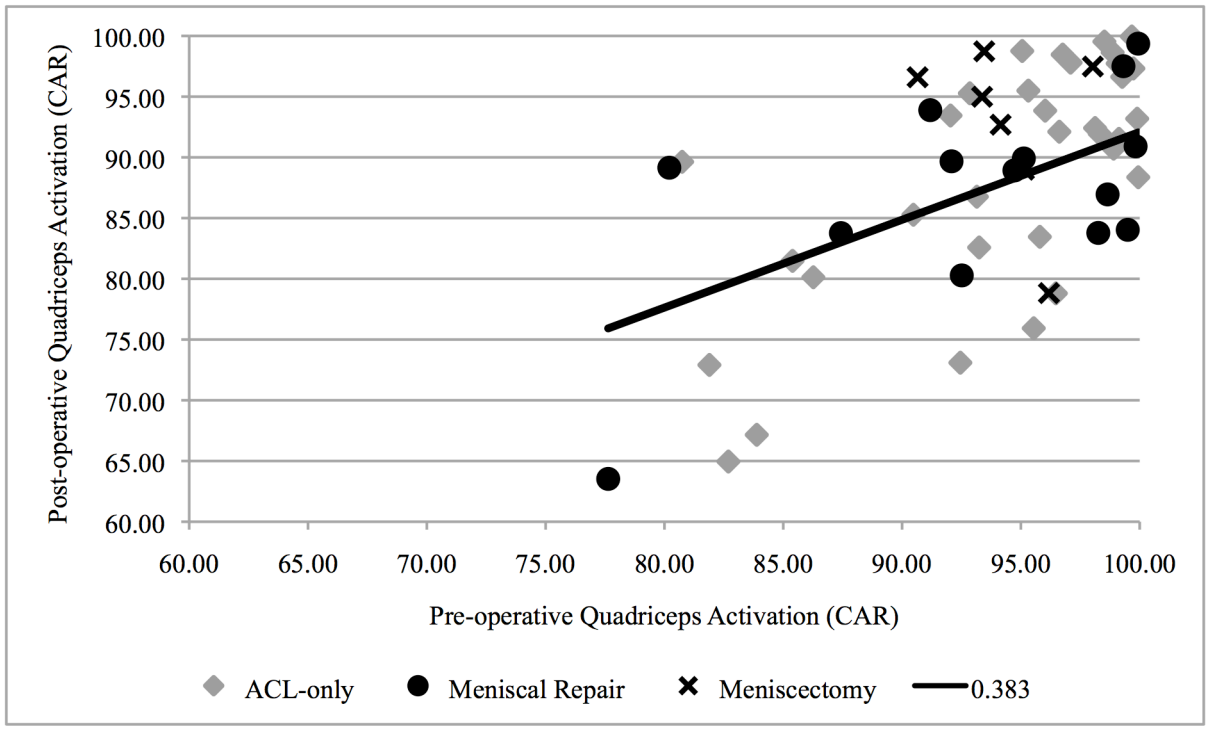


Figure 4.2 Pre-operative quadriceps activation plotted against post-operative quadriceps activation (P≤0.001).

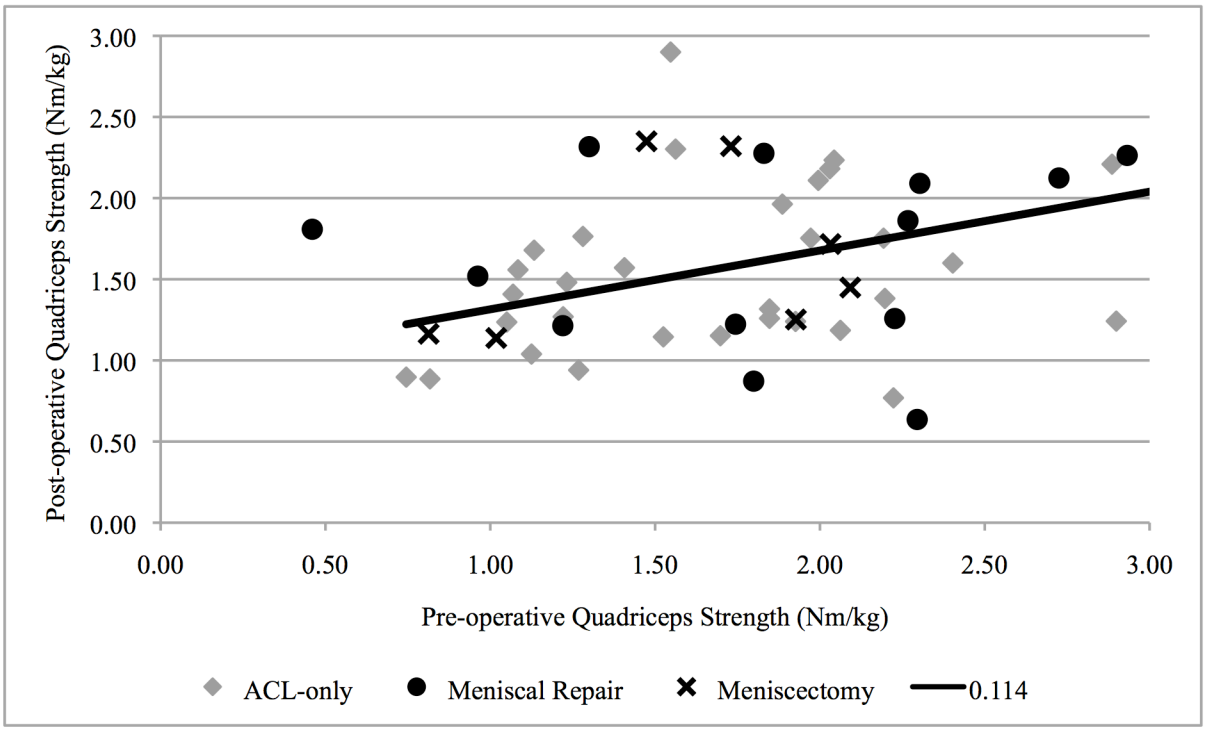


Figure 4.3 Pre-operative quadriceps isokinetic strength plotted against post-operative isokinetic strength (P=0.046).

Table 4.2 Quadriceps Activation, Strength and Index (mean±SD)

Time	Quadriceps Activation (CAR	Quadriceps Strength (Nm/kg)	Quadriceps Index
Pre-operative	94.01±5.8	1.78±0.6	73.64±30.7
Post-operative	88.80±9.1*	1.61±0.5	74.25±23.7

Abbreviations: CAR, central activation ratio
*P≤0.001 as compared to pre-operative activation

4.5 Discussion

The primary purpose of this investigation was to determine the relationship between pre-operative quadriceps QAF and post-operative quadriceps activation and strength following ACL reconstruction. Examining the relationship between these variables could help to advance pre-operative rehabilitation protocols by identifying critical factors responsible for helping to improve the recovery of quadriceps function following ACL reconstruction. It was found that

ACL patients with better pre-operative quadriceps activation and strength recovered quadriceps activation and strength better than those with lower pre-operative quadriceps function. It was also found that quadriceps activation prior to surgery was not related to post-operative strength. Furthermore, concomitant meniscal surgery does not seem to be a factor that influences these relationships.

Relationship between Pre-operative Quadriceps Activation and Post-operative Quadriceps Strength

Our results indicate that pre-operative quadriceps activation is not associated with post-operative strength (Figure 4.1). Thus, it seems pre-operative rehabilitation programs that focus on utilizing interventions to improve QAF may not positively affect post-operative quadriceps strength. Given that previous research had established a relationship between quadriceps activation and strength in healthy (Stackhouse et al., 2000) and ACL injured individuals (Lynch et al., 2012), we had anticipated that pre-operative quadriceps activation would affect the recovery of strength. It is possible that the failure to establish a relationship between pre-operative activation and post-operative strength resulted from a change in mediators of QAF from the pre-operative to post-operative time point. The current literature indicates that several triggers of QAF, such as pain, effusion, or altered afferent input from the damaged ACL, are likely present and contribute in combination to strength deficits following ACL injury and reconstruction (Hart et al., 2010; Palmieri-Smith and Thomas, 2009; Rice and McNair, 2010). Moreover, the central mechanisms that may mediate QAF such as descending cortical inhibition, pre-synaptic inhibition, Ib inhibition, and/or recurrent inhibition may have also varied between the two time points. Hence, it is possible that pre-operative QAF may be triggered and mediated by different factors than post-operative QAF, which may have affected strength differently at each time point and limited the potential relationship between pre-operative QAF and post-operative strength. Further complicating this relationship is the trauma induced by surgical reconstruction of the ligament as well as concomitant injury/subsequent repair, which may increase the magnitude of QAF from the pre- to post-operative time point (Eitzen et al., 2009). Given that our participants demonstrated significantly more QAF post-

operatively compared to pre-operative (Table 4.2), our data supports this theory that surgery may induce a higher level of QAF. Ultimately, it is unknown what triggers and mechanism(s) contribute to QAF in ACL deficient and reconstruction patients and requires further research.

In addition to the potential alterations in mediators of QAF that may have affected this relationship, it is also possible that an association was not identified because QAF and quadriceps strength were collected in different modes (QAF, isometric; strength, isokinetic) on the dynamometer. To test this as a potential cofounding source of error, we also assessed the relationship between pre-operative QAF and post-operative isometric strength. No relationship was found (P=0.186). Furthermore, we recognize that the inclusion of participants with concomitant meniscal surgeries may have affected our results. Thus to account for concomitant meniscal surgery, we included it as a covariate in the analysis, however it was found to be non-significant (Isokinetic: P=0.715, MVIC: P=0.420). Hence, it seems that the difference in mode, as well as concomitant meniscal surgery, did not influence our results.

It is interesting to note that quadriceps strength and the quadriceps index did not significantly differ between the pre- to post-operative time point, despite the fact that our participants demonstrated significantly more QAF after reconstruction than before (Table 4.2). Though previous authors have found QAF and strength to be related post-ACL injury (Lynch et al., 2012), others have found a lack of a relationship between the two following reconstruction (Krishnan and Williams, 2011). Thus, other factors, such as muscle atrophy or possibly alterations in muscle architecture, may have affected post-operative strength. Recent work by Krishnan and Williams (2011) supports the idea that quadriceps atrophy is a major contributor to weakness following ACL reconstruction and found that in individuals 2-15 years post-ACL reconstruction quadriceps atrophy is a more significant contributor than QAF to post-operative strength deficits. Again, similar to our theory about mediators of QAF, it is possible that atrophy may have mediated strength differently at each time point. More research is needed to examine the effects of quadriceps muscle atrophy and QAF at a time point when individuals are returned back to activity post-reconstruction.

Relationship between Pre-operative Quadriceps Activation and Post-operative Quadriceps Activation

Pre-operative quadriceps activation was positively related to post-operative activation (Figure 4.2), however concomitant meniscal surgery was not found to be a factor that significantly affected this relationship. Thus, individuals with better pre-operative quadriceps activation demonstrated greater volitional muscle activation following ACL reconstruction, independent of concomitant meniscal surgery. To our knowledge this is the first study to analyze this relationship. Previous investigations have found that patients with greater pre-operative quadriceps strength have greater strength post-operatively (de Jong et al., 2007; Eitzen et al., 2009; Shelbourne and Johnson, 2004). Therefore, it seems reasonable that voluntary activation of the quadriceps muscle follows this same trend. As quadriceps activation is thought to represent the proportion of the muscle one can contract voluntarily, it could be expected that having a greater portion of the muscle available prior to surgery would be beneficial for the restoration of activation post-surgery. Though our research suggests that pre-operative activation is not related to post-operative muscle strength, previous investigators have shown that alterations in quadriceps EMG activity post-ACL reconstruction are related to gait (Bulgheroni et al., 1997). Thus, it seems that volitional muscle activation post-reconstruction may be an important component of post-operative knee function. The next step for researchers and clinicians is to understand the affect that post-operative quadriceps activation has on functional outcomes such as functional performance and knee mechanics, which is important to developing more effective rehabilitation protocols.

Relationship between Pre-operative Quadriceps Strength and Post-operative Quadriceps Strength

Our results indicate that pre-operative quadriceps strength is positively related to the recovery of post-operative strength, independent of concomitant meniscal surgery (Figure 4.3). This finding is in agreement with previous work by Eitzen et al. (2009), Shelbourne and Johnson (2004), and de Jong et al. (2007). These investigators utilized isokinetic strength measures at 60°/second (de Jong et al., 2007; Eitzen et al., 2009) and 180°/second (de Jong et al., 2007;

Shelbourne and Johnson, 2004) and found that individuals with better pre-operative quadriceps strength demonstrated greater post-operative quadriceps strength (de Jong et al., 2007; Eitzen et al., 2009; Shelbourne and Johnson, 2004), better performance during hoping tasks (de Jong et al., 2007; Eitzen et al., 2009), and higher levels of self-reported function (Eitzen et al., 2009). Thus, individuals with greater strength post-ACL injury, but prior to ACL-reconstruction, may not experience as much early post-operative muscle weakness and may be able to regain strength better in the ACL limb than those with less pre-operative strength. Despite the fact that our patients were capable of regaining their pre-operative strength, it is important to note that the quadriceps index, which is an indicator of the strength of the involved limb as compared to the uninjured limb, suggests that strength deficits still exist to some degree between the ACL reconstructed limb and the contralateral limb at a time when individuals are returned back to sport (Table 4.2). These finding are important given that persistent quadriceps weakness is common following ACL reconstruction (Palmieri-Smith et al., 2008) and negatively influences knee function (Lewek et al., 2002). Hence, finding therapeutic approaches capable of minimizing post-operative strength deficits is necessary. Based on our work and the work of others (de Jong et al., 2007; Eitzen et al., 2009; Shelbourne and Johnson, 2004), we recommend that clinicians focus on maximizing strength before ACL reconstruction to improve the recovery of post-operative quadriceps strength.

4.6 Perspective

Examining the relationship between pre-and post-operative quadriceps strength and activation can help to advance pre-operative rehabilitation protocols by identifying critical factors responsible for helping to improve the recovery of quadriceps function following ACL reconstruction. Based on our results, it is recommended that rehabilitation programs continue to focus on maximizing strength prior to ACL reconstruction to improve the recovery of post-operative quadriceps strength. Furthermore it was found that pre-operative QAF is positively related to post-operative activation. Thus, therapies that target QAF prior to ACL reconstruction should improve the recovery of volitional muscle activation, however the clinical meaningfulness of this result on functional knee outcomes is unknown.

Chapter 5. Combination of Eccentric Exercise and Neuromuscular Electrical Stimulation Intervention Post-ACL Reconstruction, Part I: Recovery of Quadriceps Function

A manuscript based on the research presented in this chapter has been submitted for publication:

> Lepley LK, Wojtys EM, Palmieri-Smith RM (In review). Journal of Orthopedic & Sports Physical Therapy

5.1 Abstract

Study Design: Parallel longitudinal.

Objective: To evaluate the effectiveness of a combined neuromuscular electrical stimulation (NMES) and eccentric exercise intervention to improve the recovery of quadriceps activation and strength following anterior cruciate ligament (ACL) reconstruction.

Background: NMES has been shown to reduce quadriceps activation failure (QAF), and eccentric exercise has been shown to lessen muscle atrophy post-ACL reconstruction. Given that these are two critical components of quadriceps strength, an intervention combining these therapies may be effective at reinstituting quadriceps function.

Methods and Measures: Thirty-six individuals post-ACL injury were placed into four treatment groups (N&E, NMES and eccentrics; E-only, eccentrics only; N-only, NMES-only; STND, standard of care) and ten healthy controls participated. Groups N&E and N-only received the NMES protocol 2x per week for the first six weeks post-reconstruction. Groups N&E and E-only

received the eccentric exercise protocol 2x per week beginning six weeks post-reconstruction. Quadriceps activation was assessed via the superimposed burst technique and quantified via the central activation ratio. Quadriceps strength was assessed via maximal voluntary isomeric contractions (Nm/kg). Data was gathered on three occasions: pre-operative, 12-weeks-post-surgery and at return-to-play.

Results: No differences in pre-operative measures existed ($P>0.05$). E-only recovered quadriceps activation better than N-only or STND ($P<0.05$). N&E and E-only recovered strength better than N-only or the STND ($P<0.05$) and had strength values that were similar to healthy individuals at return-to-play ($P>0.05$).

Conclusion: Eccentric exercise was capable of restoring levels of quadriceps activation and strength that were similar to those of healthy adults and better than NMES alone.

Keys words: ACL, knee, rehabilitation, electrical muscle stimulation, eccentric exercise

5.2 Introduction

Quadriceps weakness is common following anterior cruciate ligament (ACL) reconstruction. Despite aggressive rehabilitation programs directed at improving quadriceps function, a universally effective treatment approach to reverse this muscle weakness has yet to be identified (Palmieri-Smith et al., 2008). Quadriceps weakness that accompanies ACL injury is related to reduced functional performance (Keays et al., 2003; Schmitt et al., 2012), the potential for re-injury (Hurley et al., 1992; Schmitt et al., 2012), and the development of post-traumatic osteoarthritis (Tourville et al., 2014). Given the short-and long-term consequences of quadriceps weakness, it is critical that rehabilitation approaches capable of reinstituting complete quadriceps strength are developed.

Although the precise mechanism(s) of quadriceps weakness are unknown, there is evidence to suggest that quadriceps activation failure (QAF) and muscle atrophy contribute to persistent strength deficits (Palmieri-Smith et al., 2008; Williams et al., 2005a). QAF is the inability to completely volitionally contract the muscle due to alterations in neural signaling (Hopkins and Ingersoll, 2000), and is common following ACL reconstruction (Hart et al., 2010; Ingersoll et al.,

2008). Specifically, these changes in neural signaling are thought to be caused by a reduction in alpha motorneuron recruitment and/or firing rate (Hopkins and Ingersoll, 2000). If left untreated, QAF can significantly impede strength gains (Hurley et al., 1994) by only allowing portions of the muscles to be volitionally utilized during active exercise (Hopkins and Ingersoll, 2000). Quadriceps muscle atrophy that occurs following ACL reconstruction is also thought to contribute to persistent muscle weakness (Krishnan and Williams, 2011; Williams et al., 2005a) due to alterations in muscle architecture (Kawakami et al., 2000; Narici and Cerretelli, 1998), selective fiber atrophy (Edstrom, 1970; Lopresti et al., 1988; Lorentzon et al., 1989), or even neural deficits such as QAF (Palmieri-Smith et al., 2008). Together, QAF and muscle atrophy have been reported to account for approximately 60% of the variance in quadriceps strength post-ACL injury (Williams et al., 2005a). As such, QAF and muscle atrophy are crucial factors to target in order to improve the recovery of quadriceps strength following ACL reconstruction.

Neuromuscular electrical stimulation (NMES) is a clinical modality that has the potential to treat QAF by directly stimulating the inhibited alpha motorneurons, resulting in an involuntary contraction of the muscle (Rice and McNair, 2010). Because NMES exogenously stimulates the muscle, large diameter, Type II muscle fibers are thought to be selectively recruited, resulting in a greater potential for muscle force production (Lake, 1992). Importantly, in ACL reconstructed individuals, NMES has been found to be more effective than exercise alone at improving quadriceps activation (Kim et al., 2010).

Eccentric exercise, whereby the muscle is lengthened and an external force exceeds that produced by the muscle, has been shown to be more effective than traditional concentric strengthening at minimizing muscle atrophy and improving muscle force production (LaStayo et al., 2003). Though the application of early post-operative eccentric resistance exercise to the ACL reconstructed limb has traditionally been contraindicated, as there is potential for injury to the graft, articular cartilage, or surrounding soft tissue structure (Wilk et al., 2003), recent evidence has shown that the application of early eccentrics to the ACL limb can be used to safely increase quadriceps muscle volume (Brasileiro et al., 2011; Gerber et al., 2007a) and strength (Gerber et al., 2007b, 2009).

As NMES and eccentric exercise have been shown to successfully improve two critical components of quadriceps weakness, it seems plausible, that a rehabilitation protocol utilizing both of these therapies will be effective at reinstituting quadriceps strength. Therefore, the goal of the current study was to determine if the combination of NMES and eccentric exercise would be effective at improving quadriceps muscle strength in patients following ACL reconstruction. We hypothesized that the greatest improvements in quadriceps muscle strength would be achieved in patients receiving the combined intervention, when compared to patients receiving either therapy in isolation or the standard of care following ACL reconstruction. Furthermore, we anticipated that improvements in quadriceps activation would be significantly related to gains in quadriceps strength.

5.3 Methods

Participants

Thirty-six individuals scheduled for ACL reconstruction were invited to participate in this study (Table 5.1). Potential participants were excluded if they: had a previous history of surgery to either knee, suffered a previous ACL injury, or had a known heart condition. Pregnant females were also excluded. Surgical reports were obtained to report any concomitant meniscal damage that required surgical intervention (Table 5.1). In addition to the ACL patients, 10 healthy controls were enrolled in this investigation for purposes of comparing the effectiveness of these interventions to healthy quadriceps strength and activation data. Informed consent was obtained from all subjects and approved by the University's Institutional Review Board prior to testing.

Table 5.1 Participant Demographics (mean±SD)

						Pre-operative Quadriceps Function		Surgery Details		Time-to-Test (days)		
Group	N	Gender	Age (yrs)	Height (m)	Mass (kg)	Strength (Nm/kg)	QAF (CAR)	Graft	Meniscus	ACL injury to pre-operative	12-weeks post-surgery	Return to play
N&E	8	3f/5m	23.2±6.3	1.45±0.6	77.8±16.5	2.73±0.8	95.78±3.5	PT=7 STG=1	ACL-only=7 Meniscal Repair=1	73.25±54.4	85.87±3.4	208.50±26.3
N-only	10	2f/8m	21.8±4.4	1.76±0.1	81.65±22.6	2.69±0.6	97.43±3.0	PT=10 STG=0	ACL-only=5 Meniscal Repair=4 Meniscectomy=1	51.50±12.5	85.10±2.8	215.90±30.2
E-only	8	3f/5m	23.2±5.4	1.75±0.1	77.7±10.4	2.89±1.1	95.95±4.5	PT=6 STG=2	ACL-only=6 Meniscal Repair=2	94.10±84.7	83.50±4.3	228.80±39.4
STND	10	5f/5m	18.3±3.7	1.73±0.1	75.5±24.1	2.67±0.6	94.92±5.3	PT=8 STG=2	ACL-only=5 Meniscal Repair=4 Meniscectomy=1	95.75±57.9	96.25±±26.4	220.12±27.5
Healthy	10	3f/7m	23.5±3.4	1.73±0.1	71.7±9.9	-	-	-	-	-	-	-
Total	46	17f/29m	21.9±4.9	1.69±0.2	76.8±17.6	2.74±0.8	96.04±4.1	PT=31 STG=5	ACL-only=23 Meniscal Repair=11 Meniscectomy=2	78.00±59.1	87.30±13.1	218.77±31.3

Abbreviations: CAR, central activation ratio; E-only, eccentric-only; f, female; m, male; N-only; NMES-only; N&E, NMES and eccentrics; PT, bone-patellar tendon-bone graft; STG, semitendinosus/gracilis graft; STND, standard of care

Overview of Testing and Interventions

This study utilized a parallel longitudinal design, wherein ACL patients were placed into their respective treatment groups. Figure 5.1 illustrates the participation groups as well as the study timeline. In general, all ACL patients were required to complete quadriceps activation and strength measures at three testing sessions (pre-operative, 12-week post-surgery and at return-to-play [RTP]). At the first post-operative rehabilitation appointment, patients in the combined NMES and eccentric exercise (N&E) and NMES (N-only) groups began the 6-week NMES therapy protocol. At six weeks post-operative, the N&E and eccentric (E-only) groups began the eccentric strengthening program. Patients in the standard of care (STND) group did not receive either the NMES or eccentric strengthening study protocol and underwent the standard ACL rehabilitation protocol that is utilized at our institution. Healthy participants participated in only one data collection where quadriceps activation and strength were assessed.

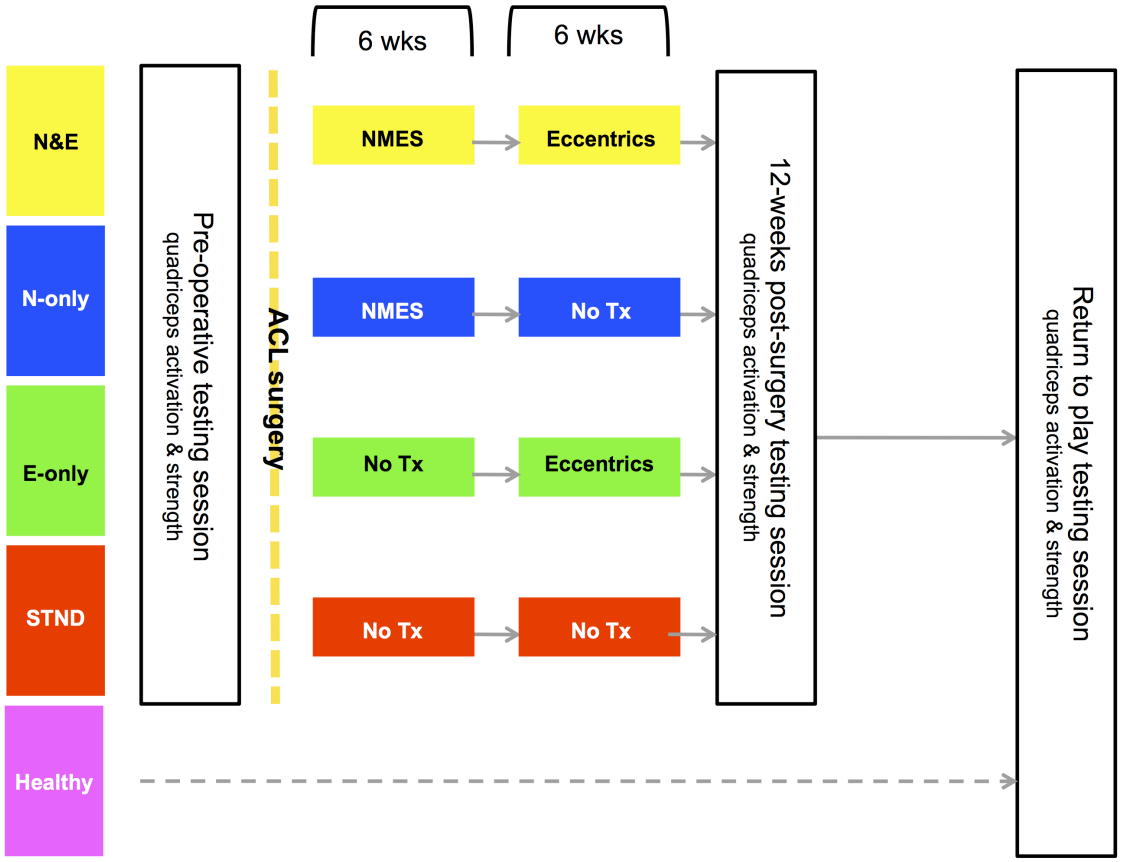


Figure 5.1 Study Testing Timeline. Upon confirmation of ACL rupture, ACL patients were place into one of four groups. Prior to ACL reconstruction, all ACL patients underwent a pre-operative testing session consisting of quadriceps muscle strength and activation measurements. ACL patients in the combined NMES and eccentric exercise (N&E) and NMES (N-only) groups began the 6-week NMES therapy protocol immediately post-surgery. At six weeks post-operative, the N&E and eccentric (E-only) groups began the eccentric strengthening program. Patients in the standard of care (STND) group did not receive either intervention. Quadriceps strength and activation measurements were collected again at 12-weeks post-surgery as well as return-to-play. Healthy participants participated in only one testing session (return-to-play) where quadriceps activation and strength were measured.

ACL patients in all groups received the same basic rehabilitation protocol (Appendix B). The NMES and eccentric treatments were considered to be adjunct treatment(s) to the overall post-operative treatment plan. As such we did not strictly control the basic rehabilitation protocol that is utilized at our institution. Essentially, we allowed each therapist that treated patients in this study to progress the rehabilitation program dependent on each patient's post-operative needs.

The NMES intervention was initiated immediately post-surgery at the first physical therapy appointment (average 6.5±2.9 days post-surgery to start of NMES). The eccentric exercise intervention was delayed until each patient was at least six weeks post-reconstruction (average 42.5±3.4 days post-surgery to start of eccentrics). This was done to ensure each patient had adequate post-operative time to have managed his or her pain, effusion, knee range of motion and quadriceps function, before the initiation of high intensity eccentric exercise. Additionally, to begin the eccentric protocol, each patient was also required to undergo an evaluation by their orthopedic surgeon where the above-mentioned criteria were assessed.

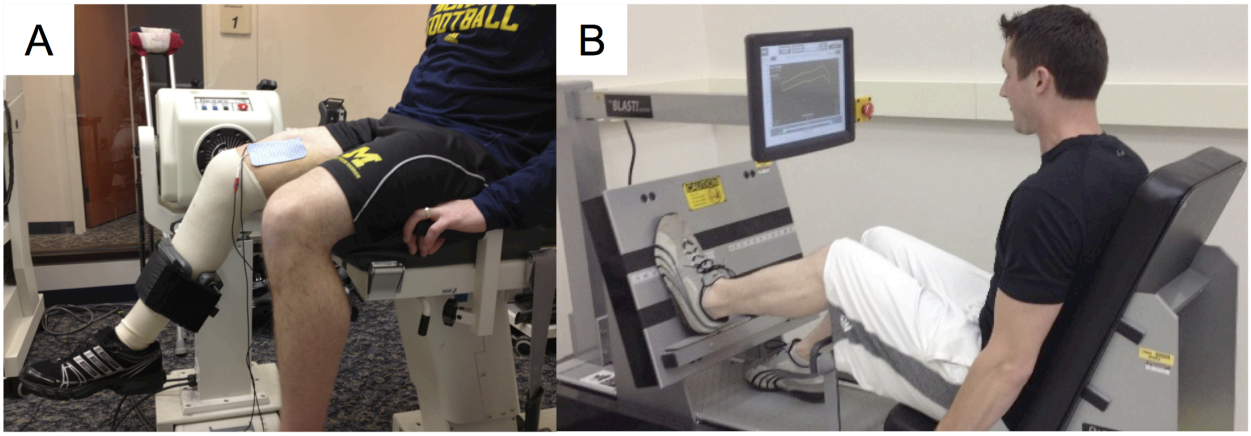


Figure 5.2 Patient receiving the NMES treatment (A) and performing the eccentric leg press (B).

Neuromuscular Electrical Stimulation Intervention

Patients placed into groups N&E and N-only received the NMES intervention two times per week for six weeks following ACL reconstruction (Figure 5.2, A). Patients in the STND and E-only groups did not receive this treatment. To deliver the therapy, patients were positioned in a Biodex Dynamometer (Biodex System 3, Biodex Medical Systems, Shirley, NY, USA) with their hips flexed to 90°, ACL knee flexed to 60° and their back supported. Self-adhesive, stimulating electrodes (Dura-Stick II [7 x 13cm] Chattanooga Group, Hixson, TN, USA) were placed over the vastus lateralis proximally and the vastus medialis distally. The Intelect Legend XT (Chattanooga Medical Supply, Chattanooga, TN) was set to deliver a 2500 Hz alternating current, modulated at 75 bursts per second, with a ramp-up time of 2 seconds, followed by a 50-second rest period

(Fitzgerald et al., 2003). Patients were encouraged to tolerate the stimulus at maximal tolerance level and to relax while the NMES was delivered in order to avoid voluntary quadriceps contraction and hamstring co-contraction (Appendix D). Ten isometric contractions lasting 10 seconds each were elicited during each session. This post-operative protocol has been demonstrated to improve quadriceps strength and activation in patients that have undergone total knee arthroplasty (Stevens et al., 2004) and ACL reconstruction (Fitzgerald et al., 2003; Snyder-Mackler et al., 1991).

Eccentric Exercise Intervention

Patients placed into Group N&E and E-only received eccentric exercise two times per week for six weeks, beginning at six weeks post-ACL reconstruction (Figure 5.2, B). N-only and STND patients did not receive this intervention. To perform the exercise, patients were positioned in a BLAST!™ Leg Press (BLAST! Leg Press version 1.2, Bio Logic Engineering Inc., Dexter, MI, USA) with their ACL-reconstructed knee range of motion limited to approximately 20 to 60° of knee flexion, following guidelines established by Gerber et al. (2007b). Once correctly positioned in the Blast!™ Leg Press, patients performed a warm-up trial consisting of a series of ten isokinetic concentric and eccentric quadriceps contractions with the ACL reconstructed limb. Following the warm-up trial, each participant performed ten isokinetic eccentric quadriceps contractions on the ACL limb. In total, patients completed four sets of ten eccentric contractions with two minutes rest in between each set. During the eccentric contractions, patients were encouraged to train at an intensity equal to 60% of their one-repetition maximum, consistent with published data indicating that load intensities of at least 60% of the one-repetition maximum are adequate to induce strength (Dwyer and Davis, 2008). The training intensity of eccentric actions was based on each participant's one-repetition maximum collected at the first session each week (Appendix D).

Quadriceps Activation and Strength Measures

To assess quadriceps strength, patients were positioned with their hips flexed to 90°, their back supported, and their testing leg and torso strapped securely into the dynamometer. At each testing session, patients performed three knee extension maximal voluntary isometric (MVIC)

trials with the knee flexed to 90°. The maximal knee extension torque produced across the three isometric trials was normalized to body weight and used for statistical analysis.

To quantify quadriceps activation the superimposed burst technique was utilized, wherein the peak torque recorded from the MVIC trials was inputted into a custom written LabVIEW (LabVIEW version 8.5, National Instruments, Austin, TX, USA) program that was set to deliver a supramaximal electrical stimulus (100 pulses/sec, 600μsec pulse duration, 10 pulse titanic train, 130 V) to the quadriceps muscle once the maximal knee extension torque had been reached and then subsequently dropped by 1 Nm (Palmieri-Smith et al., 2010). The automatic delivery of the stimulus was chosen instead of doing it manually because it has been shown to reduce measurement error by improving stimulus timing (Krishnan et al., 2009). The electrical stimulus was delivered through two self-adhesive stimulating electrodes (Dura-Stick II [7 x 13cm] Chattanooga Group, Hixson, TN, USA) applied over the vastus lateralis muscle proximally and the vastus medialis distally using a Grass S88 Dual Output Square Pulse Stimulator (S88, Grass Technologies, West Warick, RI, USA) with an SIU8T Transformer Stimulus Isolation Unit (SIU8T, Grass Technologies, West Warick, RI, USA) attached. Volitional activation of the quadriceps was determined using the central activation ratio (CAR) formula (Equation 5.1) wherein, the subject's peak torque generated immediately prior to the delivery of the stimulus was divided by the peak torque generated as a result of the electrical stimulus and multiplied by 100. A CAR of 100 was used to represent complete quadriceps activation (Kent-Braun and Le Blanc, 1996). The maximal CAR value (i.e. trial that displayed the least amount of QAF) that was collected during superimposed burst testing was used for statistical analysis.

Equation 5.1 Central Activation Ratio

$$\text{Central Activation Ratio} = \left(\frac{\text{MVIC}}{\text{MVIC} + \text{superimposed burst torque}} \right) * 100$$

Statistical Analysis

Sample size was estimated using an a priori power analysis based on previous work examining the effects of NMES on volitional muscle activation post-ACL reconstruction (Wigerstad-Lossing

et al., 1988). Based on this data (Wigerstad-Lossing et al., 1988), a projected effect size (Cohen's d, Equation 5.2) of 3.66 was calculated for quadriceps strength. Thus, in order to detect associations with an α-level of 0.05 and the 1-β 0.80, it was determined that six patients per group would be needed for this investigation.

To ensure there were no differences in baseline parameters between groups we examined the following variables; time between sessions (post-injury to pre-operative test, post-surgery to 12-week test and post-surgery to return-to-play test), pre-operative quadriceps activation, strength, and subject demographics using one-way analyses of variances (ANOVA).

To detect the immediate and prolonged effectiveness of interventions between ACL patients, percent change scores (Equation 5.3) were calculated for quadriceps strength and activation between the 1) pre-operative and 12-week post-surgery time points (Pre-to-12wks), and between the 2) pre-operative and RTP (Pre-to-RTP) time points. The percent change scores were then subsequently analyzed using one-way ANOVAs with *post hoc* independent t-tests where appropriate. To determine if gains in quadriceps activation were a mechanism leading towards gains in strength, multiple linear regressions were utilized to assess the relationship between the change in quadriceps activation and strength from 1) Pre-to-12wks and 2) Pre-to-RTP. To determine the effectiveness of interventions to restore 'healthy and/or normal' levels of quadriceps function, each treatment group's quadriceps strength and activation at RTP was compared to Healthy controls utilizing independent t-tests. Lastly, standardized effect sizes (Equation 5.2) and 95% confidence intervals (95%CI) were calculated to determine if gains in quadriceps function that were detected between groups were clinically meaningful. Effect sizes were interpreted using the guidelines described by Cohen (1977), with values less than 0.5 interpreted as weak; values ranging from 0.5-0.79 interpreted as moderate and values greater than 0.8 interpreted as strong. The α-level was set a priori at $P \leq 0.05$ for all tests. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 21.0 (IBM Corp., Armonk, NY, USA).

Equation 5.2 Cohen's d Effect Size

$$\text{Cohen's d} = \frac{\left(\text{experimental group}_1 - \text{experimental group}_2\right)}{\text{pooled standard deviation}}$$

Equation 5.3 Percent Change

$$\text{Percent Change} = \left(\frac{\left(\text{time}_2 - \text{time}_1\right)}{\text{time}_1}\right) * 100$$

5.4 Results

Pre-operative Quadriceps Function and Demographics

No significant differences in participant gender ($F_{4,45}$=0.467, P=0.759), age ($F_{4,45}$=2.107, P=0.097), height ($F_{4,45}$=1.876, P=0.133), or mass ($F_{4,45}$=0.396, P=0.811) were found between groups. Furthermore, no difference in pre-operative quadriceps function (Strength: $F_{3,35}$=0.125, P=0.945; QAF: F_{35}=0.600, P=0.619), time between injury and surgery ($F_{3,35}$=1.91, P=0.329) or between testing sessions (12-week post-surgery: $F_{3,35}$=1.746, P=0.177; RTP: $F_{3,35}$=0.641, P=0.594) were detected between treatment groups (Table 5.1).

Percent Change Scores- Quadriceps Activation

A significant change in quadriceps activation was detected between groups at the pre-operative to RTP time points ($F_{3,35}$=3.056, P=0.042), but not between groups at the pre-operative and 12-weeks post-surgery ($F_{3,35}$=1.583, P=0.213, Table 5.2) time points. Follow-up independent t-tests and effect sizes calculations revealed that group E-only demonstrated significantly greater, and strong-clinically meaningful gains in quadriceps activation at RTP as compared to STND (t_{16}=-2.630, P=0.018, d=1.25, 95%CI=0.23, 2.26) and N-only (t_{16}=-2.086, P=0.053, d=0.99, 95%CI=0.01, 1.97). Group N&E demonstrated significantly greater, and strong-clinically meaningful gains at RTP as compared to STND (t_{16}=2.225, P=0.041, d=1.05, 95%CI=0.06, 2.05). Compared to N-only, N&E demonstrated a trend towards improved quadriceps activation (t_{16}=-2.265, P=0.097, d=0.84, 95%CI=-0.13, 1.81) that was found to be clinically meaningful, but not statistically significant. No difference in quadriceps activation was detected between groups N&E and E-

only (t_{14}=-0.486, P=0.634, d=0.24, 95%CI=-0.74, 1.23) or between N-only and STND (t_{18}=-0.079, P=0.938, d=0.03, 95%CI=-0.84, 0.91).

Percent Change Scores- Quadriceps Strength

Significant changes in quadriceps strength were detected between groups at the pre-operative to 12-week post-surgery time points ($F_{3,35}$=3.621, P=0.023) and between groups at the pre-operative to RTP time points ($F_{3,35}$=3.745, P=0.021, Table 5.3). Follow-up independent t-tests and effect sizes calculations revealed that group N&E demonstrated significantly greater, and strong-clinically meaningful gains in quadriceps strength at all post-operative time points as compared to N-only group (Pre-op to 12wks: t_{16}=-2.218, P=0.041, d=1.05, 95%CI=0.06, 2.04; Pre-op to RTP: t_{16}=-2.265, P=0.038, d=1.07, 95%CI=0.08, 2.07) and STND (Pre-op to 12wks: t_{16}=2.968, P=0.009, d=1.41, 95%CI=0.37, 2.45; Pre-op to RTP: t_{16}=2.409, P=0.028, d=1.14, 95%CI=0.14, 2.14). No difference in quadriceps strength was detected between groups N&E and E-only (Pre-op to 12wks: t_{14}=1.092, P=0.293, d=0.51, 95%CI=-0.45, 1.54; Pre-op to RTP: t_{14}=1.015, P=0.327, d=0.51, 95%CI=-0.49, 1.50). E-only was statistically and clinically stronger than STND and at RTP (Pre-op to 12wks: t_{16}=-1.830, P=0.086, d=0.87, 95%CI=-0.10, 1.84; Pre-op to RTP: t_{16}=-2.381, P=0.030, d=1.13, 95%CI=0.13, 2.13), while a trend towards greater strength in the E-only group was detected when compared to N-only at RTP (Pre-op to 12wks: t_{16}=-0.968, P=0.347, d=0.46, 95%CI=-0.48, 1.40; Pre-op to RTP: t_{16}=-2.052, P=0.057, d=0.97, 95%CI=-0.01, 1.96). Lastly, no differences in strength were detected between groups N-only and STND (Pre-op to 12wks: t_{18}=1.158, P=0.262, d=0.52, 95%CI=-0.37, 1.41; Pre-op to RTP: t_{18}=0.095, P=0.925, d=0.04, 95%CI=-0.83, 0.92).

Table 5.2 Quadriceps Activation (mean±SD)

	Quadriceps Activation (CAR)			Percent Change	
Group	Pre-operative	12-weeks	RTP	Pre-to-12wks	Pre-to-RTP
N&E	95.78±3.5	94.84±4.2	97.61±2.8	-1.19±6.4	1.62±3.9[b]
N-only	97.43±3.0	91.43±8.4	91.83±4.6	-7.22±8.3	-3.47±7.3
E-only	95.95±4.5	95.02±3.8	98.11±1.2	-1.22±7.8	2.61±4.1[a]
STND	94.92±5.3	91.76±6.4	91.83±9.0	-3.60±4.2	-3.25±5.0
Healthy	-	-	96.61±2.8[c]	-	-

Abbreviations: CAR, central activation ratio

[a]P<0.05, compared to N-only and STND for Pre-to-RTP

[b]P=0.041, compared to STND for Pre-to-RTP

[c]P<0.05, compared to N-only and STND at RTP

Table 5.3 Quadriceps Strength (mean±SD)

	Quadriceps Strength (Nm/kg)			Percent Change	
Group	Pre-operative	12-weeks	RTP	Pre-to-12wks	Pre-to-RTP
N&E	2.73±0.8	2.35±0.6	2.94±0.6	-8.77±27.4[a]	15.97±39.4[a]
N-only	2.69±0.6	1.79±0.3	2.15±0.6	-31.36±15.2	-17.45±22.5
E-only	2.89±1.1	2.10±0.6	2.85±0.9	-22.60±23.3	1.05±13.0[b]
STND	2.67±0.6	1.59±0.5	2.16±0.6	-39.49±16.1	-18.35±19.8
Healthy	-	-	3.17±0.9[c]	-	-

[a]P<0.05, compared to N-only and STND for Pre-to-12wks and Pre-to-RTP

[b]P=0.030, compared to STND for Pre-to-RTP

[c]P<0.05, compared to N-only and STND at RTP

Relationship between Change in Quadriceps Activation and Strength

The change in ACL patient's quadriceps activation from Pre-to-12wks (R^2=0.146, b=0.382, P=0.021, Figure 5.3) and from Pre-to-RTP (R^2=0.125, b=0.353, P=0.035, Figure 5.4) was significantly related to improvements in quadriceps strength.

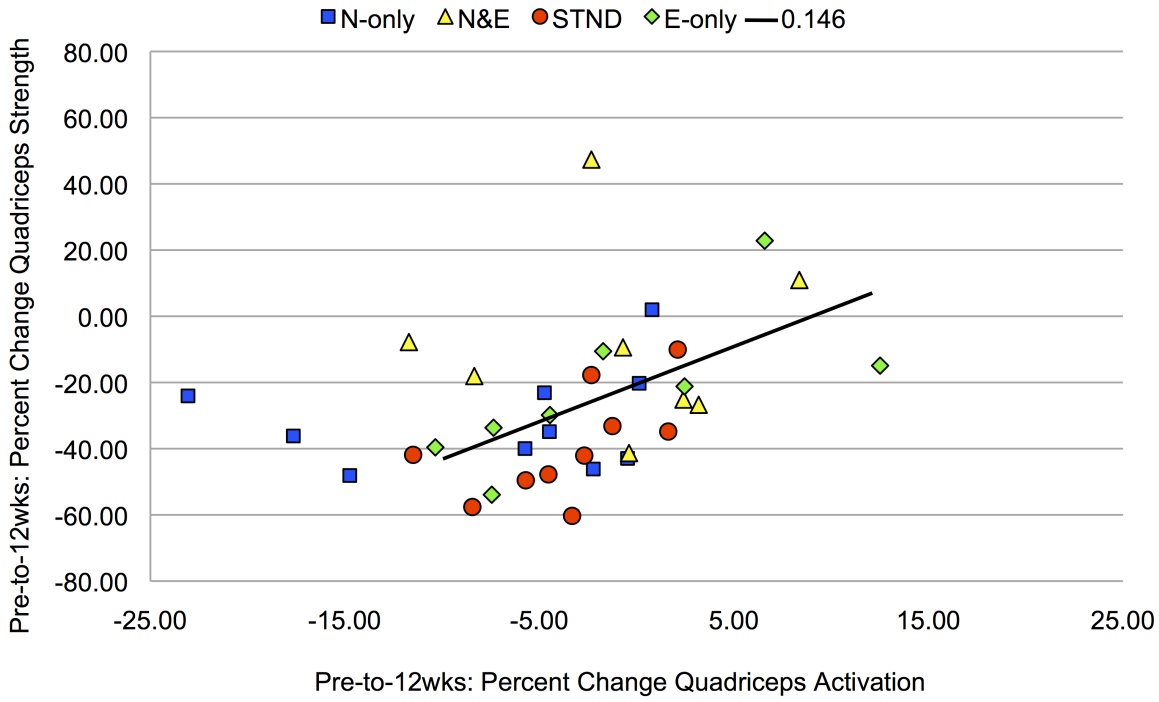


Figure 5.3 Pre-operative-to-12-weeks post-surgery percent change quadriceps activation plotted against percent change in quadriceps strength (P=0.021).

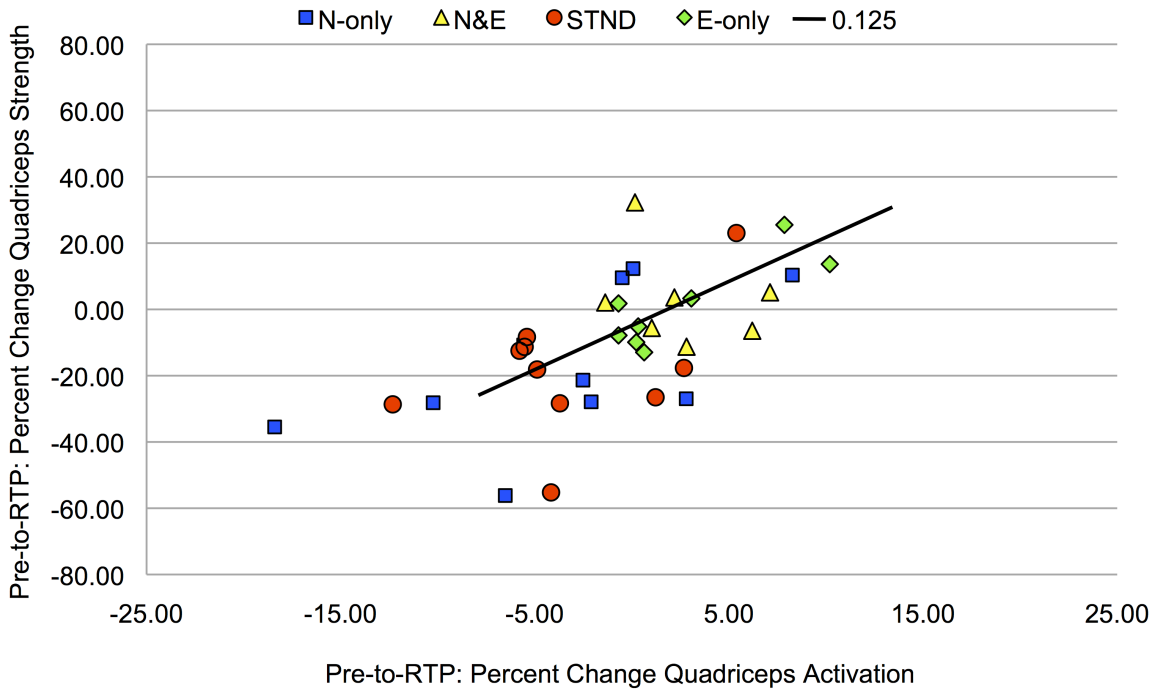


Figure 5.4 Pre-operative-to-Return-to-Play percent change quadriceps activation plotted against percent change in quadriceps strength (P=0.035).

Quadriceps Activation and Strength- compared to Healthy

As compared to Healthy, no differences in quadriceps strength or activation were detected in groups N&E (Strength: t_{16}=-0.599, P=0.557, d=0.29, 95%CI=-0.65, 1.22, Table 5.2; QAF: t_{16}=0.747, P=0.466, d=0.36, 95%CI=-0.58, 1.29, Table 5.3) and E-only (Strength: t_{16}=-0.720, P=0.482, d=0.34, 95%CI=-0.59, 1.28; QAF: t_{16}=1.376, P=0.188, d=0.66, 95%CI=-0.29, 1.61) at RTP. At RTP, group N-only demonstrated significant, strong-clinically meaningful strength deficits and QAF as compared to Healthy (Strength: t_{18}=-2.923, P=0.009, d=1.32, 95%CI=0.35, 2.29; QAF: t_{18}=-2.780, P=0.012, d=1.24, 95%CI=0.28, 2.20). Whereas Healthy was statistically and clinically stronger than STND at RTP (Strength: t_{18}=-2.789, P=0.012, d=1.32, 95%CI=0.35, 2.29), but no difference in activation was detected (QAF: t_{18}=-1.589, P=0.129, d=0.71, 95%CI=-0.19, 1.61).

5.5 Discussion

This prospective study used a combined NMES and eccentric exercise intervention designed to improve the recovery of quadriceps strength. It was found that individuals receiving the combined NMES and eccentric exercise intervention recovered quadriceps strength better than individuals that received just the NMES therapy or the standard of care following ACL reconstruction. It was also found that eccentric exercise was capable of producing similar strength gains to the combined intervention. Importantly, when compared to healthy individuals, the combined intervention and eccentric-only were capable of restoring levels of quadriceps activation and strength similar to those of healthy adults, whereas lower values in these measures still persisted for individuals that did not receive the eccentric treatment.

Quadriceps Activation

The eccentric exercise therapy, not NMES, was found to be driving factor behind improvements in quadriceps activation post-ACL reconstruction (Table 5.2). This is a novel finding, and to our knowledge, this is the first study to directly compare these two treatments. Our data are in agreement with previous research performed by Brasileiro and colleagues (2011) wherein improvements in quadriceps activation, measured via EMG, was found after six weeks of eccentric exercise post-ACL reconstruction. Importantly, Brasileiro et al. (2011) also found that improved quadriceps muscle activity strongly correlated with gains in quadriceps strength, which also corroborates the findings of our work. As such, eccentric exercise seems to be an effective therapy that is capable of combating QAF, which aids in the restoration of quadriceps strength, better than NMES alone post-ACL reconstruction.

Our measure of quadriceps activation, assessed via the superimposed burst technique, indicates that there is an improvement in an individual's ability to volitionally utilize their quadriceps muscle during isometric contractions. Though this improvement in volitional muscle activation is thought to be achieved through improved alpha motorneuron recruitment and/or firing rate (Kent-Braun and Le Blanc, 1996), the superimposed burst technique does not directly measure alpha motorneuron pool excitability. As such, the means by which an individual's volitional activation improved post-eccentrics is not entirely clear. It is possible that eccentric

exercise is capable of improving quadriceps activation through the selective recruitment of Type II muscle fibers. Evidence in healthy individuals has shown that eccentric contractions have a greater effect on Type II muscle fibers than concentric strengthening (Hortobagyi et al., 1996). Given that Type II fibers are the type of muscle fibers thought to be selectively inhibited post-ACL reconstruction (Lopresti et al., 1988; Snyder-Mackler et al., 1993), it seems possible that eccentrics may improve an individual's capability to volitionally recruit the inhibited portions of the quadriceps, resulting in improved quadriceps activation and greater capability for force production. In addition to this proposed explanation, eccentric training has been shown to produce faster neural adaptations from strength training (Hortobagyi et al., 1996), as well as increased cortical (Fang et al., 2001), and EMG activity of the quadriceps muscle (Linnamo et al., 2000). Ultimately our work helps to provide preliminary data, and future work should aim to understand the mechanism(s) by which eccentric exercise improves QAF post-reconstruction.

Our results illustrate that the NMES-only therapy produced a change in quadriceps activation that was similar to the STND group (Table 5.2). Given that previous research has shown NMES to be more effective than exercise alone at improving QAF (Fitzgerald et al., 2003; Snyder-Mackler et al., 1991; Wigerstad-Lossing et al., 1988), we had expected NMES patients to perform better than those receiving the standard of care post-reconstruction. Furthermore, due to the fact that our NMES intervention was based on protocols that have previously been shown to improve quadriceps function in ACL reconstructed individuals (Fitzgerald et al., 2003; Snyder-Mackler et al., 1991) and that all our patients were able to receive this therapy at maximal tolerance and in many instances at the equipment's maximal stimulus capacity (100 milliamps, Appendix D), this result was unexpected. Though the majority of work has found that NMES has a positive effect on quadriceps activation (Kim et al., 2010), beneficial results are not homogenous in the literature. Similar to our findings, previous studies have found that NMES does not provide any additional benefits to quadriceps function above traditional exercise (Draper and Ballard, 1991; Paternostro-Sluga et al., 1999). Previous work by Palmieri-Smith et al. (2010) in women with mild-to-moderate knee osteoarthritis found that NMES did not improve quadriceps activation or strength, and theorized that NMES may not have been

beneficial due to the lack of pre-intervention QAF exhibited in their study population. In relation to our patients, though the pre-operative level of quadriceps activation was relatively high (Table 5.1), no baseline differences existed between treatment groups. Furthermore, it seems reasonable to assume that at the time when the NMES therapy was administered (immediately post-reconstruction), a significant magnitude of QAF was likely present. As such, we feel the most likely explanation is that the equipment utilized to deliver the intervention, the Intelect Legend XT (Chattanooga Medical Supply, Chattanooga, TN), was not powerful enough to override and recruit the inhibited alpha motoneurons despite being delivered at maximal output. In clinical trials where NMES has been found to be effective, the VersaStim 380 and Empi 300 PV electrical stimulators (VersaStim 380, Electro-Med Healthy Industries, Miami Flordia; Empi 300 PV, Empi, St Paul, MN) have been utilized (Delitto et al., 1988; Fitzgerald et al., 2003; Snyder-Mackler et al., 1994b; Snyder-Mackler et al., 1991). These devices are capable of producing significantly more stimulus output then the device we used. For instance, at maximal output (100 milliamps), our equipment was only capable of generating a training intensity of ~44% of the MVIC on the ACL reconstructed limb (Appendix D). In contrast, others have found that the VersaStim is capable of generating contractions up to ~70% of the non-injured limb (Snyder-Mackler et al., 1994b). As such, we feel the difference in device is likely the driving factor as to why we did not see beneficial results. Thus, clinicians utilizing NMES to improve quadriceps activation may need to employ devices capable of generating high stimulus intensity (200 milliamps), which tend to be greater than the typical clinical electrical stimulation unit is able to deliver. Notably, the production of both the VersaStim 380 and Empi 300 PV have been discontinued and we are unaware of another device that has been shown to produce the same beneficial results as reported by previous authors post-ACL reconstruction.

Another factor that needs consideration is the post-operative graft site pain associated with patellar tendon ACL reconstruction. In our cohort, seventeen of the 18 patients that received the NMES treatment had undergone ACL reconstruction with patellar tendon graft autograft (Table 5.1). Though our patients were able to tolerate the NMES at an average intensity of ~77 milliamps with an average training intensity of ~41% of the MVIC on the ACL reconstructed limb (Appendix D), anterior knee pain during the early weeks of treatment (weeks 1-2) was common

and limited the stimulus intensity. Others (Fitzgerald et al., 2003) have delivered NMES interventions post-patellar tendon autograft ACL reconstruction, however their treatment was delivered in full knee extension. In contrast, a treatment angle of 60° of knee flexion was utilized in this investigation, which was used to track stimulus intensity, but likely induced more anterior knee pain as compared to full knee extension.

Going forward, future investigations need to take the device and patient population into consideration. Identifying if other clinical units are capable of generating the same results as the VersaStim 380 and Empi 300 PV seems critical to determining if results from research-intensive clinical settings are capable of being replicated in the typical clinic. Another consideration is graft type post-reconstruction. In our patient population, even if we had a device capable of generating very high muscle contractions, this intensity may not have been utilized due to post-operative graft site pain, patient safety and compliance.

Quadriceps Strength

It is clear that eccentric exercise was the driving factor behind improvements in quadriceps strength, given that patients exposed to this therapy recovered quadriceps strength better than NMES-only or the standard of care post-ACL reconstruction (Table 5.3). Furthermore, patients that received eccentric treatments were able to restore quadriceps strength to pre-intervention levels (or better) and did not exhibit any strength differences when compared to healthy adults (Table 5.3). Taken together, these results suggest that eccentrics are an effective therapeutic approach to combating post-operative quadriceps strength deficits. Importantly, this finding is in agreement with previous research conducted in ACL reconstructed populations wherein eccentrics was found to be a superior strength training method as compared to concentrics (Gerber et al., 2007b, 2009), and can last up to one year post-surgery (Gerber et al., 2009). From a clinical perspective, this is a significant finding, as quadriceps weakness accelerates joint degeneration (Tourville et al., 2014), leads to reduce knee function (Lewek et al., 2002) and quality of life (Logerstedt et al., 2013) post-ACL reconstruction. Hence, interventions that are capable of restoring pre-operative quadriceps strength, such as the eccentric therapeutic

approach utilized in this study, are critical to promoting both short-and-long term knee joint health.

Relationship of Quadriceps Activation and Strength

Changes in quadriceps activation were found to positively influence the recovery of quadriceps strength, however, the relationship between these two variables was relatively low (Figures 5.3 and 5.4). This result suggests that other mechanisms to improve strength were likely at work. Based on previous work in ACL reconstructed individuals (Brasileiro et al., 2011; Gerber et al., 2009), and the proposed mechanisms of eccentrics exercise, it seems plausible that changes in quadriceps morphology likely contributed to changes in quadriceps muscle strength. Although alterations in muscle architecture and volume were not measured in our study, previous authors have found significant improvements in quadriceps muscle volume post-ACL reconstruction. Specifically, eccentric exercise increased quadriceps muscle volume by 23% immediately following a 12-week intervention (Gerber et al., 2007a), and was capable of increasing quadriceps muscle volume by more than 50% at one year post-surgery (Gerber et al., 2009). Other morphological changes that may have aided in the restoration of quadriceps strength included improvements in muscle architecture, such as a change in the angle of pennation, fiber length and possible sarcomeres adaptations (Lieber and Friden, 2000). In rats, eccentric exercise has been shown to increase the number of sarcomeres in a series (Butterfield et al., 2005), as well as decrease myostatin levels (Ochi et al.). Myostatin is a protein that inhibits muscle growth, and has recently been found to be elevated in human quadriceps muscle following ACL reconstruction (Mendias et al., 2013). This study helps to provide preliminary evidence of therapies that positively affect quadriceps strength, and moving forward, it is important that more comprehensive evaluations of both neurological and morphological characteristics of muscle post-ACL reconstruction are completed.

Limitations

This study is not without limitations. First, ACL patients enrolled in this study had a variety of graft types and concomitant meniscal injuries that in some cases required surgical intervention (Table 5.1). Based on our sample size, we are not powered to consider these variables as factors

that may have affected the recovery of quadriceps function. Data emerging from our lab indicates that concomitant meniscal surgeries (meniscectomy or meniscal repair) does not affect the post-operative recovery of quadriceps strength or activation (Lepley et al., In Review). However, it is unclear whether or not graft type influences post-operative quadriceps strength, as the current literature reports inconsistent results. Thus, future investigations should continue to take graft type into consideration. Lastly, going forward, it is ideal for these treatments to be evaluated using a randomized control trial. Although no pre-operative differences in quadriceps function were detected, suggesting our study did not suffer from selection bias, to determine the true clinical effect, larger sample sizes and patient randomization is needed.

Clinical Recommendations

Based on these results, our recommendation is that clinicians consider utilizing eccentric exercise as a means to improve quadriceps activation and strength post-ACL reconstruction. From a patient perspective, the utilization of eccentrics post-reconstruction to improve quadriceps function may be an attractive alternative to NMES, given that this type of intervention can be easily delivered (two treatment per week for six weeks), is safe, and is well tolerated by patients. In comparison, in order for NMES to be beneficial it must be delivered at high intensities (that may not be achievable by all clinical units) that are often uncomfortable and may reduce patient compliance. With that, it is important for therapists to consider the devices and time in which they decide to initiate the eccentric-strengthening program post-reconstruction. Our work utilized a closed kinetic chain device. This afforded us the ability to initiate an early post-operative intervention given that the potential for strain on the ACL graft was reduced as compared to an isokinetic dynamometer. In addition to these factors, the intensity of the treatment and dose is another important clinical consideration. Our work indicates that 6-weeks of eccentric strengthening (12 treatments in total) is adequate to produce prolonged strength gains. Further, we encouraged our patients to train at, or above 60% of their one repetition maximum which was collected at the beginning of each week of the eccentric therapy.

5.6 Conclusion

Eccentric exercise post-ACL reconstruction was found to positively improve quadriceps activation and strength. Changes in quadriceps activation were positively related to changes in quadriceps strength, suggesting that by removing QAF, quadriceps strength should improve. NMES was not found to improve QAF or strength post-reconstruction. The inability of NMES to improve quadriceps muscle function may be the result of an inability to generate powerful muscle contractions due to device limitations, safety concerns for graft site safety, and post-operative pain. Importantly, when compared to healthy individuals, patients that were exposed to eccentric exercise were capable of restoring healthy levels of quadriceps activation and strength, whereas deficits in these measures still persisted for individuals not exposed to eccentric exercise.

Chapter 6. Combination of Eccentric Exercise and Neuromuscular Electrical Stimulation Intervention Post-ACL Reconstruction, Part II: Knee Mechanics

A manuscript based on the research presented in this chapter has been submitted for publication:

> Lepley LK, Wojtys EM, Palmieri-Smith RM (In review). Journal of Orthopedic & Sports Physical Therapy

6.1 Abstract

Study Design: Parallel longitudinal.

Objective: The purpose of this study was to evaluate the effects of a combined neuromuscular electrical stimulation (NMES) and eccentric exercise intervention on knee mechanics post-ACL reconstruction during a dynamic landing task.

Background: The authors previously reported that an eccentrically-based rehabilitation protocol post-anterior cruciate ligament (ACL) reconstruction induced greater quadriceps muscle activation and strength than a NMES intervention.

Methods and Measures: Thirty-six individuals post-injury were placed into four treatment groups (N&E, NMES and eccentrics; E-only, eccentrics only; N-only, NMES-only; STND, standard of care) and ten Healthy controls participated. N&E received the NMES and eccentric protocol post-reconstruction, whereas groups N-only and E-only received only the NMES or eccentric therapy, respectively. Sagittal plane knee mechanics and quadriceps strength were evaluated at

return-to-play. To evaluate knee mechanics limb symmetry, the area under the curve for knee flexion angle and extension moment was derived and then normalized to the contralateral limb. Quadriceps strength was evaluated using the quadriceps index.

Results: Compared to Healthy, reduced sagittal plane knee limb symmetry was found for N-only, E-only and STND for knee extension moment ($P<0.05$). No difference was detected between Healthy and N&E ($P>0.60$). No difference between groups was detected for knee flexion angle limb symmetry ($P>0.05$). Greater knee flexion angles and moments over stance were related to quadriceps strength.

Conclusion: N&E was found to restore sagittal plane knee limb symmetry better than the N-only, E-only or the STND post-ACL reconstruction. Greater knee flexion angles and moments over stance were related to quadriceps strength.

Keys words: ACL, knee, rehabilitation, limb symmetry index, quadriceps, strength

6.2 Introduction

The restoration of quadriceps muscle strength following anterior cruciate ligament (ACL) reconstruction is a major challenge for patients and rehabilitation specialists. Often, despite clinicians' best efforts, quadriceps weakness persists long after the rehabilitation period has ended (Palmieri-Smith et al., 2008). This persistent weakness can cause significant alterations in daily life, as it can lead to altered movement patterns (Lewek et al., 2002; Snyder-Mackler et al., 1991) that are associated with decreased functional performance and re-injury (Schmitt et al., 2012). Accordingly, rehabilitation approaches that target, and combat, quadriceps weakness may be able to reduce the biomechanical alterations that are associated with the lingering strength deficits.

Previous work has found that quadriceps strength post-ACL reconstruction is significantly related to alterations in sagittal plane knee motion (Lewek et al., 2002; Snyder-Mackler et al., 1991). Specifically, patients that exhibited greater post-operative quadriceps strength demonstrated movement patterns that were indistinguishable from non-injured individuals (Lewek et al., 2002) and their non-injured limb (Snyder-Mackler et al., 1991). Wherein patients

with quadriceps strength deficits displayed reduced knee flexion angles (Lewek et al., 2002; Snyder-Mackler et al., 1991) and extension moments during activity (Lewek et al., 2002). Thus, it seems that if clinicians can identify and implement therapeutic interventions that are capable of improving the recovery of quadriceps strength, they can positively influence sagittal plane knee mechanics, which should help to improve functional performance and possibly reduce the occurrence of re-injury (Oberländer et al., 2013).

In our own work, we have previously demonstrated that the application of a combined neuromuscular electrical stimulation (NMES) and eccentric exercise intervention is one such therapeutic approach that can induce significant and clinically meaningful gains in quadriceps strength post-ACL reconstruction (Chapter 5). This 12-week post-operative combined NMES and eccentric exercise intervention (6 weeks of NMES and followed by 6 week of eccentric exercise) was compared to the standard of care post-ACL reconstruction, and the separate application of just the NMES or eccentric exercise therapy. In general, it was found that eccentric exercise was likely the driving factor behind strength gains, as patients that were exposed to eccentrics recovered quadriceps strength better than those that were not. Furthermore patients that received the eccentric intervention demonstrated strength that was similar to non-injured matched healthy controls at a time when they were returned back into participation.

The purpose of this study was to evaluate the effects of our combined NMES and eccentric exercise intervention on knee mechanics post-ACL reconstruction during a dynamic landing task. We hypothesized that compared with the standard of care and the NMES-only intervention; an eccentrically-based rehabilitation program would result in a greater measure of sagittal plane knee limb symmetry, wherein these patients would demonstrate knee flexion angles and moments that more closely resemble their contralateral non-injured limb during dynamic activity. Furthermore, we hypothesized that greater quadriceps strength would be positively associated with greater knee mechanic limb symmetry.

6.3 Methods

Participants

This study sample consisted of the same patients and participants that participated in our previous study (Chapter 5, Table 6.1). Potential patients were excluded if they: had a previous history of surgery to either knee, suffered a previous ACL injury, or had a known heart condition. Pregnant females were also excluded. Surgical reports were obtained to detail any concomitant meniscal damage that required surgical intervention (Table 6.1). Informed consent was obtained from all subjects and approved by the University's Institutional Review Board prior to testing.

Table 6.1 Participant Demographics (mean±SD)

Group	N	Gender	Age (yrs)	Height (m)	Mass (kg)	Surgery Details		Time-to-Return-to-Play (days)
						Graft	Meniscus	
N&E	8	3f/5m	23.2±6.3	1.45±0.6	77.8±16.5	PT=7 STG=1	ACL-only=7 Meniscal Repair=1	208.50±26.3
N-only	10	2f/8m	21.8±4.4	1.76±0.1	81.65±22.6	PT=10	ACL-only=5 Meniscal Repair=4 Meniscectomy=1	215.90±30.2
E-only	8	3f/5m	23.2±5.4	1.75±0.1	77.7±10.4	PT=6 STG=2	ACL-only=6 Meniscal Repair=2	228.80±39.4
STND	10	5f/5m	18.3±3.7	1.73±0.1	75.5±24.1	PT=8 STG=2	ACL-only=5 Meniscal Repair=4 Meniscectomy=1	220.12±27.5
Healthy	10	3f/7m	23.5±3.4	1.73±0.1	71.7±9.9	-	-	-
Total	46	17f/29m	21.9±4.9	1.69±0.2	76.8±17.6	PT=31 STG=5	ACL-only=23 Meniscal Repair=11 Meniscectomy=2	218.77±31.3

Abbreviations: E-only, eccentric-only; f, female; m, male; N-only; NMES-only; N&E, NMES and eccentrics; PT, bone-patellar-tendon-bone graft; STG, semitendinosus/gracilis graft

Figure 6.1 illustrates the study timeline. The details of our intervention have been previously described (Chapter 5), however, in general, our primary investigation utilized a parallel longitudinal design, wherein ACL patients were placed into groups. At the first post-operative rehabilitation appointment, patients in the combined NMES and eccentric exercise (N&E) and NMES (N-only) groups began the 6-week NMES therapy protocol. At six weeks post-operative, the N&E and eccentric (E-only) groups began the eccentric strengthening program. Patients in the standard of care (STND) group did not receive either the NMES or eccentric strengthening study protocol and underwent the standard ACL rehabilitation protocol that is utilized at our institution. At return to play, motion capture and quadriceps strength data was collected to assess potential differences in knee mechanics and strength between groups. Healthy participants also participated in this final data collection for the purpose of comparing the effectiveness of our intervention to healthy norms.

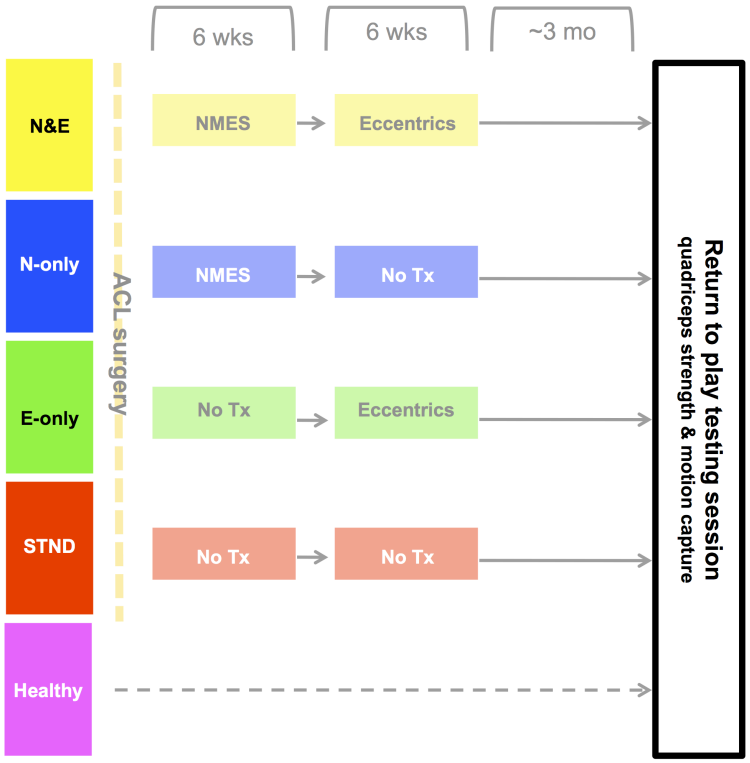


Figure 6.1 Study Testing Timeline. Upon confirmation of ACL rupture, ACL patients were place into one of four groups. All ACL patients and healthy individuals participated in one testing session at return-to-play, wherein quadriceps strength and knee mechanics were measured. The faded colors represent the intervention that was previously described in Chapter 5. Patients in the combined NMES and eccentric group (N&E) received the NMES and eccentric protocol post-reconstruction, whereas groups NMES (N-only) and eccentrics (E-only) received only the NMES or eccentric therapy, respectively.

Neuromuscular Electrical Stimulation and Eccentric Interventions

ACL patients in all groups received the same basic rehabilitation protocol (Chapter 5, Appendix B). The NMES and eccentric treatments were considered to be adjunct treatment(s) to the overall post-operative treatment plan. Thus, we did not strictly control the basic rehabilitation protocol that is utilized at our institution.

Patients placed into groups N&E and N-only received the NMES intervention two times per week for six weeks following ACL reconstruction (Figure 6.1). Patients in the STND and E-only groups did not receive this treatment. As previously described (Chapter 5), to receive the NMES

treatment, patients were positioned in a dynamometer with their hips flexed to 90°, ACL knee flexed to 60° and their back supported (Snyder-Mackler et al., 1991). Stimulating electrodes were placed over the vastus lateralis proximally and the vastus medialis distally and the Intelect Legend XT (Chattanooga Medical Supply, Chattanooga, TN) was set to deliver a 2500 Hz alternating current, modulated at 75 bursts per second, with a ramp-up time of 2 seconds, followed by a 50-second rest period (Fitzgerald et al., 2003; Snyder-Mackler et al., 1991). Patients were encouraged tolerate the stimulus at maximal tolerance level and to relax while the NMES was delivered in order to avoid voluntary quadriceps contraction and hamstring co-contraction. Ten isometric contractions lasting 10 seconds each were elicited during each session. This NMES protocol was developed based on previous work in ACL reconstructed patients that has improved post-operative quadriceps strength (Fitzgerald et al., 2003; Snyder-Mackler et al., 1991).

Patients placed into Group N&E and E-only received eccentric exercise two times per week for six weeks, beginning six weeks post-ACL reconstruction (Figure 6.1). N-only and STND patients did not receive this intervention. As previously described (Chapter 5), to perform the exercise, patients were positioned in a BLAST!™ Leg Press (BLAST! Leg Press version 1.2, Bio Logic Engineering Inc., Dexter, MI, USA) with their ACL-reconstructed knee range of motion limited to approximately 20 to 60° of knee flexion (Gerber et al., 2007b). Once correctly positioned, patients performed a warm-up trial. Following the warm-up, patients completed four sets of ten eccentric contractions with two minutes rest in between each set. During the eccentric contractions, patients were encouraged to train at an intensity equal to 60% of their one-repetition maximum, consistent with published data indicating that load intensities of at least 60% of the one-repetition maximum are adequate to induce strength (Dwyer and Davis, 2008). The training intensity of eccentric actions was based on each participant's one-repetition maximum collected at the first session each week.

Quadriceps Strength Measure

To assess quadriceps strength, patients were positioned in an isokinetic dynamometer (Biodex System 3, Biodex Medical Systems, Shirley, NY, USA) with their hips flexed to 90°, their back

supported, and their testing leg and torso strapped securely into the dynamometer. Once correctly positioned, patients performed three maximal knee extension maximal voluntary isometric (MVIC) trials with the knee flexed to 90°. The maximal knee extension torque produced across the three isometric trials with the ACL reconstructed limb was then normalized to body weight. The contralateral, non-injured limb quadriceps strength was also evaluated using the same protocol to quantify the recovery of quadriceps strength in the ACL reconstruction limb. For statistical analysis, the quadriceps index (QI) was utilized (Chmielewski et al., 2004) (Equation 6.1). Healthy individuals also underwent the same testing scheme and had the right and left limb analyzed using the same protocol, wherein all right limbs of healthy participants were arbitrarily labeled as the matched 'reconstructed limb'.

Equation 6.1 Quadriceps Index

$$\text{Quadriceps Index (QI)} = \left(\frac{\text{Max MVIC, ACL reconstructed limb}}{\text{Max MVIC, contralateral non-injured limb}} \right) * 100$$

Single-Legged Landing Task

All patients underwent motion analysis testing during a dynamic single-legged landing task. Three-dimensional biomechanical data were collected for the knee joint complex using a Vicon system (Vicon, Oxford Metrics, London, England) sampling at 240 Hz synchronized with analog data sampling at 1200 Hz. The landing task required patients to perform a single-leg forward hop onto a force plate with the ACL reconstructed limb or contralateral limb, which was pre-determined prior to the trial (OR 6-7; Advanced Medical Technology, Inc, Watertown, MA). The distance to hop was determined by each participant's leg length, defined as the tip of the greater trochanter to the tip of the lateral malleolus (Webster et al., 2004). Trials were collected until at least three successful trials were achieved on the reconstructed and non-injured limbs, or right and left limbs in the case of healthy participants. Successful trials were defined as trials in which participants landed on the force platform and were able to balance on their take-off limb without touching the floor with the contralateral limb.

Kinematic and Kinetic Data Processing

Lower limb joint rotations were defined based on three-dimensional coordinates of 32 precisely located retro-reflective markers (right and left limb; anterior and posterior superior iliac spines, iliac crest, greater trochanter, distal thigh, medial and lateral femoral epicondyles, tibial tuberosity, distal shank, lateral shank, medial and lateral malleoli, calcaneus, dorsal navicular, head of first and fifth metatarsal). An initial static trial of each participant aligned with the laboratory coordinate system was recorded, from which a kinematic model comprising of seven skeletal segments (bilateral foot, shank and thigh segments and the pelvis) and 24 degrees of freedom was created in Visual3D version 4.0 software (C-Motion; Rockville, MD)(McLean et al., 2004b). The three-dimensional marker trajectories recorded during each dynamic landing trial were subsequently processed within the respective subject's Visual3D model to solve for the generalized coordinates of each frame. Rotations were calculated utilizing the Cardan rotation sequence (Cole et al., 1993) and were expressed relative to each subject's neutral static position (McLean et al., 2007). Three-dimensional ground reaction force data was sampled and synchronized with the kinematic data and both were filtered using a fourth-order, zero-lag, low-pass Butterworth filter at 12 Hz cut-off frequency (Myer et al., 2007). Filtered kinematic and ground reaction force data were then submitted to a standard inverse dynamics approach within Visual3D (Willson and Davis, 2008). Segmental inertial properties were defined based on the previous work of Dempster (1959). The intersegmental moments at the knee joint were expressed as flexion-extension, adduction-abduction, and internal-external rotational moments with respect to the Cardan axes of the local joint coordinate system (McLean et al., 2007; McLean et al., 2005). Kinetic outputs were normalized to subject body height and mass and represented as internal moments (Chmielewski et al., 2001), wherein a positive knee extensor moment at the knee would therefore represent the moment production by the quadriceps muscles.

Biomechanical data was time normalized to 100% of the stance phase for graphical purposes, with initial contact equating to the time when the vertical ground reaction force first exceeded and fell below 10 N (Borotikar et al., 2008; McLean et al., 2007) and toe-off equating to 250 msec post-initial contact (Deneweth et al., 2010). Ensemble averages were calculated across stance for all rotations and moments (McLean et al., 2004a). From these ensemble averages,

the area under the curve (Equation 6.2) was calculated for sagittal knee joint rotations and moments over the first 50% of stance, as this is when ACL injury is most likely to occur (Griffin et al., 2006). The area under the curve was chosen over peak angle or moment values because this derivative accounts for the total contribution of a joint angle or moment towards producing motion. As such, it is thought to quantify movement more accurately than peak values (DeVita et al., 1998b). To account for baseline differences in how each patient would accomplish this landing task, the area under the curve derivatives (angle and moment) for the ACL reconstructed limb was normalized to the contralateral non-injured limb (right limb normalized to left limb for healthy participants) utilizing the limb symmetry index for knee mechanics (de Jong et al., 2007) (Equation 6.3). In this way, each participant's healthy non-injured limb was used as their own control. Though there are inherent issues with utilizing the healthy limb as a control post-ACL injury and reconstruction as potential contralateral quadriceps strength deficits have been reported (Hiemstra et al., 2007), comparing alterations in knee mechanics between limbs with the limb symmetry index is a clinically applicable technique that allowed us to account for baseline characteristics in the way each subject accomplishes the task (Teichtahl et al., 2009) (Figures 6.2 and 6.3).

Equation 6.2 Area Under the Curve

$$\text{Area under the curve} = \int_a^b f(x)dx$$

Equation 6.3 Limb Symmetry Index

$$\text{Limb Symmetry Index} = \left(\frac{\text{area under the curve, ACL reconstructed limb (moment or angle)}}{\text{area under the curve, contralateral non-injured limb (corresponding moment or angle)}} \right) * 100$$

Statistical Analysis

To determine the effectiveness of the interventions to improve limb symmetry of knee mechanics, the limb symmetry indices for knee flexion angle and moments were analyzed using one-way analyses of variances (ANOVAs) with *post hoc* Bonferroni multiple correction procedures where appropriate. To determine if differences in the limb symmetry index that were found to be statistically significant were clinically meaningful, standardized effect sizes

(Equation 6.4) and 95% confidence intervals (95%CI) were calculated. Effect sizes were interpreted using the guidelines described by Cohen (1977), with values less than 0.5 interpreted as *weak*; values ranging from 0.5-0.79 interpreted as *moderate* and values greater than 0.8 interpreted as *strong*. Lastly, to examine the relationship between quadriceps strength and knee mechanics, multiple linear regressions were utilized to evaluate the relationship between 1) QI and limb symmetry index for knee extension moment and 2) QI and limb symmetry index for knee flexion angle. The α-level was set *a priori* at P≤0.05. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 21.0 (IBM Corp., Armonk, NY, USA).

Equation 6.4 Effect Size

$$\text{Cohen's d} = \frac{\left(\text{experimental group}_1 - \text{experimental group}_2\right)}{\text{pooled standard deviation}}$$

6.4 Results

Knee Mechanics

Significant differences between groups were observed, indicating the limb symmetry indices differed between groups for the area under the curve for knee flexion angles and moments (Angle: $F_{4,45}$=2.615, P=0.049; Moment: $F_{4,45}$=5.292, P=0.002). Specifically, compared to Healthy individuals, groups N-only (P=0.020, d=1.75, 95%CI=0.72, 2.78), E-only (P=0.004, d=1.95, 95%CI=0.83, 3.09) and STND (P=0.005, d=1.97, 95%CI=0.90, 3.04) demonstrated significantly lower, and clinically meaningful, reduced limb symmetry for knee extension moments. This reduced limb symmetry was driven by small knee extension moments with the ACL reconstructed limb (Table 6.2, Figure 6.2). Group N&E observationally displayed reduced knee extension moments with their ACL reconstructed limb that were clinically meaningful (Table 6.2, d=1.61, 95%CI=0.55, 2.69), but not statistically different from Healthy controls (P=0.060). Furthermore, though an overall main effect of limb symmetry was detected for knee flexion angles, only the N-only group tended to demonstrate lower limb symmetry as compared to

Healthy (P=0.083, d=1.47, 95%CI=0.49, 2.46). No other significant post-hoc differences were noted with regards to knee flexion angle (P values range=0.323-1.000; Table 6.2, Figure 6.3).

Table 6.2 Area Under the Curve and Limb Symmetry Index (mean±SD)

	Knee Extension Moment			Knee Flexion Angle		
	Area under the curve		Limb Symmetry Index	Area under the curve		Limb Symmetry Index
Group	ACL	Healthy		ACL	Healthy	
N&E	33.26±9.7	50.80±11.1	66.72±19.0	-1362.59±256.7	-1509.59±302.3	92.38±21.1
N-only	33.40±17.2	50.03±10.2	64.22±19.0*	-1039.21±374.5	-1412.18±363.6	73.38±18.0
E-only	21.98±11.2	41.64±13.9	55.35±24.1*	-1260.83±500.3	-1499.86±469.1	83.74±23.3
STND	27.59±9.9	46.94±9.6	58.75±20.1*	-1238.67±215.9	-1601.55±161.9	78.10±15.9
Healthy	43.51±7.3	46.24±15.7	99.87±21.6	-1172.73±342.6	-1226.60±349.6	95.77±11.7

Abbreviations: E-only, eccentric-only; N-only; NMES-only; N&E, NMES and eccentrics; STND, standard of care

*P<0.05, as compared to Healthy

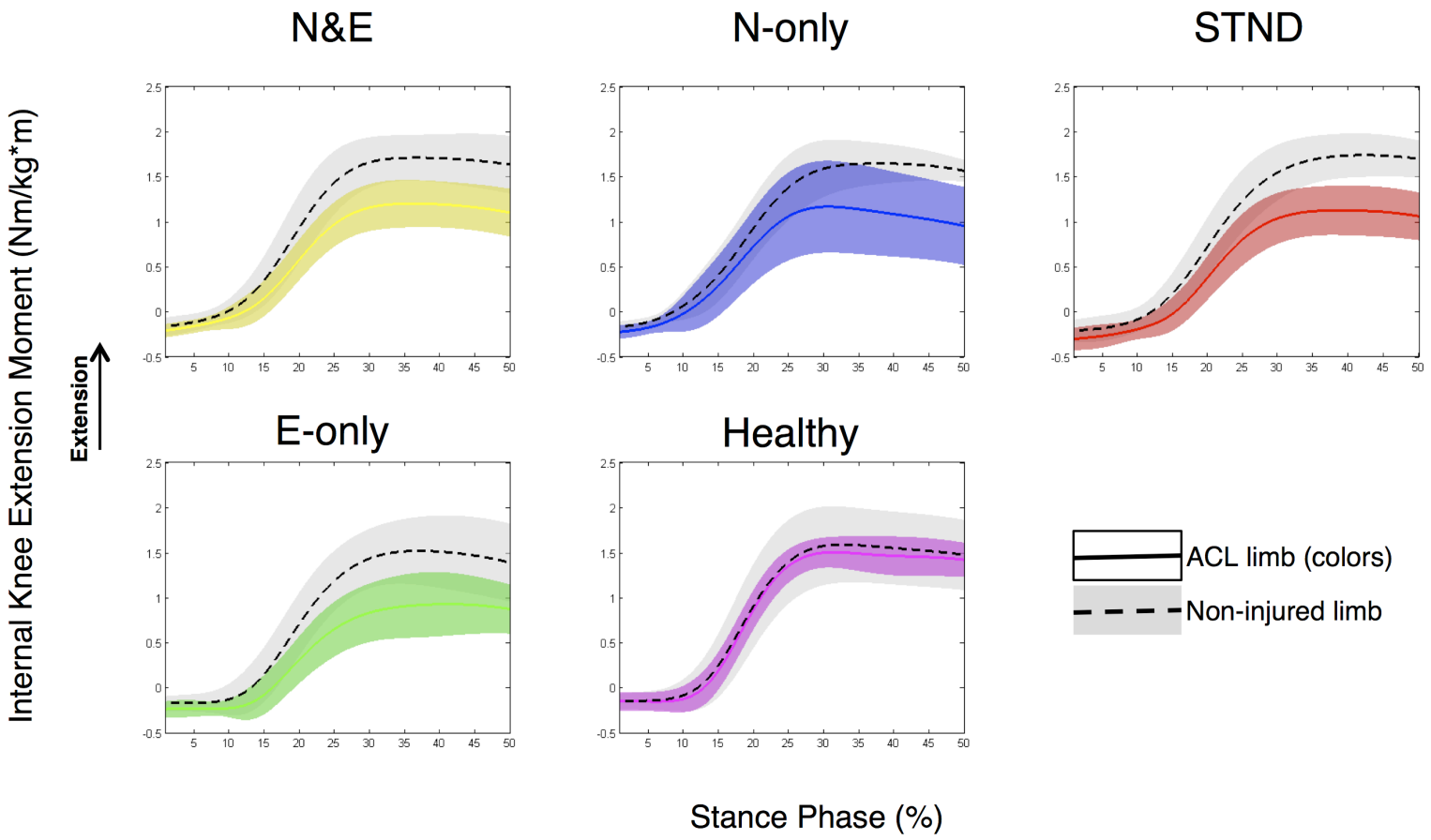


Figure 6.2 Knee Extension Moment Limb Symmetry Plots

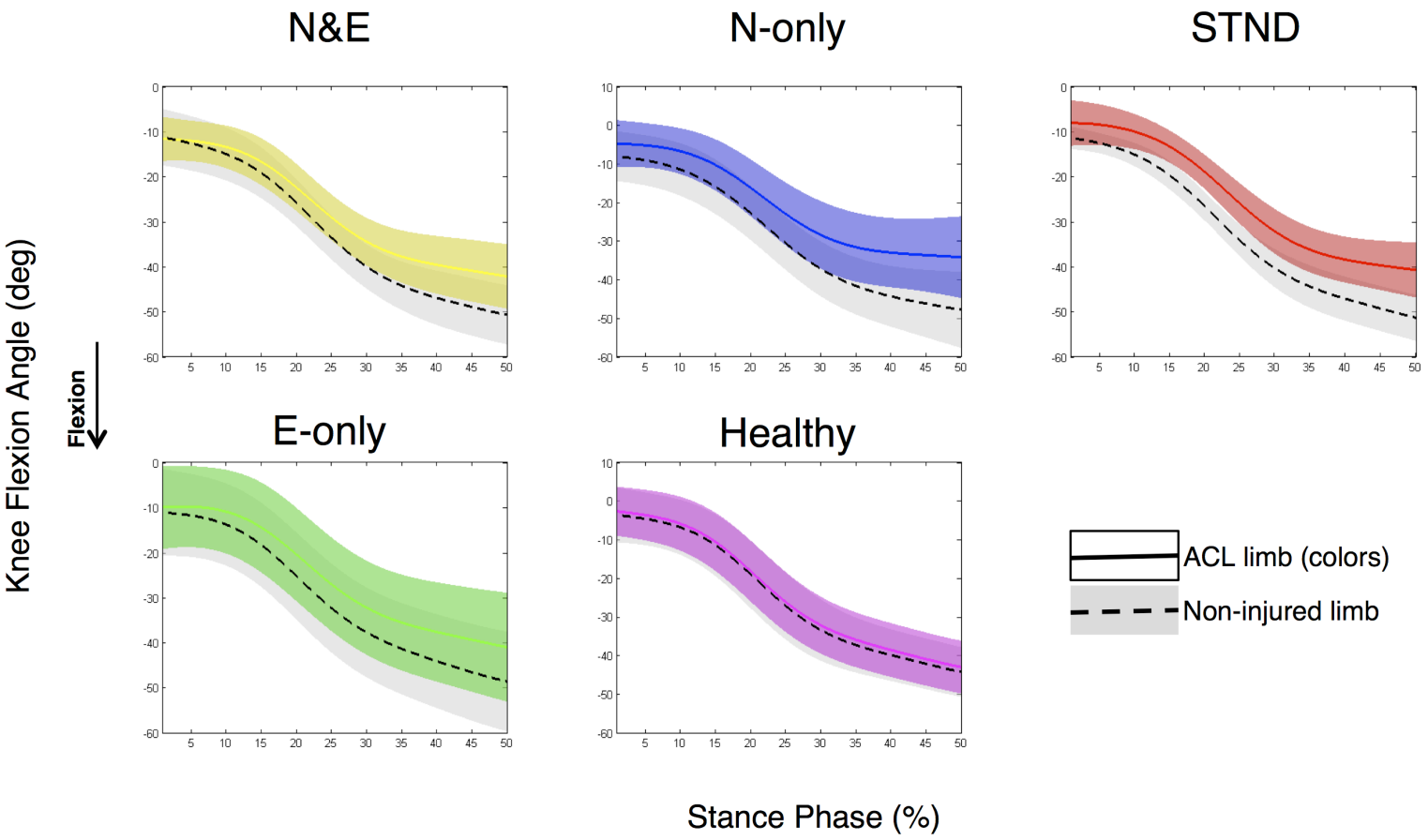


Figure 6.3 Knee Flexion Angle Limb Symmetry Plots

Relationship between Quadriceps Strength and Knee Mechanics

Among all participants, it was found that individuals with greater QIs (Table 6.3) demonstrated greater knee mechanic limb symmetry during the single-legged landing task (QI and Limb Symmetry Index knee extension moment: R^2=0.220, b=0.469, P=0.001, Figure 6.4; QI and Limb Symmetry Index knee flexion angle: R^2=0.212, b=0.460, P=0.001, Figure 6.5).

Table 6.3 Quadriceps Index (mean±SD)

Group	Quadriceps Index (QI)
N&E	84.74±12.4
N-only	67.22±14.7
E-only	84.84±10.1
STND	73.02±12.8
Healthy	94.39±7.0

Abbreviations: E-only, eccentric-only; N-only; NMES-only; N&E, NMES and eccentrics; STND, standard of care

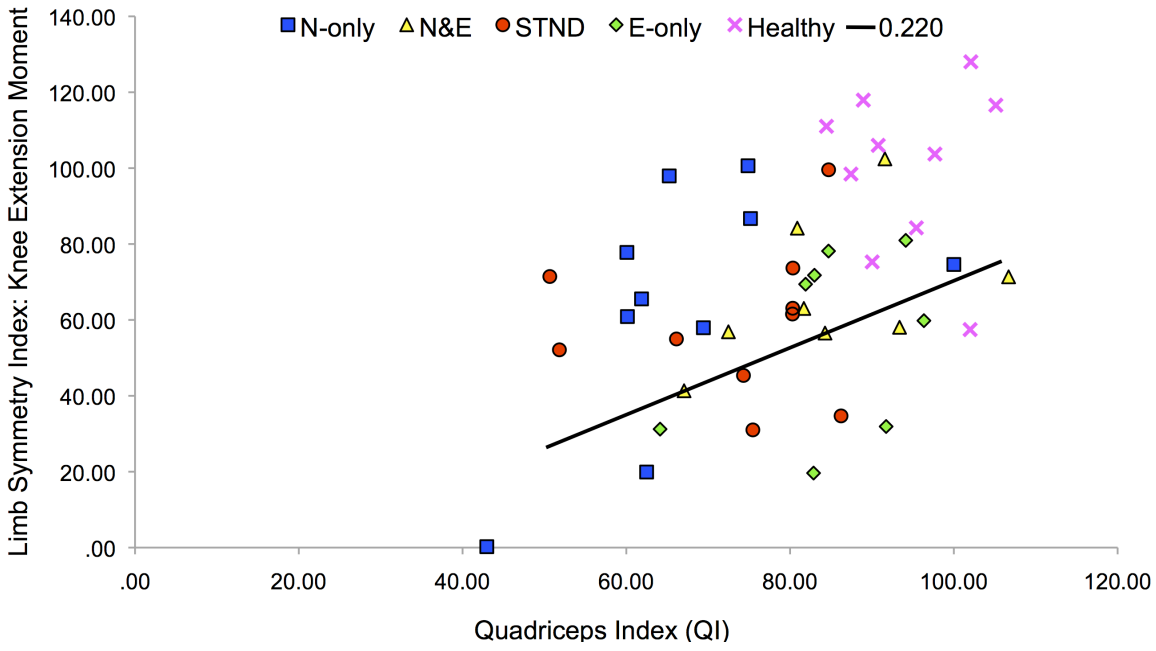


Figure 6.4 Quadriceps Index plotted against Knee Extension Moment Limb Symmetry Index (P=0.001). N-only outlier had a QI of 43.10 and a limb symmetry index of 0.24.

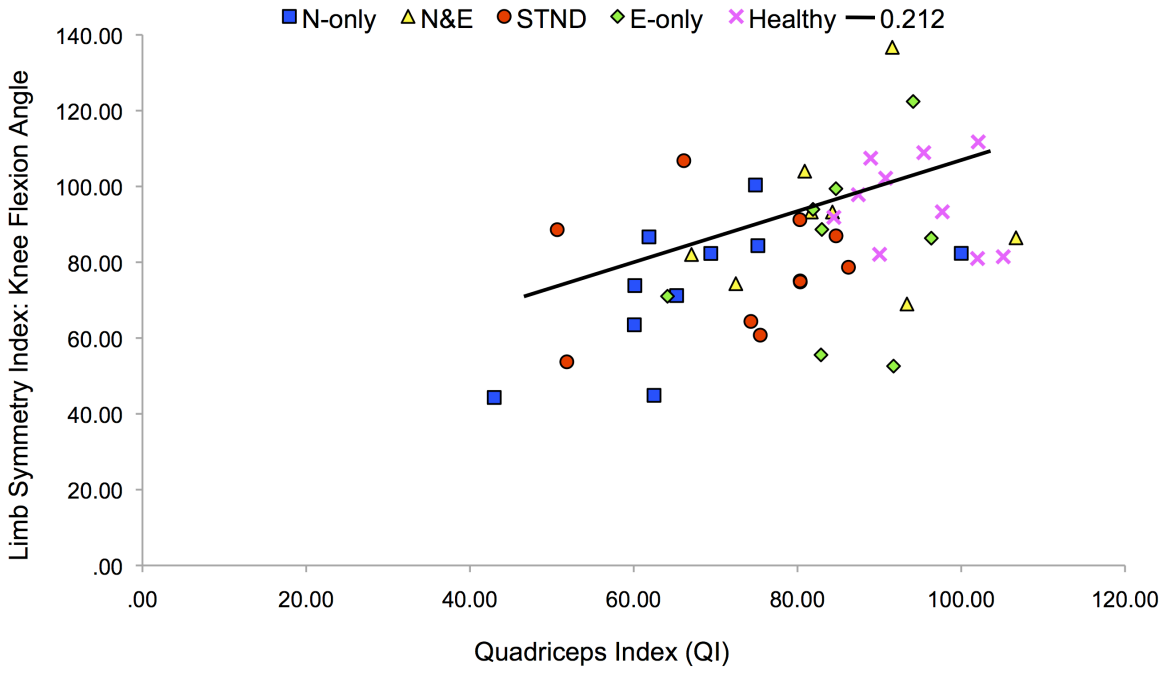


Figure 6.5 Quadriceps Index plotted against Limb Flexion Angle Limb Symmetry Index (P=0.001)

6.5 Discussion

This study was conducted to determine the effectiveness of a combined NMES and eccentric exercise intervention to restore limb symmetry, and to analyze the relationship between limb symmetry and quadriceps strength. It was found that compared to healthy individuals, patients that received the NMES-only, eccentric-only, or standard of care interventions displayed a significantly lower limb symmetry index (i.e. greater bilateral difference) in knee extension moment during a single-legged landing task. Though not statistically significant, a clinically meaningful trend towards reduced limb symmetry index was found between the combined intervention (N&E) and healthy individuals for knee extension moment. Knee flexion angles did not appear to be as affected as knee extension moment post-ACL reconstruction, as no significant group differences were identified. Lastly, quadriceps strength was found to be significantly related to limb symmetry for sagittal plane mechanics, suggesting that if quadriceps strength is improved, sagittal plane biomechanics will be positively affected. Taken together, these results suggest that our combined NMES and eccentric exercise intervention is more effective than standard of care or the separate application of NMES and eccentrics exercise therapies, which is in agreement with our previous work (Chapter 5). However, differences in knee mechanics as assessed by the limb symmetry index still existed to some extent in the ACL limb, despite the success of the combined intervention (N&E), which indicates that knee joint function is not fully restored with this combined therapeutic approach at the time patients returned to play.

Knee Mechanics

Individuals that were exposed to the combined intervention (N&E) were able to generate knee moments that most closely resemble their non-injured limb, whereas patients that received the standard of care, NMES-only or eccentrics-only demonstrated significantly less limb symmetry. This difference was driven by reduced knee extension moments with the reconstructed limb (Table 6.2). The combined group (N&E) observationally displayed reduced limb symmetry for knee extension moments that was found to be clinically meaningful, but not statistically different from Healthy individuals. This result suggests that although the combined intervention

was the most successful at reinstituting limb symmetry, alterations in knee extension moments still existed to some extent. Importantly, compared to all our ACL reconstructed patients, our Healthy group displayed very high limb symmetry indices (small inter-limb alterations) for knee mechanics, which is in agreement with previous research suggesting that there is no difference between limbs in healthy individuals during activity (Button et al., 2005). As such, inter-limb differences in knee mechanics, that reduced limb symmetry, appear to be a characteristic that was specific only to our ACL reconstructed patients, suggesting that an incomplete recovery of knee function existed at return-to-play.

Surprisingly, though our combined group (N&E) demonstrated a greater knee extension limb symmetry index than patients that were just exposed to the NMES (N-only) or standard of care (STND) intervention, the eccentric-only (E-only) group did not exhibit the same trend as group N&E. This finding is in contrast to our hypothesis, as we had anticipated that participants who received the eccentric exercise intervention would respond similarly. To our knowledge, Coury et al. (2006) is the only other study to have examined alterations in knee kinematics post-reconstruction after the application of an eccentric exercise intervention. In this cohort (Coury et al., 2006), it was observed that knee flexion improved from baseline (pre: 51° post: 58°) during level ground walking (5.0 km/h) following a 12-week eccentric exercise intervention in five male individuals that were approximately nine months post-surgery. Though this is a relatively small sample (Coury et al., 2006), and there is limited data on this topic, we had anticipated that our patients would respond similarly. From a clinical standpoint, given that the main function of the quadriceps muscle is eccentric actions, we had anticipated that participants who trained eccentrically would be better able to utilize their quadriceps muscle during activity and would therefore demonstrate sagittal plane knee movement more similar to their non-injured limb. Although it is not entirely clear as to why the eccentric-only group demonstrated reduced limb symmetry for knee extension moment as compared to the combined group (N&E), there are a couple of plausible explanations. One possibility is that exposure to the eccentric exercise treatment did not transfer to a more efficient utilization of eccentric muscle actions during the hopping task. In other words, there may have been a lack of a transfer or motor-learning effect. Similar to our work, others have found that strength

training alone is not sufficient to alter lower extremity jump landing mechanics (Herman et al., 2008). Specifically, it is thought that in addition to muscle strengthening, rehabilitation programs should include a neuromuscular component to positively influence lower extremity mechanics (Myer et al., 2005). Thus, it seems plausible that the combination of NMES and eccentric exercise may have been more effective, as a variety of modalities that are able to target both the strength as well as the neural components of muscle may have been able to better augment movement, and promote utilization of the quadriceps muscle during activity (Herman et al., 2008). Another possibility is that there was a psychological component to this single-legged hopping activity, and that individuals placed into the eccentric-only group were simply not as comfortable performing this activity as others, despite the fact that they had a similar quadriceps strength index to group N&E (Table 6.3). This potential fear of re-injury is common post-ACL reconstruction (Langford et al., 2009) and is associated with reduced function (Chmielewski et al., 2008). As such, this potential psychological factor could have resulted in the eccentric group utilizing less quadriceps function, resulting in a lower knee extension moment and larger inter-limb difference. Ultimately, our work provides some preliminary data, and indicates that an eccentric intervention with a neural component such as NMES is beneficial at improving knee mechanic limb symmetry post-reconstruction. Given the results of this study and the limited research to date, more work is needed.

Interestingly, no significant difference was found in the limb symmetry index for knee flexion angles, though it appears that the NMES-only group tended to have lower limb symmetry as compared to healthy controls for this measure (P=0.083, d=1.47, 95%CI=0.49, 2.46, Table 6.2). As such, it appears that our ACL individuals were able to maintain knee flexion angles that were similar to their non-injured knee, despite the fact that deficits in knee extension moments were identified. To accomplish this movement pattern, it is possible that our ACL participants may have adopted a forward trunk lean during landing. In this scenario, by leaning the body's center of mass anteriorly, the ground reaction force would have been repositioned closer to the knee joint complex, resulting in a smaller moment arm and a consequent reduction in the knee extension moment (Winter, 2005). This alteration in trunk flexion, leading to reduced knee extension moments and stable knee flexion angles, has recently been identified in ACL

reconstructed patients during a single-legged-forward-hop task (Oberländer et al., 2013), that is similar to the one employed in this study. As such, it seems likely that our patients may have utilized a forward trunk lean to reduce the strain on the quadriceps muscle, which resulted in a lower knee extension moment that reduced the limb symmetry index. However, due to the fact that our biomechanical model did not include a trunk segment, we cannot say with certainty that our patients adopted this movement pattern.

Relationship between Quadriceps Strength and Knee Mechanics

Individuals with less side-to-side strength deficits were able to demonstrate movement patterns that more closely resemble their non-injured limb. This result supports our hypothesis, and is in agreement with previous literature (Lewek et al., 2002; Oberländer et al., 2013; Snyder-Mackler et al., 1991), indicating that alterations in knee mechanics are in part due to residual muscle weakness. Similar to our work, Oberländer and colleagues (2013) found that at 12-months post-reconstruction, deficits in quadriceps strength assessed via MVIC were significantly correlated with reduced knee extension moments during their single-legged hopping task. This relationship has also been corroborated by Lewek et al. (2002) and Snyder-Mackler et al. (1991). Specifically, Lewek et al. (2002) found that patients with a greater recovery of quadriceps strength post-reconstruction were able to produce knee extension moments and angles that were indistinguishable from healthy controls and were significantly correlated with quadriceps strength during walking and jogging activities. Likewise, Snyder-Mackler et al. (1991) noted that patients with stronger quadriceps muscles post-reconstruction demonstrated more normal gait patterns with greater flexion-excursion gait patterns that were correlated with strength. Importantly our data indicates that only about 20% of the variability in knee joint moments and angles can be explained by quadriceps strength. As such, though improvements in quadriceps strength will likely improve knee mechanics, alterations in moment patterns are likely due to a combination of events such as alterations in neural activity and/or motor learning patterns, psychological readiness, as well as joint kinematics/kinetics of both the upper and lower kinetic chains.

Limitations

Our study is not without limitations. First, the use of contra-lateral limb as a control may have resulted in alterations in the limb symmetry index calculations. Although we do recognize that this is an imperfect method, given the potential for alterations in the neuromuscular function in the non-injured limb post-ACL injury (Hiemstra et al., 2007), this data analysis technique has previously been employed by several studies investigating the motion of the ACL deficient (Li et al., 2006) and reconstructed knees (Deneweth et al., 2010; Oberländer et al., 2013; Papannagari et al., 2006; Snyder-Mackler et al., 1991). Furthermore, work by Teichtahl et al. (2009) has shown that inter-subject variability exceeds that of intra-subject variability with regards to knee mechanics, as such we believe that the use of the contralateral limb to calculate limb symmetry was justified. Second, our biomechanical model did not include a trunk segment. Therefore we can only speculate that our ACL patients may have utilized a forward trunk lean to maintain knee flexion angles with a concurrent reduced knee extension moment. Third, this investigation utilized a mixed cohort of patients, including two graft types and patients that underwent a variety of concomitant meniscal procedures (Table 6.1). Due to the small group sample size, this investigation was not adequately powered to analyze these potential covariates as factors that may have altered sagittal plane knee mechanics. In our own work, we have found that concomitant meniscectomy and/or meniscal repair does lead to greater quadriceps strength deficits than isolated ACL reconstruction (Lepley et al., In Review). Furthermore, at this point in time, it appears that both the patellar-tendon and hamstring graft type produce similar function results (Mohtadi et al., 2011) and knee mechanics (Tashman et al., 2007). However, we do acknowledge that alterations in surgical produces between graft type and meniscal injuries may have been a factor that influences our results. Future work should take these limitations into consideration.

Clinical Implications

In ACL rehabilitation, restoring strength and bilateral limb symmetry is a primary clinical goal as asymmetries and strength deficits are thought to increase the risk of contralateral and ipsilateral limb injury (Paterno et al., 2010; Schmitt et al., 2012). It is therefore concerning that the combined ACL patients (N&E) were the only group that displayed knee mechanic limb

symmetry indices that were comparable to healthy individuals. Though the N&E group outcomes were superior to the standard of care and isolated NMES and eccentric therapies, our combined group (N&E) still displayed alterations in knee mechanics (Limb symmetry index: Moment=66%, Angle=92%), and also quadriceps strength deficits (QI=85%) below what is deemed healthy (QI>90%). Based on these results, a longer eccentric intervention post-reconstruction may be beneficial, as this therapy was found to be the driving factor behind strength gains in our previous work (Chapter 5). Additionally of the ACL patients in our study, those individuals with less side-to-side strength deficits were able to demonstrate movement patterns that more closely resemble their non-injured limb. This result is in agreement with the previous literature (Lewek et al., 2002; Oberländer et al., 2013; Snyder-Mackler et al., 1991) and indicates that interventions that are capable of improving quadriceps strength, such as the one employed in this current study, should positively improve dynamic movement in ACL reconstructed patients.

6.6 Conclusion

A combined NMES and eccentric exercise intervention was found to restore sagittal plane knee limb symmetry better than the separate application of NMES, eccentric exercise or the standard of care following ACL reconstruction at a time when patients were returned to participation. Greater knee flexion angles and moments over stance were related to quadriceps strength, suggesting that interventions capable of restoring quadriceps strength can positively influence sagittal plane knee mechanics, which should help to improve functional performance post-reconstruction.

Chapter 7. Summary and Future Directions

7.1 Introduction

The overarching goal of this dissertation was to develop novel rehabilitation approaches capable of markedly improving the recovery of quadriceps strength post-reconstruction and to gain a more detailed understanding of the effect of QAF on post-operative quadriceps function. With more than 50% of ACL reconstructed limbs suffering from joint degeneration within 10 years of injury, and the occurrence of ACL injury continually increasing, these data are essential to improving quality of life and preserving long-term knee joint health. With this purpose in mind, the specific aims of this dissertation were developed to illuminate our understanding of therapies and rehabilitation approaches capable of improving knee function post-reconstruction. Furthermore, this dissertation was developed so that data emerging from this work could immediately inform clinical decision-making and be transitioned into clinical practice. As such, a primary strength of this dissertation is the clinical applicability of this work. Below is a brief summary of each study, key outcomes and clinical implications, which clearly demonstrates that the overall goals (specific aims) of this dissertation were achieved. Additionally, study limitations and future research directions are presented.

7.2 Summary

In **Chapter 3**, the effects of eccentric exercise on cross-education strength and activation were determined in the unexercised limb. This study represented the first investigation to provide insight into the neuromuscular response of the unexercised quadriceps muscle to eccentric cross-education training using volitional muscle activation testing. Moreover, this study is unique because it is the first to determine the dose of eccentric exercise necessary to elicit

quadriceps strength and activation gains in the unexercised knee. The key outcomes from this study was that eccentric exercise resulted in both mode and velocity specific gains in quadriceps strength in the exercised and unexercised limb of healthy participants. Further, it was also found that five-weeks of eccentric cross-education training was sufficient to improve quadriceps strength in the unexercised limb. A trend towards greater quadriceps volitional activation (less QAF) was also detected in the unexercised limb, suggesting that strength gains likely occurred due to enhanced neural activity of the quadriceps muscle. From a clinical perspective these data indicate that eccentric cross-education may be an effective therapy to improve quadriceps activation and strength deficits. Though future work needs to be done to either confirm or refute these data, based on our results, it is recommend that clinicians consider utilizing this type of therapy immediately following ACL reconstruction to improve quadriceps function and then transition to eccentric exercise with the involved limb once it is clinically appropriate.

Examining the role of QAF further**, Chapter 4** investigated the relationship between pre-and post-operative quadriceps activation and strength. This investigation was undertaken to help design more effective pre-operative rehabilitation interventions by identifying the factors that contribute to the best recovery of quadriceps function post-reconstruction. It was found that pre-operative activation was positively related to post-operative activation, and pre-operative strength was positively related to post-operative strength. No relationship between pre-and post-operative quadriceps activation and strength was identified. This is first investigation to examine the effect between pre-and post-operative quadriceps activation, and our results suggest that pre-and post-operative QAF may be triggered and mediated by different factors that affect strength differently, limiting the potential relationship between these two variables. Furthermore, it was found that QAF is more extensive following ACL reconstruction than post-injury. This post-operative degradation in quadriceps neural activity is likely influenced by ACL reconstruction itself, as deficits in quadriceps neural activity were for the most part, resolved prior to surgery. Knowing that there are chronic adaptations in quadriceps neural activity that do not resolve with traditional rehabilitation is a valuable clinical point. This information is especially important as chronic QAF is hypothesized to be a mechanism of post-traumatic OA.

Based on these outcomes, it is recommended that rehabilitation programs prior to ACL reconstruction continue to focus on maximizing strength to improve the post-operative recovery of strength. Additionally it is recommended that clinicians employ therapies that target and reduce QAF prior to ACL reconstruction to improve the volitional recovery of quadriceps muscle activation post-reconstruction. Going forward, it would be ideal for future research to identify the implications of chronic QAF on post-operative outcomes as well as the extent to which these neural alterations affect activities of daily living and long-term knee joint health.

Chapters 5 and 6 detail a novel clinical investigation that was conducted to determine the effectiveness of a combined NMES and eccentric exercise intervention to improve the recovery of quadriceps strength (Chapter 5) and knee mechanics (Chapter 6) post-ACL reconstruction. Though this was a preliminary investigation, this is the first study to employ a combined therapeutic approach to combat quadriceps weakness by utilizing therapies that have been shown to remove QAF and minimize muscle atrophy. In **Chapter 5**, it was found that eccentric exercise post-ACL reconstruction was capable of restoring levels of quadriceps activation and strength that were similar to those of healthy adults and better than the separate application of NMES. Further it was found that the change in quadriceps activation was positively related to the change in strength, suggesting that by removing QAF, quadriceps strength should improve post-reconstruction. Taking these data a step further, **Chapter 6** examined the effectiveness of these interventions to improve knee mechanics post-ACL reconstruction. It was found that the combined NMES and eccentric exercise intervention was found to restore sagittal plane knee mechanic limb symmetry better than the separate application of NMES, eccentric exercise or the standard of care. Moreover, it was found that greater knee flexion angles and moments over stance were positively related to quadriceps strength. Taken together, these data suggest that a longer eccentric exercise intervention may be beneficial as this was found to be the driving factor behind strength gains (Chapter 5) and greater strength is capable of positively influencing movement post-reconstruction (Chapter 6). However, to determine the true clinical effect of these results, larger sample sizes and patient randomization is needed.

7.3 Limitations and Future Research Directions

Though the studies in this dissertation represent significant advances in rehabilitation approaches, this dissertation is not without limitations and future research is needed to continue to elucidate treatments capable of improving the recovery of quadriceps strength.

The primary limitation to this dissertation is that alterations in muscle morphology were not measured, and this was due to financial resources. However, given our results, it seems pertinent that future research utilizes methods to detect these changes. At the macro-level, it is recommended that future work measures changes in muscle cross-sectional area, pennation angle and/or volume. At the micro-level, detecting for changes in muscle fiber type and possible sarcomeres adaptations utilizing muscle biopsy and tissue staining techniques is also recommended. Moreover, tracking changes in circulating biomarkers, such as myostatin (atrophy-inducing signaling molecule) could help to explain changes in muscle fiber growth and strength. Taken together, a combination of macro- and micro- level measures as well as studying the cellular response of muscle should help to more fully clarify the precise adaptations in muscle morphology that affect strength in response to ACL injury, surgery and therapeutic interventions.

Along the same lines, another limitation is that the superimposed burst technique was the only neurological measure utilized to quantify alterations in quadriceps activation. Though the superimposed burst technique is commonly employed in the ACL literature to detect QAF, this measure does not directly measure alterations in alpha motorneuron pool excitability. Rather, this technique accounts for an individual's capability to volitionally utilize their quadriceps muscle during an isometric contraction. Accordingly, going forward, future investigations should consider utilizing a combination of neural measures to better understand the mechanisms underlying the changes in quadriceps neural activity. To accomplish this, it is recommended that future work utilize methods such as the Hoffman reflex to track alterations in spinal reflexive activity as well as the V-wave, which accounts for descending motor input. Furthermore, the use of methodology such as transcranial magnetic stimulation could account for cortical changes. Together, these spinal reflexive and cortical measures would allow for a

more precise determinant of quadriceps activation failure in addition to the superimposed burst technique.

It would also be beneficial for future work to examine the effect of graft type (patellar tendon v. semitendinosus gracilis) on quadriceps activation, as it is unknown what effect these graft types have on quadriceps neural activity. Given that University of Michigan is primarily a patellar tendon graft center, combining data sets with other institutions that primarily utilize hamstring grafts may be an approach that can help determine if differences in quadriceps activation exists between these two graft types.

Lastly, going forward, it would be ideal for our preliminary intervention work to be evaluated using a randomized control trial. Though no group selection bias was detected in the intervention trial, confirmed by the fact that no pre-operative differences in quadriceps function existed between groups, larger sample sizes and patient randomization is needed to determine the true clinical effect.

APPENDICES

APPENDIX A

Pilot Data AIM 1

Summary of Pilot Data

To ensure exposure to the testing protocol did not cause a learning effect, three subjects (Table A.i) underwent pilot testing. Paired t-tests were utilized to detect if a change in quadriceps activation (Table A.ii) and strength (Table A.iii) occurred in the non-dominant limb between A) week 1 and week 4, B) week 1 and week 8, and C) week 4 and week 8. No change in quadriceps activation or strength was found ($P>0.05$), suggesting that exposure to the equipment and testing protocol did not cause a change in quadriceps function.

Table A.i Participant Demographics

Subjects	Sex	Age (yrs)	Height (m)	Mass (kg)
Pilot 1	Male	19	1.45	66.68
Pilot 2	Female	22	1.75	68.04
Pilot 3	Male	23	1.75	83.91

Table A.ii Quadriceps Activation: Central Activation Ratio (mean)

Subjects	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8
Pilot 1	90.30	84.27	92.22	84.45	89.12	93.24	89.65	90.49
Pilot 2	95.43	98.02	97.35	97.43	97.83	97.47	98.64	96.64
Pilot 3	90.84	92.97	91.98	98.59	89.50	94.88	88.51	91.83

Table A.iii Quadriceps Strength (Nm/kg [mean])

Subjects	Mode	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8
Pilot 1	CON 30 deg/sec	2.00	1.86	2.35	2.10	2.17	2.61	2.18	2.36
Pilot 2		1.75	1.62	1.72	1.63	1.87	1.84	1.75	1.89
Pilot 3		2.11	2.16	2.34	2.26	2.55	2.58	2.61	2.27
Pilot 1	CON 60 deg/sec	1.73	1.60	2.08	1.76	1.86	2.11	1.93	1.90
Pilot 2		1.27	1.33	1.32	1.57	1.58	1.38	1.46	1.79
Pilot 3		1.78	1.49	1.95	2.04	2.51	2.03	2.03	1.80
Pilot 1	ECC 30 deg/sec	1.76	2.25	2.35	2.24	2.06	1.98	2.00	2.08
Pilot 2		2.01	2.18	1.80	1.77	1.72	1.49	1.65	1.61
Pilot 3		1.68	1.89	1.85	1.87	2.53	2.33	2.20	2.25
Pilot 1	ECC 60 deg/sec	2.43	2.72	2.73	2.18	2.10	2.17	1.83	2.08
Pilot 2		1.90	2.05	1.81	1.83	1.93	1.57	1.31	1.83
Pilot 3		2.31	1.93	1.97	1.69	2.68	2.65	2.68	2.38

Abbreviations: CON, concentric; ECC, eccentric

APPENDIX B

General Post-operative Rehabilitation Protocol

Table B.i Post-operative Guidelines for Participants Undergoing ACL Reconstruction

		Time				
Exercise	Group	1-4 weeks	5-15 weeks	3-4 months	4-5 months	6 months
Range of Motion (ROM)	ACL-only and Meniscectomy	No restrictions Bicycle				
	Meniscal Repair	0°-40°: wk1 0-50°: wk2 0-60°: wk3 0-70°: wk4	0°-80°: wk5 0-90°: wk6 No restrictions: wk7+			
	All	Patellar mobilization				
Brace	ACL-only and Meniscectomy	None	During closed chain -discontinue at wk6			
	Meniscal Repair	During closed chain				
Flexibility	All	Hamstring stretch Calf stretch Quadriceps stretch	Continue previous exercises as necessary	Continue previous exercises as necessary	Continue previous exercises as necessary	Continue previous exercises as necessary
Weight Bearing (WB)	ACL-only and Meniscectomy	25%+ WB: wks1-4	Progress to FWB: wk5+			
	Meniscal Repair	NWB: wk1 25% WB: wk2 50% WB: wk3 75% WB: wk4	Progress to FWB: wk5 Progress to FWB w/o crutches: wk6+			
Progressive Resistance Exercises	All	Quadriceps sets Straight-leg raise Hip abduction and adduction Ankle pumps	To previous exercises add the following: Hamstring curls Hip flexion and extension Leg press	Continue previous exercises as necessary	Continue previous exercises as necessary	Continue previous exercises as necessary
Closed Kinetic Chain Exercises	All	Leg Press Single-leg balance	To previous exercises add the following: Standing bilateral ankle platform system	To previous exercises add the following: Walk/jog program	To previous exercises add the following: Plyometrics -Meniscal Repair sagittal only until 6 months	To previous exercises add the following: Agility Program (Appendix 2)
	Meniscal Repair -maintain ROM /WB restrictions	Calf raises Standing knee extensions Bilateral mini squats	Stair-climbing machine Step-ups Single-leg squats	Rope jumping		Sport-specific training

*** Individual variations between protocols existed based on effusion, quadriceps control, gait, age, and individual's response to treatment***

APPENDIX C

MedSport Return-to-Play Criteria

Table C.i Agility Program Guidelines

Directions: Complete 3 sessions per week with at least 1 day of rest in between sessions. Do not complete a session if you are experiencing pain or swelling. Take rest days until symptoms are gone, and then resume the program.

	Week		
Exercise	1	2	3
Forward Run	10 reps	10 reps	10 reps
Retro Run	10 reps	10 reps	10 reps
Side Shuffles	10 reps	10 reps	10 reps
Carioca's	10 reps	10 reps	10 reps
Forward Skip	10 reps	10 reps	10 reps
Retro Skip	10 reps	10 reps	10 reps
Quick Step		5 reps x 20 seconds	5 reps x 20 seconds
Double Leg Line Hop		5 reps x 20 seconds	5 reps x 20 seconds
Double Leg Square Hop		5 reps x 20 seconds	5 reps x 20 seconds
Cutting			10 reps (1/2 basketball court)
Shuttle Run			10 reps (full basketball court)
Box Cut			10 reps (each corner basketball court)
Base Running			10 reps (on baseline of court, forward and backward)

Agility Exercise Descriptions

Side Shuffles: In a defensive stance, run sideways (laterally) with trailing foot stepping to the leading foot.

Carioca's: Run sideways (laterally) by alternately crossing trailing leg in front of the leading leg and then crossing trailing leg behind the leading leg.

Quick Step: Place a line on the floor. On toes, quickly step forward over the line with both feet, then step backward over the line, emphasizing quickness.

Double Leg Line Hop: Place a line on the floor. Start on one side of the line with feet parallel to the line. Hop with both feet to the opposite side of the line and then hop back to the starting position.

Double Leg Square Hop: Form a cross on the floor with tape. As you are facing the cross, box 1 is lower left, box 2 is upper left, box 3 is upper right, and box 4 is lower right. Start in box 1, with both feet hop forward to box 2, then hop laterally to box 3, then hop backward to box 4, then hop laterally back to box 1. Week 2 of agilities perform this pattern: 1, 2, 3, 4. Week 3 of agilities, switch to this pattern: 1, 3, 2, 4.

Cutting: Run at a 45º angle for 3-5 steps. Plant on the outside leg and cut 90º and continue another 3-5 steps. Continue this zig-zag pattern to half-court (basketball) or about 20 yards.

Shuttle Runs: Perform either on a basketball court or outside, about 40 yards total distance. Start on the baseline, run and touch the free-throw line, then return and touch the baseline. Next, run and touch half-court, then back and touch. Then run and touch the opposite free-throw line, then back and touch. Finally, run and touch the opposite baseline, then back and touch. Outside, go 10 yards, back, 20 yards, back, 30 yards, back, and 40 yards, back.

Box Cut: Use the basketball key or similar size area. Start on the baseline at one of the corners. Run forward to the free-throw line. Change direction on your outside leg and side shuffle across the free-throw line. Plant on your outside leg and run backward to the baseline. Change

direction on your outside leg and side shuffle back to your starting position. Repeat beginning from the opposite corner you started from.

Base Running: Use softball or little league bases. If you are inside, just use half a basketball court. Starting from home plate, run bases with rounded turns like you normally would. Repeat in the opposite direction.

APPENDIX D

NMES and Eccentric Exercise Interventions Treatment Intensity

Table D.i NMES Intervention Intensity (Table 1 of 3)

			Week 1		Week 2				
			Treatment 1	Treatment 2	Treatment 3				Treatment 4
Subject	Weight (kg)	Group	NMES Intensity (mA)	NMES Intensity (mA)	NMES Intensity (mA)	MVIC (Nm)	NMES Torque Production (Nm)	% Torque Production	NMES Intensity (mA)
74	127.01	N-only	31	43	50	16.90	16.04	94.89	72
79	92.98	N-only	30	36	30	17.65	6.78	38.43	37
88	46.20	N-only	40	40	55	9.83	10.92	111.08	65
92	58.20	N-only	19	19	45	5.27	1.52	28.92	45
96	89.81	N&E	45	58	58	4.62	6.40	138.47	85
97	63.50	N-only	50	50	58	10.46	8.45	80.78	60
99	79.38	N-only	47	50	60	10.07	4.07	40.38	65
102	84.39	N-only	45	50	55	27.81	6.60	23.74	60
103	86.18	N-only	33	45	75	15.97	4.34	27.17	75
104	86.21	N&E	52	60	65	5.29	1.78	33.65	65
106	83.00	N&E	50	60	85	55.53	19.75	35.58	85
107	58.97	N&E	40	60	85	29.91	9.66	32.29	85
108	97.97	N-only	46	50	70	10.29	2.29	22.22	70
109	59.42	N&E	50	50	60	16.50	5.08	30.79	60
111	80.65	N-only	32	40	50	9.66	7.51	77.79	50
113	102.51	N&E	50	55	65	6.92	2.79	40.24	65
114	83.46	N&E	37	40	80	11.87	3.29	27.73	80
126	59.37	N&E	50	50	50	6.89	3.83	55.59	50

Table D.i NMES Intervention Intensity (Table 2 of 3)

			Week 3					Week 4				
			Treatment 5				Treatment 6	Treatment 7				Treatment 8
Subject	Weight (kg)	Group	NMES Intensity (mA)	MVIC (Nm)	NMES Torque Production (Nm	% Torque Production	NMES Intensity (mA)	NMES Intensity (mA)	MVIC (Nm)	NMES Torque Production (Nm	% Torque Production	NMES Intensity (mA)
74	127.01	N-only	92	27.5	15.26	55.49	100	95	45.57	19.03	41.75	100
79	92.98	N-only	38	24.78	8.52	34.37	48	60	47.22	11.89	25.18	66
88	46.20	N-only	65	12.10	14.25	117.76	66	63	15.80	10.03	63.48	63
92	58.20	N-only	70	27.03	8.12	30.04	70	85	57.46	17.46	30.39	85
96	89.81	N&E	85	15.31	9.70	63.32	85	100	44.92	34.21	76.16	95
97	63.50	N-only	80	19.74	5.54	28.06	80	85	26.17	11.82	45.18	80
99	79.38	N-only	65	11.23	9.95	88.60	65	70	22.36	9.89	44.22	85
102	84.39	N-only	65	40.97	11.64	28.40	60	68	45.98	12.11	26.34	68
103	86.18	N-only	100	46.87	11.69	24.94	100	100	55.97	4.78	8.54	100
104	86.21	N&E	95	17.84	9.99	55.99	95	100	26.84	6.31	23.51	100
106	83.00	N&E	90	49.43	28.77	58.20	90	100	87.01	62.60	71.95	100
107	58.97	N&E	90	41.67	15.45	37.07	90	100	46.43	27.81	59.90	100
108	97.97	N-only	100	24.83	6.11	24.61	100	100	60.33	5.86	9.71	100
109	59.42	N&E	75	17.79	4.77	26.81	75	85	25.93	10.57	40.76	85
111	80.65	N-only	50	20.13	10.43	51.81	50	65	26.02	16.14	62.04	65
113	102.51	N&E	85	44.29	10.54	23.80	85	100	48.53	10.20	21.01	100
114	83.46	N&E	80	18.38	5.28	28.72	80	100	25.27	13.61	53.85	100
126	59.37	N&E	70	18.60	11.40	61.29	70	65	24.05	14.22	59.12	70

Table D.i NMES Intervention Intensity (Table 3 of 3)

			Week 5					Week 6				
			Treatment 9				Treatment 10	Treatment 11				Treatment 12
Subject	Weight (kg)	Group	NMES Intensity (mA)	MVIC (Nm)	NMES Torque Production (Nm)	% Torque Production	NMES Intensity (mA)	NMES Intensity (mA)	MVIC (Nm)	NMES Torque Production (Nm)	% Torque Production	NMES Intensity (mA)
74	127.01	N-only	100	96.346	17.15	17.80	100	88	102.76	17.40	16.93	100
79	92.98	N-only	90	62.36	10.08	16.16	96	91	60.79	8.60	14.15	100
88	46.20	N-only	71	26.89	8.51	29.75	71	71	28.97	10.14	35.00	71
92	58.20	N-only	100	67.052	17.19	25.64	100	100	79.44	28.65	36.06	100
96	89.81	N&E	100	68.039	14.70	21.61	100	100	90.46	3.89	4.30	100
97	63.50	N-only	90	43.071	8.89	20.64	90	100	69.63	21.42	30.76	100
99	79.38	N-only	90	36.792	9.89	26.88	90	100	83.92	36.82	43.87	100
102	84.39	N-only	70	54.864	14.88	27.12	70	75	84.59	44.52	52.62	100
103	86.18	N-only	100	92.35	7.17	7.76	100	100	118.57	4.74	4.00	100
104	86.21	N&E	100	29.846	7.37	24.69	100	100	40.82	21.19	51.90	100
106	83.00	N&E	100	96.275	60.47	62.81	100	100	110.92	76.57	69.03	100
107	58.97	N&E	100	49.199	28.65	58.23	100	100	57.72	45.34	78.55	100
108	97.97	N-only	100	56.686	3.99	7.04	100	100	59.08	2.67	4.52	100
109	59.42	N&E	100	51.211	12.99	25.37	100	100	69.41	36.74	52.92	100
111	80.65	N-only	85	55.02	19.25	34.99	90	100	62.67	25.24	40.26	100
113	102.51	N&E	100	56.95	13.47	23.65	100	100	105.97	10.77	10.16	100
114	83.46	N&E	100	48.12	12.45	25.87	100	100	67.28	21.71	32.26	100
126	59.37	N&E	70	24.051	14.22	59.13	70	100	35.06	30.55	87.13	100

Table D.ii Eccentric Intervention Intensity (Table 1 of 3)

			Week 1						Week 2					
			Treatment 1			Treatment 2			Treatment 3			Treatment 4		
Subject	Weight (kg)	Group	1 RM (lbs)	Avg Force	Intensity (%)	1 RM (lbs)	Avg Force	Intensity (%)	1 RM (lbs)	Avg Force	Intensity (%)	1 RM (lbs)	Avg Force	Intensity (%)
96	89.81	N&E	234.00	251.25	107.37	234.00	285.50	122.01	321.00	337.50	105.14	321.00	251.00	78.19
104	86.21	N&E	126.00	182.50	144.84	126.00	174.75	138.69	205.00	223.50	109.02	205.00	204.50	99.76
106	83.00	N&E	221.00	165.50	74.89	221.00	180.00	81.45	287.00	228.75	79.70	287.00	244.75	85.28
107	58.97	N&E	138.00	160.50	116.30	138.00	159.00	115.22	179.00	209.75	117.18	179.00	239.00	133.52
109	59.42	N&E	191.00	151.25	79.19	191.00	134.00	70.16	257.00	179.00	69.65	257.00	187.50	72.96
113	102.51	N&E	252.00	211.25	83.83	252.00	216.00	85.71	277.00	232.50	83.94	277.00	296.75	107.13
114	83.46	N&E	217.00	134.00	61.75	217.00	150.50	69.35	253.00	239.00	94.47	253.00	257.50	101.78
121	97.97	E-only	142.00	92.75	65.32	142.00	162.00	114.08	278.00	213.90	76.94	278.00	255.75	92.00
122	82.46	E-only	234.00	147.50	63.03	234.00	198.25	84.72	352.00	277.50	78.84	352.00	296.00	84.09
123	74.84	E-only	334.00	209.00	62.57	334.00	205.25	61.45	374.00	311.00	83.16	374.00	348.00	93.05
124	66.36	E-only	104.00	115.50	111.06	104.00	134.25	129.09	106.00	145.75	137.50	106.00	192.25	181.37
125	67.54	E-only	164.00	126.75	164.00	164.00	98.25	59.91	206.00	160.00	77.67	206.00	173.25	84.10
126	59.37	N&E	109.00	110.25	101.15	109.00	137.00	125.69	129.00	146.00	113.18	129.00	163.25	126.55
131	85.63	E-only	120.00	112.75	93.96	120.00	174.75	145.63	211.00	244.25	115.76	211.00	252.75	119.79

Table D.ii Eccentric Intervention Intensity (Table 2 of 3)

			Week 3						Week 4					
			Treatment 5			Treatment 6			Treatment 7			Treatment 8		
Subject	Weight (kg)	Group	1 RM (lbs)	Avg Force	Intensity (%)	1 RM (lbs)	Avg Force	Intensity (%)	1 RM (lbs)	Avg Force	Intensity (%)	1 RM (lbs)	Avg Force	Intensity (%)
96	89.81	N&E	338.00	270.50	80.03	338.00	213.25	63.09	354.00	343.25	96.96	354.00	370.25	104.59
104	86.21	N&E	271.00	297.50	109.78	271.00	338.00	124.72	304.00	316.75	104.19	304.00	315.25	103.70
106	83.00	N&E	340.00	285.00	83.82	340.00	284.25	83.60	367.00	323.50	88.15	367.00	313.50	85.42
107	58.97	N&E	256.00	267.00	104.30	256.00	288.75	112.79	281.00	284.75	101.33	281.00	230.50	82.03
109	59.42	N&E	294.00	197.50	67.18	294.00	205.50	69.90	309.00	214.00	69.26	309.00	217.00	70.23
113	102.51	N&E	336.00	296.75	88.32	336.00	344.75	102.60	430.00	397.50	92.44	430.00	397.50	92.44
114	83.46	N&E	289.00	295.25	102.16	289.00	311.50	107.79	308.00	345.00	112.01	308.00	381.00	123.70
121	97.97	E-only	309.00	269.00	87.06	309.00	333.75	108.01	324.00	338.25	104.40	324.00	335.75	103.63
122	82.46	E-only	392.00	359.25	91.65	392.00	426.75	108.86	395.00	459.00	116.20	395.00	521.50	132.03
123	74.84	E-only	489.00	451.75	92.38	489.00	511.00	104.50	500.00	482.80	96.56	500.00	482.80	96.56
124	66.36	E-only	120.00	202.50	168.75	120.00	238.25	198.54	126.00	247.00	196.03	126.00	247.00	196.03
125	67.54	E-only	245.00	224.25	91.53	245.00	244.50	99.80	297.00	263.75	88.80	297.00	320.00	107.74
126	59.37	N&E	143.00	188.50	131.82	143.00	208.25	145.63	156.00	225.00	144.23	156.00	234.25	150.16
131	85.63	E-only	234.00	275.50	117.74	234.00	315.00	134.62	256.00	335.25	130.96	256.00	380.25	148.54

Table D.ii Eccentric Intervention Intensity (Table 3 of 3)

			Week 5						Week 6					
			Treatment 9			Treatment 10			Treatment 11			Treatment 12		
Subject	Weight (kg)	Group	1 RM (lbs)	Avg Force	Intensity (%)	1 RM (lbs)	Avg Force	Intensity (%)	1 RM (lbs)	Avg Force	Intensity (%)	1 RM (lbs)	Avg Force	Intensity (%)
96	89.81	N&E	385.00	378.00	98.18	385.00	359.50	93.38	415.00	487.75	117.53	415.00	526.25	126.81
104	86.21	N&E	334.00	318.75	95.43	334.00	303.25	90.79	361.00	320.50	88.78	361.00	320.50	88.78
106	83.00	N&E	386.00	319.25	82.71	386.00	360.50	93.39	394.00	400.25	101.59	394.00	413.50	104.95
107	58.97	N&E	316.00	236.00	74.68	316.00	255.25	80.78	322.00	283.50	88.04	322.00	325.00	100.93
109	59.42	N&E	314.00	220.25	70.14	314.00	228.75	72.85	323.00	244.50	75.70	323.00	280.75	86.92
113	102.51	N&E	456.00	468.50	102.74	476.00	461.50	96.95	476.00	502.25	105.51	476.00	563.25	118.33
114	83.46	N&E	318.00	440.00	138.36	318.00	438.50	137.89	357.00	437.00	122.41	357.00	500.50	140.20
121	97.97	E-only	358.00	357.25	99.79	377.00	390.50	103.58	377.00	445.75	118.24	377.00	445.75	118.24
122	82.46	E-only	421.00	505.75	120.13	421.00	493.75	117.28	427.00	495.75	116.10	427.00	550.25	128.86
123	74.84	E-only	531.00	547.25	103.06	531.00	593.00	111.68	537.00	567.75	105.73	537.00	591.50	110.15
124	66.36	E-only	150.00	323.50	215.67	150.00	343.25	228.83	159.00	375.00	235.85	159.00	326.25	205.19
125	67.54	E-only	345.00	393.25	113.99	345.00	382.25	110.80	350.00	421.50	120.43	350.00	460.00	131.43
126	59.37	N&E	179.00	245.25	137.01	179.00	242.25	135.34	219.00	232.00	105.94	219.00	245.75	112.21
131	85.63	E-only	287.00	368.25	128.31	287.00	360.50	125.61	305.00	394.00	129.18	305.00	359.25	117.79

APPENDIX E

Supplementary Data- AIM 1

Table E.i Participant Demographics

SUBJECTS	GROUP	SEX	AGE (YRS)	HEIGHT (M)	MASS (KG)
1	EX	F	22	1.63	65.77
3	EX	M	24	1.83	86.18
4	EX	F	27	1.57	47.62
5	EX	M	25	1.68	68.20
6	EX	F	22	1.65	54.40
8	EX	M	25	1.83	81.64
10	EX	M	20	1.78	74.84
11	EX	M	22	1.85	90.72
13	EX	F	20	1.78	65.77
102	CNTRL	F	24	1.73	58.96
103	CNTRL	M	25	1.75	84.82
105	CNTRL	F	20	1.70	58.96
106	CNTRL	F	20	1.65	61.23
107	CNTRL	M	27	1.80	68.03
108	CNTRL	F	22	1.70	65.77
109	CNTRL	F	28	1.60	54.5
110	CNTRL	M	18	1.80	79.37
111	CNTRL	F	19	1.75	70.31

ABBREVIATIONS: CNRTL, CONTROL PARTICIPANT; EX, ECCENTRIC TRAINING PARTICIPANT

Table E.ii Quadriceps Activation (CAR [mean])

			TIME		
SUBJECTS	GROUP	LIMB	PRE	MID	POST
1	EX	EXERCISED	.95	.92	.96
		UN-EXERCISED	.95	.95	.94
3	EX	EXERCISED	.96	.94	.96
		UN-EXERCISED	.95	.95	.95
4	EX	EXERCISED	.89	.81	.76
		UN-EXERCISED	.80	.94	.95
5	EX	EXERCISED	.88	.92	.91
		UN-EXERCISED	.90	.95	.96
6	EX	EXERCISED	.85	.95	.96
		UN-EXERCISED	.90	.95	.93
8	EX	EXERCISED	.96	.98	.97
		UN-EXERCISED	.94	.97	.95
10	EX	EXERCISED	.88	.94	.95
		UN-EXERCISED	.95	.95	.94
11	EX	EXERCISED	.90	.94	.95
		UN-EXERCISED	.93	.98	.97
13	EX	EXERCISED	.95	.97	.98
		UN-EXERCISED	.95	.93	.97
102	CNTRL	EXERCISED	.92	.92	.97
		UN-EXERCISED	.93	.90	.96
103	CNTRL	EXERCISED	.98	.97	.95
		UN-EXERCISED	.98	.98	.95
105	CNTRL	EXERCISED	.94	.95	.96
		UN-EXERCISED	.88	.96	.94
106	CNTRL	EXERCISED	.96	.94	.94
		UN-EXERCISED	.95	.95	.93
107	CNTRL	EXERCISED	.97	.98	.97
		UN-EXERCISED	.96	.93	.91
108	CNTRL	EXERCISED	.96	.94	.95
		UN-EXERCISED	.96	.95	.92
109	CNTRL	EXERCISED	.94	.86	.93
		UN-EXERCISED	.85	.93	.84
110	CNTRL	EXERCISED	.97	.95	.93
		UN-EXERCISED	.93	.94	.90
111	CNTRL	EXERCISED	.94	.95	.96
		UN-EXERCISED	.95	.97	.97

ABBREVIATIONS: CAR; CENTRAL ACTIVATION RATIO; CNRTL, CONTROL PARTICIPANT;

EX, ECCENTRIC TRAINING PARTICIPANT

Table E.iii Quadriceps Strength Concentric Mode 30 deg/second (mean [Nm/kg])

SUBJECTS	GROUP	LIMB	TIME PRE	MID	POST
1	EX	EXERCISED	1.70	1.43	1.83
		UN-EXERCISED	1.26	1.35	1.20
3	EX	EXERCISED	1.72	2.29	2.12
		UN-EXERCISED	1.88	1.74	1.81
4	EX	EXERCISED	1.23	1.36	1.26
		UN-EXERCISED	.69	1.07	1.50
5	EX	EXERCISED	2.43	3.23	3.95
		UN-EXERCISED	1.66	3.28	3.63
6	EX	EXERCISED	1.58	2.46	2.40
		UN-EXERCISED	1.95	2.28	2.64
8	EX	EXERCISED	2.71	3.25	3.19
		UN-EXERCISED	2.47	3.21	2.78
10	EX	EXERCISED	2.69	2.97	3.61
		UN-EXERCISED	2.78	2.33	3.29
11	EX	EXERCISED	2.27	2.69	3.04
		UN-EXERCISED	2.22	2.66	2.99
13	EX	EXERCISED	2.41	2.61	2.54
		UN-EXERCISED	1.75	2.06	2.25
102	CNTRL	EXERCISED	1.83	1.70	1.76
		UN-EXERCISED	1.91	1.66	2.06
103	CNTRL	EXERCISED	1.95	2.02	2.36
		UN-EXERCISED	1.98	2.33	2.47
105	CNTRL	EXERCISED	1.54	2.33	2.20
		UN-EXERCISED	1.83	1.54	1.69
106	CNTRL	EXERCISED	2.43	2.79	3.20
		UN-EXERCISED	2.54	2.75	3.34
107	CNTRL	EXERCISED	2.46	2.50	1.98
		UN-EXERCISED	2.07	2.29	2.17
108	CNTRL	EXERCISED	2.90	2.78	2.68
		UN-EXERCISED	2.45	2.54	2.47
109	CNTRL	EXERCISED	2.29	2.13	2.67
		UN-EXERCISED	1.75	1.80	1.95
110	CNTRL	EXERCISED	2.86	2.25	2.54
		UN-EXERCISED	2.70	2.11	2.65
111	CNTRL	EXERCISED	2.70	3.03	3.21
		UN-EXERCISED	2.99	2.91	2.32

ABBREVIATIONS: CNRTL, CONTROL PARTICIPANT; EX, ECCENTRIC TRAINING PARTICIPANT

Table E.iv Quadriceps Strength Concentric Mode 60 deg/second (mean [Nm/kg])

SUBJECTS	GROUP	LIMB	TIME PRE	TIME MID	TIME POST
1	EX	EXERCISED	1.32	1.11	1.28
		UN-EXERCISED	0.60	0.86	0.98
3	EX	EXERCISED	1.52	1.76	1.58
		UN-EXERCISED	1.64	1.64	1.77
4	EX	EXERCISED	0.83	1.41	1.02
		UN-EXERCISED	0.63	0.91	1.41
5	EX	EXERCISED	1.92	2.21	3.11
		UN-EXERCISED	1.37	3.02	3.33
6	EX	EXERCISED	1.30	2.46	1.76
		UN-EXERCISED	1.52	1.81	2.35
8	EX	EXERCISED	2.38	3.15	2.77
		UN-EXERCISED	2.29	2.88	2.66
10	EX	EXERCISED	2.27	2.76	3.40
		UN-EXERCISED	1.89	2.20	3.01
11	EX	EXERCISED	1.48	2.56	2.79
		UN-EXERCISED	2.39	2.26	2.75
13	EX	EXERCISED	1.21	2.15	2.24
		UN-EXERCISED	1.32	1.77	2.07
102	CNTRL	EXERCISED	1.32	1.13	1.59
		UN-EXERCISED	1.18	1.15	1.55
103	CNTRL	EXERCISED	1.65	1.99	2.13
		UN-EXERCISED	1.57	2.32	1.98
105	CNTRL	EXERCISED	0.93	1.52	1.42
		UN-EXERCISED	1.18	1.07	1.20
106	CNTRL	EXERCISED	1.93	2.12	2.91
		UN-EXERCISED	2.10	2.61	2.97
107	CNTRL	EXERCISED	1.81	1.80	1.72
		UN-EXERCISED	2.15	1.76	1.73
108	CNTRL	EXERCISED	2.22	2.05	2.28
		UN-EXERCISED	2.04	2.03	2.15
109	CNTRL	EXERCISED	1.62	1.81	2.34
		UN-EXERCISED	1.67	1.82	1.82
110	CNTRL	EXERCISED	1.70	1.69	2.41
		UN-EXERCISED	2.32	1.78	3.43
111	CNTRL	EXERCISED	2.11	2.50	2.10
		UN-EXERCISED	2.61	2.13	1.70

ABBREVIATIONS: CNRTL, CONTROL PARTICIPANT; EX, ECCENTRIC TRAINING PARTICIPANT

Table E.v Quadriceps Strength Eccentric Mode 30 deg/second (mean [Nm/kg])

SUBJECTS	GROUP	LIMB	TIME PRE	TIME MID	TIME POST
1	EX	EXERCISED	1.73	1.92	2.60
		UN-EXERCISED	1.43	1.53	1.87
3	EX	EXERCISED	2.98	4.27	3.84
		UN-EXERCISED	3.18	3.75	3.35
4	EX	EXERCISED	1.33	2.09	1.93
		UN-EXERCISED	0.83	1.57	1.81
5	EX	EXERCISED	2.65	5.97	6.81
		UN-EXERCISED	2.24	4.92	6.13
6	EX	EXERCISED	2.24	2.75	3.25
		UN-EXERCISED	2.23	2.34	3.04
8	EX	EXERCISED	1.88	4.27	4.26
		UN-EXERCISED	2.38	3.58	3.18
10	EX	EXERCISED	2.68	3.89	5.14
		UN-EXERCISED	2.53	3.04	4.31
11	EX	EXERCISED	2.24	2.57	3.16
		UN-EXERCISED	2.21	2.43	3.28
13	EX	EXERCISED	2.36	3.58	3.62
		UN-EXERCISED	2.46	2.30	2.52
102	CNTRL	EXERCISED	2.52	2.15	2.86
		UN-EXERCISED	2.77	2.58	2.36
103	CNTRL	EXERCISED	1.80	2.01	2.53
		UN-EXERCISED	2.22	2.46	2.37
105	CNTRL	EXERCISED	2.04	2.67	2.37
		UN-EXERCISED	2.32	2.93	2.45
106	CNTRL	EXERCISED	2.32	2.73	3.56
		UN-EXERCISED	2.34	2.81	3.57
107	CNTRL	EXERCISED	2.73	3.19	3.07
		UN-EXERCISED	2.95	2.68	2.92
108	CNTRL	EXERCISED	3.64	3.65	3.56
		UN-EXERCISED	2.99	2.50	2.46
109	CNTRL	EXERCISED	2.25	1.85	2.00
		UN-EXERCISED	1.99	2.04	1.78
110	CNTRL	EXERCISED	3.55	3.09	3.91
		UN-EXERCISED	3.26	3.19	2.25
111	CNTRL	EXERCISED	3.60	3.84	2.96
		UN-EXERCISED	4.01	3.74	3.01

ABBREVIATIONS: CNRTL, CONTROL PARTICIPANT; EX, ECCENTRIC TRAINING PARTICIPANT

Table E.vi Quadriceps Strength Eccentric Mode 60 deg/second (mean [Nm/kg])

SUBJECTS	GROUP	LIMB	TIME PRE	TIME MID	TIME POST
1	EX	EXERCISED	1.56	2.25	2.70
		UN-EXERCISED	1.65	1.68	1.84
3	EX	EXERCISED	2.82	4.26	3.40
		UN-EXERCISED	3.04	3.32	3.85
4	EX	EXERCISED	1.45	2.32	1.94
		UN-EXERCISED	1.00	1.77	1.83
5	EX	EXERCISED	2.57	5.27	6.18
		UN-EXERCISED	2.33	5.71	5.98
6	EX	EXERCISED	1.80	2.88	3.36
		UN-EXERCISED	2.00	2.43	3.33
8	EX	EXERCISED	1.38	4.30	4.70
		UN-EXERCISED	1.98	4.10	3.38
10	EX	EXERCISED	2.85	4.53	5.36
		UN-EXERCISED	2.99	2.93	4.11
11	EX	EXERCISED	2.38	2.88	3.34
		UN-EXERCISED	2.94	2.92	2.97
13	EX	EXERCISED	2.51	3.55	3.73
		UN-EXERCISED	2.45	2.15	2.56
102	CNTRL	EXERCISED	2.71	2.42	2.28
		UN-EXERCISED	2.69	2.28	2.59
103	CNTRL	EXERCISED	1.85	2.41	2.60
		UN-EXERCISED	2.34	2.80	2.76
105	CNTRL	EXERCISED	2.00	2.32	2.77
		UN-EXERCISED	2.50	3.05	2.75
106	CNTRL	EXERCISED	2.43	3.02	3.91
		UN-EXERCISED	2.55	3.02	3.63
107	CNTRL	EXERCISED	2.70	2.99	2.88
		UN-EXERCISED	3.09	2.86	2.93
108	CNTRL	EXERCISED	3.83	3.50	3.28
		UN-EXERCISED	3.26	2.86	2.73
109	CNTRL	EXERCISED	2.45	2.32	2.02
		UN-EXERCISED	2.17	2.09	1.79
110	CNTRL	EXERCISED	3.48	3.15	3.97
		UN-EXERCISED	3.57	3.30	3.53
111	CNTRL	EXERCISED	3.35	4.11	3.48
		UN-EXERCISED	3.99	3.71	2.85

ABBREVIATIONS: CNRTL, CONTROL PARTICIPANT; EX, ECCENTRIC TRAINING PARTICIPANT

APPENDIX E

Supplementary Data- AIM 2

Table E.vii Participant Demographics (Table 1 of 3)

SUBJECTS	SEX	AGE (YRS)	HEIGHT (M)	MASS (KG)	TIME TO TEST (MONTHS)		CONCOMITANT MENISCAL SURGERY
					PRE-OPERATIVE: POST-INJURY	POST-OPERATIVE: POST-SURGERY	
12	FEMALE	15	1.65	58.97	0.73	7.13	ACL-ONLY
15	FEMALE	14	1.74	61.23	0.50	6.97	ACL-ONLY
16	FEMALE	15	1.68	81.65	0.67	6.63	ACL-ONLY
18	MALE	23	1.80	86.18	10.37	9.00	MENISCAL REPAIR
21	FEMALE	15	1.85	61.23	0.73	8.40	MENISCAL REPAIR
22	MALE	29	1.75	77.11	1.03	6.50	ACL-ONLY
24	MALE	19	1.84	84.37	9.20	6.87	ACL-ONLY
26	MALE	15	1.75	63.50	1.43	8.40	MENISCECTOMY
31	MALE	20	1.85	81.65	1.20	6.47	ACL-ONLY
34	MALE	17	1.73	61.23	1.43	6.07	MENISCAL REPAIR
36	MALE	28	1.65	88.45	1.30	5.23	ACL-ONLY
39	FEMALE	20	1.65	57.61	0.83	6.97	ACL-ONLY
40	MALE	17	1.80	74.84	1.70	5.87	ACL-ONLY
42	FEMALE	20	1.70	83.91	1.33	7.50	ACL-ONLY
45	FEMALE	17	1.68	56.70	2.13	6.30	MENISCAL REPAIR
48	MALE	16	1.80	70.76	0.53	6.40	MENISCECTOMY
49	FEMALE	16	1.65	93.44	1.93	8.63	ACL-ONLY
50	MALE	19	1.85	75.80	3.77	8.60	MENISCAL REPAIR
51	FEMALE	19	1.63	65.90	1.60	7.73	MENISCAL REPAIR
53	FEMALE	16	1.68	63.50	2.23	7.20	MENISCECTOMY
55	MALE	18	1.61	54.43	0.83	7.83	ACL-ONLY
58	FEMALE	22	1.70	92.98	0.90	9.20	ACL-ONLY
61	MALE	16	1.93	79.50	1.47	10.57	MENISCECTOMY

Table E.vii Participant Demographics (Table 2 of 3)

SUBJECTS	SEX	AGE (YRS)	HEIGHT (M)	MASS (KG)	TIME TO TEST (MONTHS)		CONCOMITANT MENISCAL SURGERY
					PRE-OPERATIVE: POST-INJURY	POST-OPERATIVE: POST-SURGERY	
64	FEMALE	15	1.68	62.59	1.43	6.63	ACL-ONLY
72	MALE	38	1.83	91.35	2.33	7.33	ACL-ONLY
74	MALE	25	1.91	127.01	1.80	7.43	ACL-ONLY
77	FEMALE	24	1.70	64.86	1.13	8.23	ACL-ONLY
79	MALE	22	1.88	92.98	1.87	7.87	ACL-ONLY
81	FEMALE	24	1.60	61.23	9.40	6.70	ACL-ONLY
82	FEMALE	21	1.78	71.66	5.87	7.60	MENISCAL REPAIR
87	MALE	16	1.78	66.04	2.17	6.80	ACL-ONLY
88	FEMALE	23	1.57	46.26	1.97	6.47	ACL-ONLY
90	FEMALE	16	1.75	73.93	1.47	6.47	ACL-ONLY
91	FEMALE	18	1.70	74.39	2.53	6.53	MENISCECTOMY
92	FEMALE	15	1.60	58.20	1.97	6.87	ACL-ONLY
94	MALE	16	1.75	86.18	1.77	6.10	MENISCAL REPAIR
96	MALE	28	1.87	89.81	4.17	7.00	ACL-ONLY
97	MALE	22	1.70	63.50	0.70	6.73	MENISCAL REPAIR
99	MALE	23	1.79	79.38	1.67	6.00	MENISCAL REPAIR
101	MALE	17	1.80	136.53	1.17	9.30	MENISCECTOMY
102	MALE	24	1.83	84.39	1.60	6.80	MENISCAL REPAIR
103	MALE	30	1.83	86.18	1.97	9.67	MENISCAL REPAIR
104	MALE	22	1.17	86.21	1.03	8.37	ACL-ONLY
105	FEMALE	16	1.80	75.21	2.43	8.97	ACL-ONLY
106	MALE	18	0.02	83.00	0.80	6.57	ACL-ONLY
107	FEMALE	17	1.68	58.97	1.30	6.03	ACL-ONLY

Table E.vii Participant Demographics (Table 3 of 3)

SUBJECTS	SEX	AGE (YRS)	HEIGHT (M)	MASS (KG)	TIME TO TEST (MONTHS)		CONCOMITANT MENISCAL SURGERY
					PRE-OPERATIVE: POST-INJURY	POST-OPERATIVE: POST-SURGERY	
108	MALE	17	1.73	97.97	2.20	7.20	MENISCECTOMY
109	FEMALE	25	1.60	59.42	5.83	6.07	ACL-ONLY
110	MALE	15	1.83	74.84	2.03	6.10	MENISCAL REPAIR
111	MALE	17	1.83	80.65	1.43	6.93	ACL-ONLY
112	FEMALE	17	1.68	58.51	1.43	7.93	ACL-ONLY
114	MALE	33	1.80	83.46	3.37	6.57	ACL-ONLY
116	MALE	17	1.78	76.66	1.50	6.40	ACL-ONLY
118	MALE	16	1.77	73.20	1.57	6.10	MENISCAL REPAIR

Table E.viii Quadriceps Activation (CAR [max] Table 1 of 3)

SUBJECTS	LIMB	TIME	
		PRE-OPERATIVE	POST-OPERATIVE
12	ACL	74.36	90.92
	HEALTHY	91.26	91.28
15	ACL	94.30	77.45
	HEALTHY	87.02	75.30
16	ACL	82.29	61.61
	HEALTHY	81.55	70.30
18	ACL	82.11	79.21
	HEALTHY	76.87	77.91
21	ACL	94.27	85.76
	HEALTHY	87.10	71.22
22	ACL	98.36	95.08
	HEALTHY	99.88	97.53
24	ACL	76.59	65.44
	HEALTHY	74.78	83.42
26	ACL	93.78	67.95
	HEALTHY	91.82	70.05
31	ACL	94.28	75.32
	HEALTHY	97.58	95.75
34	ACL	71.02	87.04
	HEALTHY	72.03	92.21
36	ACL	87.48	67.93
	HEALTHY	80.15	94.47
39	ACL	98.80	97.06
	HEALTHY	98.80	90.13
40	ACL	83.02	79.00
	HEALTHY	63.78	81.93
42	ACL	96.87	90.93
	HEALTHY	98.20	97.79
45	ACL	75.86	62.60
	HEALTHY	77.95	94.67
48	ACL	91.25	91.68
	HEALTHY	94.54	94.12
49	ACL	85.65	75.86
	HEALTHY	88.87	90.17
50	ACL	89.31	87.65
	HEALTHY	92.89	96.31

Table E.viii Quadriceps Activation (CAR [max] Table 2 of 3)

SUBJECTS	LIMB	TIME	
		PRE-OPERATIVE	POST-OPERATIVE
51	ACL	99.33	98.72
	HEALTHY	94.39	98.38
53	ACL	94.13	87.60
	HEALTHY	90.54	85.16
55	ACL	95.81	92.02
	HEALTHY	94.77	95.13
58	ACL	92.41	80.77
	HEALTHY	86.79	88.44
61	ACL	91.82	91.58
	HEALTHY	92.59	93.15
64	ACL	94.14	96.69
	HEALTHY	90.70	92.86
72	ACL	88.76	84.25
	HEALTHY	95.95	94.12
74	ACL	92.64	88.98
	HEALTHY	92.13	96.02
77	ACL	99.41	93.01
	HEALTHY	90.36	93.71
79	ACL	91.04	87.53
	HEALTHY	88.53	87.75
81	ACL	92.65	83.63
	HEALTHY	93.45	93.21
82	ACL	86.33	82.92
	HEALTHY	96.21	86.03
87	ACL	78.94	88.31
	HEALTHY	91.98	90.84
88	ACL	94.92	97.06
	HEALTHY	94.66	98.03
90	ACL	94.34	81.41
	HEALTHY	92.75	94.67
91	ACL	87.00	95.44
	HEALTHY	95.72	92.64
92	ACL	99.31	86.72
	HEALTHY	98.45	90.16
94	ACL	96.51	81.59
	HEALTHY	97.38	95.56

Table E.viii Quadriceps Activation (CAR [max] Table 3 of 3)

		TIME	
SUBJECTS	LIMB	PRE-OPERATIVE	POST-OPERATIVE
96	ACL	98.25	98.65
	HEALTHY	98.17	98.44
97	ACL	87.76	91.87
	HEALTHY	92.76	99.15
99	ACL	99.01	89.58
	HEALTHY	96.19	93.86
101	ACL	91.86	98.38
	HEALTHY	90.24	98.28
102	ACL	99.17	83.14
	HEALTHY	96.40	83.14
103	ACL	98.33	84.87
	HEALTHY	98.24	91.88
104	ACL	95.22	90.34
	HEALTHY	88.81	91.66
105	ACL	80.24	69.59
	HEALTHY	83.69	71.42
106	ACL	93.65	94.55
	HEALTHY	92.56	92.61
107	ACL	99.60	99.14
	HEALTHY	98.43	99.30
108	ACL	94.90	96.18
	HEALTHY	98.06	97.13
109	ACL	95.87	98.29
	HEALTHY	97.62	97.78
110	ACL	92.97	87.19
	HEALTHY	85.28	87.97
111	ACL	97.94	85.86
	HEALTHY	92.84	96.24
112	ACL	98.91	94.67
	HEALTHY	94.86	93.47
114	ACL	94.35	97.49
	HEALTHY	95.14	97.76
116	ACL	90.24	92.85
	HEALTHY	93.13	85.50
118	ACL	99.23	96.54
	HEALTHY	97.06	93.77

Table E.ix Quadriceps Strength (MVIC [Nm/kg] {max} Table 1 of 3)

		TIME	
SUBJECTS	LIMB	PRE-OPERATIVE	POST-OPERATIVE
12	ACL	1.97	2.95
	HEALTHY	3.04	3.03
15	ACL	1.83	1.84
	HEALTHY	1.89	1.87
16	ACL	1.65	1.19
	HEALTHY	2.07	1.61
18	ACL	1.82	2.21
	HEALTHY	2.06	2.16
21	ACL	1.73	1.28
	HEALTHY	1.95	1.10
22	ACL	3.62	3.11
	HEALTHY	4.64	4.00
24	ACL	2.63	2.15
	HEALTHY	2.71	3.77
26	ACL	2.48	2.19
	HEALTHY	3.45	2.73
31	ACL	2.29	1.57
	HEALTHY	3.75	3.58
34	ACL	1.45	2.44
	HEALTHY	1.82	3.59
36	ACL	2.00	1.61
	HEALTHY	2.28	3.19
39	ACL	2.80	1.85
	HEALTHY	3.24	2.87
40	ACL	2.00	2.66
	HEALTHY	1.74	2.73
42	ACL	1.56	1.17
	HEALTHY	3.10	3.03
45	ACL	2.05	1.18
	HEALTHY	2.12	3.62
48	ACL	2.49	2.50
	HEALTHY	3.28	3.78
49	ACL	1.82	1.17
	HEALTHY	2.00	1.92
50	ACL	4.03	2.67
	HEALTHY	4.05	4.14

Table E.ix Quadriceps Strength (MVIC [Nm/kg] {max} Table 2 of 3)

		TIME	
SUBJECTS	LIMB	PRE-OPERATIVE	POST-OPERATIVE
51	ACL	3.10	2.38
	HEALTHY	3.17	3.00
53	ACL	2.39	2.97
	HEALTHY	2.95	3.14
55	ACL	3.56	2.28
	HEALTHY	3.50	3.60
58	ACL	1.61	1.78
	HEALTHY	1.64	2.30
61	ACL	2.67	2.86
	HEALTHY	2.84	3.33
64	ACL	2.19	2.30
	HEALTHY	2.42	2.73
72	ACL	1.90	2.08
	HEALTHY	2.98	3.14
74	ACL	2.18	1.61
	HEALTHY	2.16	2.64
77	ACL	2.53	1.26
	HEALTHY	2.47	2.32
79	ACL	1.97	1.39
	HEALTHY	2.53	2.23
81	ACL	2.06	1.67
	HEALTHY	2.60	3.40
82	ACL	2.50	1.91
	HEALTHY	3.43	3.34
87	ACL	2.02	2.62
	HEALTHY	3.64	3.79
88	ACL	1.67	1.92
	HEALTHY	2.80	3.18
90	ACL	3.32	1.72
	HEALTHY	3.14	3.09
91	ACL	2.21	2.16
	HEALTHY	3.44	2.86
92	ACL	2.59	1.89
	HEALTHY	3.13	2.66
94	ACL	2.37	1.72
	HEALTHY	3.00	3.18

Table E.ix Quadriceps Strength (MVIC [Nm/kg] {max} Table 3 of 3)

		TIME	
SUBJECTS	LIMB	PRE-OPERATIVE	POST-OPERATIVE
96	ACL	3.60	3.31
	HEALTHY	3.99	3.93
97	ACL	2.68	2.89
	HEALTHY	3.87	4.48
99	ACL	3.17	2.97
	HEALTHY	4.03	3.98
101	ACL	1.80	2.20
	HEALTHY	1.98	3.34
102	ACL	3.13	2.02
	HEALTHY	3.52	2.02
103	ACL	3.36	1.49
	HEALTHY	3.95	3.41
104	ACL	1.25	2.65
	HEALTHY	2.15	2.80
105	ACL	1.87	1.38
	HEALTHY	2.47	1.71
106	ACL	4.03	4.19
	HEALTHY	3.88	3.91
107	ACL	1.98	2.65
	HEALTHY	3.10	3.13
108	ACL	1.94	2.10
	HEALTHY	3.28	3.35
109	ACL	2.95	3.03
	HEALTHY	3.49	3.38
110	ACL	3.14	2.78
	HEALTHY	3.30	3.40
111	ACL	3.63	2.83
	HEALTHY	3.44	3.76
112	ACL	3.03	2.79
	HEALTHY	3.84	3.32
114	ACL	2.74	2.46
	HEALTHY	3.01	3.36
116	ACL	3.73	3.14
	HEALTHY	4.24	3.72
118	ACL	2.95	2.61
	HEALTHY	3.70	3.55

Table E.x Quadriceps Strength (Isokinetic [Nm/kg] {max} Table 1 of 3)

		TIME	
SUBJECTS	LIMB	PRE-OPERATIVE	POST-OPERATIVE
12	ACL	1.19	1.09
	HEALTHY	1.69	1.60
15	ACL	0.88	1.14
	HEALTHY	1.37	1.40
16	ACL	0.97	0.98
	HEALTHY	1.08	0.94
18	ACL	1.73	1.70
	HEALTHY	1.12	1.49
21	ACL	0.65	1.04
	HEALTHY	1.05	1.41
22	ACL	1.97	1.67
	HEALTHY	2.79	2.38
24	ACL	1.57	1.21
	HEALTHY	1.63	2.15
26	ACL	0.55	0.99
	HEALTHY	1.93	2.26
31	ACL	0.83	0.68
	HEALTHY	2.07	1.15
34	ACL	1.08	1.74
	HEALTHY	1.90	2.20
36	ACL	0.94	0.80
	HEALTHY	1.70	1.84
39	ACL	0.44	0.79
	HEALTHY	1.66	1.19
40	ACL	0.97	1.55
	HEALTHY	1.63	2.14
42	ACL	0.54	0.83
	HEALTHY	1.55	1.93
45	ACL	1.22	0.79
	HEALTHY	1.46	2.07
48	ACL	1.49	2.15
	HEALTHY	1.68	2.26
59	ACL	1.04	1.03
	HEALTHY	0.77	1.05
50	ACL	2.72	1.90
	HEALTHY	2.35	2.75

Table E.x Quadriceps Strength (Isokinetic [Nm/kg] {max} Table 2 of 3)

		TIME	
SUBJECTS	LIMB	PRE-OPERATIVE	POST-OPERATIVE
51	ACL	1.91	1.73
	HEALTHY	2.07	2.30
53	ACL	1.34	2.14
	HEALTHY	0.75	1.84
55	ACL	2.28	0.98
	HEALTHY	2.55	2.20
58	ACL	0.85	1.22
	HEALTHY	1.15	1.27
61	ACL	0.99	0.97
	HEALTHY	1.80	1.44
64	ACL	0.98	1.33
	HEALTHY	0.96	1.35
72	ACL	1.23	1.20
	HEALTHY	1.72	1.36
74	ACL	1.57	1.08
	HEALTHY	1.58	2.53
77	ACL	0.95	0.97
	HEALTHY	1.08	1.58
79	ACL	1.20	0.95
	HEALTHY	1.89	1.92
81	ACL	1.11	0.98
	HEALTHY	1.38	1.57
82	ACL	1.54	1.06
	HEALTHY	1.71	2.02
87	ACL	1.62	1.62
	HEALTHY	1.56	1.42
88	ACL	0.70	0.89
	HEALTHY	1.41	0.91
90	ACL	1.61	1.06
	HEALTHY	1.92	2.22
91	ACL	0.90	1.27
	HEALTHY	1.77	1.56
92	ACL	1.09	0.94
	HEALTHY	1.80	1.18
94	ACL	1.27	1.13
	HEALTHY	2.02	2.08

Table E.x Quadriceps Strength (Isokinetic [Nm/kg] {max} Table 3 of 3)

		TIME	
SUBJECTS	LIMB	PRE-OPERATIVE	POST-OPERATIVE
51	ACL	1.91	1.73
	HEALTHY	2.07	2.30
53	ACL	1.34	2.14
	HEALTHY	0.75	1.84
55	ACL	2.28	0.98
	HEALTHY	2.55	2.20
58	ACL	0.85	1.22
	HEALTHY	1.15	1.27
61	ACL	0.99	0.97
	HEALTHY	1.80	1.44
64	ACL	0.98	1.33
	HEALTHY	0.96	1.35
72	ACL	1.23	1.20
	HEALTHY	1.72	1.36
74	ACL	1.57	1.08
	HEALTHY	1.58	2.53
77	ACL	0.95	0.97
	HEALTHY	1.08	1.58
79	ACL	1.20	0.95
	HEALTHY	1.89	1.92
81	ACL	1.11	0.98
	HEALTHY	1.38	1.57
82	ACL	1.54	1.06
	HEALTHY	1.71	2.02
87	ACL	1.62	1.62
	HEALTHY	1.56	1.42
88	ACL	0.70	0.89
	HEALTHY	1.41	0.91
90	ACL	1.61	1.06
	HEALTHY	1.92	2.22
91	ACL	0.90	1.27
	HEALTHY	1.77	1.56
92	ACL	1.09	0.94
	HEALTHY	1.80	1.18
94	ACL	1.27	1.13
	HEALTHY	2.02	2.08

APPENDIX E

Supplementary Data- AIM 3

Table E.xi Participant Demographics (Table 1 of 2)

							Time		
Subjects	Group	Sex	Height (m)	Weight (kg)	Graft Type	Surgery details	Pre	12 week	Return to play
74	N-only	M	1.905	127.01	PT	ACL only	54	92	223
77	STND	F	1.702	64.86	PT	ACL only	140	79	247
79	N-only	M	1.880	92.98	PT	ACL only	56	84	236
88	N-only	F	1.575	46.26	PT	ACL only	59	87	194
92	N-only	F	1.600	58.20	PT	ACL only	59	86	206
94	STND	M	1.753	86.18	PT	Meniscal repair	53	86	183
95	STND	F	1.575	46.26	STG	Meniscal repair	311	85	247
96	N&E	M	1.867	89.81	PT	ACL only	125	85	210
97	N-only	M	1.702	63.5	PT	Meniscal repair	21	82	202
99	N-only	M	1.791	79.38	PT	Meniscal repair	50	84	180
101	STND	M	1.803	136.53	PT	Meniscectomy	35	82	279
102	N-only	M	1.829	84.39	PT	Meniscal repair	48	84	204
103	N-only	M	1.829	86.18	PT	Meniscal repair	59	85	290
104	N&E	M	1.173	86.21	PT	ACL only	31	84	251
105	STND	F	1.803	75.206	PT	ACL only	73	84	269
106	N&E	M	0.018	83	PT	ACL only	24	86	197
107	N&E	F	1.676	58.97	PT	ACL only	39	84	181
108	N-only	M	1.727	97.97	PT	Meniscectomy	66	85	216
109	N&E	F	1.600	59.421	PT	ACL only	175	83	182
110	STND	M	1.829	74.844	STG	ACL only	61	93	183
111	N-only	M	1.829	80.65	PT	ACL only	43	82	208
112	STND	F	1.676	58.514	PT	ACL only	43	83	238
113	N&E	M	1.854	102.510	STG	ACL only	44	94	205
114	N&E	M	1.803	83.460	PT	ACL only	101	86	197

Abbreviations: E-only, eccentric group; N&E, neuromuscular electrical stimulation and eccentric group; N-only, neuromuscular electrical stimulation group; STND; standard of care group

Table E.xi Participant Demographics (Table 2 of 2)

							Time	
Subjects	Group	Sex	Height (m)	Weight (kg)	Graft Type	Surgery details	Pre	12 week	Return to play
116	STND	M	1.778	76.658	PT	ACL only	45	80	192
118	STND	M	1.765	73.200	PT	Meniscal repair	47	78	183
119	STND	F	1.651	63.095	PT	Meniscal repair	133	85	267
121	E-only	M	1.892	97.977	PT	Meniscal repair	55	160	273
122	E-only	M	1.753	82.464	PT	ACL only	108	92	189
123	E-only	M	1.880	74.844	PT	ACL only	218	85	210
124	E-only	F	1.702	66.361	STG	ACL only	131	89	244
125	E-only	M	1.727	67.541	PT	ACL only	46	77	202
126	N&E	F	1.676	59.376	PT	Meniscal repair	47	85	245
128	E-only	F	1.626	74.844	PT	Meniscal repair	44	96	231
130	E-only	M	1.829	72.576	PT	ACL only	81	84	210
131	E-only	F	1.613	85.639	STG	ACL only	83	87	202
132	Healthy	F	1.740	71.215	No surgery	Healthy	-	-	-
133	Healthy	M	1.753	72.574	No surgery	Healthy	-	-	-
134	Healthy	M	1.702	72.576	No surgery	Healthy	-	-	-
135	Healthy	M	1.829	78.471	No surgery	Healthy	-	-	-
136	Healthy	F	1.716	60.238	No surgery	Healthy	-	-	-
137	Healthy	F	1.664	76.740	No surgery	Healthy	-	-	-
138	Healthy	F	1.540	55.000	No surgery	Healthy	-	-	-
139	Healthy	M	1.753	90.537	No surgery	Healthy	-	-	-
140	Healthy	M	1.829	74.840	No surgery	Healthy	-	-	-
141	Healthy	M	1.807	65.700	No surgery	Healthy	-	-	-

Abbreviations: E-only, eccentric group; N&E, neuromuscular electrical stimulation and eccentric group; N-only, neuromuscular electrical stimulation group; STND; standard of care group

Table E.xii Quadriceps Activation (CAR [max] Table 1 of 4)

			Time		
Subjects	Group	Limb	Pre	12 week	Post
74	N-only	ACL	96.62	82.12	92.11
		Healthy	93.42	91.03	99.4
77	STND	ACL	99.89	96.68	93.18
		Healthy	93.73	86.83	95.9
79	N-only	ACL	92.85	75.45	95.28
		Healthy	90.25	78.89	90.94
88	N-only	ACL	98.86	99.65	98.63
		Healthy	96.23	99.7	98.92
92	N-only	ACL	99.94	99.47	88.36
		Healthy	99.2	96.62	90.66
94	STND	ACL	98.26	90.6	83.78
		Healthy	98.52	89.68	99.47
95	STND	ACL	96.63	95.44	98.98
		Healthy	97.2	91.34	99.29
96	N&E	ACL	98.51	98.13	99.53
		Healthy	98.65	99.58	99.53
97	N-only	ACL	91.19	86.23	93.89
		Healthy	93.31	93.46	99.4
99	N-only	ACL	99.83	99.96	90.91
		Healthy	96.98	97.14	94.56
101	STND	ACL	93.46	95.47	98.73
		Healthy	91.82	95.58	98.77
102	N-only	ACL	99.5	86.71	84.03
		Healthy	97.94	99.94	84.03

Abbreviations: E-only, eccentric group; N&E, neuromuscular electrical stimulation and eccentric group; N-only, neuromuscular electrical stimulation group; STND; standard of care group

Table E.xii Quadriceps Activation (CAR [max] Table 2 of 4)

			Time		
Subjects	Group	Limb	Pre	12 week	Post
103	N-only	ACL	98.65	94.41	96.95
		Healthy	98.57	97.46	92.61
104	N&E	ACL	99.13	96.87	91.52
		Healthy	91.7	97.13	94.29
105	STND	ACL	81.89	78.34	69.85
		Healthy	84.26	71.28	72.91
106	N&E	ACL	95.31	94.65	95.5
		Healthy	95.74	96.09	94.02
107	N&E	ACL	99.67	89.22	99.95
		Healthy	98.6	98.62	99.83
108	N-only	ACL	98.03	93.59	97.48
		Healthy	99.23	97.09	97.54
109	N&E	ACL	96.76	99.14	98.46
		Healthy	98.66	99.2	98.92
110	STND	ACL	94.73	96.29	88.92
		Healthy	85.89	95.3	89.54
111	N-only	ACL	98.9	96.74	90.72
		Healthy	93.87	97.15	96.47
112	STND	ACL	99.26	93.91	96.63
		Healthy	97.2	94.41	94.17
113	N&E	ACL	89.53	97.7	97.92
		Healthy	89.36	99.15	95.45
114	N&E	ACL	95.06	87.73	98.76
		Healthy	96.32	94.55	97.81

Abbreviations: E-only, eccentric group; N&E, neuromuscular electrical stimulation and eccentric group; N-only, neuromuscular electrical stimulation group; STND; standard of care group

Table E.xii Quadriceps Activation (CAR [max] Table 3 of 4)

			Time		
Subjects	Group	Limb	Pre	12 week	Post
116	STND	ACL	92.04	82.55	93.45
		Healthy	96.03	88.58	87.75
118	STND	ACL	99.32	97.05	97.51
		Healthy	97.06	95.12	94.12
119	STND	ACL	93.82	91.36	97.25
		Healthy	80.83	82.14	90.46
121	E-only	ACL	98.61	96.94	97.72
		Healthy	99.16	98.71	97.93
122	E-only	ACL	99.53	92.71	99.5
		Healthy	99.41	99.4	99.85
123	E-only	ACL	96.14	98.57	99.31
		Healthy	96.86	99.88	99.18
124	E-only	ACL	86.37	99.73	95.91
		Healthy	99.04	92.79	96.18
125	E-only	ACL	99.52	95.27	99.32
		Healthy	94.27	94.93	98.84
126	N&E	ACL	92.3	95.34	99.31
		Healthy	98.89	97.95	99.37
128	E-only	ACL	97.3	90.55	98.06
		Healthy	96.47	96.48	97.92
130	E-only	ACL	98.26	89.04	96.83
		Healthy	98.63	98.27	98.48
131	E-only	ACL	91.92	98.4	98.26
		Healthy	98.82	99.03	99.76

Abbreviations: E-only, eccentric group; N&E, neuromuscular electrical stimulation and eccentric group; N-only, neuromuscular electrical stimulation group; STND; standard of care group

Table E.xii Quadriceps Activation (CAR [max] Table 4 of 4)

			Time		
Subjects	Group	Limb	Pre	12 week	Post
132	Healthy	ACL "R"	-	-	98.35
		Healthy "L"	-	-	99.46
133	Healthy	ACL "R"	-	-	98.64
		Healthy "L"	-	-	96.25
134	Healthy	ACL "R"	-	-	91.47
		Healthy "L"	-	-	113.35
135	Healthy	ACL "R"	-	-	94.66
		Healthy "L"	-	-	99.24
136	Healthy	ACL "R"	-	-	99.01
		Healthy "L"	-	-	98.5
137	Healthy	ACL "R"	-	-	93.02
		Healthy "L"	-	-	97.32
138	Healthy	ACL "R"	-	-	96.92
		Healthy "L"	-	-	97.52
139	Healthy	ACL "R"	-	-	99.94
		Healthy "L"	-	-	98.18
140	Healthy	ACL "R"	-	-	98.69
		Healthy "L"	-	-	99.25
141	Healthy	ACL "R"	-	-	95.44
		Healthy "L"	-	-	97.02

Abbreviations: E-only, eccentric group; N&E, neuromuscular electrical stimulation and eccentric group; N-only, neuromuscular electrical stimulation group; STND; standard of care group

Table E.xiii Quadriceps Strength MVIC (Nm/kg [max] Table 1 of 4)

			Time		
Subjects	Group	Limb	Pre	12 week	Post
74	N-only	ACL	2.29	1.46	1.68
		Healthy	2.21	2.52	2.79
77	STND	ACL	2.82	1.12	1.26
		Healthy	2.62	1.79	2.49
79	N-only	ACL	1.99	1.51	1.43
		Healthy	2.57	2.34	2.29
88	N-only	ACL	1.73	1.77	1.95
		Healthy	2.88	3.46	3.24
92	N-only	ACL	2.65	1.51	1.91
		Healthy	3.29	2.96	2.75
94	STND	ACL	2.40	1.02	1.76
		Healthy	3.09	2.43	3.40
95	STND	ACL	2.00	1.34	1.65
		Healthy	2.64	1.72	2.05
96	N&E	ACL	3.62	2.12	3.41
		Healthy	4.06	4.13	4.05
97	N-only	ACL	2.71	1.62	2.99
		Healthy	3.91	3.73	4.58
99	N-only	ACL	3.36	2.68	3.00
		Healthy	4.21	3.94	3.99
101	STND	ACL	1.80	1.62	2.22
		Healthy	2.08	2.36	3.36
102	N-only	ACL	3.21	1.67	2.07
		Healthy	3.69	3.86	2.07

Abbreviations: E-only, eccentric group; N&E, neuromuscular electrical stimulation and eccentric group; N-only, neuromuscular electrical stimulation group; STND; standard of care group

Table E.xiii Quadriceps Strength MVIC (Nm/kg [max] Table 2 of 4)

			Time		
Subjects	Group	Limb	Pre	12 week	Post
103	N-only	ACL	3.41	2.22	1.50
		Healthy	3.98	3.66	3.48
104	N&E	ACL	1.29	1.91	2.69
		Healthy	2.19	2.82	2.88
105	STND	ACL	1.96	1.02	1.40
		Healthy	2.51	1.53	1.74
106	N&E	ACL	4.15	3.76	4.23
		Healthy	4.04	4.08	3.97
107	N&E	ACL	2.03	1.87	2.69
		Healthy	3.14	2.96	3.29
108	N-only	ACL	1.97	1.52	2.16
		Healthy	3.33	3.08	3.49
109	N&E	ACL	3.01	2.25	3.11
		Healthy	3.52	3.19	3.40
110	STND	ACL	3.20	2.09	2.80
		Healthy	3.31	3.60	3.49
111	N-only	ACL	3.66	1.97	2.88
		Healthy	3.48	3.43	3.85
112	STND	ACL	3.15	1.59	2.89
		Healthy	4.04	3.51	3.35
113	N&E	ACL	2.56	2.84	2.40
		Healthy	3.37	3.20	3.57

Abbreviations: E-only, eccentric group; N&E, neuromuscular electrical stimulation and eccentric group; N-only, neuromuscular electrical stimulation group; STND; standard of care group

Table E.xiii Quadriceps Strength MVIC (Nm/kg [max] Table 3 of 4)

			Time		
Subjects	Group	Limb	Pre	12 week	Post
114	N&E	ACL	2.78	2.28	2.47
		Healthy	3.11	3.75	3.41
116	STND	ACL	3.89	2.26	3.19
		Healthy	4.3	3.36	3.76
118	STND	ACL	2.98	2.45	2.64
		Healthy	3.72	3.89	3.55
119	STND	ACL	2.54	1.47	1.82
		Healthy	2.31	2.39	2.41
121	E-only	ACL	2.30	2.06	2.12
		Healthy	2.25	2.52	2.25
122	E-only	ACL	4.63	3.07	4.39
		Healthy	4.92	5.02	5.30
123	E-only	ACL	3.88	3.05	4.00
		Healthy	3.73	4.20	4.16
124	E-only	ACL	1.80	1.53	2.04
		Healthy	2.57	2.15	2.49
125	E-only	ACL	2.99	2.10	3.04
		Healthy	3.44	3.76	4.75
126	N&E	ACL	2.44	1.79	2.57
		Healthy	3.43	2.65	3.18
128	E-only	ACL	2.72	1.25	2.37
		Healthy	2.81	2.67	2.58
130	E-only	ACL	3.47	2.09	3.12
		Healthy	3.87	3.89	3.76

Abbreviations: E-only, eccentric group; N&E, neuromuscular electrical stimulation and eccentric group; N-only, neuromuscular electrical stimulation group; STND; standard of care group

Table E.xiii Quadriceps Strength MVIC (Nm/kg [max] Table 4 of 4)

			Time		
Subjects	Group	Limb	Pre	12 week	Post
131	E-only	ACL	1.39	1.71	1.75
		Healthy	2.64	2.03	2.06
132	Healthy	ACL "R"	-	-	3.04
		Healthy "L"	-	-	3.35
133	Healthy	ACL "R"	-	-	5.09
		Healthy "L"	-	-	4.99
134	Healthy	ACL "R"	-	-	2.70
		Healthy "L"	-	-	3.09
135	Healthy	ACL "R"	-	-	2.54
		Healthy "L"	-	-	2.82
136	Healthy	ACL "R"	-	-	2.19
		Healthy "L"	-	-	2.46
137	Healthy	ACL "R"	-	-	2.11
		Healthy "L"	-	-	2.49
138	Healthy	ACL "R"	-	-	3.05
		Healthy "L"	-	-	2.90
139	Healthy	ACL "R"	-	-	3.35
		Healthy "L"	-	-	3.43
140	Healthy	ACL "R"	-	-	3.41
		Healthy "L"	-	-	3.34
141	Healthy	ACL "R"	-	-	4.29
		Healthy "L"	-	-	4.49

Abbreviations: E-only, eccentric group; N&E, neuromuscular electrical stimulation and eccentric group; N-only, neuromuscular electrical stimulation group; STND; standard of care group

Table E.xiv Area Under the Curve Sagittal Plane Knee Mechanics (Table 1 of 4)

			Knee Extension Moment		Knee Flexion Angle	
Subjects	Group	Limb	Area Under the Curve	Limb Symmetry Index	Area Under the Curve	Limb Symmetry Index
74	N-ONLY	ACL	41.57	77.79	-1000.41	63.49
		Healthy	53.44		-1575.62	
77	STND	ACL	30.74	71.44	-1468.48	88.59
		Healthy	43.03		-1657.53	
79	N-ONLY	ACL	7.24	19.91	-474.18	44.88
		Healthy	36.35		-1056.60	
88	N-ONLY	ACL	40.94	60.88	-533.45	73.84
		Healthy	67.25		-722.44	
92	N-ONLY	ACL	31.07	57.94	-1670.27	82.32
		Healthy	53.63		-2028.95	
94	STND	ACL	32.75	52.12	-924.39	53.73
		Healthy	62.85		-1720.55	
95	STND	ACL	43.93	73.67	-1084.49	74.81
		Healthy	59.63		-1449.61	
96	N&E	ACL	34.25	56.54	-1452.56	93.25
		Healthy	60.57		-1557.64	
97	N-ONLY	ACL	36.18	97.95	-1108.08	71.21
		Healthy	36.94		-1556.10	
99	N-ONLY	ACL	51.55	86.72	-1112.48	84.37
		Healthy	59.45		-1318.53	
101	N&E	ACL	26.58	54.98	-1361.09	106.80
		Healthy	48.34		-1274.45	
102	N-ONLY	ACL	40.52	74.61	-1283.29	82.35
		Healthy	54.30		-1558.34	

Abbreviations: E-only, eccentric group; N&E, neuromuscular electrical stimulation and eccentric group; N-only, neuromuscular electrical stimulation group; STND; standard of care group

Table E.xiv Area Under the Curve Sagittal Plane Knee Mechanics (Table 2 of 4)

			Knee Extension Moment		Knee Flexion Angle	
Subjects	Group	Limb	Area Under the Curve	Limb Symmetry Index	Area Under the Curve	Limb Symmetry Index
103	N-ONLY	ACL	0.09	0.24	-709.85	44.32
		Healthy	37.47		-1601.68	
104	N&E	ACL	28.84	58.06	-1262.78	68.99
		Healthy	49.68		-1830.46	
105	STND	ACL	24.76	63.08	-1216.09	75.07
		Healthy	39.25		-1619.88	
106	N&E	ACL	43.31	71.36	-1652.93	86.45
		Healthy	60.70		-1911.99	
107	N&E	ACL	37.43	63.02	-952.79	93.26
		Healthy	59.39		-1021.68	
108	N-ONLY	ACL	32.21	65.54	-1352.64	86.69
		Healthy	49.14		-1560.37	
109	N&E	ACL	48.88	102.44	-1572.14	136.71
		Healthy	47.72		-1149.28	
110	STND	ACL	28.23	61.55	-1434.57	91.23
		Healthy	45.86		-1572.47	
111	N-ONLY	ACL	52.72	100.62	-1147.50	100.38
		Healthy	52.40		-1143.19	
112	STND	ACL	14.61	34.70	-1232.19	78.68
		Healthy	42.10		-1566.09	
113	N&E	ACL	24.42	41.33	-1237.09	82.04
		Healthy	59.08		-1507.89	
114	N&E	ACL	19.43	56.87	-1130.07	74.35
		Healthy	34.16		-1520.03	

Abbreviations: E-only, eccentric group; N&E, neuromuscular electrical stimulation and eccentric group; N-only, neuromuscular electrical stimulation group; STND; standard of care group

Table E.xiv Area Under the Curve Sagittal Plane Knee Mechanics (Table 3 of 4)

			Knee Extension Moment		Knee Flexion Angle	
Subjects	Group	Limb	Area Under the Curve	Limb Symmetry Index	Area Under the Curve	Limb Symmetry Index
116	STND	ACL	38.44	99.57	-1549.88	86.96
		Healthy	38.60		-1782.29	
118	STND	ACL	25.44	45.37	-1175.99	64.39
		Healthy	56.07		-1826.48	
119	STND	ACL	10.47	31.02	-939.54	60.77
		Healthy	33.75		-1546.18	
121	E-ONLY	ACL	14.09	80.96	-1102.23	122.42
		Healthy	17.40		-900.40	
122	E-ONLY	ACL	7.96	19.64	-488.96	55.55
		Healthy	40.53		-880.14	
123	E-ONLY	ACL	31.45	59.81	-1608.10	86.35
		Healthy	52.59		-1862.33	
124	E-ONLY	ACL	38.70	69.41	-1902.22	93.95
		Healthy	55.76		-2024.74	
125	E-ONLY	ACL	17.08	31.22	-1255.13	71.02
		Healthy	54.70		-1767.23	
126	N&E	ACL	29.58	84.18	-1641.38	104.03
		Healthy	35.14		-1577.79	
128	E-ONLY	ACL	12.44	31.91	-667.22	52.59
		Healthy	38.98		-1268.60	
130	E-ONLY	ACL	34.00	71.77	-1756.04	88.65
		Healthy	47.38		-1980.89	
131	E-ONLY	ACL	20.17	78.15	-1306.79	99.41
		Healthy	25.81		-1314.59	

Abbreviations: E-only, eccentric group; N&E, neuromuscular electrical stimulation and eccentric group; N-only, neuromuscular electrical stimulation group; STND; standard of care group

Table E.xiv Area Under the Curve Sagittal Plane Knee Mechanics (Table 4 of 4)

			Knee Extension Moment		Knee Flexion Angle	
Subjects	Group	Limb	Area Under the Curve	Limb Symmetry Index	Area Under the Curve	Limb Symmetry Index
132	HEALTHY	ACL	45.95	106.00	-1469.20	102.17
		Healthy	43.34		-1437.99	
133	HEALTHY	ACL	45.37	57.46	-1402.91	80.99
		Healthy	78.96		-1732.28	
134	HEALTHY	ACL	49.65	98.44	-1780.11	97.81
		Healthy	50.44		-1819.88	
135	HEALTHY	ACL	35.17	75.28	-1066.19	82.08
		Healthy	46.72		-1298.90	
136	HEALTHY	ACL	41.29	117.93	-1166.19	107.45
		Healthy	35.01		-1085.67	
137	HEALTHY	ACL	32.04	111.02	-802.28	91.85
		Healthy	28.86		-873.50	
138	HEALTHY	ACL	35.73	116.59	-690.36	81.45
		Healthy	30.65		-847.59	
139	HEALTHY	ACL	49.28	103.71	-800.96	93.31
		Healthy	47.51		-858.42	
140	HEALTHY	ACL	45.85	128.02	-1217.05	111.75
		Healthy	35.82		-1089.13	
141	HEALTHY	ACL	54.86	84.27	-1331.74	108.92
		Healthy	65.10		-1222.72	

Abbreviations: E-only, eccentric group; N&E, neuromuscular electrical stimulation and eccentric group; N-only, neuromuscular electrical stimulation group; STND; standard of care group

APPENDIX F

Institutional Review Board Consent- AIM 1

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. *Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.*

GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

Study title: The Benefit of a Single-Legged Eccentric Training Program for the Muscles Around the Untrained Knee.

Names, degrees, and affiliations of the researchers conducting the study:
Principal Investigator: Lindsey Klykken, MEd, ATC – School of Kinesiology, University of Michigan
Faculty Advisor: Riann Palmieri-Smith, PhD, ATC – School of Kinesiology, University of Michigan

INVITATION TO PARTICIPATE IN A RESEARCH STUDY

The above-named researchers invite you to participate in a research study aimed at determining whether strength training provided to a single leg can improve thigh muscle strength in the leg not being trained. We hope to better understand how many training sessions are necessary to create improvements in thigh muscle function. If we find that strength training on one leg can lead to strength gains in the opposite leg, we plan to use a similar protocol in the future to improve rehabilitation practices following knee injury. We will recruit a total of 40 subjects to participate in this investigation.

DESCRIPTION OF HUMAN SUBJECT INVOLVEMENT

What exactly will be done to me if I participate in this study?

If you choose to participate, you will be randomly assigned to receive strength training (training group) or no strength training (control group). Participants in ALL groups will be asked to report for testing on 3 occasions over a period of 8 weeks. Participants in the training group will also receive training 3 times per week for 8 weeks. All testing and training sessions will be conducted in the Neuromuscular Research Laboratory within the School of Kinesiology at The University of Michigan.

Testing Sessions (ALL GROUPS)
All participants will be asked to report for 3 testing sessions. One session will occur upon study entry, one session will occur 4 weeks into the study, and the last session will occur at the 8th week of study. Subjects randomized to the training group will also have testing done during one of your training session each week. In all testing sessions, you will have measures of your muscle strength recorded.

Measures of Muscle Strength
Two large pads will be placed on the front of your thigh and secured with bandages. Once all of the pads are attached to your leg, you will be positioned in a device that measures muscle strength. You will be asked to sit in

a chair attached to the device with your knees bent. Once you are positioned in the device, you will be asked to kick your leg out against a pad as hard as you can. As soon as you feel comfortable with the kick, the researchers will apply a group of shocks to the skin of your thigh while you are resting. We will deliver the shocks thru the pads we attached earlier. In order to help you get use to the shocks, we will start giving them to you at a low level and will then increase the level in small amounts. We eventually need the level of the shocks to reach 130 volts each. If these shocks were delivered separately they would feel like a shock of static electricity like when you walk across a carpet and touch a doorknob, except a shock of static electricity can reach up to 1,000 volts. The series of 10 shocks will last less than 1 second and are delivered very close together, so you shouldn't be able to feel individual shocks. The group of shocks will allow your muscle to contract even when you are resting. These shocks may be slightly uncomfortable; the discomfort you experience in the muscle is normal. If at anytime during the procedures you feel as if the shocks are too strong and you don't want to continue, please notify the researchers immediately. Once you are comfortable with the shocks, you will again be asked to kick out as hard as you can. Once the researchers see that you are contracting as hard as you can by watching a computer screen (usually in about 2 seconds), they will deliver the series of shocks on top of your muscle. This technique, where we deliver shocks on top of a muscle contraction, will be repeated 3 times for each leg.

You will also be asked to contract your thigh muscles several times while no shocks are delivered. This will also be done on both legs.

Measure of knee muscles size
We will assess the size of your knee muscles by wrapping a cloth measuring tape around your thigh. We will do this on both thighs.

Scales to assess activity level
In order to quantify activity level, subjects will be asked to complete the two activity level scales. These scales will allow us to track activity level of all subjects throughout the intervention. Subjects in the training group will complete the scales during the last training session of each week. Subjects in the control group will be contacted by email weekly and provided an electronic copy of the scales to complete and return to the primary investigator.

Training Sessions (Training group ONLY)
If you assigned to the training group, you will be asked to participate in 24 training sessions with each lasting approximately 30 minutes. At the training session, you will be seated in a device that measures muscle strength. You will be asked to perform 4 sets of 10 repetitions of resistance training for your knee muscles. You will be given a rest period between each set throughout the session. If you are uncomfortable with the training session, you can stop at any time.

5. BENEFITS

Although you may not receive direct benefit from participation, others may ultimately benefit from the knowledge obtained in this study. Specifically, your participation in this study may help us to gather knowledge that may be beneficial for patients with knee injury, particularly for patients who have had a knee surgery and are unable to exercise their injured limb for a period of time.

6. RISKS & DISCOMFORTS OF PARTICIPATION

- The researchers have taken steps to minimize risk of this study. Even so, you may still experience some risks related to your participation, even when researchers are careful to avoid them. Please tell the researchers about any concerns or problems you have during the study. You should also tell your regular health care provider. By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.
- The stimuli delivered during muscle strength testing are short but intense and you may experience some mild discomfort during testing (COMMON). It is also possible that you might experience muscle soreness after the strength testing because of repeated muscle contractions (INFREQUENT). These

effects are similar to those that would be felt in any muscle after new exercise. In order to make the shocks as comfortable as possible, large pads will be used to apply the shocks.

- You may experience muscle soreness after performing the muscle contractions associated with the training (COMMON). In order to minimize the likelihood of the discomfort, you will be encouraged to warm-up and stretch the muscles before participation.
- You may suffer a muscle or tendon injury when performing the repeated muscle contractions (INFREQUENT). Lindsey Klykken, the principal investigator, and Dr. Palmieri-Smith, the faculty advisor on this study, are both certified athletic trainers equipped with the knowledge to evaluate and manage musculoskeletal injuries. Thus, if an injury were to occur, Ms. Klykken and Dr. Palmieri-Smith would provide immediate care and refer you to a physician for further evaluation.
- There is also the potential risk of loss of confidentiality through participation in this study. Every effort will be made to keep the your information confidential, however, this cannot be guaranteed.
- As with any research study, there may be unanticipated risks.

7. COMPENSATION

You will receive $25 for each of the three testing sessions that you complete, for a total of $75. Those persons assigned to the training group will also receive $10 for each week of training, for a total of $80. Thus, if you are in the control group you can receive a total of $75 for participating and for persons in the training group you can receive a total of $155 for participating. Payments for the testing sessions will be mailed to you at an address you provide within 2 weeks from the date you report for testing. Payments for the training sessions will be mailed to you upon completion of all training sessions (at the end of the 8 weeks). If you drop out of the training group, you would receive your payment for the portion of the study you completed, following your last training session.

8. CONFIDENTIALITY

We will put the information collected about you during the study into a research record. This research record will not show your name, but will have codes entered in it, that will allow the information to be linked to you. However, we will keep your research record confidential, to the extent provided by federal, state, and local law. We will not allow anyone to see your record, other than the members of this research team. You will not be identified in any reports from this study.

To keep your information safe, the researchers will lock any information that contains your name (i.e. this signed consent form) in a file cabinet. Researchers other than those listed on this study will not have access to that file cabinet. Any information we record on a computer will be listed by a study number given to your name by the researchers and will not be linked in any way to your name.

9. STORAGE AND FUTURE USE OF DATA

The data you provide will be stored on a secure server. All files will be password protected. The researchers will retain the data for five years. The data will not be made available to other researchers for other studies following the completion of this research study and will not contain information that could identify you.

10. VOLUNTARY NATURE OF THE STUDY

Participating in this study is completely voluntary. Even if you decide to participate now, you may change your mind and request that you stop at any time. If you decide to withdraw early, we will utilize the data that we had collected prior to your withdrawal in our findings.

The researchers can also decide to remove you from the study at any time. This might happen if you become injured or fail to comply with the study as outlined above. It is important that you tell the researchers if you become injured during the course of the study so they can deem whether it is safe for you to continue to

participate. For example, if you hurt a knee ligament while playing basketball it would be important for the researchers to know this information. If you are assigned to the training intervention and fail to report more than three times you will also be removed from the study as this could influence our research results.

11. CONTACT INFORMATION

If you have questions about this research, including questions about scheduling or compensation for participating, you may contact:

Principle Investigator: Lindsey Klykken, MEd., ATC
Mailing Address: 1230B CCRB, School of Kinesiology, University of Michigan, 401 Washtenaw Avenue, Ann Arbor, MI, 48109-2214
Telephone: 734-647-3871
Email: klykkenl@umich.edu

Faculty Advisor: Riann Palmieri-Smith, Ph.D., ATC
Mailing Address: 4745G CCRB, School of Kinesiology, University of Michigan, 401 Washtenaw Avenue, Ann Arbor, MI, 48109-2214
Telephone: 734-615-3154
Email: riannp@umich.edu

If you have questions about your rights as a research participant, or wish to obtain information, ask questions or discuss any concerns about this study with someone other than the researcher(s), please contact the University of Michigan Health Sciences and Behavioral Sciences Institutional Review Board, 540 E Liberty, Ste 202, Ann Arbor, MI 48104-2210, (734) 936-0933 [or toll free, (866) 936-0933], [for international calls including the US Calling Code 1 and the exit number for the country of origin XXX+1+734-936-0933], irbhsbs@umich.edu.

12. CONSENT OF THE SUBJECT

By signing this document, you are agreeing to participate in this study. You will be given a copy of this document for your records and one copy will be kept with the study records. Be sure that questions you have about the study have been answered and that you understand what your being asked to do. You may contact the researcher if you think of a question later.

I agree to participate in the study.

_____
Printed Name

_____ _____
Signature of Subject Date

APPENDIX F

Institutional Review Board Consent- AIM 2

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

1.1 Study title:
Neuromechanical Dysfunction Associated with ACL Injury

1.2 Company or agency sponsoring the study:
This study is funded by The University of Michigan Bone and Joint Injury Prevention & Rehabilitation Center. Additional funding is provided by the National Institutes of Health.

1.3 Names, degrees, and affiliations of the researchers conducting the study:
Riann Palmieri-Smith, PhD, ATC – University of Michigan, School of Kinesiology
Asheesh Bedi, MD – University of Michigan, Department of Orthopedics
Catherine Brandon, MD – University of Michigan, Department of Radiology
Elizabeth Sibilsky Eisenman, MEd, ATC – University of Michigan, Department of Orthopaedics
Lindsey Lepley, MEd, ATC – University of Michigan, School of Kinesiology
Scott McLean, PhD - University of Michigan, School of Kinesiology
Christopher Mendias, PhD, ATC – University of Michigan, School of Kinesiology
Daryl Montie, DPT, CSCS, MA – University of Michigan, MedSport
Edward Wojtys, MD – University of Michigan, Department of Orthopedics

2. PURPOSE OF THIS STUDY

2.1 Study purpose:
Thigh muscle weakness often accompanies anterior cruciate ligament (ACL) injury. This study is designed to examine how thigh muscle weakness that accompanies ACL injury affects lower body positions and forces. We will also examine whether electrical stimulation therapy can improve thigh muscle strength.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

Subjects between the ages of 14-45 will be recruited to participate. All study participants cannot have any previous history of ACL injury or ACL surgery and cannot have a cardiac demand-type pacemaker. Furthermore, volunteers who are females and are pregnant are not eligible to participate. Healthy volunteers cannot have any current knee pain and/or have had any lower body injury in the previous 6 months. It is very important that you accurately report your medical history.

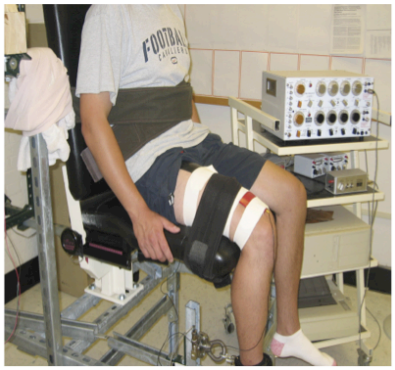
3.2 How many people (subjects) are expected to take part in this study?

We will enroll 234 participants in this part of the study and 60 participants in another part of the study

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

If you agree to participate in this study, you will be asked to report to the MedSport Clinic located in Domino Farms for testing. You will be asked to participate in a minimum of one testing session and a maximum of three testing sessions. If you are a volunteer that has torn your ACL, you will be asked to report for testing prior to your surgery, ~6 months following your surgery, and in some cases ~8 months to 3 years following your surgery. If you are a healthy, uninjured volunteer you will be asked to report for up to 3 sessions approximately 6 months apart. We will schedule these session on days/times that are convenient for you.



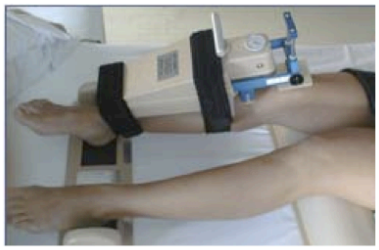
Picture 1. Muscle Strength Test

At all testing sessions, your muscle strength, the looseness of your knee joints, and a measure of the swelling in your knees will be taken. Additionally, you will be asked to fill out a questionnaire that asks questions about your pain level and functional abilities.

Measures of Muscle Strength: Two large pads will be placed on the front of both of your thighs and secured with bandages. Once all of the pads are attached to your leg, you will be positioned in a device that measures muscle strength. You will be asked to sit in a chair attached to the device with your knees bent (Picture 1). Once you are positioned in the device, you will be asked to kick your leg out against a pad as hard as you can. As soon as you feel comfortable with the kick, the researchers will apply a group of shocks to the skin of your thigh while you are resting. We will deliver the shocks thru the pads we attached earlier. In order to help you get use to the shocks, we will start giving them to you at a low level and will then increase the level in small amounts. We eventually need the level of the shocks to reach 150 volts each (if these shock were delivered separately they would feel like a shock of static electricity like when you walk across a carpet and touch a door knob, except a shock of static electricity can reach up to 1,000 volts) The series of 10 shocks will last less than 1 second and are delivered very close together, so you shouldn't be able to feel individual shocks. The group of shocks will allow your muscle to contract even when you are resting. These shocks may be slightly uncomfortable, the discomfort you experience in the muscle is normal. If at anytime during the procedures you feel as if the shocks are too strong and you don't want to continue, please notify the

researchers immediately. Once you are comfortable with the shocks, you will again be asked to kick out as hard as you can. Once the researchers see that you are contracting as hard as you can by watching the computer screen (usually in about 2 seconds), they will deliver the series of shocks on top of your muscle. This technique, where we deliver shocks on top of a muscle contraction, will be repeated 3 times for each leg.

Measure of looseness of your knee joint: In order to see how loose your knees are, we will place each knee into a device, one at a time. You will be asked to lay on your back and we will place a pad under both of your legs. The device will be secured to your leg, at the ankle and calf, by Velcro straps (see picture 2). Once your knee is in the device, the investigators will pull a handle on the device, which causes the shin bone to move forward. The investigators will pull on the handle 3 times for each knee.

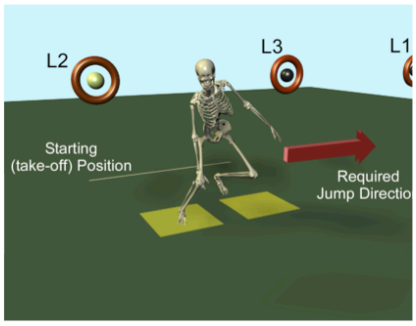


Picture 2. Knee Looseness Testing

Measure of knee swelling: We will assess how much fluid is in your knee by wrapping a cloth measuring tape around your kneecap. We will do this on both knees.

Picture 4. Forward Hop

Once your physician says it is ok for you to return to activity you may be asked to complete the following tests either one or two times. At the second and third (if applicable) testing sessions, you will repeat all of the tests done in the first session and may also be asked to complete several jump landings before and after being fatigued and 10 forward hops. Not all people will be asked to do the fatigue testing. If the investigator wishes to have you take part in this testing he or she will ask you prior to your arrival at a testing session.



Picture 3. Jump Landing Task.

Jump Landings: The jump landing tasks will include both double and single leg take-offs. Upon landing, you will be required to quickly jump to the left, right or straight up. You will be informed in which direction to jump by a light (Picture 3). The first light (L1) is fixed to the left and in front of a force plate (similar to a scale that measures forces). If this light comes on, you will land on the left foot only and then jump to the right. A second light (L2) will be similarly positioned to the right of the force plates, and will require you to land on the right foot only and jump to the left. A third light (L3) will be placed between the two force plates. When this light comes on you will be required to land on both feet and jump straight up. The researchers will demonstrate the jump landings before you are asked to do it.

Following the initial jump landing trials, you may again be required to perform the above tasks, only this time while being exposed to a general fatigue protocol. As a reminder, not all volunteers are being asked to do this part of the study. The researchers will ask you before you come in for testing if they would like you to complete the fatigue testing. Specifically, you will be asked to perform continuous

sets of three single or double leg squats between the jump trials. You will alternate between squats and jumps until fatigue is reached, being defined as the point when you can no longer perform three squats in succession. You will be able to place the non-fatigued leg on a platform for stability during the single leg squats. From our previous work, we expect that you will be able to perform approximately 50 jump trials (150 squats) prior to maximum fatigue.

During all of the the jump landings you will have 28 reflective markers attached to your body, which will enable us to measure the movements of your lower body. The markers will be secured directly to the skin using adhesive tape and will not cause you any discomfort. As some markers are required to be attached to the thigh and hips, you will be asked to wear bicycle shorts and sports brassier during testing.

Forward Hops: The forward hop requires you to jump and land on a single leg. We will ask you to complete the hop for both legs. Before you hop, you will be asked to stand on the leg we are testing (picture 4), with your hands on your hips. When you are ready, you will be asked to jump forward as far as you can and stick the landing, if possible. You will be asked to hop 5 times for each leg.

Measures of brain and spinal cord output: For these tests we will obtain measures of brain and spinal cord function known as the H-reflex, M-wave, and, V-wave. To obtain the H-reflex and M-wave one small area, on both legs, will be shaved, rubbed gently with sand paper, and cleaned with isopropyl alcohol. Four round stickers (electrodes) will be applied to this area and an additional electrode will be applied to the bone on the inside of your ankle. These electrodes will be outlined with a black marker to ensure they are in the same place throughout the entire testing session. Next, you will be given a small round disc to place near your groin. A diagram will be provided to demonstrate the correct placement. Additionally, we will ask you to place a large rubber electrode on your buttocks. Several measurements will be taken while you are lying down. These measurements include a 1-millisecond shock. The intensity of this shock will vary depending on which response is being elicited. Lower intensities (50-100V) will be needed to obtain an H-reflex where higher intensities (100-200V) are needed to elicit an M-wave. The shocks in this study feel similar to a shock of static electricity, like when you are walking across a carpet and then touch a door knob, except the voltage is much lower (A shock of static electricity can provide up to thousands of volts of electricity). To obtain the V-wave, the same technique utilized to gather the H-reflex and M-wave will be used, except that you will be asked to contract your quadriceps, by kicking out your leg, as hard as you can against resistance. The shocks will be applied atop of the quadriceps contraction.

MRI measures

For this test, you will be asked to report to The University of Michigan Hospital so an MRI of your thigh muscles can be obtained. The MRI machine uses a strong magnet and radiowaves to make images of the inside of your body. The scanning procedure is very much like an x-ray or a CT scan. You will be asked to lie on a long narrow couch for approximately 1 hour while the machine gathers data. During this time you will not be exposed to x-rays, but rather a magnetic field. Your will not feel anything during the test. You will, however, hear repetitive knocking noises that arise from the MR scanner. The space within the large magnet in which you will lie is somewhat confined. If you feel discomfort at any time, notify the operator and you can discontinue the exam.

If an injury or potentially significant health condition is identified by one of the investigators during the MRI examination, both you and your treating physician (ACL-injured subjects) will be notified. Please note that the MRIs are for research only and will not be read by your clinical provider(s).

If you have already undergone an MRI as a part of your clinical care you will still need to have an additional MRI for research purposes only.

4.2 How much of my time will be needed to take part in this study?

The testing sessions that take place at MedSport will last no longer than 2.5 hours. You may be asked to report for testing from 1-3 times. Therefore, the maximum amount time you would need to report for testing would be 7.5 hours. If you are asked to have an MRI scan, this testing will take about 1 additional hour. The maximum total testing time would be approximately 8.5 hours (testing at MedSport + MRI).

4.3 When will my participation in the study be over?

Most subjects will complete their part of the study within 1 year. The entire study is expected to last about 5 years.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

The known or expected risks are:

- You may experience some discomfort when the electrical shocks are applied to your skin. In order to make the shocks as comfortable as possible, large pads will be used to apply the shocks.
- You may experience muscle soreness after performing repeated muscle contractions. You will be offered ice bags following the experiment to minimize the chances of muscle soreness.
- You may suffer a joint or muscle injury during the study when performing the landing tasks. Dr. Palmieri-Smith, the lead researcher on this study, is a certified athletic trainer equipped with the knowledge to evaluate and manage musculoskeletal injuries. Thus, if an injury were to occur Dr. Palmieri-Smith would manage the condition and refer you to a physician for further evaluation.
- You may suffer a muscle or tendon injury when performing the repeated muscle contractions. Dr. Palmieri-Smith, the lead researcher on this study, is a certified athletic trainer equipped with the knowledge to evaluate and manage musculoskeletal injuries. Thus, if an injury were to occur, Dr. Palmieri-Smith would manage the condition and refer you to a physician for further evaluation.
- The magnet that is a part of the MRI may attract metals that are implanted within your body. Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience a strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged. You will be provided a way to secure these items. If you have any history of head or eye injury involving metal fragments or if you have ever worked in a metal shop you should notify the operator/investigator.
- If you are pregnant the fetus may be affected if you have an MRI scan. Currently, the effects of MRI on a fetus are unknown and international safety standards recommend that MRI is utilized cautiously for pregnant women. Therefore if you are pregnant, you are ineligible to participate

in the investigation. If at any time during the course of the study you become or suspect that you may be pregnant, please notify the PI so you can be removed from the investigation.

- There is also the potential risk of loss of confidentiality through participation in this study. Every effort will be made to keep your information confidential, however, this cannot be guaranteed. Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions and you may take a break at any time during the study. You may stop your participation in this study at any time.
- As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?

The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors.

5.3 If I take part in this study, can I also participate in other studies?

Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?

You may not receive any personal benefits from being in this study. Your participation will be of benefit to medical science.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?

Since your participation is voluntary, you may decide not to take part in the study at any time without penalty. Your only other option is not to participate.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the

study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information" (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

No harm will occur if you decide to leave the study early.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's **medical reviewer.**

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?

You will receive $25 for each session in which you participate. If you are asked to get an MRI scan you will receive $25 for your participation. You will receive this payment in the mail approximately 4 weeks after each testing session.

8.3 Who could profit or financially benefit from the study results?
No person or organization has a financial interest in the outcome of the study.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?
We will put the information collected about you during the study into a research record. This research record will not show your name, but will have codes entered in it, that will allow the information to be linked to you. However, we will keep your research record confidential, to the extent provided by federal, state, and local law. We will not allow anyone to see your record, other than people who have a right to see it. You will not be identified in any reports from this study.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- All records relating to your ACL injury, the treatment you have received, and your response to the treatment
- Billing information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
  - Make sure the study is done safely and properly
  - Learn more about side effects
  - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.

- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study may be published or presented at a scientific meeting. If your name and pictures will be used in any publications or presentation, the researchers will ask for your separate written permission.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

9.3 What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over. Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan Notice of Privacy Practices. This information is also available on the web at http://www.med.umich.edu/hipaa/npp.htm. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Riann Palmieri-Smith, Ph.D., ATC
Mailing Address: 4745G CCRB, School of Kinesiology, University of Michigan, 401 Washtenaw Avenue, Ann Arbor, MI, 48109-2214
Telephone: 734-615-3154

You may also express a concern about a study by contacting the Institutional Review Board listed below, or by calling the University of Michigan Compliance Help Line at 1-888-296-2481.

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

☐ This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*

12. SIGNATURES

Research Subject:

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Signature of Subject: _____ Date: _____

Name (Print legal name): _____

Patient ID:_____ Date of Birth: _____

Legal Representative (if applicable):

Signature of Person #1 Legally Authorized to Give Consent_____ Date: _____

Name (Print legal name): _____ Phone: _____

Address: _____

Check Relationship to Subject:

☐Parent ☐Spouse ☐Child ☐Sibling ☐Legal Guardian ☐Other: _____

Signature of Person #2 Legally Authorized to Give Consent_____ Date: _____

Name (Print legal name): _____ Phone: _____

Address: _____

Check Relationship to Subject:

☐Parent ☐Spouse ☐Child ☐Sibling ☐Legal Guardian ☐Other: _____

If this consent is for a child who is a ward of the state (for example a foster child), please tell the study team immediately. The researchers may need to contact the IRBMED.

Reason subject is unable to sign for self:_____

_____

Principal Investigator (or Designee):

I have given this research subject (or his/her legally authorized representative, if applicable) information about this study that I believe is accurate and complete. The subject has indicated that he or she understands the nature of the study and the risks and benefits of participating.

Name: _____ Title: _____

Signature: _____ Date of Signature: _____

APPENDIX F

Institutional Review Board Consent- AIM 3

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

1.1 Study title:
Neuromechanical Dysfunction Associated with ACL Injury

1.2 Company or agency sponsoring the study:
This study is funded by The National Institutes of Health and The University of Michigan Bone & Joint Injury Prevention & Rehabilitation Center.

1.3 Names, degrees, and affiliations of the researchers conducting the study:
Riann Palmieri-Smith, PhD, ATC – University of Michigan, School of Kinesiology
Asheesh Bedi, MD – University of Michigan, Department of Orthopedics
Catherine Brandon, MD – University of Michigan, Department of Radiology
Elizabeth Sibilsky Eisenman, MEd, ATC – University of Michigan, Department of Orthopaedics
Lindsey Lepley, MEd, ATC – University of Michigan, School of Kinesiology
Scott McLean, PhD - University of Michigan, School of Kinesiology
Christopher Mendias, PhD, ATC – University of Michigan, School of Kinesiology
Bruce Miller, MD- University of Michigan, Department of Orthopedics
Daryl Montie, DPT, CSCS, MA – University of Michigan, MedSport
Edward Wojtys, MD – University of Michigan, Department of Orthopedics

2. PURPOSE OF THIS STUDY

2.1 Study purpose:
Thigh muscle weakness often accompanies anterior cruciate ligament (ACL) injury. This study is designed to examine how thigh muscle weakness that accompanies ACL injury affects lower body positions and forces. We will also examine whether electrical stimulation therapy and knee muscle strengthening can improve thigh muscle strength.

We are asking you to help us test an intervention to improve thigh (quadriceps) muscle strength. The quadriceps muscle has an important role as a shock absorber for the knee. It often becomes weak

following ACL injury and therefore its ability to serve as a shock absorber is diminished, and cartilage in the knee must increasingly assume these loads. This can result in deterioration of the joint.

Quadriceps muscle strength can be improved by muscle use. Muscle use can be achieved by voluntary intensive physical activity or with stimulation of muscle activation by electrical stimulation.
We are testing the effectiveness of two interventions to improve quadriceps muscle strength. The first therapy we are testing is called neuromuscular electric stimulation (NMES). NMES therapy has been shown to improve quadriceps strength immediately following therapy and this should allow the muscle to better serve as a protective agent and shock absorber. In the second portion of the study we are testing the effectiveness of a combined intervention of NMES and eccentric strengthening to improve thigh muscle strength. Eccentric muscle strengthening is the lowering phase of an exercise. Following ACL reconstruction eccentric strengthening has also been shown to improve quadriceps muscle strength. This study will determine if NMES therapy or a combined NMES and eccentric protocol improves quadriceps strength and lower body positions and loads.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

Sixty volunteers, between the ages of 14-45, who have torn their ACL or sustained a serious knee injury to their articular cartilage or collateral ligaments and are scheduled to undergo surgical repair will be recruited to participate in this part of the study. All study participants cannot have any previous history of serious ACL injury or ACL surgery or a demand-type cardiac pacemaker. Furthermore, volunteers who are females and are pregnant are not eligible to participate. It is very important that you accurately report your medical history.

3.2 How many people (subjects) are expected to take part in this study?

We will enroll 60 participants in this part of the study and 214 participants in another part of the study.

4. INFORMATION ABOUT STUDY PARTICIPATION

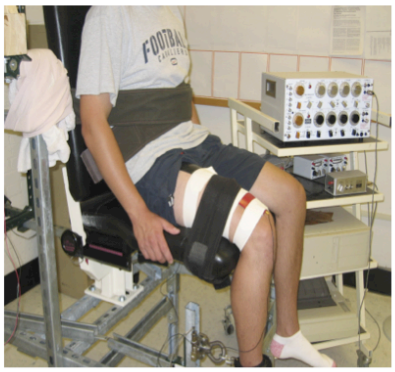
4.1 What will happen to me in this study?

If you choose to participate, you will be randomly assigned or placed into a group to receive either short duration NMES therapy after surgery only (therapy group 1), long duration NMES therapy after surgery only (therapy group 2), NMES therapy and eccentric strengthening after surgery (therapy group3), or no therapy (therapy group 4). *Participants in ALL groups* will undergo a standard ACL rehabilitation protocol and will be asked to report for testing on 3 occasions over a period of 6 months. Participants in therapy group 1 and 2 will also receive NMES therapy 2-3 times per week for up to 6 weeks. Participants in therapy group 3 will receive the NMES therapy 2-3 times per week for the first 6 weeks post-surgery followed by 6 weeks of eccentric strengthening 2-3 times per week. The therapy sessions will take place during your normally scheduled physical therapy appointments at MedSport. All therapy and testing sessions will be done at the University of Michigan MedSport Clinic, in Domino's Farms (Lobby A) in Ann Arbor on Plymouth Road.

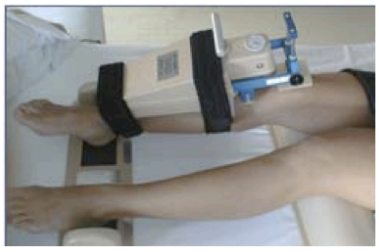
TESTING SESSIONS (ALL GROUPS)

All groups will be asked to report for 3 testing sessions. One session will occur before your operation and 2 sessions will occur after your operation (12 weeks and 6 months post-surgery). In the testing session before your operation, you will be asked to walk with specialized stickers attached to your skin. You will also have measures of your muscle strength and looseness of your knee joints recorded. You will also be asked to fill out a questionnaire that asks questions about your pain level and functional abilities. Some participants may be asked to have an MRI of their muscles taken. At the session 12 weeks following your surgery, you will be asked to walk, have measures of knee looseness recorded, and fill out the questionnaire. At approximately 6 months following your surgery, you will be asked to repeat all of the tests done in the previous sessions and will also be asked to complete about 30 jump landings and 10 forward hops.

Measures of Muscle Strength: Two large pads will be placed on the front of both of your thighs and secured with bandages. Once all of the pads are attached to your leg, you will be positioned in a device that measures muscle strength. You will be asked to sit in a chair attached to the device with your knees bent (Picture 1). Once you are positioned in the device, you will be asked to kick your leg out against a pad as hard as you can. As soon as you feel comfortable with the kick, the researchers will apply a group of shocks to the skin of your thigh while you are resting. We will deliver the shocks thru the pads we attached earlier. In order to help you get use to the shocks, we will start giving them to you at a low level and will then increase the level in small amounts. We eventually need the level of the shocks to reach 150 volts each (if these shock were delivered separately they would feel like a shock of static electricity like when you walk across a carpet and touch a door knob, except a shock of static electricity can reach up to 1,000 volts) The series of 10 shocks will last less than 1 second and are delivered very close together, so you shouldn't be able to feel individual shocks. The group of shocks will allow your muscle to contract even when you are resting. These shocks may be slightly uncomfortable, the discomfort you experience in the muscle is normal. If at anytime during the procedures you feel as if the shocks are too strong and you don't want to continue, please notify the researchers immediately. Once you are comfortable with the shocks, you will again be asked to kick out as hard as you can. Once the researchers see that you are contracting as hard as you can by watching the computer screen (usually in about 2 seconds), they will deliver the series of shocks on top of your muscle. This technique, where we deliver shocks on top of a muscle contraction, will be repeated 3 times for each leg.



Picture 1. Muscle Strength Test



Picture 2. Knee Looseness Testing

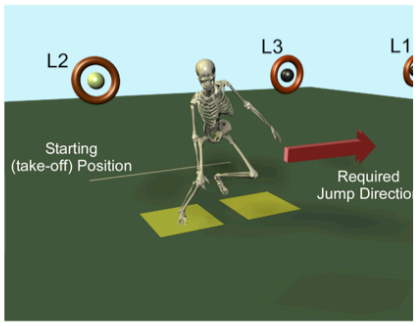
Measure of looseness of your knee joint: In order to see how loose your knees are, we will place each knee into a device, one at a time. You will be asked to lay on your back and we will place a pad under both of your legs. The device will be secured to your leg, at the ankle and calf, by Velcro straps (see picture 2). Once your knee is in the device, the investigators will pull a handle on the device, which causes the shin bone to move forward, or to the left or right. The investigators will pull on the handle 9 times for each knee.

Measure of knee swelling: We will assess how much fluid is in your knee by wrapping a cloth measuring tape around your kneecap. We will do this on both knees.

Walking: In order to understand the forces that your knee sustains during everyday activities, we will ask you to walk about 100 meters with reflective markers attached to your skin. You will be asked to walk this length about 5 times.

Jump Landings: The jump landing tasks will include both double and single leg take-offs. Upon landing, you will be required to quickly jump to the left, right or straight up. You will be informed in which direction to jump by a light (Picture 3). The first light (L1) is fixed to the left and in front of a force plate (similar to a scale that measures forces), If this light comes on, you will land on the left foot only and then jump to the right. A second light (L2) will be similarly positioned to the right of the force plates, and will require you to land on the right foot only and jump to the left. A third light (L3) will be placed between the two force plates. When this light comes on you will be required to land on both feet and jump straight up. The researchers will demonstrate the jump landings before you are asked to do it.

Following the initial jump landing trials, you will again be required to perform the above tasks, only this time while being exposed to a general fatigue protocol. Specifically, you will be asked to perform continuous sets of three single or double leg squats between the jump trials. You will alternate between squats and jumps until fatigue is reached, being defined as the point when you can no longer perform three squats in succession. You will be able to place the non-fatigued leg on a platform for stability during the single leg squats. From our previous work, we expect that you will be able to perform approximately 50 jump trials (150 squats) prior to maximum fatigue.



Picture 3. Jump Landing Task.

During the jump landing you will have 28 reflective markers attached to your body, which will enable us to measure the movements of your lower body. The markers will be secured directly to the skin using adhesive tape and will not cause you any discomfort. As some markers are required to be attached to the thigh and hips, you will be asked to wear bicycle shorts and sports brassier during testing.


Picture 4. Forward Hop

Forward Hops: The forward hop requires you to jump and land on a single leg. We will ask you to complete the hop for both legs. Before you hop, you will be asked to stand on the leg we are testing (picture 4), with your hands on your hips. When you are ready, you will be asked to jump forward as far as you can and stick the landing, if possible. You will be asked to hop 5 times for each leg.

Measures of brain and spinal cord output: For these tests we will obtain measures of brain and spinal cord function known as the H-reflex, M-wave, and, V-wave. To obtain the H-reflex and M-wave one small area, on both legs, will be shaved, rubbed gently with sand paper, and cleaned with isopropyl

alcohol. Four round stickers (electrodes) will be applied to this area and an additional electrode will be applied to the bone on the inside of your ankle. These electrodes will be outlined with a black marker to ensure they are in the same place throughout the entire testing session. Next, you will be given a small round disc to place near your groin. A diagram will be provided to demonstrate the correct placement. Additionally, we will ask you to place a large rubber electrode on your buttocks. Several measurements will be taken while you are lying down. These measurements include a 1-millisecond shock. The intensity of this shock will vary depending on which response is being elicited. Lower intensities (50-100V) will be needed to obtain an H-reflex where higher intensities (100-200V) are needed to elicit an M-wave. The shocks in this study feel similar to a shock of static electricity, like when you are walking across a carpet and then touch a door knob, except the voltage is much lower (A shock of static electricity can provide up to thousands of volts of electricity). To obtain the V-wave, the same technique utilized to gather the H-reflex and M-wave will be used, except that you will be asked to contract your quadriceps, by kicking out your leg, as hard as you can against resistance. The shocks will be applied atop of the quadriceps contraction.

MRI measures

For this test, you will be asked to report to The University of Michigan Hospital so an MRI of your thigh muscles can be obtained. The MRI machine uses a strong magnet and radiowaves to make images of the body interior. The scanning procedure is very much like an x-ray or a CT scan. You will be asked to lie on a long narrow couch for approximately 1 hour while the machine gathers data. During this time you will not be exposed to x-rays, but rather a magnetic field. Your will not feel anything during the test. Your will, however, hear repetitive knocking noises that arise from the MR scanner. The space within the large magnet in which you will lie is somewhat confined. If you feel discomfort at any time, notify the operator and you can discontinue the exam at anytime.

If an injury or potentially significant health condition is identified by one of the investigators during the MRI examination, both you and your treating physician (ACL-injured subjects) will be notified. Please note that the MRIs are for research only and will not be read by your clinical provider(s).

If you have already undergone an MRI as a part of your clinical care you will still need to have an additional MRI for research purposes only.

NMES SESSIONS (THERAPY GROUPS 1, 2, 3 ONLY)

If you are assigned to the therapy group 1, 2 or 3, you will be asked to participate in between 12-18 NMES therapy sessions after surgery. NMES sessions in therapy groups 1 and 3 will last approximately 10 minutes each, while NMES sessions in therapy group 2 will last approximately 20 minutes each. The number of sessions you participate in depends on the number of physical therapy visits you do at MedSport. At the NMES sessions, you will be sitting in device that measures muscle strength with two electrodes applied to your thigh muscle. While relaxed, an electrical stimulation will be delivered to your thigh muscle, causing it to contract. If you are assigned to therapy groups 1 or 3 you will have the electrical stimulation delivered 10 times per session. If you are assigned to therapy group 2 the electrical stimulation will be delivered 20 times per session. Regardless of group assignment, following each contraction, you will be given a period of rest. The intensity of the electrical stimulation will be increased gradually throughout each session. If you are uncomfortable with the therapy sessions, you can stop it at any time.

ECCENTRIC SESSIONS (THERAPY GROUP 3 ONLY)

If you are assigned to therapy group 3, you will be asked to participate in between 12-18 eccentric strengthening sessions. These sessions will begin six weeks after surgery, once the NMES intervention

is complete. Each session will last approximately 20 minutes. The number of sessions you participate in depends on the number of physical therapy visits you do at MedSport. At the eccentric strengthening session, you will be seated in a leg press machine that will apply a weight to your thigh muscles. You will be asked to perform a total of four sets consisting of ten muscle contractions with two minutes rest between each set. The intensity of the eccentric strengthening will be gradually increased over the course of the intervention. If you are uncomfortable with the eccentric therapy sessions, you can stop at any time.

4.2 How much of my time will be needed to take part in this study?

Testing sessions will last approximately 2-3 hours each. Each therapy session (NMES or eccentric strengthening) will last between 10-20 minutes and will take place before, after, or during your normal physical therapy appointments at MedSport. For participants in therapy group 1 you will have a maximum of 3 hours of NMES treatment post-surgery. For participants in therapy group 2 you will have a maximum of 6 hours of NMES treatment post-surgery. For participants in therapy group 3 you will have a maximum of 3 hours of NMES treatment and a maximum a 6 hours of eccentric strengthening following your surgery. All participants, regardless of group assignment, will be asked to report for testing on 3 occasions with each testing session lasting between 2-3 hours (maximum testing time for all sessions 9 hours). For participants in therapy group 1 your maximum total time for participation in this study would be 12 hours (3 possible hours of NMES and 9 possible hours for testing). For participants in therapy group 2 your maximum total time for participation in this study would be 15 hours (6 possible hours of NMES and 9 possible hours for testing). For participants in therapy group 3 your maximum total time for participation in this study would be 18 hours (3 possible hours of NMES, 6 possible hours of eccentric strengthening and 9 possible hours for testing). For participants in therapy group 3 your maximum total time for participation in this study would be 9 hours (9 possible hours for testing).

4.3 When will my participation in the study be over?

Most subjects will complete their part of the study within 6 months. The entire study is expected to last about 5 years.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

The known or expected risks are:

- You may experience some discomfort when the electrical shocks are applied to you skin. In order to make the shocks as comfortable as possible, large pads will be used to apply the shocks.
- You may experience muscle soreness after performing repeated muscle contractions. You will be offered ice bags following the experiment to minimize the chances of muscle soreness.
- You may suffer a joint or muscle injury during the study when performing the landing/hopping tasks. Dr. Palmieri-Smith, the lead researcher on this study, is a certified athletic trainer equipped with the knowledge to evaluate and manage musculoskeletal injuries. Thus, if an injury were to occur Dr. Palmieri-Smith would manage the condition and refer you to a physician for further evaluation.
- You may suffer a muscle or tendon injury when performing the repeated muscle contractions. Dr. Palmieri-Smith, the lead researcher on this study, is a certified athletic trainer equipped with the knowledge to evaluate and manage musculoskeletal injuries. Thus, if an injury were to occur, Dr. Palmieri-Smith would manage the condition and refer you to a physician for further evaluation.

- Dr. Palmieri-Smith has recently been made aware of a patient who had undergone ACL reconstruction and broke her knee cap during an NMES treatment. It is critical that you make members of the study team aware if you are feeling pain inside your knee or in your knee cap during the treatment. Members of the study team will ask you about whether you are experiencing any discomfort during the treatment. If you are experiencing pain in the knee the treatment will be terminated. It should be mentioned that we are only aware of a single case in the United States where this has occurred and this is a common treatment, used daily, for a number of joint injuries. In the case where the knee cap was broken, the young woman was experiencing pain in her knee and failed to alert clinicians.
- The magnet that is a part of the MRI may attract metals that are implanted within your body. Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience a strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged. You will be provided a way to secure these items. If you have any history of head or eye injury involving metal fragments or if you have ever worked in a metal shop you should notify the operator/investigator.
- If you are pregnant the fetus may be affected if you have an MRI scan. Currently, the effects of MRI on a fetus are unknown and international safety standards recommend that MRI is utilized cautiously for pregnant women. Therefore if you are pregnant, you are ineligible to participate in the investigation. If at any time during the course of the study you become or suspect that you may be pregnant, please notify the PI so you can be removed from the investigation.
- There is also the potential risk of loss of confidentiality through participation in this study. Every effort will be made to keep your information confidential, however, this cannot be guaranteed. Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions and you may take a break at any time during the study. You may stop your participation in this study at any time.
- As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?

The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors.

5.3 If I take part in this study, can I also participate in other studies?

Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?

You may not receive any personal benefits from being in this study. Your participation will be of benefit to medical science.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?

Since your participation is voluntary, you may decide not to take part in the study at any time without penalty. Your only other option is not to participate.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information" (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

No harm will occur if you decide to leave the study early.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's **medical reviewer.**

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?

You will receive $25 for the first testing session, $35 for the second testing session and $50 for the third testing session. You will receive these payments at the time of testing. Those persons assigned to the therapy groups will also receive $10 for each week of NMES therapy and $10 for each week of eccentric strengthening. You will receive upon completion of all therapy sessions. If you drop out of therapy group 1 or 2, you would receive your payment upon completion of your last therapy session.

8.3 Who could profit or financially benefit from the study results?

No person or organization has a financial interest in the outcome of the study.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?

We will put the information collected about you during the study into a research record. This research record will not show your name, but will have codes entered in it, that will allow the information to be linked to you. However, we will keep your research record confidential, to the extent provided by federal, state, and local law. We will not allow anyone to see your record, other than people who have a right to see it. You will not be identified in any reports from this study.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- All records relating to your ACL injury, the treatment you have received, and your response to the treatment
- Billing information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
  - Make sure the study is done safely and properly
  - Learn more about side effects
  - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study may be published or presented at a scientific meeting. If your name and pictures will be used in any publications or presentation, the researchers will ask for your separate written permission.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

9.3 What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be

used or disclosed, even after you have canceled your permission or the study is over. Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan Notice of Privacy Practices. This information is also available on the web at http://www.med.umich.edu/hipaa/npp.htm. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Riann Palmieri-Smith, Ph.D., ATC
Mailing Address: 4745G CCRB, School of Kinesiology, University of Michigan, 401 Washtenaw Avenue, Ann Arbor, MI, 48109-2214
Telephone: 734-615-3154

You may also express a concern about a study by contacting the Institutional Review Board listed below, or by calling the University of Michigan Compliance Help Line at 1-888-296-2481.

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 200, Room 2086

Ann Arbor, MI 48109-2800
Telephone: 734-763-4768
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy, contact the University of Michigan Health System Privacy Officer at 1-888-296-2481.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

☐ This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*

12. SIGNATURES

Research Subject:

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Signature of Subject: _____ Date: _____

Name (Print legal name): _____

Patient ID:_____ Date of Birth: _____

Legal Representative (if applicable):

Signature of Person #1 Legally Authorized to Give Consent_____ Date: _____

Name (Print legal name): _____ Phone: _____

Address: _____

Check Relationship to Subject:

☐Parent ☐Spouse ☐Child ☐Sibling ☐Legal Guardian ☐Other: _____

Signature of Person #2 Legally Authorized to Give Consent_____ Date: _____

Name (Print legal name): _____ Phone: _____

Address: _____

Check Relationship to Subject:

☐Parent ☐Spouse ☐Child ☐Sibling ☐Legal Guardian ☐Other: _____

If this consent is for a child who is a ward of the state (for example a foster child), please tell the study team immediately. The researchers may need to contact the IRBMED.

Reason subject is unable to sign for self:_____

_____

Principal Investigator (or Designee):

I have given this research subject (or his/her legally authorized representative, if applicable) information about this study that I believe is accurate and complete. The subject has indicated that he or she understands the nature of the study and the risks and benefits of participating.

Name: _____ Title: _____

Signature: _____ Date of Signature: _____

APPENDIX G

Collections Forms- AIM 1

Eccentric Cross-Education Study
Isokinetic Data Collection Sheet

Study Participant #:	Group: CONTROL

Testing Session 1 (Pre). Test Date:_____

		Concentric (Trained: R/L)		Eccentric (Trained: R/L)	
		30°	60°	30°	60°
Torque	1				
	2				
	3				
		Concentric (Un-Trained: R/L)		Eccentric (Un-Trained: R/L)	
		30°	60°	30°	60°
Torque	1				
	2				
	3				

Testing Session 2 (Mid, wk4). Test Date:_____

		Concentric (Trained: R/L)		Eccentric (Trained: R/L)	
		30°	60°	30°	60°
Torque	1				
	2				
	3				
		Concentric (Un-Trained: R/L)		Eccentric (Un-Trained: R/L)	
		30°	60°	30°	60°
Torque	1				
	2				
	3				

Testing Session 3 (Post, wk8). Test Date:_____

Torque		Concentric (Trained: R/L)		Eccentric (Trained: R/L)	
		30°	60°	30°	60°
	1				
	2				
	3				
Torque		Concentric (Un-Trained: R/L)		Eccentric (Un-Trained: R/L)	
		30°	60°	30°	60°
	1				
	2				
	3				

Eccentric Cross-Education Study
Isokinetic Data Collection Sheet

Study Participant #:	Group: ECCENTRIC

Testing Session 1 (Pre). Test Date:_____

		Concentric (Trained: R/L)		Eccentric (Trained: R/L)	
		30°	60°	30°	60°
Torque	1				
	2				
	3				
		Concentric (Un-Trained: R/L)		Eccentric (Un-Trained: R/L)	
		30°	60°	30°	60°
Torque	1				
	2				
	3				

Testing Session 2 (wk 1). Test Date:_____

		Concentric (Un-Trained: R/L)		Eccentric (Un-Trained: R/L)	
		30°	60°	30°	60°
Torque	1				
	2				
	3				

Testing Session 3 (wk 2). Test Date:_____

		Concentric (Un-Trained: R/L)		Eccentric (Un-Trained: R/L)	
		30°	60°	30°	60°
Torque	1				
	2				
	3				

Testing Session 4 (wk 3). Test Date:_____

		Concentric (Un-Trained: R/L)		Eccentric (Un-Trained: R/L)	
		30°	60°	30°	60°
Torque	1				
	2				
	3				

Testing Session 5 (Mid, wk4). Test Date:_____

		Concentric (Trained: R/L)		Eccentric (Trained: R/L)	
		30°	60°	30°	60°
Torque	1				
	2				
	3				
		Concentric (Un-Trained: R/L)		Eccentric (Un-Trained: R/L)	
		30°	60°	30°	60°
Torque	1				
	2				
	3				

Testing Session 6 (wk5). Test Date:_____

		Concentric (Trained: R/L)		Eccentric (Trained: R/L)	
		30°	60°	30°	60°
Torque	1				
	2				
	3				

Testing Session 7 (wk6). Test Date:_____

		Concentric (Un-Trained: R/L)		Eccentric (Un-Trained: R/L)	
		30°	60°	30°	60°
Torque	1				
	2				
	3				

Testing Session 8 (wk7). Test Date:_____

		Concentric (Un-Trained: R/L)		Eccentric (Un-Trained: R/L)	
		30°	60°	30°	60°
Torque	1				
	2				
	3				

Testing Session 9 (Post, wk8). Test Date:_____

Torque		Concentric (Trained: R/L)		Eccentric (Trained: R/L)	
		30°	60°	30°	60°
	1				
	2				
	3				
Torque		Concentric (Un-Trained: R/L)		Eccentric (Un-Trained: R/L)	
		30°	60°	30°	60°
	1				
	2				
	3				

Participant ID#_____ Date:_____

Testing Session:_____

TEGNER ACTIVITY LEVEL SCALE

Please indicate in the spaces below the HIGHEST level of activity that you participated in **BEFORE STUDY ENROLLMENT** and the highest level you are able to participate in **CURRENTLY**.

BEFORE STUDY: Level_____ CURRENT: Level_____

Level 10	Competitive sports-soccer, football, rugby (national elite)
Level 9	Competitive sports-soccer, football, rugby (lower divisions), ice hockey, wrestling, gymnastics, basketball
Level 8	Competitive sports-racquetball or bandy, squash or badminton, track and field athletics (jumping, etc.), down-hill skiing
Level 7	Competitive sports- tennis, running, motorcars speedway, handball Recreational sports- soccer, football, rugby, bandy , ice hockey, basketball, squash, racquetball, running
Level 6	Recreational sports- tennis and badminton, handball, racquetball, down-hill skiing, jogging at least 5 times per week
Level 5	Work-heavy labor (construction, etc.) Competitive sports – cycling, cross-country skiing Recreational sports- jogging on uneven ground at least twice weekly
Level 4	Work- moderately heavy labor (e.g. truck driving, etc.)
Level 3	Work-light labor (nursing, etc.)
Level 2	Work- light labor Walking on uneven ground possible, but impossible to back pack or hike
Level 1	Work-sedentary (secretarial, etc.)
Level 0	Sick leave or disability pension because of knee problems

Y Tegner and J Lysom. *Rating Systems in the Evaluation of Knee Ligament Injuries*. Clinical Othropedics and Related Research. Vol. 198: 43-49, 1985.

Participant ID#:_____ Date:_____
Testing Session:_____

MARX ACTIVITY LEVEL SCALE

Please indicate how often you performed each activity in your healthiest and most active state, **in the past year.**

	Less than one time in a month	One time in a month	One time in a week	2 or 3 times in a week	4 or more times in a week
Running: running while playing a sport or jogging	☐	☐	☐	☐	☐
Cutting: changing directions while running	☐	☐	☐	☐	☐
Decelerating: coming to a quick stop while running	☐	☐	☐	☐	☐
Pivoting: turning your body with you foot planted while play a sport. For example: skiing, skating, kicking, throwing, hitting a ball (golf, tennis, squash), etc.	☐	☐	☐	☐	☐

APPENDIX G

Collections Forms- AIMS 2 & 3

ACL Pre-Post Quadriceps Activation Data Collection Sheet

Study Participant #:	Age:
Ht.	Wt:

Testing Session 1 (Pre-op 1). Test Date:_____

		Right		Left	
		Vol.	Burst	Vol.	Burst
Torque @ 90°	1				
	2				
	3				

Testing Session 2 (6 months). Test Date:_____

		Right		Left	
		Vol.	Burst	Vol.	Burst
Torque @ 90°	1				
	2				
	3				

ACL NMES + ECC Quadriceps Activation Data Collection Sheet

Study Participant #:	Age:
Ht.	Wt:

Testing Session 1 (Pre-op). Test Date:_____

		Right		Left	
		Vol.	Burst	Vol.	Burst
Torque @ 90°	1				
	2				
	3				

Testing Session 2 (Post-op 12 wk). Test Date:_____

		Right		Left	
		Vol.	Burst	Vol.	Burst
Torque @ 90°	1				
	2				
	3				

Testing Session 3 (Post-op 6 month). Test Date:_____

		Right		Left	
		Vol.	Burst	Vol.	Burst
Torque @ 90°	1				
	2				
	3				

2000 IKDC SUBJECTIVE KNEE EVALUATION FORM

Your Full Name_____

Today's Date: _____/_____/_____ (Day / Month / Year) Date of Injury: _____/_____/_____ (Day / Month / Year)

SYMPTOMS*:

*Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.

1. What is the highest level of activity that you can perform without significant knee pain?

   ❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   ❑Strenuous activities like heavy physical work, skiing or tennis
   ❑Moderate activities like moderate physical work, running or jogging
   ❑Light activities like walking, housework or yard work
   ❑Unable to perform any of the above activities due to knee pain

2. During the past 4 weeks, or since your injury, how often have you had pain?

	0	1	2	3	4	5	6	7	8	9	10	
Never	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	Constant

3. If you have pain, how severe is it?

	0	1	2	3	4	5	6	7	8	9	10	
No pain	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	Worst pain imaginable

4. During the past 4 weeks, or since your injury, how stiff or swollen was your knee?

   ❑Not at all
   ❑Mildly
   ❑Moderately
   ❑Very
   ❑Extremely

5. What is the highest level of activity you can perform without significant swelling in your knee?

   ❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   ❑Strenuous activities like heavy physical work, skiing or tennis
   ❑Moderate activities like moderate physical work, running or jogging
   ❑Light activities like walking, housework, or yard work
   ❑Unable to perform any of the above activities due to knee swelling

6. During the past 4 weeks, or since your injury, did your knee lock or catch?

   ❑Yes ❑No

7. What is the highest level of activity you can perform without significant giving way in your knee?
   ❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   ❑Strenuous activities like heavy physical work, skiing or tennis
   ❑Moderate activities like moderate physical work, running or jogging
   ❑Light activities like walking, housework or yard work
   ❑Unable to perform any of the above activities due to giving way of the knee

Page 2 – 2000 IKDC SUBJECTIVE KNEE EVALUATION FORM

SPORTS ACTIVITIES:

8. What is the highest level of activity you can participate in on a regular basis?

❑Very strenuous activities like jumping or pivoting as in basketball or soccer
❑Strenuous activities like heavy physical work, skiing or tennis
❑Moderate activities like moderate physical work, running or jogging
❑Light activities like walking, housework or yard work
❑Unable to perform any of the above activities due to knee

9. How does your knee affect your ability to:

		Not difficult at all	Minimally difficult	Moderately Difficult	Extremely difficult	Unable to do
a.	Go up stairs	❑	❑	❑	❑	❑
b.	Go down stairs	❑	❑	❑	❑	❑
c.	Kneel on the front of your knee	❑	❑	❑	❑	❑
d.	Squat	❑	❑	❑	❑	❑
e.	Sit with your knee bent	❑	❑	❑	❑	❑
f.	Rise from a chair	❑	❑	❑	❑	❑
g.	Run straight ahead	❑	❑	❑	❑	❑
h.	Jump and land on your involved leg	❑	❑	❑	❑	❑
i.	Stop and start quickly	❑	❑	❑	❑	❑

FUNCTION:

10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

FUNCTION PRIOR TO YOUR KNEE INJURY:

Cannot perform daily activities	0	1	2	3	4	5	6	7	8	9	10	No limitation in daily activities
	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	

CURRENT FUNCTION OF YOUR KNEE:

Cannot perform daily activities	0	1	2	3	4	5	6	7	8	9	10	No limitation in daily activities
	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	

Participant ID #:_____ Date:_____
Testing Session:_____

TEGNER ACTIVITY LEVEL SCALE

Please indicate in the spaces below the HIGHEST level of activity that you participated in BEFORE YOUR INJURY and the highest level you are able to participate in CURRENTLY.

BEFORE INJURY: Level_____ CURRENT: Level_____

Level 10	**Competitive sports- soccer, football, rugby (national elite)**
Level 9	**Competitive sports- soccer, football, rugby (lower divisions), ice hockey, wrestling, gymnastics, basketball**
Level 8	**Competitive sports- racquetball or bandy, squash or badminton, track and field athletics (jumping, etc.), down-hill skiing**
Level 7	**Competitive sports- tennis, running, motorcars speedway, handball** **Recreational sports- soccer, football, rugby, bandy, ice hockey, basketball, squash, racquetball, running**
Level 6	**Recreational sports- tennis and badminton, handball, racquetball, down-hill skiing, jogging at least 5 times per week**
Level 5	**Work- heavy labor (construction, etc.)** **Competitive sports- cycling, cross-country skiing,** **Recreational sports- jogging on uneven ground at least twice weekly**
Level 4	**Work- moderately heavy labor (e.g. truck driving, etc.)**
Level 3	**Work- light labor (nursing, etc.)**
Level 2	**Work- light labor** **Walking on uneven ground possible, but impossible to back pack or hike**
Level 1	**Work- sedentary (secretarial, etc.)**
Level 0	**Sick leave or disability pension because of knee problems**

Y Tegner and J Lysolm. *Rating Systems in the Evaluation of Knee Ligament Injuries.* Clinical Orthopedics and Related Research. Vol. 198: 43-49, 1985.

ACL NMES+ECC
Hopping Tasks Collection Sheet

Participant ID #:_____
Date:___/___/___

Testing Session: 6 mos f/u

Single Leg Forward Hop For Distance

Trial #	Limb	Distance (in)	Distance (cm)
1	R		
2	R		
3	R		
4	L		
5	L		
6	L		

Unanticipated ForwardHop Trials (forwardhop#)

Trial #	Limb		Good Trial?	
1	R	L	Y	N
2	R	L	Y	N
3	R	L	Y	N
4	R	L	Y	N
5	R	L	Y	N
6	R	L	Y	N
7	R	L	Y	N
8	R	L	Y	N
9	R	L	Y	N
10	R	L	Y	N
11	R	L	Y	N
12	R	L	Y	N
13	R	L	Y	N
14	R	L	Y	N
15	R	L	Y	N
16	R	L	Y	N
17	R	L	Y	N
18	R	L	Y	N
19	R	L	Y	N
20	R	L	Y	N
21	R	L	Y	N
22	R	L	Y	N
23	R	L	Y	N
24	R	L	Y	N
25	R	L	Y	N

ACL NMES + ECC
NMES Treatment Log

Study Participant #:_____

Each treatment should consist of the following:

Pad Placement: 6.9 x 12.7 self adhesive electrodes will be placed over the vastus lateralis proximally and the vastus medialis distally.

Patient setup:
1) ACLr leg and torso secured to Biodex chair with Velcro straps
2) Seated with knee at **60°of flexion** record MVIC.
3) Seated with knee at **60°of flexion** NMES intervention.

Stimulation setup: After determining the participants average MVIC over 3 trials, the participant will be delivered a 2500-Hz alternating current, modulated at 75 bursts per second, with a ramp-up/ramp-down time of 2 seconds, followed by a 50-second rest period. If using the Chattanooga stimulator in the BJIPRC lab, use the protocol titled "ACL NMES." To select this protocol, push the center button on the stimulator unit (the one that looks like a file folder), select "user defined protocols" in the upper right hand corner, select the "ACL NMES" protocol. **The intensity of the current needs to be set at the participant's maximum tolerance.** The intensity will be increased throughout each session as tolerated. The patient should be instructed to relax while the NMES is applied to avoid voluntary quadriceps contraction and hamstring co-contraction. Ten, 10-second contractions will be elicited, via NMES, during each session.

Treatment time: ~10-12 minutes

Study Participant #:_____

Session #	Date	Avg. MVIC (across 3 trials)	NMES Torque Production (N*m)	% Torque Production	NMES Intensity (mA)
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					

ACL NMES + ECC
Eccentric Treatment Log

Study Participant #:_____

Each treatment should consist of the following:

1.
    a. Blast Leg Press System
        i. Tower located on side beneath force plate
2. Open up Blast LabVIEW folder (located on the top left of the touch screen)
    a. Double click and then stay clear of the equipment- allow for equipment to "warm-up"
3. Select 'Browse Return Users' (ex. ACL095)
4. For Warm-up select 'Training Mode'
    a. Step 1' select
        i. Target type: 1RM
        ii. Leg mode: ACL leg only (Right or Left)
        iii. Kinetic Training Mode: Bidirectional
        iv. Target Template: Extended Roll Off
    b. 'Step 2' select Training Program
        i. ACL Warm-up
    c. 'Step 3' select 'Begin Training"
        i. Target band controls will provide a real time visual target of the force the subject needs to produce to stay within the identified range for the set
        ii. *Enable Expert Transition*
    d. After warm-up completion select 'Back" (upper left hand of screen)
5. For Eccentric Exercise change the 'Training Program' to 'ACL ECCENTRIC' then begin training.
    a. After the completion of eccentric protocol (4 sets of 10 reps) select 'Back" (upper left hand of screen)

6. Record intensity of training
    a. From the Main Menu select 'Data Recall' then 'Single Session Recall'
        i. Choose the appropriate date/time of the ACL ECCENTRIC training program.
    b. On the plot side of the screen navigate to 'Mean Force' and record the mean IN force (blue plot) on the treatment log for set 1. Then on the right side of the screen navigate to set 2 and record the mean for force for this set. Continue to do this until all 4 sets from that session have been recorded on the treatment log. Then calculate the average over all 4 sets and record.

Study Participant #:_____

Session #	Date	1 RM Mean force (lbs)	Set Mean Force				Avg. Force Across Sets	Eccentric Intensity (% of 1 RM)
			Set1	Set2	Set3	Set4		
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								

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