Neuromuscular Mechanisms and Clinical Utility of Blood Flow Restriction Therapy

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APPROVAL OF THE DISSERTATION

This dissertation, "Neuromuscular Mechanisms and Clinical Utility of Blood Flow Restriction Therapy", has been approved by the Graduate Faculty of the School of Education and Human Development in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

Lower extremity muscle weakness is a major, and potentially costly, concern for many load-restricted patient populations (e.g., elderly individuals, post-surgical patients, etc.). If left untreated, prolonged deficits in muscle function can lead to a variety of negative health outcomes including altered biomechanics, increased risk for injury, and decreased patient reported quality of life. To overcome this problem, low load exercise with blood flow restriction therapy (LL-BFRT) has been suggested as an alternative treatment approach for improving muscle strength when high load resistance exercise may be unachievable or contraindicated. However, to determine the potential benefits and clinical utility of LL-BFRT, we must investigate the underlying neuromuscular mechanisms and overall effects of LL-BFRT in healthy and clinical populations.

Therefore, the purpose of manuscript I was to determine the effects of LL-BFRT on motor unit recruitment and motor unit behavior compared to standard LL exercise without BFRT in healthy adults. In this study, compared to LL exercise without BFRT, we identified that exercising under BFRT increased overall motor unit recruitment and altered motor unit behavior of the vastus lateralis and significantly increased participant's rating of perceived exertion. These results indicate that LL-BFRT may be an effective method for increasing muscle activation and perceived exercise difficulty without increasing load and mechanical tension during exercise.

The purpose of manuscript II was to examine the effects of LL-BFRT on muscle strength and limb symmetry in patients with quadriceps strength deficits following anterior cruciate ligament reconstruction (ACLR) compared to a true control condition. We identified that female patients treated with LL-BFRT experienced significant improvements in

isokinetic quadriceps strength and limb symmetry at 90 º/s when controlling for baseline values. However, no significant between group differences were found for isokinetic or isometric quadriceps strength and limb symmetry at 180 º/s and 90 º of knee flexion, respectively. These results provide preliminary evidence to support the utilization of LL-BFRT for improving quadriceps strength in patients with lingering strength deficits after undergoing ACLR and traditional post-surgical rehabilitation programs.

Lastly, the purpose of manuscript III was to examine the effects of LL-BFRT on patient reported outcome measures (PROMS) in patients with quadriceps strength deficits following ACLR compared to a true control condition. We found that compared to a control condition, female patients treated with LL-BFRT reported significant improvements in the overall condition of their injured limb as well as noteworthy decreases in knee-related pain and fear of reinjury and increases in psychological readiness, subjective reported knee function, and knee-related quality of life. Therefore, the results of this exploratory study suggest that LL-BFRT may be an effective treatment intervention for improving various psychological components of recovery in patients with significant quadriceps strength deficits following ACLR.

By utilizing novel sEMG technology we were able to quantify changes in motor unit recruitment and behavior during LL-BFRT to provide support for one of the primary proposed mechanisms of this complementary treatment intervention. Additionally, through pilot testing we were able to preliminarily explore both the physiological (i.e., strength and limb symmetry) and psychological responses to LL-BFRT in patients with persistent quadriceps strength deficits following ACLR. These studies have provided foundational evidence to support the neuromuscular mechanisms of LL-BFRT and have also provided

clinicians and researchers with suggestive evidence to promote the usage and investigation of LL-BFRT as a multifunctional intervention to combat physiological and psychological deficits in patients recovering from ACLR.

TABLE OF CONTENTS

LIST OF TABLES

Manuscript I

Manuscript II

Manuscript III

Appendix C

Appendix D

LIST OF FIGURES

Manuscript I

Manuscript II

Manuscript III

Appendix B

Appendix D

SECTION II: MANUSCRIPTS

MANUSCRIPT I:

MOTOR UNIT RECRUITMENT DURING LOW LOAD EXERCISE WITH BLOOD FLOW RESTRICTION THERAPY

Abstract

Background: Low-load exercise with blood flow restriction therapy (LL-BFRT) has been speculated to enhance muscle strength, size, and function by metabolically stimulating a greater number of motor units during exercise, despite a low production of mechanical tension. Unfortunately, this proposed mechanism of LL-BFRT has not been substantiated at the individual motor unit level during exercise. **Purpose:** To determine the effects of LL-BFRT on motor unit recruitment and behavior compared to low-load (LL) exercise without blood flow restriction therapy (BFRT). **Study Design:** Laboratory-based crossover study. **Methods:** Twenty-eight healthy, physically active adults (age = 20.46 ± 1.55 years; sex = 22 females, 6 males; height = 164.19 ± 9.97 cm; mass = 64.15 ± 8.03 kg) were recruited via convenience sampling. The primary independent and dependent variables were the exercise condition (LL-BFRT vs. LL) and motor unit behavior characteristics, respectively. Both conditions consisted of 4 sets of isokinetic knee extension and flexion exercise (30x15x15x15 repetitions) completed at approximately 20% of the individual's peak knee extension and flexion torque and a single 30-second maximal isometric fatigue trial at 90° of knee flexion. A pneumatic tourniquet cuff was inflated to 60% of an individual's limb occlusion pressure during the LL-BFRT condition. Motor unit behavior was assessed at the distal one-third of the dominant limb's vastus lateralis using a Trigno Galileo EMG device (Delsys Inc., Natick, MA). Following data collection, raw EMG signals were processed and decomposed using NeuroMap software (Delsys Inc., Natick, MA). An accuracy threshold of ≥ 80% was set for all identified motor unit action potential waveforms. To control for the amount torque exerted during each exercise, the total number of motor units recruited was divided by the average peak knee extension torque during each condition and set of exercise.

Differences in motor unit behavior between conditions during sets 1-4 were examined using a 2 (condition) x 4 (set 1-4) repeated-measures multivariate analysis of variance (RM-MANOVA), and a one-way RM-MANOVA was conducted to evaluate differences between conditions during the isometric fatigue trial. Additionally, a paired samples t-test was utilized to examine changes in rating of perceived exertion (RPE) between exercise conditions. **Results:** A greater number of motor units were recruited during the LL-BFRT condition compared to the LL condition during sets 1-4 (MD = 2.85 NMU/(Nm/kg), $p = 0.02$) and the isometric fatigue trial (MD = 4.12 NMU/(Nm/kg), $p < 0.001$). Participants also reported higher RPE values following the LL-BFRT condition compared to the LL condition (MD = 3.39, $p < 0.001$). **Conclusions:** The inclusion of BFRT during LL knee extension and flexion exercise increased motor unit activation of the vastus lateralis in healthy adults compared to standard LL exercise without BFRT. While these results support our hypothesis and a potential benefit of LL-BFRT, additional research is warranted to further explore the underlying mechanisms associated with usage of LL-BFRT during patient care.

Introduction

Low-load exercise with blood flow restriction therapy (LL-BFRT) may offer clinicians and researchers an alternative therapeutic intervention for achieving neuromuscular improvements while mitigating the potentially harmful adverse events often associated with increased joint stress during high load (HL) resistance exercise. This treatment technique requires the restriction of arterial inflow and complete occlusion of venous outflow via the application of a tourniquet-like mechanism during either anaerobic or aerobic-based exercise.[1] Blood flow restriction therapy (BFRT) is typically used in conjunction with low-load (LL) resistance exercise between 20% to 40% of an individual's one-repetition maximum (1RM) to elicit similar strength and hypertrophy gains to those acquired through traditional HL resistance exercise (i.e., 80% of an individual's 1RM).[2,3] However, by drastically decreasing load intensity during exercise, LL-BFRT minimizes the amount of stress on the affected joint and surrounding tissues.[4] Therefore, this complementary approach to rehabilitation and strength training may be a viable treatment option for healthy individuals,[2,5,6] elderly patients,[7,8] and various load-restricted populations (e.g., following severe sport-related injuries or surgical intervention).[9]

Current research has shown that LL-BFRT has the potential to increase muscle strength, hypertrophy, and activation when HL resistance exercise may be contraindicated.[10–14] Unfortunately, the proposed mechanisms of LL-BFRT have yet to be substantially supported. There has been speculation that LL-BFRT works to enhance muscle function by three primary mechanisms: 1) increased intracellular swelling, 2) decreased oxygen availability, and 3) increased metabolite accumulation.[15–18] These factors, as well as a lowered intramuscular pH, may act further stimulate group III and group IV afferent fibers

leading to earlier neuromuscular fatigue of type I (i.e., slow-twitch oxidative) muscle fibers.[15–18] This fatigued, hypoxic state and increased presence of metabolic byproducts has been suggested to promote the early recruitment of high threshold motor units and Type IIA/Type IIX muscle fibers during exercise in order to maintain a desired force output.[10,15] This altered motor unit recruitment can then lead to increases in muscle strength and hypertrophy, despite exercises being completed under low mechanical tension, by metabolically stimulating an increased number of muscle fibers and causing a more widespread hypertrophic stimulus within the muscle.[9,15]

Quantifying muscle activation during exercise can help to describe an individual's ability to generate muscle force by recruiting varying numbers of motor units and modulating their behavior characteristics such as their firing rate. Historically, muscle activation during LL-BFRT has been primarily quantified using surface electromyographic (sEMG) techniques (e.g., root mean squared (RMS), integrated EMG (iEMG), peak of the EMG signal (EMGpeak), average EMG amplitude, etc.).[19–22] However, this general measurement of electrical currents has not provided specific information regarding individual motor unit behavior during exercise. Novel sEMG technology with motor unit decomposition capabilities may counter this limitation.[23] The Trigno Galileo Senor (Delsys Inc, Boston, MA) is a small, unobtrusive sEMG device that has been designed to assess motor unit behavior including firing rates, recruitment thresholds, and action potential amplitudes during functional activities. This four-pin sensor array measures differential combinations of electrical signals that are then amplified, filtered, stored, and later decomposed using built-in proprietary software algorithms. Additional information regarding the decomposition algorithms and Artificial Intelligence framework can be found in a report by De Luca et al.[23]

Overall, these recent technological advancements may allow researchers to further investigate how alterations in motor unit recruitment and behavior may contribute to the underlying mechanisms and benefits of utilizing LL-BFRT in patient care.

To the best of our knowledge, functional and real-time changes in motor unit behavior during LL-BFRT compared to standard LL exercise have yet to be investigated. Therefore, the primary aim of the study was to determine the effects of LL-BFRT on motor unit recruitment and behavior compared to LL exercise without BFRT. We hypothesized that LL-BFRT would increase overall motor unit recruitment compared to LL exercise without BFRT.

Methods

Study Design

Motor unit behavior of the dominant vastus lateralis was examined using a cross-sectional crossover study design to determine the effects of LL-BFRT on muscle activity in healthy adults. The independent variable was the exercise condition (LL-BFRT and LL), and the dependent variables included motor unit recruitment, motor unit firing rates (i.e., peak, average, initial, and terminal motor unit firing rate), and motor unit action potential amplitudes (i.e., peak and average motor unit action potential amplitude) measured using sEMG and processed via proprietary decomposition software. Our secondary dependent variable was rating of perceived exertion (RPE) measured using the Borg scale.[24]

Participants

Twenty-eight healthy, physically active adults (age = 20.46 ± 1.55 years; sex = 22 females, 6 males; height = 164.19 ± 9.97 cm; mass = 64.15 ± 8.03 kg) were recruited for study participation via convenience sampling. Inclusion criteria included being 18 years of age or older and having a Godin Leisure-Time Exercise Questionnaire score of ≥ 14 or a Tegner Activity Scale score of ≥ 5. Participants were excluded from the study if they had a lower extremity injury within the past 6 months, lower extremity surgery within the past 12 months, history or current diagnosis of a metabolic, pulmonary, or cardiovascular disease (e.g., Peripheral Artery Disease and/or Peripheral Vascular Disease, diabetes, venous thromboembolism, deep vein thrombosis, impaired circulation or peripheral vascular compromise, sickle cell anemia, and severe hypertension), current use of anti-coagulant medication, current diagnosis of cancer, and if the participant was pregnant or unable to provided informed consent.

An a-priori sample size estimation was performed using G*Power 3.1 with an alpha level of 0.05, power of 0.95, and an estimated Cohen's d effect size of 1.37 based on the results of a previous study examining the effects of BFRT on motor unit behavior of the vastus lateralis.[10] This estimation resulted in a suggested sample size of 8 participants in order to detect significant between-condition changes in motor unit behavior. However, given differences in our study methodology and a possible attrition rate of 20%, our sample size was set to 28 participants. This research protocol was approved by the University of Virginia's Institutional Review Board for Health Sciences Research (IRB-HSR#210058), and informed, written consent was provided by all participants before enrollment.

Procedures

Prior to participation, all participants were required to answer several screening questions regarding their age and medical history in order to determine their eligibility for this study. Those that qualified for participation were asked to refrain from taking part in any strenuous physical activity of their lower extremities for 24 hours prior to their scheduled session.

Upon arrival for the study, participants were instructed to provide additional demographic information (i.e., age, sex, height, weight, and dominant leg) and complete two physical activity questionnaires (i.e., Tegner Activity Scale and Godin Leisure-Time Exercise Questionnaire). Participants were then randomly allocated to receive each of the exercise conditions in a randomized order starting with either the LL-BFRT condition or the LL condition. Study procedures were conducted in the following order: 1) muscle morphology assessment, 2) maximal voluntary isokinetic contraction assessment, 3) exercise condition 1, 4) RPE for exercise condition 1 and a 5-minute rest period, 5) exercise condition 2, and 6) RPE for exercise condition 2.

Muscle Morphology

Following the completion of the demographic and physical activity questionnaires, morphological characteristics of the dominant vastus lateralis including cross-sectional area, thickness, subcutaneous fat tissue thickness, and echogenicity were assessed via B-mode diagnostic ultrasound (ACUSON Freestyle, Siemens Medical Solutions, USA) using an 8-3 MHz linear-array probe. The assessment site was determined by measuring the distance from the superior pole of the patella to the greater trochanter of the femur in line with the lateral aspect of the thigh (i.e., bisecting the vastus lateralis). The distal 1/3 of this measurement was marked and used for ultrasound and sEMG assessment.

Muscle thickness and subcutaneous fat tissue thickness were assessed by capturing three images in the direction of muscle fiber orientation at the marked assessment site. Muscle cross-sectional area was determined by transversely marking the skin every 2cm from the assessment site towards the medial and lateral portions of the thigh (5-6 marks total).[8] The superior edge of the ultrasound probe was then aligned with the lateral aspect of each mark, and images were captured sequentially in a medial to lateral direction. High viscosity ultrasound gel and minimal probe pressure were applied to mitigate unwanted muscle distortion.

Muscle Activity

After ultrasound measurements were taken, the assessment site of the vastus lateralis and a reference location on the iliotibial band were prepped for the placement of a noninvasive sEMG sensor (Trigno Galileo Sensor, Delsys Inc, Natick, MA, USA: 80 dB common mode rejection rate and 11 mV signal input range). Skin preparation included the shaving of any hair and dead skin cells as well as extensive cleaning of the sites using sterile gauze and alcohol prep pads. The two-part sensor included a rectangular reference electrode (27 x 46 x 13 mm) and a circular head electrode (23 x 30 x 7 mm) consisting of the previously described sensor array (Figure 1.1). The reference electrode was secured over the prepared location on iliotibial band while the head electrode was attached to the assessment site over the distal vastus lateralis. To limit unwanted motion, a non-adhesive wrapping was applied circumferentially over the sensor and distal thigh. Signals of muscle activation were acquired, monitored, and live-streamed to EMGworks (Delsys Inc.) at sampling rate of 2222.22 Hz and a preset bandwidth of 20-450Hz.

Muscle Strength

Strength was assessed via maximal voluntary isokinetic contractions (MVIC) of the quadriceps and hamstring muscles using an isokinetic dynamometer (Biodex Systems III Isokinetic Dynamometer, Biodex Medical Systems) at a set speed of 120 °/s. Participants were positioned in the chair with their hips flexed to 90° and the distal third of their shank secured to the arm of the dynamometer. Several practice repetitions were provided prior to maximal strength testing. Participants were then instructed to complete three consecutive maximal repetitions of knee extension and flexion through their full knee range of motion. The average peak torque across each of the three trials was then exported and used for further analysis. Twenty percent of the participant's average peak torque for knee extension and flexion was determined and utilized as self-regulated targets during both exercise conditions.

Rating of Perceived Exertion

RPE was measured following the completion of each exercise condition using the Borg scale.[24] This scale ranged from 0, no exertion at all, to 10, maximal exertion. Participants were asked to use this scale in order to identify their level of perceived difficulty during the preceding exercise.

Exercise Protocols

Each exercise condition consisted of the same primary components: 4 sets of isokinetic knee extension and flexion exercise (30x15x15x15 repetitions) and a 30 second maximal isometric fatigue trial. Isokinetic repetitions were performed at approximately 20% of the individual's predetermined MVIC for knee flexion and extension using a set speed of 120 °/s. Before beginning the first set of isokinetic repetitions for each exercise condition, the participants were instructed on their torque targets (i.e., 20% MVIC for knee flexion and

extension) and given practice trials for familiarization. Verbal and visual feedback were provided throughout each condition to ensure that exercises were completed at the correct speed, intensity, and through an individual's full knee range of motion. A 30 second rest period was provided following each set of exercise. For the maximal isometric fatigue trial, participants were positioned in 90° of hip and knee flexion and were instructed to kick out as hard as possible for 30 seconds. Five minutes of rest was provided after the first exercise condition. The LL-BFRT condition was completed with tourniquet cuff application while the LL exercise condition was performed as a control.

Blood Flow Restriction

An automated pneumatic tourniquet cuff (Delfi Personalized Tourniquet System, Delfi Medical Vancouver, BC) was used to create the LL-BFRT condition. After the contoured cuff was secured around the most proximal portion of dominant lower extremity, the tourniquet system was calibrated and inflated to determine the participant's total limb occlusion pressure (LOP; i.e., the amount of pressure needed to completely occlude arterial and venous blood flow). At the start of the LL-BFRT condition the cuff was inflated to 60% of the individual's predetermined LOP. The cuff remained inflated throughout all sets, repetitions, and interset rest periods. Cuff pressure was only released at the end of the maximal isometric fatigue trial for each condition.

Data Processing

Muscle Morphology

After data collection, the cross-sectional area images of the vastus lateralis were reconstructed in PowerPoint (Microsoft, Redmond, WA, USA) and measured following protocols previously described by Reeves et al[25] and Lixandrão et al.[8] Each image was individually opened, rotated, and aligned with the fascial border of the previous image until the entire fascia of the vastus lateralis was recreated. The cross-sectional area of the reconstructed image as well as the echogenicity, muscle thickness, and subcutaneous fat tissue thickness were then measured using ImageJ software (National Institutes of Health, Bethesda, MD). To ensure accurate measurement, pixel conversion was set based on the depth of the original ultrasound image.

Muscle Activity

As previously stated, each of the raw sEMG signals were processed and decomposed using a proprietary decomposition software (NeuroMap Software, Delsys Inc, Natick, MA, USA). By characterizing unique motor unit action potential (MUAP) waveforms, NeuroMap is capable of identifying individual motor unit behavior parameters such as total motor unit recruitment, peak and average motor unit firing rates, initial and terminal motor unit firing rates, as well as peak and average motor unit action potential amplitudes. An accuracy threshold for decomposed MUAP waveforms was set to $\geq 80\%$.[26] After motor units identified with below 80% accuracy were excluded, the average of each motor unit behavior characteristic was calculated per set and condition and used for further analysis. To control for the influence of self-regulated torque exerted during each condition and set of exercise, the total number of motor units recruited (NMU) was then divided by the average peak knee extension torque controlling for body mass (Nm/kg) during the respective exercise set per condition ([NMU/(Nm/kg)]).

Statistical Analysis

Participant demographic information, vastus lateralis morphological characteristics, and the raw number of motor units recruited during each condition and set of exercise were examined using descriptive statistics including means and standard deviations as represented in Table 1.1, Table 1.2, and Table 1.3, respectively. A 2 (condition) X 4 (exercise set 1-4) repeated measures multivariate analysis of variance (RM-MANOVA) was conducted to examine differences in each dependent measure of motor unit recruitment and behavior between conditions and across sets 1 to 4. An additional one-way RM-MANOVA was conducted to evaluate differences between conditions for each dependent variable during the maximal isometric fatigue trial. In the event of statistically significant findings, separate univariate analyses and post hoc pairwise comparisons with Bonferroni adjustments were conducted to examine the source of these differences. A paired samples t-test was utilized to examine changes in RPE between exercise conditions. Effect size was calculated as partial eta squared (η_p^2) for the multivariate and univariate analyses and Cohen's d for the paired samples t-test. Partial eta squared statistics of 0.01, 0.06, and 0.14 represented small, medium and large effects, respectively; whereas Cohen's d effect sizes of 0.2, 0.5, and 0.80 were categorized as small, medium, and large, respectively.[27] Alpha was set a priori to 0.05. All statistical analyses were conducted using IBM Statistics (v28.0.1.1, SPSS, Inc. Chicago, IL, USA) and R (RStudio Inc., v2022.07.0).

Results

Motor Unit Behavior by Condition and Set 1-4

Due to missing data (i.e., no motor units accurately detected during one or more set of exercise), 3 participants were excluded from the 2 (condition) X 4 (set 1-4) RM-MANOVA. Overall results of the 2X4 RM-MANOVA revealed significant within-subjects effects for condition ($\lambda = 0.41$, $F = 3.62$, $p = 0.013$, $\eta_p^2 = 0.58$) and exercise set ($\lambda = 0.18$, $F = 7.51$, $p < 0.001$, $\eta_p^2 = 0.44$) (Table 1.4). However, no significant condition X exercise set interaction was identified ($\lambda = 0.72$, $F = 1.11$, $p = 0.341$, $\eta_p^2 = 0.10$; Table 1.4).

Univariate analyses for the main effect of condition identified significant differences in the number of motor units recruited ($F = 5.97$, $p = 0.022$, $\eta_p^2 = 0.20$), peak motor unit action potential amplitude ($F = 14.57$, $p < 0.001$, $\eta_p^2 = 0.38$), average motor unit action potential amplitude ($F = 13.86$, $p = 0.001$, $\eta_p^2 = 0.37$), and peak firing rate ($F = 6.53$, $p = 0.017$, $\eta_p^2 = 0.21$) (Table 1.5). Post hoc pairwise comparisons indicated that compared to the LL condition, the LL-BFRT condition resulted in a significantly greater number of motor units recruited (Mean Difference [MD] with 95% Confidence Interval [CI]= 2.85 NMU/(Nm/kg), [0.44, 5.26]; Figure 1.2) with higher peak motor unit action potential amplitudes (MD = 16.36 μV, [7.51, 25.21]; Figure 1.3), average motor unit action potential amplitudes (MD = 12.18 μV, [5.43, 18.94]; Figure 1.4), and peak firing rates (MD = 0.65 pps, [0.12, 1.17]; Figure 1.5) (Table 1.6). No significant between group differences were found for average firing rate (Figure 1.6), initial firing rate (Figure 1.7), or terminal firing rate (Figure 1.8).

For the main effect of exercise set, univariate analyses highlighted significant differences in the number of motor units recruited ($F = 51.68$, $p < 0.001$, $\eta_p^2 = 0.68$), peak firing rate ($F = 18.91$, $p < 0.001$, $\eta_p^2 = 0.44$), average firing rate ($F = 11.31$, $p < 0.001$, $\eta_p^2 = 0.32$), and initial firing rate ($F = 7.58$, $p < 0.001$, $\eta_p^2 = 0.24$) (Table 1.5). Post hoc pairwise

comparisons revealed a significantly greater number of motor units recruited with higher peak, average, and initial firing rates during set 1 compared to sets 2 through 4 (Table 1.7 and Figure 1.2, 1.5, 1.6, and 1.7, respectively).

Motor Unit Behavior by Condition During Maximal Isometric Fatigue Trial

The one-way RM-MANOVA revealed a significant main effect for condition (λ = 0.23, F = 9.86, p <0.001, η_p^2 = 0.77; Table 1.8). Univariate analyses identified significant differences in the number of motor units recruited (F = 34.63, p < 0.001, η_p^2 = 0.56), peak motor unit action potential amplitude (F = 11.06, p = 0.003, η_p^2 = 0.29), average motor unit action potential amplitude (F = 13.77, p < 0.001, η_p^2 = 0.34), peak firing rate (F = 7.49, p = 0.011, η_p^2 = 0.22), average firing rate (F = 27.81, p < 0.001, η_p^2 = 0.51), and initial firing rate (F = 4.89, p = 0.036, η_p^2 = 0.15) between exercise conditions (Table 1.9). Additionally, no significant between group differences were noted for terminal firing rate during the maximal isometric fatigue trial (Figure 1.8).

Additional post hoc pairwise comparisons demonstrated that compared to the LL condition, the LL-BFRT condition resulted in a significantly greater number of motor units recruited (MD = 4.12 NMU/(Nm/kg), [2.69, 5.56]; Figure 1.2) with significantly lower peak motor unit action potential amplitudes (MD = -69.78 μV, [-112.84, -26.72]; Figure 1.3), average motor unit action potential amplitudes (MD = -54.85 μV, [-85.18, -24.52]; Figure 1.4), peak firing rates (MD = -1.44 pps, [-2.52, -0.36]; Figure 1.5), average firing rates (MD = -2.48 pps, [-3.44, -1.51]; Figure 1.6), and initial firing rates (MD = -0.77 pps, [-1.49, -0.06]; Figure 1.7) (Table 1.10).

RPE by Condition

The paired samples t-test exploring differences in RPE during each exercise condition revealed significantly higher reported RPE values following the LL-BFRT condition compared to the LL condition as illustrated in Figure 1.9 (MD = 3.39, t = 14.63, p <0.001, d = 2.76; Table 1.11).

Discussion

LL-BFRT has been commonly suggested to improve muscle strength and function by enhancing motor unit recruitment during submaximal exercise.[9,15] While previous literature has quantified alterations in muscle activation before and after LL-BFRT using indirect measures of sEMG, these methods have been unable to accurately assess changes at the individual motor unit level during exercise.[19–22] Therefore, to our knowledge, this has been the first study to investigate real-time changes in motor unit recruitment of the vastus lateralis during LL-BFRT compared to standard LL exercise. By utilizing novel sEMG decomposition technology, our study sought to provide additional evidence regarding the influence of LL-BFRT on motor unit behavior and describe how these changes may relate to the proposed neuromuscular mechanisms of LL-BFRT. Overall, the results of our study provide support for our primary hypothesis as LL-BFRT increased motor unit recruitment of the vastus lateralis and altered various motor unit behavior characteristics compared to LL exercise without the implementation BFRT.

In terms of motor unit recruitment, we found significant increases in the number of motor units recruited during LL-BFRT compared to standard LL exercise when controlling for average peak knee extension torque during sets 1-4 as well as during the maximal

isometric fatigue trial. These results suggest that LL-BFRT may be an effective method for increasing muscle activation and motor unit recruitment without increasing the overall mechanical load applied during exercise. This finding may be of particular importance for patient populations where HL resistance training is contraindicated (e.g., elderly individuals, post-surgical patients, injured individuals, etc.).[7,9] For these individuals, LL-BFRT could be a potential complementary treatment approach for enhancing motor unit recruitment and improving muscle function while mitigating the amount of stress imposed on the affected joints and surrounding tissues. Previous literature investigating the effects of LL-BFRT on muscle activation has also identified significant increases in muscle excitation during LL-BFRT compared to exercise without BFRT.[19] However, findings related to myoelectric activity during LL-BFRT compared to LL and HL resistance exercise without BFRT have been inconclusive, likely due to the limited availability of high-quality evidence and vast methodological heterogeneity.[19,20,22] A recent meta-analysis conducted by Cerqueira et al[22] expressed that differences in muscle activation also appear to be dependent on whether or not exercise is performed to volitional fatigue, where greater short-term increases in muscle excitability during LL-BFRT compared to standard LL exercise were observed only during non-fatiguing protocols. Conversely, no significant differences in acute muscle excitation were identified between LL-BFRT and LL conditions when exercise was performed to volitional failure.[22] However, in the present study we identified notable increases in motor unit recruitment during a standard exercise scheme of LL-BFRT as well as during a fatiguing, maximal isometric contraction completed under BFRT. Considering these differences, future research should aim to further investigate how various types of exercise

and LL-BFRT parameters may influence muscle activation, hypertrophy, and performance-based outcomes across various patient populations.

Along with changes in overall motor unit recruitment, our results also demonstrated significant differences in several motor unit behavior characteristics between exercise conditions. When performing exercise sets 1 through 4 under the LL-BFRT condition, individuals presented with significantly higher peak and average motor unit action potential amplitudes and higher peak firing rates. As previously stated, LL-BFRT has been commonly suggested to promote the early recruitment of large motor units,[10,15] often characterized as having greater action potential amplitudes and potentially higher firing rates according to the After-Hyperpolarization (AHP) scheme,[28,29] in order to maintain the desired torque output during exercise. In agreement with current research,[10] our results have provided additional evidence to support this theorized mechanism of LL-BFRT. Utilizing high-density sEMG and similar decomposition algorithms, Fatela et al[10] also aimed to measure and characterize changes in motor unit behavior including motor unit action potential amplitudes, firing rates, and recruitment thresholds of the vastus lateralis before and after LL exercise with and without BFRT. Results of this study indicated greater decrements in the linear slope co-efficient of the regression line between motor unit recruitment threshold and firing rate as well as a shift towards an increased recruitment of motor units with greater action potential amplitudes following LL-BFRT compared to standard LL exercise.[10] It was suggested that these findings demonstrate the early recruitment of high threshold, low firing rate motor units, which would typically only be recruited during HL resistance training, as a result of including BFRT during submaximal exercise.[10,19]

However, the aforementioned effects were not consistent during our maximal isometric fatigue trial. When completing this sustained maximal contraction with the inclusion of BFRT compared to without, motor units appeared to present with significantly lower peak and average action potential amplitudes as well as significantly lower peak, average, and initial firing rates. In contrast to the AHP scheme, the Onion-Skin scheme suggests that an inverse relationship exists between motor unit recruitment thresholds and firing rates.[30] This scheme indicates that during voluntary, constant-force contractions motor units initially recruited display and maintain higher firing rates than motor units recruited later on as fatigue begins to develop.[29] Considering our findings during the maximal isometric fatigue trial, it is reasonable to assume that including BFRT during exercise encouraged the recruitment of additional motor units with higher recruitment thresholds and lower firing rates compared to exercise without BFRT. Therefore, our results are consistent with each of these hypotheses (i.e., AHP scheme and Onion-Skin scheme) and show that the influence of BFRT on motor unit behavior is likely dependent on the type of exercise being performed and whether or not it elicited fatigue. Additionally, given that participants reported significantly higher RPE values following the LL-BFRT condition compared to the LL condition, it is reasonable to assume that while the exercises were performed under comparable mechanical loads, the incorporation of BFRT significantly increased the perceived difficulty of the prescribed exercises, likely due to the fatiguing effects of BFRT.[21,31]

Limitations

Given the cross-sectional, crossover design of our study, we could not determine the longitudinal influences of LL-BFRT on motor unit behavior. However, the results of this study provide strong preliminary evidence to support the immediate effects of LL-BFRT on motor unit recruitment. Additionally, our sample within this study was primarily comprised of young females which may decrease the overall generalizability of our results to other patient populations. Future studies should aim to recruit a more diverse sample to identify how the impact of LL-BFRT may differ across participants with various demographic characteristics. Due to the lack of synchronization between our measures of sEMG and torque output, we were unable to identify individual motor unit recruitment thresholds as it relates to torque production during each set of exercise. By synchronizing these outcome measures, future researchers can aim identify whether the incorporation of BFRT promotes the early recruitment of high threshold motor units during a standard protocol of LL exercise. Nevertheless, the results of this study indicated a shift in motor unit firing rates and action potential amplitudes which may be associated with the recruitment of additional, high threshold motor units due to the early fatigue of active low threshold motor units during LL-BFRT. It is also important to consider that the size of our sEMG detection zone was much smaller than that of the entire the vastus lateralis muscle. Taking this into account, it was not possible to describe how whole-muscle motor unit recruitment differed between exercise conditions.

Conclusions

The inclusion of BFRT during isometric and isokinetic knee extension and flexion exercise was found to increase motor unit recruitment and alter motor unit behavior of the vastus lateralis in healthy adults compared to exercise without BFRT. While these results support our primary hypothesis and a potential benefit of LL-BFRT, additional research is warranted to further explore the underlying neuromuscular mechanisms associated with usage of LL-BFRT during patient care.

References

1. Scott BR, Loenneke JP, Slattery KM, Dascombe BJ. Exercise with blood flow restriction: an updated evidence-based approach for enhanced muscular development. *Sports Med Auckl NZ*. 2015;45(3):313-325. doi:10.1007/s40279-014-0288-1

2. Lixandrão ME, Ugrinowitsch C, Berton R, et al. Magnitude of Muscle Strength and Mass Adaptations Between High-Load Resistance Training Versus Low-Load Resistance Training Associated with Blood-Flow Restriction: A Systematic Review and Meta-Analysis. *Sports Med Auckl NZ*. 2018;48(2):361-378. doi:10.1007/s40279-017-0795-y

3. Dayton SR, Padanilam SJ, Sylvester TC, Boctor MJ, Tjong VK. Blood Flow Restriction Therapy Impact on Musculoskeletal Strength and Mass. *Video J Sports Med*. 2021;1(5):26350254211032680. doi:10.1177/26350254211032681

4. Schoenfeld BJ, Grgic J, Ogborn D, Krieger JW. Strength and Hypertrophy Adaptations Between Low- vs. High-Load Resistance Training: A Systematic Review and Meta-analysis. *J Strength Cond Res*. 2017;31(12):3508-3523. doi:10.1519/JSC.0000000000002200

5. Loenneke JP, Wilson JM, Marín PJ, Zourdos MC, Bemben MG. Low intensity blood flow restriction training: a meta-analysis. *Eur J Appl Physiol*. 2012;112(5):1849-1859. doi:10.1007/s00421-011-2167-x

6. Slysz J, Stultz J, Burr JF. The efficacy of blood flow restricted exercise: A systematic review & meta-analysis. *J Sci Med Sport*. 2016;19(8):669-675. doi:10.1016/j.jsams.2015.09.005

7. Centner C, Wiegel P, Gollhofer A, König D. Effects of Blood Flow Restriction Training on Muscular Strength and Hypertrophy in Older Individuals: A Systematic Review and Meta-Analysis. *Sports Med Auckl NZ*. 2019;49(1):95-108. doi:10.1007/s40279-018-0994-1

8. Lixandrão ME, Ugrinowitsch C, Bottaro M, et al. Vastus Lateralis Muscle Cross-sectional Area Ultrasonography Validity for Image Fitting in Humans. *J Strength Cond Res*. 2014;28(11):3293-3297. doi:10.1519/JSC.0000000000000532

9. Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. *Br J Sports Med*. 2017;51(13):1003-1011. doi:10.1136/bjsports-2016-097071

10. Fatela P, Mendonca GV, Veloso AP, Avela J, Mil-Homens P. Blood Flow Restriction Alters Motor Unit Behavior During Resistance Exercise. *Int J Sports Med*. 2019;40(9):555-562. doi:10.1055/a-0888-8816

11. Cook SB, Scott BR, Hayes KL, Murphy BG. Neuromuscular Adaptations to Low-Load Blood Flow Restricted Resistance Training. *J Sports Sci Med*. 2018;17(1):66-73.

12. Lauver JD, Cayot TE, Rotarius T, Scheuermann BW. The effect of eccentric exercise with blood flow restriction on neuromuscular activation, microvascular oxygenation, and the repeated bout effect. *Eur J Appl Physiol*. 2017;117(5):1005-1015. doi:10.1007/s00421-017-3589-x

13. Hammer SM, Alexander AM, Didier KD, Barstow TJ. Influence of blood flow occlusion on muscular recruitment and fatigue during maximal-effort small muscle-mass exercise. *J Physiol*. 2020;598(19):4293-4306. doi:10.1113/JP279925

14. Killinger B, Lauver JD, Donovan L, Goetschius J. The Effects of Blood Flow Restriction on Muscle Activation and Hypoxia in Individuals With Chronic Ankle Instability. *J Sport Rehabil*. 2020;29(5):633-639. doi:10.1123/jsr.2018-0416

15. Lorenz D, Bailey L, Wilk K, et al. Current Clinical Concepts: Blood Flow Restriction Training. *J Athl Train*. Published online January 22, 2021. doi:10.4085/418-20

16. Pearson SJ, Hussain SR. A review on the mechanisms of blood-flow restriction resistance training-induced muscle hypertrophy. *Sports Med Auckl NZ*. 2015;45(2):187-200. doi:10.1007/s40279-014-0264-9

17. Rossi FE, de Freitas MC, Zanchi NE, Lira FS, Cholewa JM. The Role of Inflammation and Immune Cells in Blood Flow Restriction Training Adaptation: A Review. *Front Physiol*. 2018;9. doi:10.3389/fphys.2018.01376

18. Jessee M, Mattocks K, Buckner S, et al. Mechanisms of Blood Flow Restriction: The New Testament. *Tech Orthop*. 2018;33(2):72-79. doi:10.1097/BTO.0000000000000252

19. Centner C, Lauber B. A Systematic Review and Meta-Analysis on Neural Adaptations Following Blood Flow Restriction Training: What We Know and What We Don't Know. *Front Physiol*. 2020;11:887. doi:10.3389/fphys.2020.00887

20. Hedt C, McCulloch PC, Harris JD, Lambert BS. Blood Flow Restriction Enhances Rehabilitation and Return to Sport: The Paradox of Proximal Performance. *Arthrosc Sports Med Rehabil*. 2022;4(1):e51-e63. doi:10.1016/j.asmr.2021.09.024

21. de Queiros VS, de França IM, Trybulski R, et al. Myoelectric Activity and Fatigue in Low-Load Resistance Exercise With Different Pressure of Blood Flow Restriction: A Systematic Review and Meta-Analysis. *Front Physiol*. 2021;12. Accessed August 23, 2022. https://www.frontiersin.org/articles/10.3389/fphys.2021.786752

22. Cerqueira MS, Maciel DG, Barboza JAM, et al. Low-Load Blood-Flow Restriction Exercise to Failure and Nonfailure and Myoelectric Activity: A Meta-Analysis. *J Athl Train*. 2022;57(4):402-417. doi:10.4085/1062-6050-0603.20

23. De Luca CJ, Adam A, Wotiz R, Gilmore LD, Nawab SH. Decomposition of surface EMG signals. *J Neurophysiol*. 2006;96(3):1646-1657. doi:10.1152/jn.00009.2006

24. Borg G. *Borg's Perceived Exertion and Pain Scales*. Human Kinetics; 1998.

25. Reeves ND, Maganaris CN, Narici MV. Ultrasonographic assessment of human skeletal muscle size. *Eur J Appl Physiol*. 2004;91(1):116-118. doi:10.1007/s00421-003-0961-9

26. Madarshahian S, Latash ML. Synergies at the level of motor units in single-finger and multi-finger tasks. *Exp Brain Res*. Published online July 26, 2021. doi:10.1007/s00221-021-06180-y

27. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Lawrence Erlbaum Associates; 1988.

28. Eccles JC, Eccles RM, Lundberg A. The action potentials of the alpha motoneurones supplying fast and slow muscles. *J Physiol*. 1958;142(2):275-291. doi:10.1113/jphysiol.1958.sp006015

29. De Luca CJ, Contessa P. Biomechanical benefits of the Onion-Skin motor unit control scheme. *J Biomech*. 2015;48(2):195-203. doi:10.1016/j.jbiomech.2014.12.003

30. De Luca CJ, Erim Z. Common drive of motor units in regulation of muscle force. *Trends Neurosci*. 1994;17(7):299-305. doi:10.1016/0166-2236(94)90064-7

31. Hill EC, Rivera PM, Proppe CE, Gonzalez Rojas DH, Wizenberg AM, Keller JL. Greater neuromuscular fatigue following low-load blood flow restriction than non-blood flow restriction resistance exercise among recreationally active men. *J Neurophysiol*. 2022;128(1):73-85. doi:10.1152/jn.00028.2022

Tables

Table 1.1. Participant demographics and vastus lateralis morphological characteristics

	Variable	Mean ± SD (n = 28)
Demographic Characteristics	Age (years)	20.46 ± 1.55
	Sex (female/male)	22 F / 6 M
	Dominant leg (right/left)	24 R / 4 L
	Body mass (kg)	64.15 ± 8.03
	Height (cm)	164.19 ± 9.97
	Tegner	6.14 ± 1.18
	Godin Leisure	77.64 ± 19.80
Morphological Characteristics	Cross-sectional area (cm^2)	20.17 ± 4.86
	Thickness (cm)	2.09 ± 0.38
	SATT (cm)	0.59 ± 0.27
	Echogenicity	44.28 ± 7.35

Abbreviations: SD, standard deviation; SATT, subcutaneous adipose tissue thickness

Table 1.2. Total motor unit recruitment and accuracy by condition

	Total		≥80% Accuracy	
Condition	Count	Mean ± SD	Count	Mean ± SD
LL-BFRT	2209	78.89 ± 28.26	1751	62.54 ± 22.72
LL	2174	77.64 ± 28.14	1671	59.68 ± 22.51
Difference	35	1.25 ± 13.98	80	2.86 ± 11.91
Total	4383	78.27 ± 27.95	3422	61.11 ± 22.45

Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LL, low load exercise; SD, standard deviation

Table 1.3. Raw number of accurate motor units recruited by condition and set

	LL-BFRT		LL		
Exercise set	Total	Mean ± SD	Total	Mean ± SD	Mean Difference ± SD
Set 1	450	16.07 ± 5.89	431	15.39 ± 7.00	0.68 ± 5.16
Set 2	256	9.14 ± 5.38	216	7.71 ± 4.23	1.43 ± 3.98
Set 3	240	8.57 ± 5.81	226	8.07 ± 4.90	0.50 ± 2.94
Set 4	252	9.00 ± 5.54	219	7.82 ± 4.88	1.18 ± 3.77
Isometric trial	459	16.39 ± 4.69	485	17.32 ± 4.10	-0.93 ± 6.39
Total	1751	62.54 ± 22.72	1671	59.68 ± 22.51	2.86 ± 11.91

Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LL, low load exercise; SD, standard deviation

Table 1.4. RM-MANOVA: motor unit behavior by condition and set 1-4

		Wilks' Lambda	F statistic	p-value	η^2_p
Within Subjects Effects	Condition	0.41	3.62	0.013*	0.58
	Set	0.18	7.51	<0.001*	0.44
	Condition*Set	0.72	1.11	0.341	0.10

** Statistically significant at $p \leq 0.05$*
Abbreviations: RM-MANOVA, repeated measures multivariate analysis of variance

Table 1.5. Univariate Analyses: motor unit behavior by condition and set 1-4

Characteristic	Effect	F-statistic	p-value	η^2_p
# Motor Units/ AVG Torque	Condition	5.97	0.022*	0.20
	Set	51.68	<0.001*	0.68
Peak MUAP	Condition	14.57	<0.001*	0.38
	Set	0.61	0.608	0.02
Average MUAP	Condition	13.86	0.001*	0.37
	Set	0.95	0.419	0.04
Peak firing rate	Condition	6.53	0.017*	0.21
	Set	18.91	<0.001*	0.44
Average firing rate	Condition	0.35	0.562	0.01
	Set	11.31	<0.001*	0.32
Initial firing rate	Condition	3.22	0.086	0.12
	Set	7.58	<0.001*	0.24
Terminal firing rate	Condition	1.69	0.206	0.07
	Set	2.26	0.088	0.09

** Statistically significant at $p \leq 0.05$*
Abbreviations: # Motor Units/AVG Torque, number of motor units divided by average peak torque; MUAP, motor unit action potential amplitude

Table 1.6. Pairwise Comparisons: motor unit behavior by condition

Characteristic	Comparison (Mean (SE))			Mean Difference (SE)	p-value	95% CI
	LL-BFRT		LL			
# Motor Units/ AVG Torque ([NMU/(Nm/kg)])	24.86 (2.05)	-	22.01 (1.88)	2.85 (1.17)	0.022*	(0.44, 5.26)
Peak MUAP (μV)	87.95 (14.40)	-	71.59 (11.46)	16.36 (4.29)	<0.001*	(7.51, 25.21)
Average MUAP (μV)	68.41 (10.82)	-	56.22 (8.61)	12.18 (3.27)	0.001*	(5.43, 18.94)
Peak firing rate (pps)	12.99 (0.51)	-	12.34 (0.47)	0.65 (0.25)	0.017*	(0.12, 1.17)

** Statistically significant at $p \leq 0.05$*
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LL, low load exercise; # Motor Units/AVG Torque, number of motor units divided by average peak torque; MUAP, motor unit action potential amplitude; SE, standard error; CI, confidence interval

Table 1.7. Pairwise Comparisons: motor unit behavior by set 1-4

Characteristic	Comparison				Mean Difference (SE)	p-value	95% CI
	Set	Mean (SE)	Set	Mean (SE)			
# Motor Units/ AVG Torque ([NMU/(Nm/kg)])	1	34.33 (2.58)	- 2	19.34 (1.67)	15.00 (1.54)	<0.001*	10.56 – 19.43
			- 3	20.04 (1.91)	14.29 (1.78)	<0.001*	9.17 – 19.42
			- 4	20.02 (2.02)	14.31 (1.40)	<0.001*	10.29 – 18.33
Peak Firing Rate (pps)	1	13.80 (0.54)	- 2	12.18 (0.54)	1.62 (0.18)	<0.001*	1.11 – 2.13
			- 3	12.34 (0.45)	1.46 (0.27)	<0.001*	0.67 – 2.24
			- 4	12.33 (0.47)	1.47 (0.27)	<0.001*	0.68 – 2.25
Average Firing Rate (pps)	1	4.56 (0.23)	- 2	3.94 (0.20)	0.62 (0.10)	<0.001*	0.32 – 0.92
			- 3	4.04 (0.18)	0.52 (0.15)	0.009*	0.10 – 0.94
			- 4	4.08 (0.20)	0.48 (0.12)	0.005*	0.12 – 0.83
Initial Firing Rate (pps)	1	5.18 (0.27)	- 2	4.57 (0.22)	0.61 (0.16)	0.006*	0.14 – 1.07
			- 3	4.67 (0.19)	0.51 (0.17)	0.038*	0.02 – 0.99
			- 4	4.51 (0.19)	0.67 (0.20)	0.017*	0.09 – 1.24

** Statistically significant at $p \leq 0.05$*
Abbreviations: # Motor Units/AVG Torque, number of motor units divided by average peak torque; SE, standard error; CI, confidence interval

Table 1.8. One-Way RM-MANOVA: motor unit behavior by condition (isometric fatigue trial)

		Wilks' Lambda	F statistic	p-value	η^2_p
Within Subjects Effects	Condition	0.23	9.86	<0.001*	0.77

** Statistically significant at $p \leq 0.05$*
Abbreviations: RM-MANOVA, repeated measures multivariate analysis of variance

Table 1.9. Univariate Analyses: motor unit behavior (isometric fatigue trial)

Characteristic	F-statistic	p-value	η^2_p
# Motor Units/ AVG Torque	34.63	<0.001*	0.56
Peak MUAP	11.06	0.003*	0.29
Average MUAP	13.77	<0.001*	0.34
Peak firing rate	7.49	0.011*	0.22
Average firing rate	27.81	<0.001*	0.51
Initial firing rate	4.89	0.036	0.15
Terminal firing rate	0.70	0.412	0.03

** Statistically significant at $p \leq 0.05$*
Abbreviations: # Motor Units/AVG Torque, number of motor units divided by average peak torque; MUAP, motor unit action potential amplitude

Table 1.10. Pairwise Comparisons: motor unit behavior (isometric fatigue trial)

Characteristic	Comparison (Mean (SE))			Mean Difference (SE)	p-value	95% CI
	LL-BFRT		LL			
# Motor Units/ AVG Torque ([NMU/(Nm/kg)])	10.70 (0.65)	-	6.58 (0.36)	4.12 (0.70)	<0.001*	(2.69, 5.56)
Peak MUAP (μV)	124.24 (18.44)	-	194.02 (32.19)	-69.78 (20.99)	0.003*	(-112.84, -26.72)
Average MUAP (μV)	96.02 (13.81)	-	150.87 (23.28)	-54.85 (14.78)	<0.001*	(-85.18, -24.52)
Peak firing rate (pps)	17.77 (0.59)	-	19.21 (0.48)	-1.44 (0.53)	0.011*	(-2.52, -0.36)
Average firing rate (pps)	10.67 (0.46)	-	13.15 (0.36)	-2.48 (0.47)	<0.001*	(-3.44, -1.51)
Initial firing rate (pps)	4.09 (0.32)	-	4.86 (0.27)	-0.77 (0.35)	0.036*	(-1.49, -0.06)

** Statistically significant at $p \leq 0.05$*
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LL, low load exercise; # Motor Units/AVG Torque, number of motor units divided by average peak torque; MUAP, motor unit action potential amplitude; SE, standard error; CI, confidence interval

Table 1.11. Paired samples t-test: rating of perceived exertion by condition

LL-BFRT			LL		Mean Difference	t-statistic	p-value	Effect size
Mean ± SD	Min – Max		Mean ± SD	Min – Max				
7.32 ± 1.44	4 – 9	-	3.93 ± 1.05	2 – 6	3.39	14.63	<0.001*	2.76

** Statistically significant at $p \leq 0.05$*
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LL, low load exercise; SD, standard deviation

Figures

Figure 1.1. Delsys Trigno Galileo sensor.

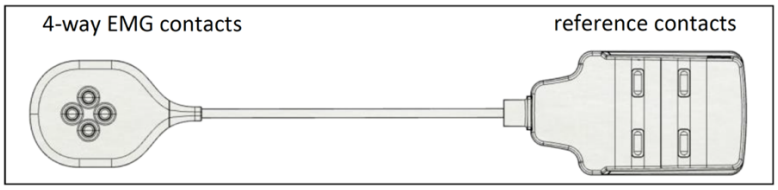
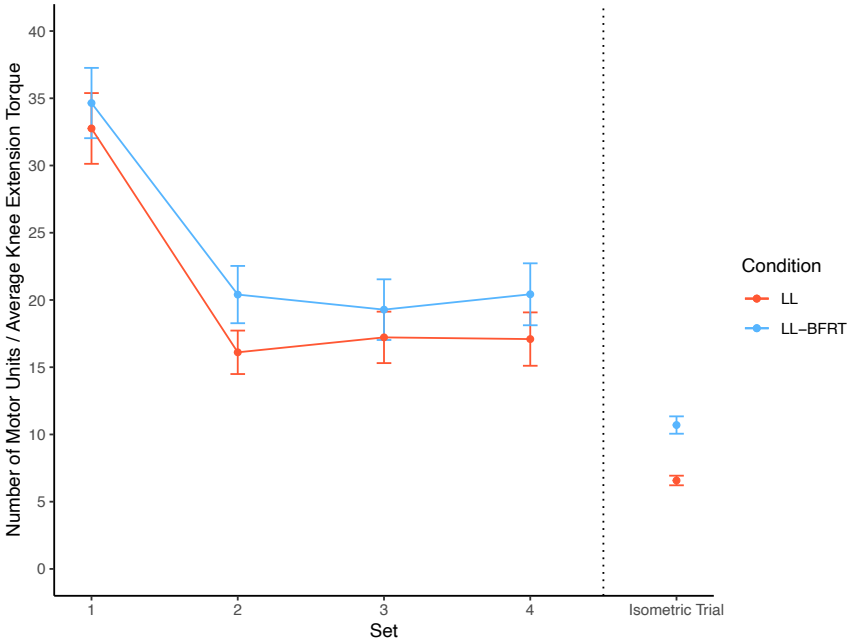
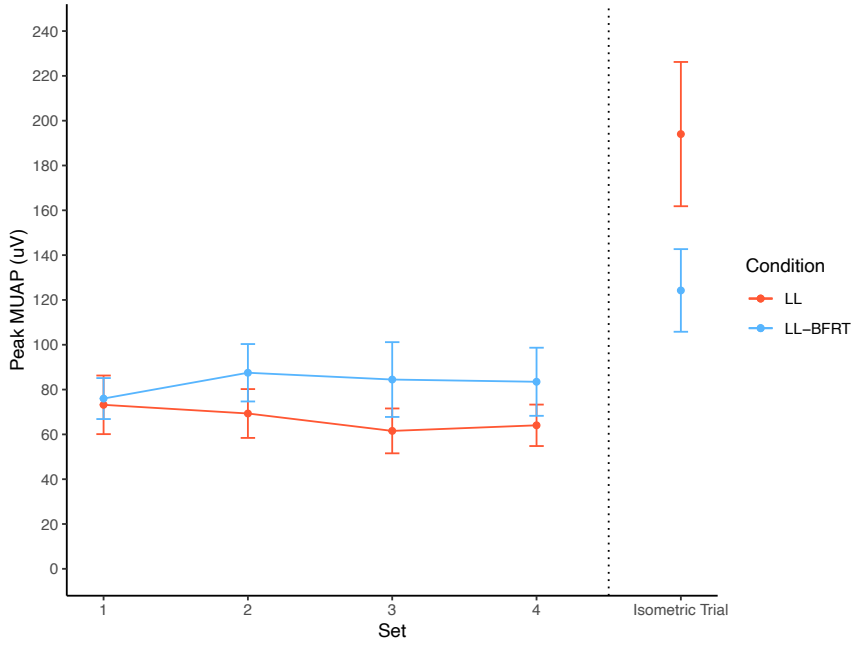


Figure 1.2. Motor unit recruitment by condition and set.



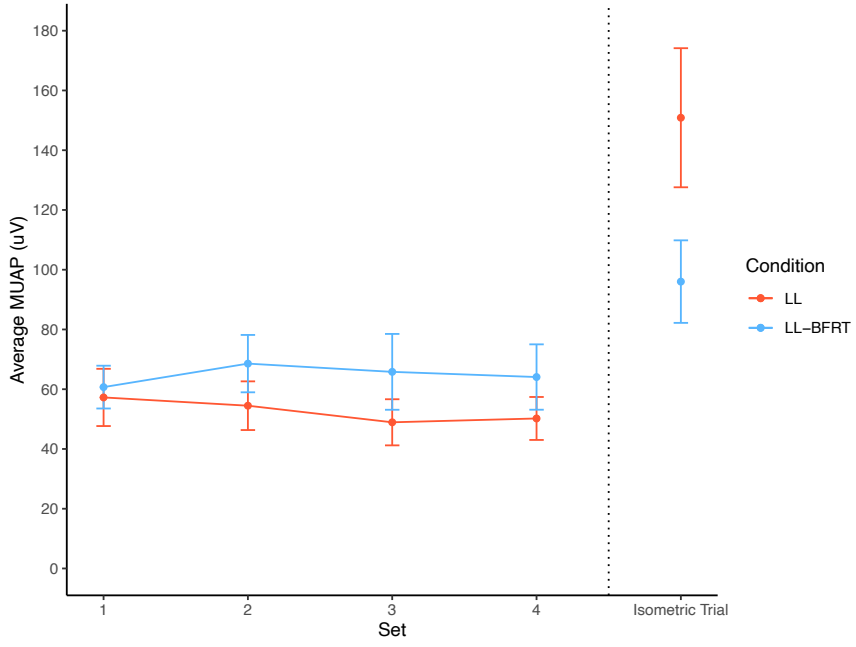
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LL, low load exercise

Figure 1.3. Peak motor unit action potential amplitude by set and condition.



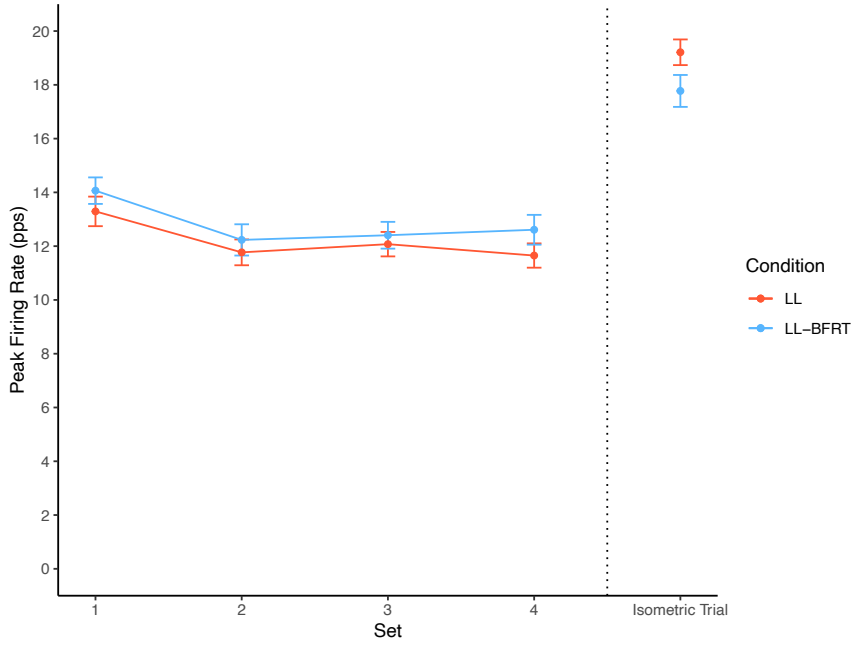
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LL, low load exercise; MUAP, motor unit action potential amplitude

Figure 1.4. Average motor unit action potential amplitude by set and condition.



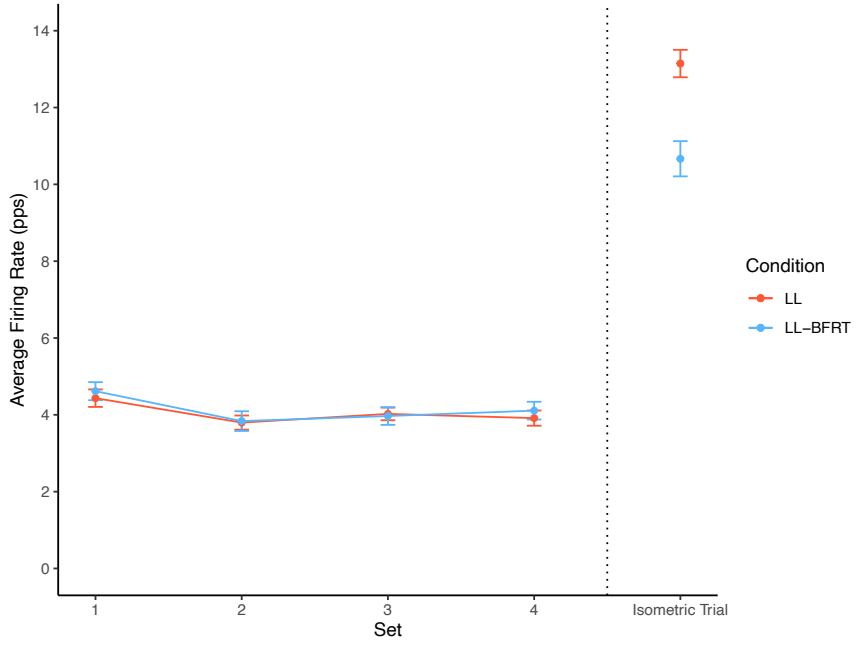
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LL, low load exercise; MUAP, motor unit action potential amplitude

Figure 1.5. Peak motor unit firing rate by set and condition.



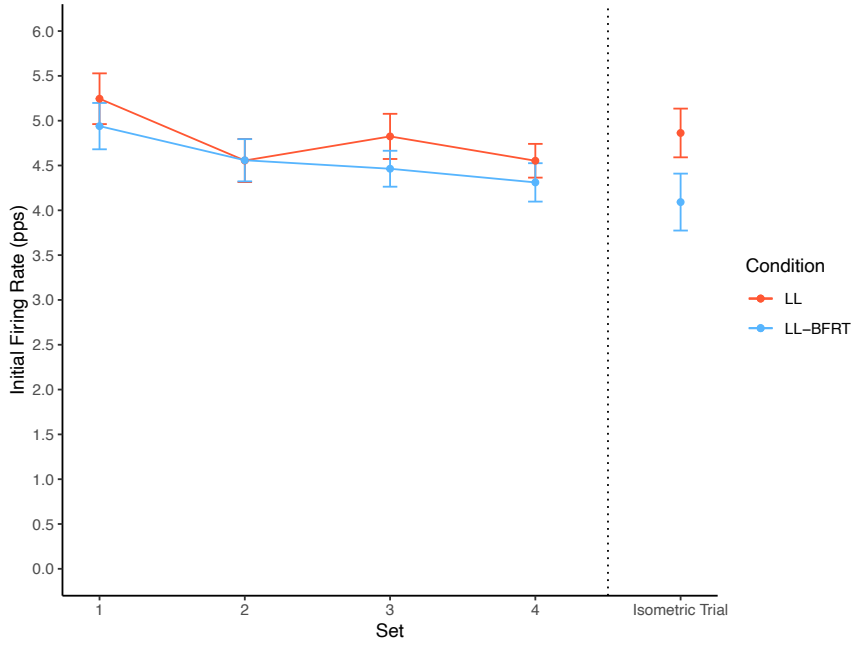
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LL, low load exercise

Figure 1.6. Average motor unit firing rate by set and condition.



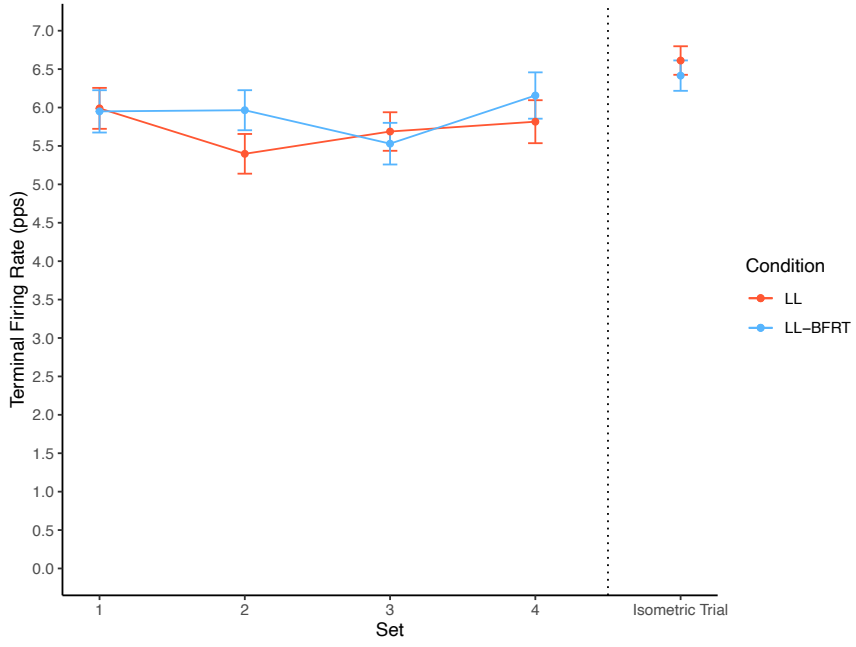
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LL, low load exercise

Figure 1.7. Initial motor unit firing rate by set and condition.



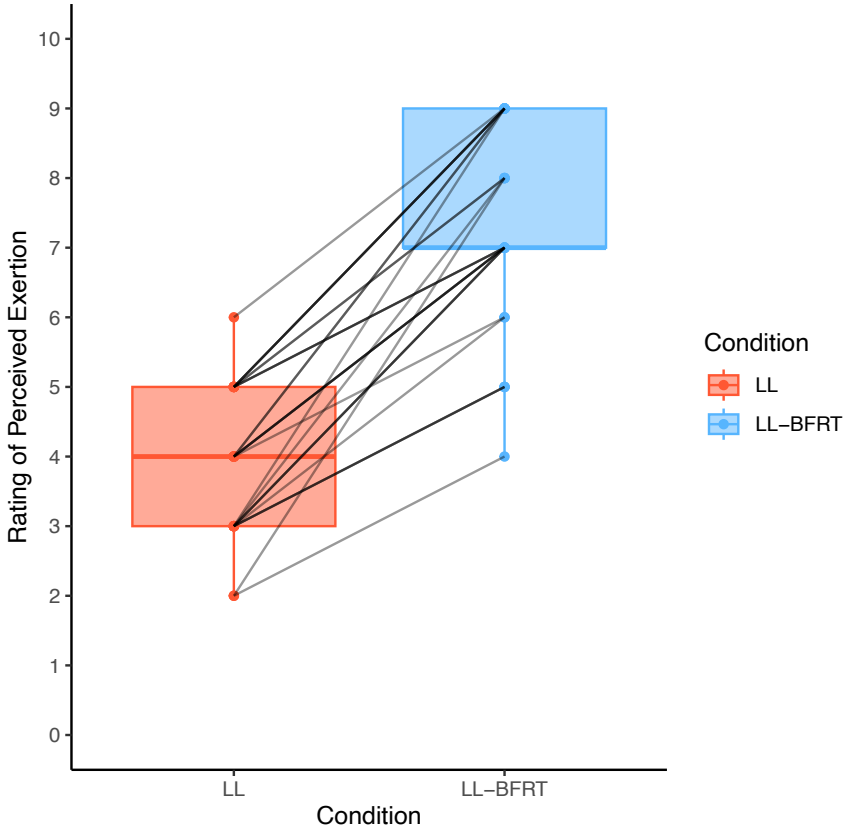
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LL, low load exercise

Figure 1.8. Terminal motor unit firing rate by set and condition.



Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LL, low load exercise

Figure 1.9. Rating of perceived exertion by condition.



Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LL, low load exercise

MANUSCRIPT II:

INFLUENCE OF BLOOD FLOW RESTRICTION THERAPY ON QUADRICEPS WEAKNESS IN PATIENTS POST-ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

Abstract

Background: Despite receiving clearance for unrestricted physical activity after participating in post-surgical rehabilitation, many individuals continue to suffer from persistent quadriceps weakness following anterior cruciate ligament reconstruction (ACLR). While there is no true standard of care for patients failing to respond to these more traditional rehabilitative methods, low load exercise with blood flow restriction therapy (LL-BFRT) may offer clinicians a complementary treatment approach for improving muscle function in patients post-ACLR. **Purpose:** To examine the effects of LL-BFRT on muscle strength and limb symmetry in patients with quadriceps strength deficits following ACLR compared to a control condition. **Study Design:** Randomized controlled pilot study. **Methods:** Ten female participants with quadriceps strength deficits following an ACLR were enrolled in this pilot study (LL-BFRT (n=5): age= 23.52±9.16 years, height= 166.85±4.12 cm, mass= 69.38±10.35 kg, time since surgery (TSS)= 16.31±16.86 months; Control (n=5): age= 21.88±3.91 years, height= 166.24±8.06 cm, mass= 69.13±11.64 kg, TSS= 48.03±41.34 months). Individuals were recruited using convenience sampling and randomly assigned to either the control group or the LL-BFRT group. At baseline, bilateral isokinetic (i.e., 90 º/s and 180 º/s) and isometric quadriceps strength was assessed using an isokinetic dynamometer. Those allocated to LL-BFRT group were required to complete 2 supervised sessions of LL-BFRT each week for a total of 4 weeks. Participants performed 4 sets (30x15x15x15 repetitions) of 5 unilateral exercises (i.e., knee extension, hamstring curl, hip abduction, hip extension, and leg press) using loads of 20-40 % of their predicted one repetition maximum under 60 % limb occlusion pressure. Following the intervention timeframe, participants in both groups were instructed to return for two follow-up

assessments. Separate 2X2 repeated measures analyses of covariance were used to examine between group differences for changes in limb symmetry and involved limb knee extension strength. The clinical significance of these changes was also evaluated by examining the proportion of participants per group that exceeded a 10 % improvement in limb symmetry at each follow-up assessment compared to baseline. **Results:** Compared to participants in the control group, those treated with LL-BFRT experienced significant increases in limb symmetry (Mean Difference [MD] with 95 % Confidence Interval [CI]= 27.32 %, [3.12, 51.51]) and involved limb strength ([MD] = 0.36 Nm/kg, [0.02, 0.71]) for peak knee extension torque during isokinetic strength testing at 90 º/s. No significant between group differences were identified for limb symmetry or involved limb strength during isokinetic strength testing at 180 º/s or isometric strength testing. **Conclusions:** The utilization of LL-BFRT elicited significant improvements in involved limb strength and limb symmetry during isokinetic strength testing at 90 º/s for females with substantial quadriceps strength deficits following a unilateral ACLR. Clinicians may consider implementing LL-BFRT into their patient care methods to improve persistent quadriceps strength deficits and potentially mitigate the development of long-term health consequences often associated with these limitations in patients post-ACLR.

Introduction

Sprain or rupture of the anterior cruciate ligament (ACL) is one of the most common, costly, and severe knee-related ligamentous injuries, especially among young, physically active individuals and athletes.[1] It has been suggested that the rate of ACL injury and surgical ACL reconstruction (ACLR) has increased by over 60 % in the past 20 years.[2,3] In the United States, an estimated 250,000 ACL injuries are sustained per year with many patients electing to undergo surgical reconstruction followed by postoperative physical therapy.[1] While the structure and components of post-surgical ACLR rehabilitation programs may vary, protocols typically focus on restoring knee function and increasing muscle strength in order to return patients to preinjury levels of physical activity and reduce the risk of subsequent injury.

It has been commonly recommended that postoperative ACLR rehabilitation should begin immediately following surgical intervention and continue for approximately 9 to 12 months prior to clearing patients for unrestricted physical activity.[4] However, a recent epidemiological study investigating the temporal utilization of supervised physical therapy after ACLR found that of those that completed physical therapy, 52 % of their visits were utilized in the first 6 weeks following surgery, 75 % in the first 10 weeks following surgery, and 90 % in the first 16 weeks following surgery.[5] This suggests that patients only receive about 10 % of their allotted physical therapy visits between 4 and 12 months post-surgery.[5] While the factors influencing an individual's access to physical therapy may differ (i.e., insurance, cost, time, etc.), the results of this study are largely concerning given that patients often continue to suffer from persistent quadriceps weakness and substantial limb asymmetries (i.e., [strength of involved limb/strength of uninvolved limb]*100) after they no

longer have access to physical therapy in the later phases of rehabilitation when clearance for activity is often considered.[5–7] A review by Lepley et al[7] reported average side-to-side quadriceps strength deficits of 23 % (range: 3-40 %) 6-months post-ACLR and 14 % (range 3-28 %) 12-months post-ACLR. This is particularly troublesome given that side-to-side strength deficits of less than 10-15 % are often recommended prior to clearing patients for an unrestricted return to physical activity.[7,8] Although the primary cause of persistent quadriceps weakness and strength asymmetries following ACLR remains elusive, several factors have been suggested to contribute to these deficits including muscle atrophy,[9–11] incomplete or insufficient rehabilitation,[9] reduced motor unit output,[12] and quadriceps activation failure.[13,14] These lingering muscle weaknesses have also been attributed to altered movement mechanics such as compensatory gait, hopping, and other functional tasks, which have been suggested to contribute to both an increased risk of reinjury and the development of knee osteoarthritis.[15–17]

Unfortunately, there is no true standard of care for patients that have failed to respond to traditional ACLR rehabilitation in terms of muscle weakness and atrophy. Low load exercise with blood flow restriction therapy (LL-BFRT) has been recently investigated as a potential prehabilitative[18–20] and rehabilitative[21–29] treatment technique for improving muscle strength after ACLR. Unfortunately, the methodology and results of these studies are inconsistent regarding the overall benefits of LL-BFRT compared to high load resistance exercise and control interventions in patients post-ACL injury. A recent study by Noyes et al[29] investigated the effects of LL-BFRT on quadriceps and hamstring strength deficits in patients failing to respond to traditional rehabilitation after knee surgery. This study found that a majority of patients had improvements in both quadriceps and hamstring strength

deficits of at least 10 % following 9 sessions of LL-BFRT and 20 % following 18 sessions of LL-BFRT.[29] However, this study reported relatively small effect sizes and had a very diverse patient population in terms of the type of knee surgery patients underwent.[29] Therefore, it is still largely unknown how LL-BFRT may affect muscle strength in patients with quadriceps weakness and limb asymmetries in the later stages of recovery following ACLR. Therefore, the primary aim of this study was to examine the effects of LL-BFRT on muscle strength and limb symmetry in patients with quadriceps strength deficits following ACLR compared to a control condition. We hypothesize that those treated with LL-BFRT will experience improvements quadriceps strength and limb symmetry compared to those exposed to a control condition.

Methods

Study Design

The influence of LL-BFRT on quadriceps strength deficits in patients post-ACLR was examined using a randomized controlled pilot study design. The independent variable was the intervention group, LL-BFRT or control, and the primary dependent variable was knee extension strength assessed via limb symmetry index (i.e., LSI = [involved limb strength/uninvolved limb strength] *100) and normalized peak and average peak torque output measured via isokinetic and isometric dynamometry.

Participants

Potential participants were recruited via fliers and study information sheets distributed across the local university, surrounding community, and associated health system.

Participants were eligible to take part in this study if they were between 15-64 years of age, at least 3 months post-unilateral ACLR, and had a LSI for isokinetic or isometric knee extension strength of less than 80 %. Participants were excluded if they experienced graft failure or severe surgical complications, had a history or current diagnosis of any cardiovascular, metabolic, or neurological disorders, were currently using anti-coagulant medication, had known pregnancy, malignancy, serious infection near the lower limb, muscular abnormalities, or had formal experience with LL-BFRT during their traditional post-surgical ACLR rehabilitation program. The study was approved by the University of Virginia's Institutional Review Board for Health Sciences Research (IRB-HSR#210507).

Fourteen participants provided written consent to participate in this pilot study. Upon completion of baseline strength testing, four participants were excluded from continued participation as they exceeded the 80% LSI threshold on each of our knee extension strength assessments. Therefore, ten female participants fully qualified for participation in this study (LL-BFRT (n=5): age= 23.52±9.16 years, height= 166.85±4.12 cm, mass= 69.38±10.35 kg, time since surgery (TSS)= 16.31±16.86 months; Control (n=5): age= 21.88±3.91 years, height= 166.24±8.06 cm, mass= 69.13±11.64 kg, TSS= 48.03±41.34 months). Additional demographic information is highlighted in Table 2.1 as well as Additional Results Table D2.1, D2.2, and D2.3.

Procedures

Baseline Visit

All participants reported to the Exercise and Sport Injury Laboratory at the University of Virginia for a required baseline assessment. Upon arrival participants provided informed

consent, were randomly allocated into either the control group or LL-BFRT group, and completed several demographic questionnaires, patient reported outcome measures (as described in Manuscript III), and the International Physical Activity Questionnaire (IPAQ) Short Form prior to beginning the strength testing procedures.

Baseline Visit – Muscle Strength

Isometric and isokinetic knee extension strength was measured bilaterally by a blinded assessor using a Biodex Systems IV dynamometer (Biodex Medical Systems, Inc. Shirley, NY). Participants were positioned in 90 º of hip flexion with the axis of the isokinetic dynamometer aligned with the lateral joint line of the knee. The distal third of the lower limb was secured to the arm of the dynamometer via a padded Velcro strap. To limit unwanted movement, participants were instructed to cross their arms over their chest with their back placed firmly against the chair and a belt secured over their lap. Knee range of motion was set from 0 º to 110 º of flexion. All strength assessments were performed on the participant's uninvolved limb followed by their involved surgical limb. Practice repetitions were completed prior to each strength assessment and 30 seconds of rest was provided at the conclusion of each assessment. Concentric peak and average peak torque for knee extension were assessed isokinetically at two speeds of 90 º/sec and 180 º/sec. Beginning with the 90 º/s isokinetic assessment, participants were instructed to perform 8 maximal repetitions through their full knee range of motion at each speed while receiving verbal encouragement. After completing each isokinetic assessment, isometric peak torque for knee extension was evaluated at 90 º of knee flexion. For testing, participants were instructed to exert maximal knee extension effort for 30 seconds. The maximum torque output produced during this trial

was recorded as the individual's peak isometric torque (Acq-Knowledge software, Biopac Systems).

Baseline Visit – Intervention Familiarization

For participants that were randomly allocated into the LL-BFRT group, one-repetition maximum (1RM) testing and intervention familiarization were completed at the end of the baseline assessment. A participant's 1RM was predicted for each exercise within the LL-BFRT intervention program by assessing their five-repetition maximum (5RM) following a modified version of the National Strength and Conditioning Association's 1RM testing protocol and 1RM estimation table.[30] Participants were then given the opportunity to practice the LL-BFRT exercise protocol to ensure proper execution of each exercise under LL-BFRT.

LL-BFRT Program

Following the baseline visit, participants in the LL-BFRT group completed 2 sessions of LL-BFRT per week for 4 weeks, for a total of 8 supervised sessions. Each session consisted of 5 single leg exercises completed under LL-BFRT in the following order: 1) knee extension, 2) hamstring curl, 3) hip abduction, 4) hip extension, and 5) leg press. Exercises were performed only on the involved limb. Before initiating their first exercise, participants completed a 5-minute self-selected warm-up on a stationary bike. After a period of rest, a skin protection sleeve and contoured Easi-Fit Tourniquet Cuff (Delfi Medical Innovations Inc.) were applied to the most proximal portion of the participant's involved limb. Subjects were instructed to lay in a relaxed, supine position on a treatment table while an automated pneumatic tourniquet system (Delfi Personalized Tourniquet System II, Delfi Medical Vancouver, BC) was used to determine their total limb occlusion pressure (LOP). During each exercise, the tourniquet cuff was inflated to 60 % of the participants predetermined

LOP. The tourniquet cuff remained inflated during all sets, repetitions, and interset rest periods and was only deflated during rest between exercises.

Subjects performed 4 sets of 30x15x15x15 repetitions at an execution speed of 2s concentric:eccentric and 20-40 % of their predicted 1RM per exercise. Thirty seconds of rest was provided between each set of exercise and 2 minutes of rest was provided between each type of exercise. To document exercise difficulty and guide progression, participants were asked to rate their level of perceived exertion (RPE) following each exercise from no effort (0) to maximal effort (10) using the Borg scale.[31] At the beginning of each session the amount of weight utilized during each exercise was modified based on the individuals reported RPE from the previous session. With a goal of achieving an RPE of 7 during each exercise, weight was either increased or maintained to ensure adequate exercise difficulty. For an RPE less than 7, weight was incrementally increased in the following session, and for an RPE of greater than or equal to 7, weight was maintained in the following session.

Weekly Physical Activity

To quantify an individual's amount of physical activity per week, participants in both groups completed an online IPAQ Short Form at the end of each week during the intervention timeframe.

Follow-Up Visits

After the completion of the one-month intervention timeframe, all participants returned for two additional follow-up visits. The initial follow-up assessment occurred within one week of completing the intervention and the secondary follow-up assessment occurred at least one month following the completion of the intervention. During each follow-up visit all measures of muscle strength were reassessed using the previously described methodology.

Data Processing

Unilateral measures of isokinetic and isometric peak and average peak torque were normalized to the participants body mass (Nm/kg). Additionally, LSI values for each measure of knee extension strength were determined using the following equation:

$$\boldsymbol{LSI} = [(\boldsymbol{involved\ limb})/(\boldsymbol{uninvolved\ limb}) * \mathbf{100}]$$

To determine the amount of change in each measure of muscle strength and limb symmetry across time, change scores were calculated between baseline and each follow-up assessment (i.e., follow-up #1 – baseline and follow-up #2 – baseline). Additionally, in accordance with the IPAQ Short Form guidelines for data processing and analysis,[32] a participant's weekly physical activity was calculated as the number of MET-minutes per week using the following formula:

$$\boldsymbol{MET\text{-}min/week} = [(\mathbf{3.3} * \boldsymbol{walking\ minutes} * \boldsymbol{walking\ days}) + (\mathbf{4.0} * \boldsymbol{moderate\ intensity\ activity\ minutes} * \boldsymbol{moderate\ days}) + (\mathbf{8.0} * \boldsymbol{vigorous\ intensity\ activity\ minutes} * \boldsymbol{vigorous\ intensity\ days})]$$

Statistical Analyses

All statistical analyses were conducted using IBM Statistics (v28.0.1.1, SPSS, Inc. Chicago, IL, USA) and R (RStudio Inc., v2022.07.0). To compare participants' demographic information (i.e., age, height, mass, weekly physical activity level, and time since surgery)

and baseline strength and LSI values between groups, descriptive analyses were completed using independent samples t-tests. Between group differences for changes in muscle strength and LSI were calculated using separate repeated measures analyses of covariance (RM-ANCOVA) with baseline values for the selected dependent variable included as a covariate in each model. For these analyses, group was included as a between-subjects factor and time (i.e., follow-up #1 value, follow-up #2 value) was included as a within-subjects factor. Where significance was observed, post-hoc analyses with Bonferroni adjustments were evaluated to determine the source and magnitude of these differences. Partial eta squared statistics were calculated to identify the magnitude of significant between group differences and categorized as small (0.01), medium (0.06), or large (0.14). Additionally, to explore the clinical relevance of these results, proportions were calculated based on the number of participants per group that experienced at least a 10 % improvement from baseline to follow-up #1 and from baseline to follow-up #2 for each of the LSI outcome measures. Alpha was set a priori to 0.05 for all analyses.

Results

Grouped and individual participant demographic information is presented in Table 2.1. With the exception of pre-surgical Tegner activity level, no significant between group differences in demographic characteristics were noted. Due to inaccurate reporting, the amount of physical activity completed by one participant in the LL-BFRT group during week 2 of the intervention was excluded from analysis. No significant differences were found between groups when evaluating weekly physical activity level (Table 2.2). Additionally,

summary statistics for LSI, involved limb knee extension strength, and knee extension strength deficits by group and time are reported in Table 2.3 and Table 2.4, respectively.

Limb Symmetry Index

Results of the 2X2 RM-ANCOVAs revealed no significant within-subjects effects for time or group X time interactions for any of the LSI measures including peak and average peak knee extension torque at 90 º/s, peak and average peak knee extension torque at 180 º/s, and peak isometric knee extension torque at 90 º of knee flexion (Table 2.5). However, a significant between-subjects effect was identified for peak knee extension torque at 90 º/s ($F = 7.13$, $p = 0.032$, $\eta_p^2 = 0.50$; Table 2.5). Compared to the control group, participants in the LL-BFRT group experienced significant increases in LSI for peak knee extension torque at 90 º/s following the intervention timeframe when controlling for baseline LSI values (Mean Difference [MD] with 95% Confidence Interval [CI]= 27.32 %, [3.12, 51.51]; Table 2.6 and Figure 2.1A).

Though lacking statistical significance, noteworthy between group differences were also identified when examining improvements in LSI for average peak torque at 90 º/s following the LL-BFRT intervention (MD = 24.89 %, [-4.60, 54.38], $p = 0.086$; Figure 2.1B). No significant between group differences in LSI were found for peak and average peak knee extension torque at 180 º/s (Figure 2.2) or peak isometric knee extension torque (Figure 2.3) when controlling for baseline differences in these LSI metrics.

Involved Limb Strength

When examining changes in normalized knee extension strength of the involved surgical limb, no significant time effects or interaction terms were identified for peak and average peak knee extension torque at 90 º/s, peak and average peak knee extension torque at 180 º/s, or peak isometric knee extension torque at 90 º of knee flexion (Table 2.7). Nevertheless, a significant between-subjects effect for group was identified for peak knee extension torque at 90 º/s ($F = 6.34$, $p = 0.040$, $\eta_p^2 = 0.48$; Table 2.7). Compared to participants in the control group, individuals treated with LL-BFRT experienced significant increases in peak knee extension torque of their involved limb at 90 º/s when controlling for differences at baseline ([MD] = 0.36 Nm/kg, [0.02, 0.71]; Table 2.8 and Figure 2.4A). Although nonsignificant, comparable between group differences were also found when exploring changes in average peak knee extension torque of the involved limb during isokinetic testing at 90 º/s (MD = 0.35 Nm/kg, [-0.03, 0.73], $p = 0.064$; Figure 2.4B). No significant between group differences were identified for involved limb knee extension strength during isokinetic strength testing at 180 º/s (Figure 2.5) or isometric strength testing (Figure 2.6) when controlling for involved limb knee extension strength at baseline.

Improvements in Knee Extension Strength Deficits

As presented in Table 2.9, over half of the participants in the LL-BFRT exceeded a 10 % improvement in LSI from baseline to the first follow-up assessment for peak and average peak knee extension torque at 90 º/s (3/5 and 4/5, respectively) as well as peak isometric knee extension torque at 90 º of knee flexion (3/5). Comparatively, only two participants in the control group exceed a 10 % improvement in LSI for peak isometric knee extension torque,

and only one participant exceeded this threshold for average peak knee extension torque at 90 º/s.

At the second follow-up assessment, all participants in the LL-BFRT group exceeded a 10 % improvement in LSI for peak and average peak knee extension torque at 90 º/s, and all but one participant exceeded this threshold for peak isometric knee extension torque. Conversely, only one participant in the control group exceeded the LSI improvement threshold for average peak knee extension torque at 90 º/s and peak isometric knee extension torque at 90 º of knee flexion.

Discussion

Long-term deficits in quadriceps strength and limb symmetry have continued to be a concerning challenge for many individuals following ACLR. While LL-BFRT has been investigated as a rehabilitative tool during the preoperative and early postoperative stages of recovery,[33] few studies have examined how this intervention technique may benefit patients with significant strength deficits during the mid to late stages of recovery when individuals may no longer have access to supervised physical therapy.[27,34] Supporting the primary hypothesis of this pilot study, our results indicate that females at least 5 months post-ACLR treated with 8 sessions of LL-BFRT experienced significant improvements in isokinetic quadriceps strength and limb symmetry at 90 º/s compared to those exposed to a true control condition. Additionally, these beneficial changes appeared to persist for at least one month after discontinuing the intervention. However, no significant between group differences in knee extension strength or LSI were identified at either follow-up assessment during isometric strength testing or isokinetic strength testing at 180 º/s. These findings have

provided preliminary evidence to support the utilization of LL-BFRT for improving quadriceps strength deficits in female patients post-ACLR.

On average, participants treated with LL-BFRT experienced a 25 % improvement (range: 8.34 – 59.34 %) in LSI and a 0.42 Nm/kg (range: 0.16 – 0.80 Nm/kg) improvement in involved limb knee extension strength for peak and average peak torque during isokinetic testing at 90 º/s immediately following the intervention timeframe. However, one month after completing the intervention these improvements appeared to decrease to approximately 15 % (range: -2.69 – 46.43 %) and 0.32 Nm/kg (range: 0.04 – 0.55 Nm/kg). Though different strength assessment techniques and LL-BFRT protocols were utilized, similar improvements have been reported in previous research investigating the effects of LL-BFRT on quadriceps strength and limb symmetry in patients following ACLR and other lower extremity-related surgeries.[29,34,35] Hylden et al.[34] completed a case series to investigate the effects of 6 sessions of LL-BFRT on persistent muscle weakness in 7 active duty service members following a traumatic lower extremity injury and surgical intervention. Similar to the findings of our study, the authors identified mean changes in peak knee extension torque of 33.4 ± 23.8 % (range: 2.5 – 65.8 %) during isokinetic testing at 90 º/s and 16.5 ± 18.7 % (range: -15.3 – 35.8 %) during isokinetic testing at 300 º/s after 2 weeks of treatment with LL-BFRT. Furthermore, in a study by Kilgas et al,[27] individuals at least 2 years post-ACLR presenting with persistent quadriceps strength deficits (≤ 10 % symmetry deficit) participated in a 4 week (5 x per week) home-based LL-BFRT intervention program. Upon completion of the intervention, participants treated with LL-BFRT experienced significant increases in knee extensor strength and knee extensor strength symmetry by 20 ± 14 % and 11 ± 2 %, respectively.[27] Noyes et al.[29] also reported comparable improvements in average quadriceps

strength deficits of approximately 7 % following 9 sessions of LL-BFRT and 10 % following 18 sessions of LL-BFRT in patients who failed to respond to traditional rehabilitation following knee surgery. These findings, and the results from our study, suggest that utilizing LL-BFRT with moderate to high LOP (i.e., 60-80 %) may be an effective alternative or complementary treatment approach for inducing significant changes in quadriceps strength and limb symmetry in patients with persistent quadriceps weakness following knee surgery. However, future large-scale studies are needed to explore when in the recovery process (i.e., presurgical, immediate postsurgical, mid-recovery, or late-recovery) may be the most appropriate and effective time to implement LL-BFRT into patient care programs for improving quadriceps strength in individuals following ACLR and other severe knee-related surgeries.

Conversely, during isometric and isokinetic knee extension strength testing at 180 º/s, no statistically significant between group differences were identified for involved limb quadriceps strength or LSI. Nevertheless, while nonsignificant, participants in the LL-BFRT group experienced average improvements of approximately 5 % and 18 % in LSI as well as 0.14 Nm/kg and 0.30 Nm/kg in involved limb knee extension strength during isokinetic testing at 180 º/s and isometric testing, respectively. Given that the demands of the exercises performed during the LL-BFRT intervention more closely emulated that of our isokinetic testing procedures at 90 º/s, we speculate that the lack of significant changes in these metrics may be related to the exercise parameters utilized during the intervention. For example, participants were encouraged to execute each exercise at an approximate 2s:2s (eccentric:concentric) contraction ratio which is similar to that of the slower, 90 º/s isokinetic testing speed compared to the faster, 180 º/s testing speed. Additionally, the exercises that

were used during the LL-BFRT intervention were primarily reliant on participants performing isotonic muscle contractions and did not include any isometric exercises. With consideration to the concept of training specificity (i.e., the SAID principle),[30] it is likely that the anticipated benefits of LL-BFRT on different strength and functional assessments may be dependent on the type of exercises and associated protocols utilized during the intervention program. Therefore, although future research is needed to investigate how altering these factors (i.e., exercise execution speed, contraction types, fixed repetition scheme vs. repetitions to fatigue, etc.) may influence patient outcomes, healthcare professionals should aim to incorporate different types of exercise with varying LL-BFRT parameters to create a comprehensive rehabilitative experience for their patients in order to target and achieve an individual's specific goals.

In addition to our aforementioned findings, we also identified noteworthy results regarding the number of participants per group that experienced greater than a 10 % improvement in LSI on each of our strength tests. At the first follow-up assessment, we found that over half (i.e., 60-80 %) of the participants in the LL-BFRT group experienced more than a 10 % improvement in LSI for peak isometric knee extension torque as well as peak and average peak knee extension torque at 90 º/s (3/5, 3/5, 4/5, respectively). In contrast, only one participant in the control group exceeded this threshold for average peak knee extension torque at 90 º/s and two participants for peak isometric knee extension torque. Hence, participants in the LL-BFRT group were 4 times more likely to meet the LSI improvement threshold for average peak torque at 90 º/s compared to participants in the control group. Noyes et al.[29] reported similar findings where approximately 69 % of their 26 patients treated with 9 sessions of LL-BFRT experienced more than a 10 % increase in

quadriceps strength deficits and peak isometric knee extension torque. Additionally, one month after completing the intervention all participants allocated to the LL-BFRT group of our study presented with more than a 10 % improvement in LSI for peak and average peak knee extension torque at 90 °/s, and all but one participant exceeded this threshold for peak isometric knee extension torque. Although participants in this study and previous research appear to have highly individualized responses to LL-BFRT (Additional Results Table D2.1-2.4),[27,29,34] these proportions indicate that 8 sessions of unilateral LL-BFRT may be sufficient for improving select quadriceps strength deficits by 10 % or more in female participants following ACLR. Yet, future research should continue to explore what factors such as a participant's demographic, biological, and psychological characteristics may influence their response, or lack thereof, to LL-BFRT across various load-restricted populations.

Limitations

There were several limitations associated with this study. First of all, our small, female sample limits our ability to apply the results of this study to other patient populations. Nevertheless, this pilot study has provided foundational evidence to guide future research and support the utilization of LL-BFRT for improving persistent quadriceps strength deficits in females following ACLR. Individuals within this study also enrolled at varying stages in their recovery process. While this confounding factor needs to be considered when interpreting our findings, it has also increased the generalizability of our results indicating that LL-BFRT may be useful for treating patients with muscle weakness regardless of their time since surgery. In terms of our LL-BFRT intervention protocol, 8 sessions of LL-BFRT using 60 % LOP and 20-40 % of an individual's predicted 1RM may not have been strenuous

enough in order to induce the anerobic response needed to elicit optimal neuromuscular adaptations. However, our results demonstrate that compared to a true control condition, LL-BFRT may be effective for helping patients overcome lingering strength deficits following an extensive lower extremity surgical intervention. Future research is warranted to explore how manipulating various LL-BFRT parameters including, but not limited to, the number of sessions and exercises prescribed, amount of LOP utilized, execution speed, and the type and intensity of the exercises performed, may influence patient outcomes and expand the benefits of this treatment technique across different types of neuromuscular, functional, and sport-specific assessments.

Conclusions

Compared to a true control condition, eight sessions of LL-BFRT elicited significant improvements in muscle strength and LSI in females with noteworthy quadriceps strength deficits following a unilateral ACLR. For patients failing to respond to traditional rehabilitative methods, clinicians may consider implementing LL-BFRT into their patient care methods to improve quadriceps strength and potentially mitigate the development of long-term health consequences often associated with persistent quadriceps weakness after ACLR.

References

1. Griffin LY, Albohm MJ, Arendt EA, et al. Understanding and preventing noncontact anterior cruciate ligament injuries: a review of the Hunt Valley II meeting, January 2005. *Am J Sports Med*. 2006;34(9):1512-1532. doi:10.1177/0363546506286866

2. Kuenze C, Bell DR, Grindstaff TL, et al. A Comparison of Psychological Readiness and Patient-Reported Function Between Sexes After Anterior Cruciate Ligament Reconstruction. *J Athl Train*. Published online December 28, 2020. doi:10.4085/1062-6050-0034.20

3. Mall NA, Chalmers PN, Moric M, et al. Incidence and trends of anterior cruciate ligament reconstruction in the United States. *Am J Sports Med*. 2014;42(10):2363-2370. doi:10.1177/0363546514542796

4. Melick N van, Cingel REH van, Brooijmans F, et al. Evidence-based clinical practice update: practice guidelines for anterior cruciate ligament rehabilitation based on a systematic review and multidisciplinary consensus. *Br J Sports Med*. 2016;50(24):1506-1515. doi:10.1136/bjsports-2015-095898

5. Burroughs PJ, Kahan JB, Moore HG, Grauer JN, Gardner EC. Temporal Utilization of Physical Therapy Visits After Anterior Cruciate Ligament Reconstruction. *Orthop J Sports Med*. 2021;9(2):2325967120982293. doi:10.1177/2325967120982293

6. Palmieri-Smith RM, Thomas AC, Wojtys EM. Maximizing quadriceps strength after ACL reconstruction. *Clin Sports Med*. 2008;27(3):405-424, vii-ix. doi:10.1016/j.csm.2008.02.001

7. Lepley LK. Deficits in Quadriceps Strength and Patient-Oriented Outcomes at Return to Activity After ACL Reconstruction: A Review of the Current Literature. *Sports Health*. 2015;7(3):231-238. doi:10.1177/1941738115578112

8. Burgi CR, Peters S, Ardern CL, et al. Which criteria are used to clear patients to return to sport after primary ACL reconstruction? A scoping review. *Br J Sports Med*. 2019;53(18):1154-1161. doi:10.1136/bjsports-2018-099982

9. Thomas AC, Wojtys EM, Brandon C, Palmieri-Smith RM. Muscle Atrophy Contributes to Quadriceps Weakness after ACL Reconstruction. *J Sci Med Sport Sports Med Aust*. 2016;19(1):7-11. doi:10.1016/j.jsams.2014.12.009

10. Lepley LK, Davi SM, Burland JP, Lepley AS. Muscle Atrophy After ACL Injury: Implications for Clinical Practice. *Sports Health*. 2020;12(6):579-586. doi:10.1177/1941738120944256

11. Krishnan C, Williams GN. Factors explaining chronic knee extensor strength deficits after ACL reconstruction. *J Orthop Res Off Publ Orthop Res Soc*. 2011;29(5):633-640. doi:10.1002/jor.21316

12. Rice DA, McNair PJ. Quadriceps arthrogenic muscle inhibition: neural mechanisms and treatment perspectives. *Semin Arthritis Rheum*. 2010;40(3):250-266. doi:10.1016/j.semarthrit.2009.10.001

13. Hart JM, Pietrosimone B, Hertel J, Ingersoll CD. Quadriceps Activation Following Knee Injuries: A Systematic Review. *J Athl Train*. 2010;45(1):87-97. doi:10.4085/1062-6050-45.1.87

14. Konishi Y, Fukubayashi T. Relationship between muscle volume and muscle torque of the hamstrings after anterior cruciate ligament reconstruction. *J Sci Med Sport*. 2010;13(1):101-105. doi:10.1016/j.jsams.2008.08.001

15. Di Stasi SL, Logerstedt D, Gardinier ES, Snyder-Mackler L. Gait patterns differ between ACL-reconstructed athletes who pass return-to-sport criteria and those who fail. *Am J Sports Med*. 2013;41(6):1310-1318. doi:10.1177/0363546513482718

16. Palmieri-Smith RM, Thomas AC, Karvonen-Gutierrez C, Sowers MF. Isometric Quadriceps Strength in Women with Mild, Moderate, and Severe Knee Osteoarthritis. *Am J Phys Med Rehabil Assoc Acad Physiatr*. 2010;89(7):541-548. doi:10.1097/PHM.0b013e3181ddd5c3

17. Tourville TW, Jarrell KM, Naud S, Slauterbeck JR, Johnson RJ, Beynnon BD. Relationship between isokinetic strength and tibiofemoral joint space width changes after anterior cruciate ligament reconstruction. *Am J Sports Med*. 2014;42(2):302-311. doi:10.1177/0363546513510672

18. Grapar Zargi T, Drobnic M, Jkoder J, Strazar K, Kacin A. The effects of preconditioning with ischemic exercise on quadriceps femoris muscle atrophy following anterior cruciate ligament reconstruction: a quasi-randomized controlled trial. *Eur J Phys Rehabil Med*. 2016;52(3):310-320.

19. Žargi T, Drobnič M, Stražar K, Kacin A. Short-Term Preconditioning With Blood Flow Restricted Exercise Preserves Quadriceps Muscle Endurance in Patients After Anterior Cruciate Ligament Reconstruction. *Front Physiol*. 2018;9:1150. doi:10.3389/fphys.2018.01150

20. Kacin A, Drobnič M, Marš T, et al. Functional and molecular adaptations of quadriceps and hamstring muscles to blood flow restricted training in patients with ACL rupture. *Scand J Med Sci Sports*. 2021;31(8):1636-1646. doi:10.1111/sms.13968

21. Takarada Y, Takazawa H, Ishii N. Applications of vascular occlusion diminish disuse atrophy of knee extensor muscles. *Med Sci Sports Exerc*. 2000;32(12):2035-2039. doi:10.1097/00005768-200012000-00011

22. Ohta H, Kurosawa H, Ikeda H, Iwase Y, Satou N, Nakamura S. Low-load resistance muscular training with moderate restriction of blood flow after anterior cruciate ligament reconstruction. *Acta Orthop Scand*. 2003;74(1):62-68. doi:10.1080/00016470310013680

23. Iversen E, Røstad V, Larmo A. Intermittent blood flow restriction does not reduce atrophy following anterior cruciate ligament reconstruction. *J Sport Health Sci*. 2016;5(1):115-118. doi:10.1016/j.jshs.2014.12.005

24. Hughes L, Paton B, Haddad F, Rosenblatt B, Gissane C, Patterson SD. Comparison of the acute perceptual and blood pressure response to heavy load and light load blood flow restriction resistance exercise in anterior cruciate ligament reconstruction patients and non-injured populations. *Phys Ther Sport Off J Assoc Chart Physiother Sports Med*. 2018;33:54-61. doi:10.1016/j.ptsp.2018.07.002

25. Hughes L, Patterson SD, Haddad F, et al. Examination of the comfort and pain experienced with blood flow restriction training during post-surgery rehabilitation of anterior cruciate ligament reconstruction patients: A UK National Health Service trial. *Phys Ther Sport Off J Assoc Chart Physiother Sports Med*. 2019;39:90-98. doi:10.1016/j.ptsp.2019.06.014

26. Hughes L, Rosenblatt B, Haddad F, et al. Comparing the Effectiveness of Blood Flow Restriction and Traditional Heavy Load Resistance Training in the Post-Surgery Rehabilitation of Anterior Cruciate Ligament Reconstruction Patients: A UK National Health Service Randomised Controlled Trial. *Sports Med Auckl NZ*. Published online July 12, 2019. doi:10.1007/s40279-019-01137-2

27. Kilgas MA, Lytle LLM, Drum SN, Elmer SJ. Exercise with Blood Flow Restriction to Improve Quadriceps Function Long After ACL Reconstruction. *Int J Sports Med*. 2019;40(10):650-656. doi:10.1055/a-0961-1434

28. Curran MT, Bedi A, Mendias CL, Wojtys EM, Kujawa MV, Palmieri-Smith RM. Blood Flow Restriction Training Applied With High-Intensity Exercise Does Not Improve Quadriceps Muscle Function After Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial. *Am J Sports Med*. 2020;48(4):825-837. doi:10.1177/0363546520904008

29. Noyes FR, Barber-Westin S, Sipes L. Blood Flow Restriction Training Can Improve Peak Torque Strength in Chronic Atrophic Postoperative Quadriceps and Hamstrings Muscles. *Arthrosc J Arthrosc Relat Surg Off Publ Arthrosc Assoc N Am Int Arthrosc Assoc*. Published online March 31, 2021. doi:10.1016/j.arthro.2021.03.040

30. National Strength & Conditioning Association. *Essentials of Strength Training and Conditioning*. 4th ed. Human Kinetics; 2015.

31. Borg G. *Borg's Perceived Exertion and Pain Scales*. Human Kinetics; 1998.

32. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ) – Short and Long Forms. Published online November 2005. https://sites.google.com/site/theipaq/scoring-protocol

33. Wengle L, Migliorini F, Leroux T, Chahal J, Theodoropoulos J, Betsch M. The Effects of Blood Flow Restriction in Patients Undergoing Knee Surgery: A Systematic Review and

Meta-analysis. *Am J Sports Med*. Published online August 18, 2021:3635465211027296. doi:10.1177/03635465211027296

34. Hylden C, Burns T, Stinner D, Owens J. Blood flow restriction rehabilitation for extremity weakness: a case series. *J Spec Oper Med Peer Rev J SOF Med Prof*. 2015;15(1):50-56.

35. Colapietro M, Portnoff B, Miller SJ, Sebastianelli W, Vairo GL. Effects of Blood Flow Restriction Training on Clinical Outcomes for Patients with ACL Reconstruction: A Systematic Review. *Sports Health*. Published online February 8, 2022:19417381211070830. doi:10.1177/19417381211070834

Tables

Table 2.1. Individual participant demographic information by group

Group	Participant (#)	Age (y)	Height (cm)	Mass (kg)	Graft (type)	TSS (m)	Tegner Score	
							Pre	Post
LL-BFRT	2	21.81	161.29	67.40	PT	10.08	7	7
	3	18.76	169.42	86.45	H	45.56	7	2
	4	18.61	165.10	63.14	Q	5.58	8	7
	7	18.68	166.37	59.69	PT	15.28	8	6
	14	39.72	172.08	70.21	Q	5.06	6	2
	Group Mean ± SD	23.52± 9.16	166.85 ±4.12	69.38± 10.35		16.31± 16.86	7.20± 0.84	4.80± 2.59
Control	1	18.55	158.75	65.04	Q	7.78	9	8
	9	28.60	175.26	73.94	PT	78.22	9	6
	10	21.46	171.45	84.46	H	99.74	9	6
	12	20.03	156.84	52.80	BEAR	46.75	9	3
	16	20.75	168.91	69.40	PT	7.66	9	5
	Group Mean ± SD	21.88± 3.91	166.24 ±8.06	69.13± 11.64		48.03±41.34	9.00± 0.00	5.60± 1.82
Mean Difference ± SE (p-value)		1.64 ± 4.45 (0.723)	0.61 ± 4.05 (0.884)	0.25 ± 6.97 (0.972)		-31.71 ± 19.97 (0.151)	-1.80± 0.37 (0.009)*	-0.80± 1.41 (0.587)

** Statistically significant at $p \leq 0.05$*

Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; TSS, time since surgery; SD, standard deviation; SE, standard error; PT, patellar tendon; H, hamstring; Q, quadriceps; BEAR, bridge-enhanced anterior cruciate ligament repair

Table 2.2. Weekly IPAQ physical activity level between groups

	MET-min/week (Mean ± SD)			
Visit	LL-BFRT	Control	Mean Difference ± SE	p-value
Baseline	4,573.80 ± 3,390.73	3,107.40 ± 2,567.30	1,466.40 ± 1,902.00	0.463
Week #1	4,361.60 ± 2,388.34	3,525.30 ± 2,957.91	836.30 ± 1,700.20	0.636
Week #2*	4,066.62 ± 2,466.83	2,571.00 ± 1,222.06	1,495.62 ± 1,248.04	0.270
Week #3	5,196.20 ± 3,006.98	2,306.00 ± 1,362.57	2,890.20 ± 1,476.38	0.086
Week #4	4,736.60 ± 2,680.21	2,447.10 ± 1,460.03	2,289.50 ± 1,364.93	0.132
Follow-up #1	4,964.00 ± 2,605.06	2,634.50 ± 1,408.15	2,329.50 ± 1,324.33	0.117
Follow-up #2	4,010.10 ± 1,898.07	3,040.50 ± 2,028.87	969.60 ± 1,242.49	0.458

**One participant in LL-BFRT group excluded from week 2 summary statistics*
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; SD, standard deviation; SE, standard error

Table 2.3. Knee extension strength and limb symmetry index by group and time

		Mean ± SD					
		Limb Symmetry Index (%)		Involved Limb Strength (Nm/kg)		Uninvolved Limb Strength (Nm/kg)	
Timepoint	Variable	LL-BFRT	Control	LL-BFRT	Control	LL-BFRT	Control
Baseline	PK at 90°/s	63.09 ± 17.70	81.97 ± 13.52	1.31 ± 0.33	1.61 ± 0.30	2.14 ± 0.51	1.97 ± 0.27
	AVG at 90°/s	63.61 ± 19.52	83.55 ± 15.88	1.20 ± 0.32	1.49 ± 0.29	1.96 ± 0.55	1.80 ± 0.31
	PK at 180°/s	76.52 ± 22.28	84.52 ± 11.30	1.19 ± 0.43	1.21 ± 0.29	1.54 ± 0.28	1.42 ± 0.25
	AVG at 180°/s	73.28 ± 21.15	83.72 ± 11.23	1.03 ± 0.41	1.07 ± 0.25	1.38 ± 0.29	1.28 ± 0.23
	Isometric at 90°	59.12 ± 26.28	64.62 ± 17.62	1.29 ± 0.61	1.53 ± 0.46	2.47 ± 1.54	2.38 ± 0.45
Follow-up #1	PK at 90°/s	88.78 ± 34.45	82.48 ± 13.68	1.74 ± 0.46	1.66 ± 0.32	2.05 ± 0.44	2.02 ± 0.27
	AVG at 90°/s	89.14 ± 34.97	83.20 ± 11.32	1.62 ± 0.47	1.55 ± 0.28	1.90 ± 0.43	1.86 ± 0.22
	PK at 180°/s	81.13 ± 28.55	84.72 ± 11.53	1.33 ± 0.47	1.29 ± 0.24	1.64 ± 0.26	1.52 ± 0.15
	AVG at 180°/s	79.88 ± 28.58	83.58 ± 8.96	1.20 ± 0.44	1.12 ± 0.18	1.50 ± 0.27	1.35 ± 0.14
	Isometric at 90°	77.32 ± 37.71	68.95 ± 7.72	1.59 ± 0.61	1.50 ± 0.15	2.40 ± 1.25	2.19 ± 0.30
Follow-up #2	PK at 90°/s	78.88 ± 29.36	81.23 ± 15.41	1.63 ± 0.46	1.62 ± 0.32	2.16 ± 0.52	2.00 ± 0.25
	AVG at 90°/s	80.58 ± 32.23	80.64 ± 12.51	1.53 ± 0.44	1.46 ± 0.21	2.01 ± 0.51	1.82 ± 0.25
	PK at 180°/s	81.78 ± 28.16	89.30 ± 17.02	1.34 ± 0.42	1.29 ± 0.23	1.68 ± 0.28	1.46 ± 0.19
	AVG at 180°/s	82.37 ± 25.51	90.09 ± 14.98	1.24 ± 0.39	1.16 ± 0.20	1.52 ± 0.27	1.30 ± 0.17
	Isometric at 90°	69.53 ± 24.46	76.34 ± 7.89	1.65 ± 0.83	1.44 ± 0.11	2.55 ± 1.36	1.91 ± 0.26
ΔFollow-up #1 – Baseline	PK at 90°/s	25.69 ± 21.99	0.50 ± 5.26	0.42 ± 0.29	0.05 ± 0.16	-0.09 ± 0.21	0.04 ± 0.08
	AVG at 90°/s	25.52 ± 22.66	-0.35 ± 8.75	0.42 ± 0.31	0.06 ± 0.15	-0.06 ± 0.21	0.06 ± 0.10
	PK at 180°/s	4.61 ± 15.36	0.20 ± 6.93	0.14 ± 0.23	0.09 ± 0.12	0.10 ± 0.06	0.10 ± 0.12
	AVG at 180°/s	6.59 ± 22.23	-0.13 ± 4.24	0.16 ± 0.30	0.05 ± 0.11	0.12 ± 0.09	0.07 ± 0.09
	Isometric at 90°	18.21 ± 38.94	4.32 ± 17.19	0.30 ± 0.33	-0.03 ± 0.32	-0.07 ± 0.47	-0.19 ± 0.25
ΔFollow-up #2 – Baseline	PK at 90°/s	15.79 ± 16.39	-0.74 ± 4.68	0.32 ± 0.19	0.01 ± 0.15	0.02 ± 0.23	0.03 ± 0.13
	AVG at 90°/s	16.97 ± 20.11	-2.91 ± 5.49	0.33 ± 0.22	-0.03 ± 0.14	0.05 ± 0.27	0.02 ± 0.16
	PK at 180°/s	5.26 ± 18.39	4.78 ± 7.71	0.15 ± 0.21	0.09 ± 0.16	0.12 ± 0.09	0.04 ± 0.15
	AVG at 180°/s	9.08 ± 20.16	6.37 ± 6.66	0.21 ± 0.22	0.09 ± 0.14	0.14 ± 0.05	0.02 ± 0.14
	Isometric at 90°	10.41 ± 26.30	11.72 ± 24.88	0.36 ± 0.37	-0.08 ± 0.43	0.08 ± 0.37	-0.47 ± 0.44

Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; SD, standard deviation; PK, peak knee extension torque; AVG, average peak knee extension torque

Table 2.4. Knee extension strength deficits by group and time

LSI Measure	Timepoint	Mean ± SD			Mean Difference (SE)	p-value
		Total	LL-BFRT	Control		
Peak Torque for 90 °/s (%)	Baseline	27.47 ± 17.88	36.91 ± 17.70	18.03 ± 13.52	18.88 (9.96)	0.095
	Follow-up #1	14.37 ± 24.93	11.22 ± 34.45	17.52 ± 13.68	-6.30 (16.58)	0.719
	Follow-up #2	19.95 ± 22.14	21.12 ± 29.36	18.77 ± 15.41	2.35 (14.83)	0.878
Average Peak Torque for 90 °/s (%)	Baseline	26.42 ± 19.79	36.39 ± 19.52	16.45 ± 15.88	19.94 (11.25)	0.114
	Follow-up #1	13.83 ± 24.70	10.86 ± 34.97	16.79 ± 11.32	-5.93 (16.44)	0.733
	Follow-up #2	19.39 ± 23.05	19.42 ± 32.23	19.36 ± 12.51	0.05 (15.46)	0.997
Peak Torque for 180 °/s (%)	Baseline	19.48 ± 17.18	23.48 ± 22.28	15.47 ± 11.30	8.00 (11.17)	0.494
	Follow-up #1	17.07 ± 20.62	18.87 ± 28.55	15.28 ± 11.53	3.59 (13.77)	0.801
	Follow-up #2	14.46 ± 22.29	18.22 ± 28.16	10.70 ± 17.02	7.52 (14.71)	0.623
Average Peak Torque for 180 °/s (%)	Baseline	21.50 ± 16.88	26.72 ± 21.15	16.28 ± 11.23	10.44 (10.71)	0.358
	Follow-up #1	18.27 ± 20.06	20.12 ± 28.58	16.41 ± 8.96	3.71 (13.39)	0.789
	Follow-up #2	13.77 ± 20.14	17.63 ± 25.51	9.91 ± 14.98	7.72 (13.22)	0.575
Peak Torque for Isometric (%)	Baseline	38.13 ± 21.29	40.88 ± 26.28	35.38 ± 17.62	5.51 (14.15)	0.707
	Follow-up #1	26.87 ± 26.04	22.68 ± 37.71	31.05 ± 7.72	-8.38 (17.22)	0.640
	Follow-up #2	27.06 ± 17.51	30.47 ± 24.46	23.66 ± 7.89	6.81 (11.49)	0.570

Abbreviations: LSI, limb symmetry index; LL-BFRT, low load exercise with blood flow restriction therapy; SD, standard deviation; SE, standard error

Table 2.5. Separate RM-ANCOVAs: Limb Symmetry Index for knee extension strength by group and time

	LSI Measure	Source	F statistic	p-value	η^2_p
Within Subjects Effects	Peak Torque for 90 °/s (%)	Time	0.02	0.902	0.00
		Time*Baseline value	0.10	0.765	0.01
		Time*Group	2.69	0.145	0.28
	Average Peak Torque for 90 °/s (%)	Time	0.36	0.570	0.05
		Time*Baseline value	0.00	0.998	0.00
		Time*Group	1.64	0.241	0.19
	Peak Torque for 180 °/s (%)	Time	0.01	0.931	0.00
		Time*Baseline value	0.01	0.927	0.00
		Time*Group	0.45	0.525	0.06
	Average Peak Torque for 180 °/s (%)	Time	0.02	0.892	0.00
		Time*Baseline value	0.05	0.838	0.01
		Time*Group	0.50	0.502	0.07
	Peak Torque for Isometric (%)	Time	1.19	0.312	0.15
		Time*Baseline value	1.35	0.284	0.16
		Time*Group	3.70	0.096	0.35
Between Subjects Effects	Peak Torque for 90 °/s (%)	Baseline value	19.79	0.003*	0.74
		Group	7.13	0.032*	0.50
	Average Peak Torque for 90 °/s (%)	Baseline value	10.99	0.013*	0.61
		Group	3.98	0.086	0.36
	Peak Torque for 180 °/s (%)	Baseline value	15.41	0.006*	0.69
		Group	0.10	0.758	0.01
	Average Peak Torque for 180 °/s (%)	Baseline value	6.59	0.037*	0.48
		Group	0.09	0.774	0.01
	Peak Torque for Isometric (%)	Baseline value	0.34	0.580	0.05
		Group	0.02	0.899	0.00

** Statistically significant at $p \leq 0.05$*
Abbreviations: RM-ANCOVA, repeated measures analysis of covariance; LSI, limb symmetry index

Table 2.6. Pairwise Comparisons: Limb Symmetry Index for knee extension strength

LSI Measure	Comparison (Mean (SE))			Mean Difference (SE)	p-value	95% CI
	LL-BFRT		Control			
Peak Torque for 90 °/s (%)	96.50 (6.65)	-	69.18 (6.65)	27.32 (10.23)	0.032*	3.12 – 51.51
Average Peak Torque for 90 °/s (%)	95.83 (8.17)	-	70.95 (8.17)	24.89 (12.47)	0.086	-4.60 – 54.38
Peak Torque for 180 °/s (%)	85.62 (6.01)	-	82.85 (6.01)	2.77 (8.64)	0.758	-17.65 – 23.20
Average Peak Torque for 180 °/s (%)	85.57 (7.32)	-	82.39 (7.32)	3.18 (10.64)	0.774	-21.98 – 28.35
Peak Torque for Isometric (%)	74.01 (10.37)	-	72.06 (10.37)	1.95 (14.73)	0.899	-32.89 – 36.78

** Statistically significant at $p \leq 0.05$*
Abbreviations: LSI, limb symmetry index; LL-BFRT, low load exercise with blood flow restriction therapy; SE, standard error; CI, confidence interval

Table 2.7. Separate RM-ANCOVAs: Involved limb knee extension strength by group and time

	Strength Measure	Source	F statistic	p-value	η^2_p
Within Subjects Effects	Peak Torque for 90 °/s (Nm/kg)	Time	0.98	0.355	0.12
		Time*Baseline value	0.53	0.488	0.07
		Time*Group	0.07	0.799	0.01
	Average Peak Torque for 90 °/s (Nm/kg)	Time	0.05	0.825	0.01
		Time*Baseline value	0.03	0.867	0.00
		Time*Group	0.00	0.985	0.00
	Peak Torque for 180 °/s (Nm/kg)	Time	0.66	0.443	0.09
		Time*Baseline value	0.64	0.450	0.08
		Time*Group	0.02	0.900	0.00
	Average Peak Torque for 180 °/s (Nm/kg)	Time	0.05	0.832	0.01
		Time*Baseline value	0.01	0.931	0.00
		Time*Group	0.01	0.908	0.00
	Peak Torque for Isometric (Nm/kg)	Time	1.15	0.319	0.14
		Time*Baseline value	1.32	0.288	0.16
		Time*Group	1.06	0.337	0.13
Between Subjects Effects	Peak Torque for 90 °/s (Nm/kg)	Baseline value	22.60	0.002*	0.76
		Group	6.34	0.040*	0.48
	Average Peak Torque for 90 °/s (Nm/kg)	Baseline value	13.97	0.007*	0.67
		Group	4.84	0.064	0.41
	Peak Torque for 180 °/s (Nm/kg)	Baseline value	24.68	0.002*	0.78
		Group	0.24	0.641	0.03
	Average Peak Torque for 180 °/s (Nm/kg)	Baseline value	14.05	0.007*	0.67
		Group	0.73	0.422	0.09
	Peak Torque for Isometric (Nm/kg)	Baseline value	10.90	0.013*	0.61
		Group	2.09	0.191	0.23

** Statistically significant at $p \leq 0.05$*
Abbreviations: RM-ANCOVA, repeated measures analysis of covariance

Table 2.8. Pairwise Comparisons: Involved limb knee extension strength

Strength Measure	Comparison (Mean (SD)) LL-BFRT		Control	Mean Difference (SE)	p-value	95% CI
Peak Torque for 90 º/s (Nm/kg)	1.84 (0.10)	-	1.48 (0.10)	0.36 (0.14)	0.040*	0.02 – 0.71
Average Peak Torque for 90 º/s (Nm/kg)	1.72 (0.11)	-	1.36 (0.11)	0.35 (0.16)	0.064	-0.03 – 0.73
Peak Torque for 180 º/s (Nm/kg)	1.34 (0.08)	-	1.29 (0.08)	0.05 (0.11)	0.641	-0.21 – 0.32
Average Peak Torque for 180 º/s (Nm/kg)	1.24 (0.09)	-	1.13 (0.09)	0.11 (0.12)	0.422	-0.19 – 0.40
Peak Torque for Isometric (Nm/kg)	1.71 (0.16)	-	1.38 (0.16)	0.32 (0.22)	0.191	-0.20 – 0.85

** Statistically significant at $p \leq 0.05$*
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; SD, standard deviation; SE, standard error; CI, confidence interval

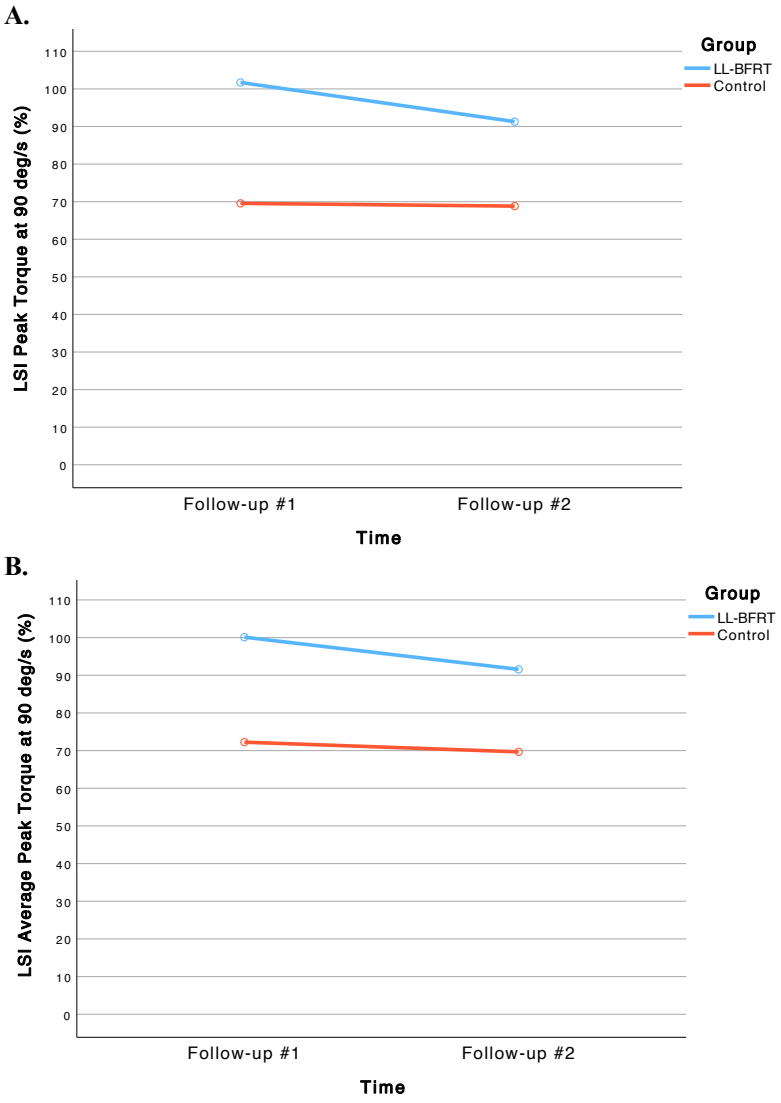
Table 2.9. Improvements in knee extension strength deficits by time

LSI Variable	Achieved > 10% Improvement (*no.* / *total no. (%)*) ΔFollow-up #1 – Baseline LL-BFRT	Control	Relative Risk	ΔFollow-up #2 – Baseline LL-BFRT	Control	Relative Risk
Peak Torque for 90 º/s	3/5 (60)	0/5 (0)	NC	5/5 (100)	0/5 (0)	NC
Average Peak Torque for 90 º/s	4/5 (80)	1/5 (20)	4	5/5 (100)	1/5 (20)	5
Peak Torque for 180 º/s	1/5 (20)	1/5 (20)	1	2/5 (40)	1/5 (20)	2
Average Peak Torque for 180 º/s	1/5 (20)	0/5 (0)	NC	2/5 (40)	1/5 (20)	2
Peak Torque for Isometric	3/5 (60)	2/5 (40)	1.5	4/5 (80)	1/5 (20)	4

Abbreviations: LSI, limb symmetry index; LL-BFRT, low load exercise with blood flow restriction therapy; NC, not computable

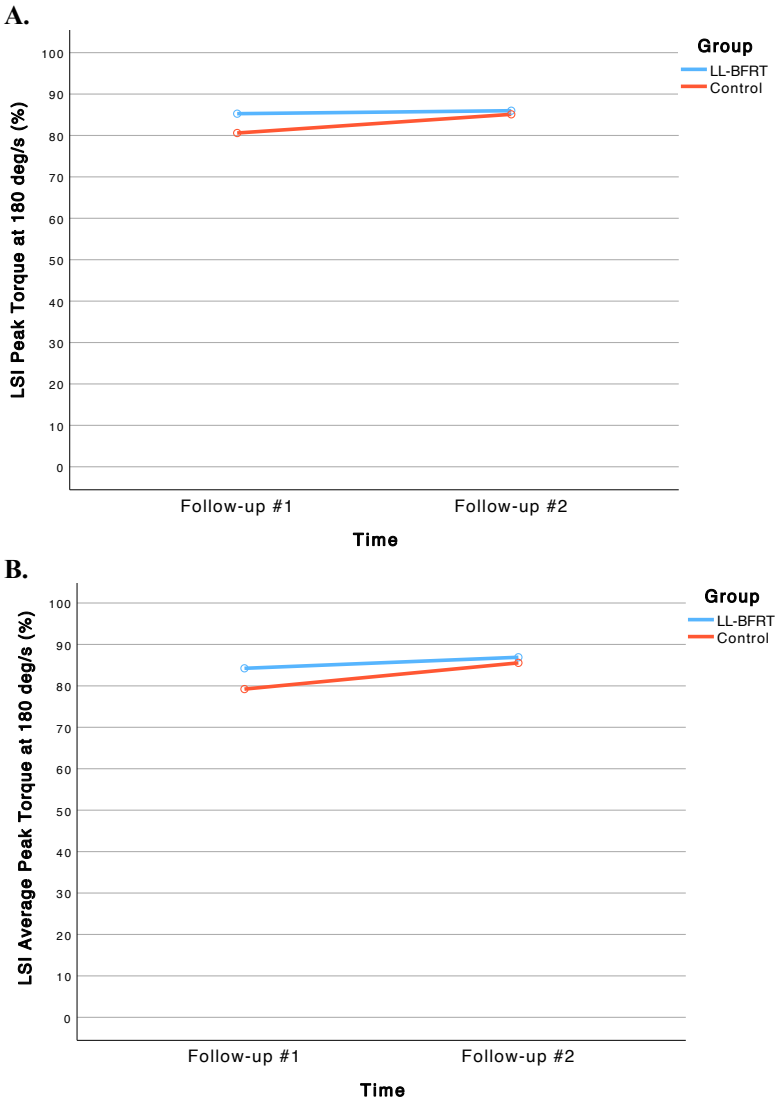
Figures

Figure 2.1. Limb symmetry index for isokinetic strength testing at 90 °/s ([A] peak knee extension torque, [B] average peak knee extension torque) by group and time controlling for baseline values.



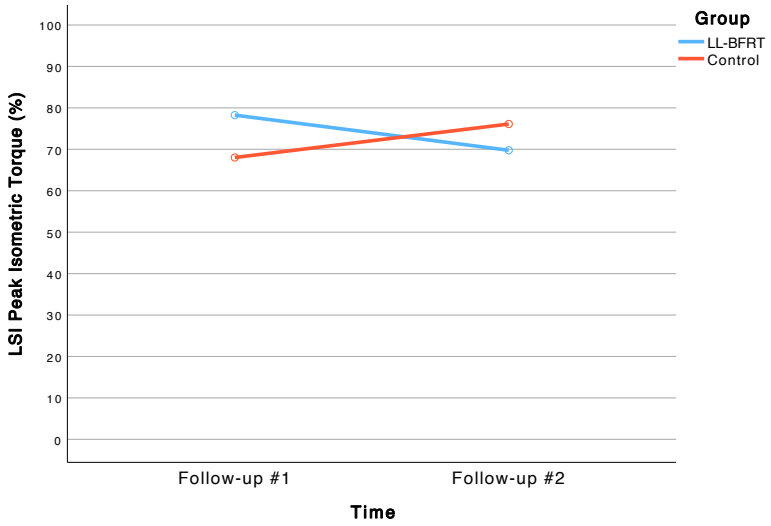
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LSI, limb symmetry index

Figure 2.2. Limb symmetry index for isokinetic strength testing at 180 °/s ([A] peak knee extension torque, [B] average peak knee extension torque) by group and time controlling for baseline values.



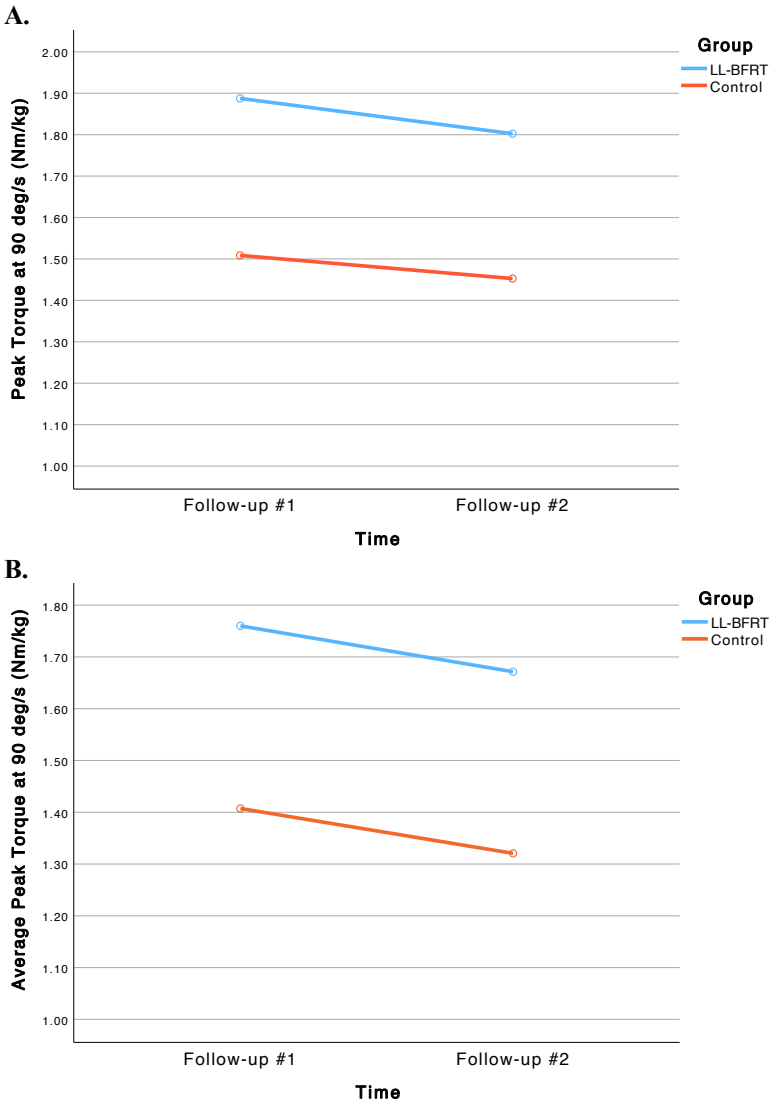
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LSI, limb symmetry index

Figure 2.3. Limb symmetry index for peak knee extension torque during isometric strength testing at 90 º of knee flexion by group and time controlling for baseline values.



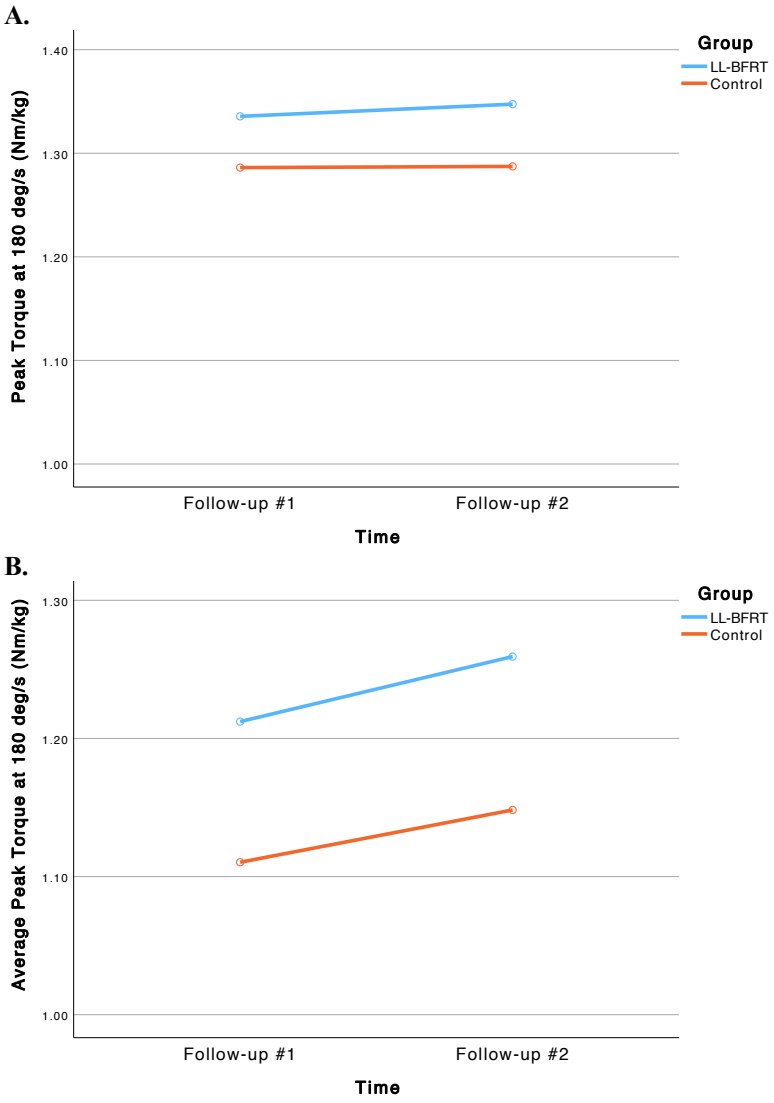
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; LSI, limb symmetry index

Figure 2.4. Involved limb knee extension strength for isokinetic testing at 90 °/s ([A] peak knee extension torque, [B] average peak knee extension torque) by group and time controlling for baseline values.



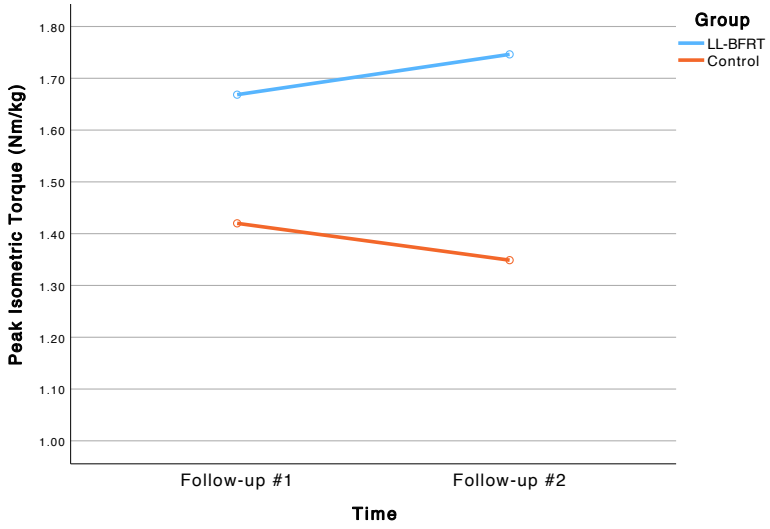
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy

Figure 2.5. Involved limb knee extension strength for isokinetic testing at 180 °/s ([A] peak knee extension torque, [B] average peak knee extension torque) by group and time controlling for baseline values.



Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy

Figure 2.6. Involved limb knee extension strength for isometric testing at 90 º of knee flexion by group and time controlling for baseline values.



Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy

MANUSCRIPT III:

PSYCHOLOGICAL RESPONSES TO BLOOD FLOW RESTRICTION THERAPY IN PATIENTS FOLLOWING ANTERIOR CRUICIATE LIGAMENT RECONSTRUCTION

Abstract

Background: Following anterior cruciate ligament reconstruction (ACLR), many individuals suffer from persistent physiological and psychological limitations despite participation in traditional post-surgical rehabilitation. Therefore, exploring the utilization of complementary interventions, such as low load exercise with blood flow restriction therapy (LL-BFRT), to address both the physical and psychological components of recovery could improve the rehabilitative process in this patient population. **Purpose:** To explore the effects of LL-BFRT on patient reported outcome measures (PROMs) in patients with quadriceps strength deficits following ACLR compared to a control condition. **Study Design:** Exploratory pilot study. **Methods:** Ten female participants with quadriceps strength deficits following an ACLR were enrolled in this exploratory pilot study (LL-BFRT (n=5): age= 23.52±9.16 years, height= 166.85±4.12 cm, mass= 69.38±10.35 kg, time since surgery (TSS)= 16.31±16.86 months; Control (n=5): age= 21.88±3.91 years, height= 166.24±8.06 cm, mass= 69.13±11.64 kg, TSS= 48.03±41.34 months). Participants were recruited via convenience sampling and randomly allocated into either the control group or LL-BFRT group. During the baseline assessment, participants completed several PROMs including the International Knee Documentation Committee (IKDC) Subjective Knee Evaluation, Knee Injury and Osteoarthritis Outcome Score (KOOS), Tampa Scale for Kinesiophobia (TSK), and Anterior Cruciate Ligament – Return to Sport Index (ACL-RSI). Individuals randomized into the LL-BFRT group completed 2 supervised sessions of LL-BFRT each week for a total of 4 weeks. Participants were instructed to perform 4 sets (30x15x15x15 repetitions) of 5 unilateral exercises (i.e., knee extension, hamstring curl, hip abduction, hip extension, and leg press) under 60 % limb occlusion pressure and 20-40 % of their predicted one repetition maximum.

All participants returned for two follow-up assessments after finishing the intervention and completed each PROM as well as the Global Rating of Change (GRoC) scale. Separate 2X2 repeated measures analyses of variance (RM-ANOVA) were used to explore differences in change scores for the sum of each questionnaire between groups and across time. The clinical significance of these changes was also evaluated by examining the proportion of participants per group that met or exceeded the minimally clinically important difference (MCID) for each respective PROM. **Results:** Compared to participants in the control group, those treated with LL-BFRT experienced significant improvements on the GRoC scale as well as the pain and quality of life subscales of the KOOS (Mean Difference [MD], 95 % Confidence Interval [CI]; GRoC: MD = 4.50, [2.35, 6.65], $KOOS_{pain}$: MD = 7.78, [0.69, 14.87], $KOOS_{QoL}$: MD = 16.25, [3.36, 29.14]). Additionally, over half of the participants in the LL-BFRT group met or exceeded the MCID for the ACL-RSI, TSK, IKDC, as well as the sport and quality of life subscales of the KOOS. **Conclusions:** Compared to a control condition, individuals treated with LL-BFRT reported substantial improvements in the overall condition of their involved limb, decreases in knee-related pain and fear of reinjury, and increases in psychological readiness and knee-related quality of life. Therefore, LL-BFRT may be an effective treatment intervention for improving the psychological components of recovery in patients with significant quadriceps strength deficits following ACLR.

Introduction

Although assessments regarding an individual's physical abilities (i.e., strength and functional performance) often dominate the return to sport evaluation following anterior cruciate ligament (ACL) injury, psychological characteristics are critical factors to consider when examining an individual's response to injury and readiness for unrestricted physical activity following an ACL reconstruction (ACLR). Subjective factors including fear of reinjury, unsatisfactory knee function, and lack of knee confidence have been identified as barriers for the return to physical activity and sport following ACLR.[1] In a recent systematic review evaluating the available evidence regarding the psychological factors related to return to play after ACLR, there was only a 63.4 % rate of return to play in patients post-ACLR and 36.6 % of those that did return to play could not perform at their pre-injury level of sport participation.[1] For patients that did not return to play, 64.7 % reported a psychological reason for their lack of return to play including fear of reinjury (76.7 %), lack of confidence in their reconstructed knee (14.8 %), depression (5.6 %), and lack of interest or motivation (2.5 %).[1] On a similar note, fear of re-injury has also been found to be the highest rated barrier for adherence to rehabilitation in patients post-ACLR, thus further highlighting the importance of considering the psychological aspects of a patient's recovery throughout the rehabilitative process (i.e., preoperatively, immediate postoperatively, early recovery, mid recovery, late recovery).[2]

Given their significant contribution to return to sport decision making, the relationship between muscle function (i.e., quadriceps strength) and patient reported outcome measures (PROMs) has started to be explored. Direct relationships have been identified between various psychological limitations and persistent quadriceps weakness in patients

post-ACLR.[3,4] It has been reported that individuals with International Knee Documentation Committee (IKDC) Subjective Knee Evaluation scores greater than or equal to 90 are 3 times more likely to present with a limb symmetry index (LSI) for quadriceps strength of 90 % or greater.[3] However, quadriceps strength normalized to body mass has been suggested as a stronger predictor of self-reported knee function when compared to LSI in an ACLR population.[5,6] Additionally, a study by Lepley et al[4] found significant associations between decreased quadriceps strength and lower self-reported knee function, psychological readiness to return to sport, and emotional response to injury in patients returning to unrestricted physical activity after ACLR. Therefore, exploring interventions that may address both the physical and psychological components of recovery could potentially improve short- and long-term outcomes in this patient population.

Low load exercise with blood flow restriction therapy (LL-BFRT) has been primarily explored as a complementary rehabilitative approach for enhancing muscle function in various patient populations including those post-ACLR.[7–10] This treatment technique incorporates the application of an external restrictive device (i.e., pneumatic tourniquet cuff, band, or strap) to partially occlude arterial blood flow and completely occlude venous blood flow to and from distal musculature, typically while an individual performs low intensity exercise (i.e., 20-40 % 1-repetition maximum).[11] Compared to traditional high load resistance exercise (i.e., >70 % 1-repetition maximum) that is reliant on the production of mechanical tension for inducing improvements in muscle strength and hypertrophy,[12,13] LL-BFRT has been shown to elicit comparable benefits while minimizing the amount of stress imposed on the targeted joints and surrounding structures by increasing metabolic stress (i.e., lactate,

hydrogen ions, inorganic phosphate) as a result of prolonged tourniquet cuff application during exercise.[14,15]

Although the physiological effects of LL-BFRT have been the primary area of research focus in patients post-ACLR, recent studies have also begun to investigate the effects of LL-BFRT for improving common PROMs in patients following various knee-related surgical interventions.[16] Beginning 2 weeks following a nonreconstructive knee arthroscopy, Tennent et al[17] explored the physical and psychological effects of 12 sessions of supervised physical therapy with and without blood flow restriction therapy (BFRT). The results of this study found significant improvements for all subscales of the Knee Injury and Osteoarthritis Outcome Score (KOOS) as well as the physical component of the Veterans RAND 12-Item Health Survey (VR-12) in both the BFRT and conventional therapy groups.[17] However, significant improvements in the mental component of the VR-12 were only identified in the BFRT group.[17] Similarly, compared to traditional high load resistance training, Hughes et al[18] found significantly greater increases in IKDC, Lower Extremity Function Scale (LEFS), Lysholm Knee-Scoring Scale (LKSS), and KOOS subscale scores in patients treated with 16 sessions of BFRT starting 2 weeks following an ACLR. While the aforementioned studies have provided promising results regarding the effects of LL-BFRT when implemented in the early recovery phase following knee surgery, the overall psychological impact of LL-BFRT has not yet been fully investigated in patients with persistent quadriceps weakness in the mid to late stages of recovery after ACLR.

Gaining a better understanding of the physiological and psychological responses to LL-BFRT is critical for evaluating its various potential benefits in an ACLR population. Therefore, the primary aim of this study was to explore the effects of LL-BFRT on PROMs

in patients with quadriceps strength deficits following an ACLR compared to a control condition. Additionally, we secondarily aimed to evaluate the relationship between changes in quadriceps strength and changes in PROMs.

Methods

Study Design

The psychological influence of LL-BFRT in patients post-ACLR was examined using an exploratory pilot study design. The independent variable was the intervention group (i.e., LL-BFRT vs. control). The dependent variables included self-reported knee function and knee-related symptomology/pain as measured by the IKDC and KOOS, kinesiophobia as measured by the Tampa Scale for Kinesiophobia (TSK), psychological readiness as measured by the Anterior Cruciate Ligament – Return to Sport Index (ACL-RSI), and patient perceived change in the overall condition of their injured limb as measured by the Global Rating of Change (GRoC) scale.

Participants

Potential participants were recruited for this study via convenience sampling through the distribution of fliers and study information sheets across the local university, surrounding community, and associated health system. In order to be eligible for participation, individuals were required to be between 15-64 years of age and at least 3 months post-ACLR. Individuals also had to report being diagnosed with a unilateral ACLR and present with a LSI of less than 80% for isokinetic or isometric knee extension strength at their baseline assessment. Exclusion criteria included graft failure or any surgical complications, history or

current diagnosis of any cardiovascular, metabolic, or neurological disorders, currently using anti-coagulant medication, known pregnancy, malignancy, serious infection near the lower limb, muscular abnormalities, or formal experience with LL-BFRT during their traditional post-surgical rehabilitation program. The study was approved by the University of Virginia's Institutional Review Board for Health Sciences Research (IRB-HSR#210507), and all participants provided written, informed consent.

Fourteen participants provided informed consent for participation in this exploratory pilot study. However, four participants were excluded from continued participation as they exceeded the 80% LSI threshold on each of our knee extension strength assessments during their baseline session. Therefore, ten female participants were formally enrolled in this study (LL-BFRT (n=5): age= 23.52±9.16 years, height= 166.85±4.12 cm, mass= 69.38±10.35 kg, time since surgery (TSS)= 16.31±16.86 months; Control (n=5): age= 21.88±3.91 years, height= 166.24±8.06 cm, mass= 69.13±11.64 kg, TSS= 48.03±41.34 months). Detailed participant demographic information is presented in Table 3.1 as well as Additional Results Table D2.1, D2.2, and D2.3.

Instrumentation – Patient Reported Outcome Measures

IKDC

Changes in subjectively reported knee symptomology, function, and sports activity after ACLR were measured using the IKDC.[19] This 18 item questionnaire included three primary domains: 1) symptoms (i.e., pain, stiffness, swelling, locking/catching, and giving way), 2) sports and daily activities, and 3) current knee function and knee function prior to injury.[19] Individual items were scored using an ordinal method with a possible total score of

0-100, where a total score of 0 indicated high symptoms and low function, and a total score of 100 indicated no symptoms and no limitations with activities of daily living or sport-related activities.[20] The IKDC has been shown to be both reliable and valid in patients post-ACLR.[20]

KOOS

The KOOS was utilized to evaluate a patient's opinions regarding the health of their knee as well as any short-term or long-term knee-related problems.[20,21] This questionnaire included 42 items across 5 subscales of symptoms, pain, activities of daily living, sport and recreation, and knee-related quality of life.[21] Each item was scored from 0-4 and each subscale was separately scored from 0-100 based on the sum of its corresponding items, where 0 indicated extreme knee-related problems and 100 indicated no knee-related problems. This scale has demonstrated good validity and reliability in an ACLR population.[20,21]

TSK

Fear of movement (i.e., kinesiophobia) and reinjury as well as fear avoidance was quantified using the full version of the TSK.[22] Individual scores on the TSK ranged from 1-4 and total scores ranged from 17-68 with higher scores suggesting increased degrees of kinesiophobia.[22,23] Patients are considered to suffer from kinesiophobia if their total score is greater than 37.[24] However, this PROM has not yet been validated in an ACLR patient population.

ACL-RSI

Psychological readiness (i.e., emotions, confidence in performance, and risk appraisal) associated with the return to sport and physical activity after ACLR was measured

using the ACL-RSI. This tri-component questionnaire was comprised of 12 items with scores ranging from 1-10. Total scores were calculated by adding the values from each individual item and calculating their relationship to 100. This scale has been shown to have acceptable reliability and validity.[25]

GRoC

The clinical change perceived by participants following the intervention timeframe was evaluated using the GRoC scale.[26] This scale asked participants to respond to the following statement, "With respect to your ACL injury, please rate the overall condition of your injured limb from the time that you began this study until now". Participants were prompted to respond to this statement on a scale from +7 (i.e., a very great deal better) to -7 (i.e., a very great deal worse).

Procedures

Baseline Assessment

Prior to beginning baseline assessment procedures, participants were randomly allocated into either the control group or LL-BFRT group. Participants then completed several PROMs including a general health history questionnaire, injury history questionnaire, Tegner Activity Scale, International Physical Activity Questionnaire (IPAQ) Short Form, ACL-RSI, TSK, IKDC, and KOOS. Bilateral assessment of the quadriceps muscles was then performed including isokinetic and isometric measures of muscle strength (as described in Manuscript II). For those in the LL-BFRT group, one-repetition maximum (1RM) testing and intervention familiarization was completed at the end of the baseline visit. To determine appropriate exercise loading, an individual's 1RM was predicted for each exercise by

assessing their five-repetition maximum (5RM) following a modified version of the National Strength and Conditioning Association's 1RM testing protocol and 1RM estimation table.[27]

LL-BFRT Program

Participants allocated to the LL-BFRT group then completed 2 sessions of LL-BFRT each week for a total of 4 weeks. During these sessions participants were instructed to perform 5 exercises under LL-BFRT using only their involved surgical limb including knee extension, hamstring curl, hip abduction, hip extension, and leg press. Participants performed 4 sets of each exercise at an initial estimated 30 % of their predetermined 1RM. Each exercise began with one set of 30 repetitions followed by 3 sets of 15 repetitions completed at an approximate execution speed of 2s concentric:eccentric. Thirty seconds of rest was provided following each set of exercise, and 2 minutes of rest was provided at the end of each exercise type. Following each exercise participants were asked to rate their level of perceived exertion (RPE) from no effort (0) to maximal effort (10) using the Borg scale in order to gauge exercise intensity and guide progression.[28] The amount of weight utilized during each exercise was modified at the start of each session based on the individuals reported RPE from the previous session. With the goal of achieving an RPE of at least 7 during each exercise, weight was either increased or maintained to ensure optimal exercise difficulty.

At the start of each exercise session, participants completed a 5-minute self-selected warm-up on a stationary bike. After a period of rest, a skin protection sleeve and Easi-Fit Tourniquet Cuff (Delfi Medical Innovations Inc.) were applied to the most proximal portion of the participant's involved thigh. To determine an individual's personalized tourniquet pressure, participants were first asked to lay in a relaxed, supine position while an automated

pneumatic tourniquet system (Delfi Personalized Tourniquet System II, Delfi Medical Vancouver, BC) inflated to their total limb occlusion pressure (LOP). The cuff was then inflated to 60 % of this LOP during exercise and was only deflated during rest between each type of exercise.

Weekly Physical Activity

The type and amount of physical activity participants performed during the intervention timeframe was measured using an online IPAQ Short Form.[29] The overall amount of physical activity was calculated as the number of MET-minutes per week using the following formula:

$$\boldsymbol{MET\text{-}min/week} = [(\mathbf{3.3} * \boldsymbol{walking\ minutes} * \boldsymbol{walking\ days}) + (\mathbf{4.0} * \boldsymbol{moderate\ intensity\ activity\ minutes} * \boldsymbol{moderate\ days}) + (\mathbf{8.0} * \boldsymbol{vigorous\ intensity\ activity\ minutes} * \boldsymbol{vigorous\ intensity\ days})]$$

Follow-Up Assessments

All participants returned for two additional follow-up assessments after the completion of the intervention timeframe. The first follow-up assessment was conducted within one week of completing the intervention and the second follow-up assessment was conducted at least one month following the completion of the intervention. During each of these assessments all baseline measures were reassessed including the aforementioned PROMs as well as the GRoC scale.

Data Processing

The amount of change in each PROM was calculated as the difference between scores reported at baseline and each post-intervention follow-up assessment (i.e., follow-up #1 – baseline and follow-up #2 – baseline). To explore the clinical importance of any treatment benefits sustained following LL-BFRT, participant's change scores were classified based on whether or not they met the minimally clinically important difference (MCID) threshold established for each PROM. These thresholds aim to represent the smallest amount of change needed for the patient to perceive the change as clinically important.[30] As suggested by previous literature investigating the MCID for each PROM in an ACLR population, the following MCID thresholds were utilized in this study: an increase of ≥ 9 points on the IKDC,[31,32] an increase of ≥ 8-10 points on the KOOS,[33,34] and an increase of ≥ 10 points on the ACL-RSI.[35] Although no MCID threshold has been established for the full 17-item TSK in this patient population, a decrease of ≥ 6 points was considered clinically valuable based on previous research investigating the responsiveness of the TSK in patients after 4 weeks of cognitive-behavioral rehabilitation following a lumbar fusion.[36] Similarly, while not established in an ACLR population, the MCID threshold for the GRoC scale was set to an increase or decrease of ≥ 5 points based on findings from previous research.[37]

Statistical Analyses

Statistical analyses were completed using IBM Statistics (v28.0.1.1, SPSS, Inc. Chicago, IL, USA) and R (RStudio Inc., v2022.07.0). Initially, between group differences in participant's demographic information (i.e., age, height, mass, physical activity, and time since surgery) and baseline values for the sum score of each PROM questionnaire were examined using independent samples t-tests. Given no significant differences between groups

at baseline, separate 2X2 repeated measures analyses of variance (RM-ANOVA) were used to explore differences in change scores for the sum of each questionnaire (e.g., IKDC, ACL-RSI, TSK, KOOS, GRoC) between groups and across time (i.e., follow-up #1, follow-up #2). Effect size was calculated to evaluate the magnitude of significant findings using partial eta squared statistics (η_p^2) and interpreted as small (0.01), medium (0.06), or large (0.14). The clinical significance of changes in each PROM were evaluated by examining the proportion of participants per group that met or exceeded the previously described MCID for each respective PROM. Additionally, to explore the potential relationship between improvements in physical and psychological outcome measures in this patient population, Pearson correlations were calculated between changes in each PROM and changes in involved limb quadriceps strength and limb symmetry as reported in Manuscript II. Alpha was set a priori to 0.05 for all analyses.

Results

Participant's demographic information, group based physical activity per week, mean PROM sum scores by group and time, and change scores for each PROM are presented in Table 3.1, Table 3.2, Table 3.3, and Table 3.4, respectively. With the exception of pre-surgical Tegner activity level, no significant between group differences were found for any of the demographic variables or baseline sum scores for each PROM. Due to inaccurate reporting, the amount of physical activity completed by one participant in the LL-BFRT group during week 2 of the intervention was excluded from analysis.

Change Scores for PROMs

Overall results of the separate 2X2 RM-ANOVAs are reported in Table 3.5. A significant interaction was found between group and time for changes on the IKDC ($F = 6.99$, $p = 0.030$, $\eta_p^2 = 0.47$) (Table 3.5). This interaction indicated that while participants in the control group experienced insignificant decreases for change scores on the IKDC over time, participants in the LL-BFRT group presented with significantly greater increases in IKDC change scores from follow-up #2 to baseline compared to follow-up #1 to baseline (Figure 3.1, Table 3.6). No other significant interactions were noted.

When examining between-subjects effects for group, significant between group differences were identified for changes on the GRoC scale ($F = 23.28$, $p = 0.001$, $\eta_p^2 = 0.74$; Figure 3.2) as well as the pain ($F = 6.40$, $p = 0.035$, $\eta_p^2 = 0.44$; Figure 3.3) and quality of life ($F = 8.45$, $p = 0.020$, $\eta_p^2 = 0.51$; Figure 3.3) subscales of the KOOS (Table 3.5). Subsequent post-hoc pairwise comparisons revealed significantly greater improvements on each of the aforementioned PROMs for participants in the LL-BFRT group compared to those in the control group (GRoC: MD = 4.50, [2.35, 6.65], $KOOS_{pain}$: MD = 7.78, [0.69, 14.87], $KOOS_{QoL}$: MD = 16.25, [3.36, 29.14]) (Table 3.7). No significant between group differences were found for changes on the ACL-RSI (Figure 3.4), TSK (Figure 3.5), IKDC (Figure 3.1), or the remaining subscales of the KOOS (Figure 3.3).

In terms of main effects for time, significant findings were identified for changes on the GRoC scale ($F = 7.36$, $p = 0.027$, $\eta_p^2 = 0.48$; Figure 3.2), TSK ($F = 6.25$, $p = 0.037$, $\eta_p^2 = 0.44$; Figure 3.5), and IKDC ($F = 5.35$, $p = 0.049$, $\eta_p^2 = 0.40$; Figure 3.1) (Table 3.5). Post hoc pairwise comparisons highlighted continued improvements on each of these outcome measures from follow-up #1 to follow-up #2 (Mean Difference [MD], 95 % Confidence

Interval [CI]; GRoC: MD = 0.90, [0.14, 1.66], TSK: MD = -2.20, [-4.23, -0.17], IKDC: MD = 3.22, [0.01, 6.43]) (Table 3.8).

MCID Proportions

Results regarding the number of participants that met or exceeded the predefined MCID threshold for each PROM are represented in Table 3.9. At the first follow-up assessment, over half of the participants in the LL-BFRT met or exceeded the MCID threshold for the ACL-RSI (3/5), GRoC (4/5), as well as the sport (4/5) and quality of life (4/5) subscales of the KOOS. In comparison, only one participant in the control experienced changes that exceeded these thresholds at the first follow-up assessment. Furthermore, at the second follow-up assessment, all participants in the LL-BFRT group met or exceeded the MCID for the GRoC and 4 out of the 5 of these participants also met or exceeded the MCID for the ACL-RSI, TSK, as well as the sport and quality of life subscales of the KOOS.

Quadriceps Strength and PROMs

Significant relationships were identified between improvements in quadriceps strength and limb symmetry with improvements on several of the PROMs collected in this study including the ACL-RSI, TSK, IKDC, subscales of the KOOS (i.e., symptom, pain, and composite score), and the GRoC scale (Table 3.10).

Discussion

Overall, this study produced several interesting findings regarding the potential psychologically-related benefits of LL-BFRT in female patients with considerable quadriceps

strength deficits following ACLR. First and foremost, we identified that patients treated with 4 weeks of LL-BFRT described the overall condition of their injured limb from the time that they began the study until each follow-up assessment as "(+4) moderately better" to "(+7) a very great deal better" as reported on the GRoC scale. Conversely, only two participants in the control group reported any change in the overall condition of their injured limb at either follow-up assessment. Additionally, although this exploratory pilot study was not sufficiently powered to find significant between group differences, noteworthy improvements were identified for several of the collected PROMs following the LL-BFRT intervention. At the first follow-up assessment, participants in the LL-BFRT group experienced average improvements of 20.76 points on the ACL-RSI, 7.40 points on the TSK, 5.52 points on the IKDC, and 7.14 points on the composite score of the KOOS. Furthermore, one month after completing the intervention these improvements appeared to increase to 26.06 points, 9.20 points, 12.41 points, and 9.05 points, respectively. In comparison, participants in the control group experienced minimal change across time on each of these subjectively reported outcome measures. Therefore, these results suggest that LL-BFRT may be a viable treatment option for improving an individual's psychological responses following an ACLR and postoperative rehabilitation including their overall perception of their injured limb, fear of movement and reinjury, subjective reported knee function, and perceived readiness to return to sport or physical activity.

At our baseline assessment, 70 % of the participants enrolled in this study [LL-BFRT = 4/5 (80 %), Control = 3/5 (60 %)] indicated that the current state of their knee was unsatisfactory when taking into account their activities of daily living, levels of pain, and activity limitations and participation restrictions. However, we found that all participants

treated with 8 sessions LL-BFRT experienced substantial improvements in the overall condition of their injured limb following the intervention compared to participants in the control group. On average, these participants indicated that the condition of their injured limb was "(+5) quite a bit better" at the initial follow-up assessment and "(+6) a great deal better" at the second follow-up assessment. These results indicate that incorporating LL-BFRT into patient care programs, even in the mid-to-late stages of recovery, may be an effective approach for improving a patient's perception of their injured limb, and subsequently, their overall knee satisfaction following an ACLR. Previous research has also found that 63% of patients treated with LL-BFRT after failing to respond to traditional post-surgical rehabilitation reported experiencing significantly better results than their previous rehabilitation program and had a mean patient satisfaction score of 8.9 out of 10 following the intervention.[38] These findings are extremely important as studies investigating patient satisfaction levels after ACLR have reported mean satisfaction scores of only 7.4 out of 10 with approximately 28 % of patients being dissatisfied with their knee-related outcomes at least a year after surgery and 73.3 % feeling unready to return to their preinjury activity when discharged from postoperative physical therapy.[39–41] Considering increased levels of patient satisfaction have been strongly associated with a higher likelihood of patients returning to preinjury levels of physical activity and reporting increased scores on PROMs such as the ACL-RSI and IKDC,[40–42] it is possible that incorporating LL-BFRT into patient care following ACLR could also improve these critical aspects of recovery. Nevertheless, future research should aim explore how utilizing LL-BFRT during postoperative rehabilitation may influence overall patient satisfaction and the rate of return to play compared to traditional

post-surgical rehabilitation programs in larger, more representative cohorts of patients post-ACLR.

While evidence related to the psychological implications of LL-BFRT remains sparce, recent research has begun to secondarily examine how this complementary treatment approach may influence patient reported knee function and knee-related problems in patients following an ACLR.[17,18,43,44] These reports have concluded that BFRT could be equally or more effective at improving patient reported knee function, as measured by the IKDC and KOOS, when implemented in the early postoperative phase of recovery (i.e., immediate post-surgery to 2 weeks post-surgery) compared to other intervention techniques such as general postoperative rehabilitation,[17,43,44] exercise with neuromuscular electrical stimulation,[43] and high load resistance training.[18] However, in one study examining the effects of high load resistance training with and without BFRT beginning 10 weeks post-ACLR, patients treated with 16 sessions of BFRT experienced average improvements of 16.49 points on the IKDC with no significant between group differences.[45] In contrast, although we did not identify any significant group differences for changes in the IKDC, over half of our participants allocated to the LL-BFRT group experienced improvements that exceeded the MCID for the IKDC at both follow-up assessments compared to their baseline assessment. Additionally, participants in the LL-BFRT were found to report significantly greater improvements on both the pain and quality of life subscales of the KOOS compared to participants in the control group. Therefore, while it has been suggested that clinically significant improvements in these PROMs typically cease within the first year following an ACLR,[46] these findings highlight that LL-BFRT may be an effective treatment technique for improving various aspects of subjective function and patient well-being when used in the later stages of recovery.

Considering the degree of these benefits may be dependent on when this intervention is incorporated into a patient's rehabilitative process, future studies should aim to identify the most appropriate time to include LL-BFRT into patient care following an ACL injury.

To the best of our knowledge, this was the first study to investigate the influence of LL-BFRT on fear of reinjury and psychological readiness in patients post-ACLR as measured by the TSK and ACL-RSI, respectively. Prior to treatment participants in the intervention group presented with average TSK scores of nearly 39 points. This is largely concerning as a threshold of 37 points or more on the TSK is often considered to be indicative of kinesiophobia which has been associated with various negative health-related and performance-based outcomes.[24,47–49] However, one month after completing the LL-BFRT intervention, 4 out of 5 participants presented with change scores exceeding the MCID threshold set for the TSK, and the preceding group mean decreased to approximately 29.60 points. Similar trends were noted for improvements on the ACL-RSI, where average sum scores for participants in the LL-BFRT group increased from 55.30 points to 81.36 points, with 80 % of these participants exceeding the MCID by their final follow-up assessment. These results are of particular importance as decreased fear of reinjury and increased psychological readiness have been strongly associated with positive changes in quadriceps strength and limb symmetry,[50] adherence to rehabilitation,[2] as well as rate of return to play and physical activity level in patients post ACLR.[24,47] In agreement, we also identified significant relationships between quadriceps strength and several of our PROMs when examining changes in each of these metrics from baseline to both follow-up assessments. Our results suggest that as quadriceps strength and limb symmetry improved, participants also reported increases in psychological readiness and patient reported knee function, decreases in

kinesiophobia and knee-related pain, and improvements in the overall condition of a patient's injured limb. Whilst the mechanisms influencing these relationships and psychophysiological responses to LL-BFRT have yet to be fully investigated, this study has provided preliminary evidence to support usage of LL-BFRT for improving physical and psychological outcome measures in patients long after receiving an ACLR. To further explore these benefits of LL-BFRT, future longitudinal studies utilizing mixed methodological designs are required to gain a comprehensive assessment of the overall effects of LL-BFRT in this patient population.

Limitations

This study was not without limitations. Considering we enrolled a relatively small, female sample, making between group comparisons and generalizing our results to patients with other demographic characteristics remains challenging. However, this exploratory study has provided clinicians and researchers with suggestive evidence to promote the usage and investigation of LL-BFRT as a multifunctional intervention to combat physiological and psychological deficits in patients recovering from ACLR. Additionally, the amount of elapsed time between when participants received surgical intervention to when they enrolled in this study varied widely. Nevertheless, the results of our study suggest that LL-BFRT may be an effective treatment approach for improving various psychological factors including a patient's perception of their injured limb, fear of reinjury, and psychological readiness, regardless of their time since surgery. Unfortunately, due to our study design and methodological constraints, we are unable to determine how a participant's previous or ongoing post-surgical rehabilitation experiences may have influenced their responses to LL-

BFRT and how their responses to these subjective outcome measures may have changed throughout their recovery process. Therefore, future researchers should consider utilizing qualitative or mixed methods study designs to explore how the incorporation of LL-BFRT into post-surgical rehabilitation programs may influence a patient's overall psychological characteristics and long-term health outcomes compared to more general postoperative rehabilitation programs.

Conclusions

The utilization of LL-BFRT was found to improve several patient reported outcomes in females with substantial quadriceps strength deficits following ACLR. Compared to a true control condition, individuals treated with 8 sessions of LL-BFRT reported considerable improvements in the overall condition of their injured limb with noteworthy decreases in knee-related pain and fear of reinjury as well as increases in psychological readiness, subjective reported knee function, and knee-related quality of life. Additionally, significant associations were identified between improvements in quadriceps strength and several of our PROMs in this patient population. Therefore, LL-BFRT may be an effective treatment intervention for improving not only quadriceps strength deficits, but also the psychological components of recovery in female patients following ACLR.

References

1. Nwachukwu BU, Adjei J, Rauck RC, et al. How Much Do Psychological Factors Affect Lack of Return to Play After Anterior Cruciate Ligament Reconstruction? A Systematic Review. *Orthop J Sports Med*. 2019;7(5):2325967119845313. doi:10.1177/2325967119845313

2. Walker A, Hing W, Lorimer A, Rathbone E. Rehabilitation characteristics and patient barriers to and facilitators of ACL reconstruction rehabilitation: A cross-sectional survey. *Phys Ther Sport Off J Assoc Chart Physiother Sports Med*. 2021;48:169-176. doi:10.1016/j.ptsp.2021.01.001

3. Zwolski C, Schmitt LC, Quatman-Yates C, Thomas S, Hewett TE, Paterno MV. The influence of quadriceps strength asymmetry on patient-reported function at time of return to sport after anterior cruciate ligament reconstruction. *Am J Sports Med*. 2015;43(9):2242-2249. doi:10.1177/0363546515591258

4. Lepley AS, Pietrosimone B, Cormier ML. Quadriceps Function, Knee Pain, and Self-Reported Outcomes in Patients With Anterior Cruciate Ligament Reconstruction. *J Athl Train*. 2018;53(4):337-346. doi:10.4085/1062-6050-245-16

5. Pietrosimone B, Lepley AS, Harkey MS, et al. Quadriceps Strength Predicts Self-reported Function Post-ACL Reconstruction. *Med Sci Sports Exerc*. 2016;48(9):1671-1677. doi:10.1249/MSS.0000000000000946

6. Kuenze C, Hertel J, Saliba S, Diduch DR, Weltman A, Hart JM. Clinical thresholds for quadriceps assessment after anterior cruciate ligament reconstruction. *J Sport Rehabil*. 2015;24(1):36-46. doi:10.1123/jsr.2013-0110

7. Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. *Br J Sports Med*. 2017;51(13):1003-1011. doi:10.1136/bjsports-2016-097071

8. Centner C, Wiegel P, Gollhofer A, König D. Effects of Blood Flow Restriction Training on Muscular Strength and Hypertrophy in Older Individuals: A Systematic Review and Meta-Analysis. *Sports Med Auckl NZ*. 2019;49(1):95-108. doi:10.1007/s40279-018-0994-1

9. Koc BB, Truyens A, Heymans MJLF, Jansen EJP, Schotanus MGM. Effect of Low-Load Blood Flow Restriction Training After Anterior Cruciate Ligament Reconstruction: A Systematic Review. *Int J Sports Phys Ther*. 2022;17(3):334-346. doi:10.26603/001c.33151

10. Caetano D, Oliveira C, Correia C, Barbosa P, Montes A, Carvalho P. Rehabilitation outcomes and parameters of blood flow restriction training in ACL injury: A scoping review. *Phys Ther Sport Off J Assoc Chart Physiother Sports Med*. 2021;49:129-137. doi:10.1016/j.ptsp.2021.01.015

11. Scott BR, Loenneke JP, Slattery KM, Dascombe BJ. Exercise with blood flow restriction: an updated evidence-based approach for enhanced muscular development. *Sports Med Auckl NZ*. 2015;45(3):313-325. doi:10.1007/s40279-014-0288-1

12. Goldberg AL, Etlinger JD, Goldspink DF, Jablecki C. Mechanism of work-induced hypertrophy of skeletal muscle. *Med Sci Sports*. 1975;7(3):185-198.

13. Schoenfeld BJ. The Mechanisms of Muscle Hypertrophy and Their Application to Resistance Training. *J Strength Cond Res*. 2010;24(10):2857-2872. doi:10.1519/JSC.0b013e3181e840f3

14. Pearson SJ, Hussain SR. A review on the mechanisms of blood-flow restriction resistance training-induced muscle hypertrophy. *Sports Med Auckl NZ*. 2015;45(2):187-200. doi:10.1007/s40279-014-0264-9

15. Lixandrão ME, Ugrinowitsch C, Berton R, et al. Magnitude of Muscle Strength and Mass Adaptations Between High-Load Resistance Training Versus Low-Load Resistance Training Associated with Blood-Flow Restriction: A Systematic Review and Meta-Analysis. *Sports Med Auckl NZ*. 2018;48(2):361-378. doi:10.1007/s40279-017-0795-y

16. Wengle L, Migliorini F, Leroux T, Chahal J, Theodoropoulos J, Betsch M. The Effects of Blood Flow Restriction in Patients Undergoing Knee Surgery: A Systematic Review and Meta-analysis. *Am J Sports Med*. Published online August 18, 2021:3635465211027296. doi:10.1177/03635465211027296

17. Tennent DJ, Hylden CM, Johnson AE, Burns TC, Wilken JM, Owens JG. Blood Flow Restriction Training After Knee Arthroscopy: A Randomized Controlled Pilot Study. *Clin J Sport Med Off J Can Acad Sport Med*. 2017;27(3):245-252. doi:10.1097/JSM.0000000000000377

18. Hughes L, Rosenblatt B, Haddad F, et al. Comparing the Effectiveness of Blood Flow Restriction and Traditional Heavy Load Resistance Training in the Post-Surgery Rehabilitation of Anterior Cruciate Ligament Reconstruction Patients: A UK National Health Service Randomised Controlled Trial. *Sports Med Auckl NZ*. Published online July 12, 2019. doi:10.1007/s40279-019-01137-2

19. Irrgang JJ, Anderson AF, Boland AL, et al. Development and Validation of the International Knee Documentation Committee Subjective Knee Form. *Am J Sports Med*. 2001;29(5):600-613. doi:10.1177/03635465010290051301

20. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res*. 2011;63 Suppl 11:S208-228. doi:10.1002/acr.20632

21. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther*. 1998;28(2):88-96. doi:10.2519/jospt.1998.28.2.88

22. Miller RP, Kori SH, Todd DD. The Tampa Scale: a Measure of Kinisophobia. *Clin J Pain*. 1991;7(1):51.

23. Pool JJM, Hiralal S, Ostelo RWJG, et al. The applicability of the Tampa Scale of Kinesiophobia for patients with sub-acute neck pain: a qualitative study. *Qual Quant*. 2009;43(5):773-780. doi:10.1007/s11135-008-9203-x

24. Liu H, Huang L, Yang Z, Li H, Wang Z, Peng L. Fear of Movement/(Re)Injury: An Update to Descriptive Review of the Related Measures. *Front Psychol*. 2021;12. Accessed March 1, 2022. https://www.frontiersin.org/article/10.3389/fpsyg.2021.696762

25. Webster KE, Feller JA, Lambros C. Development and preliminary validation of a scale to measure the psychological impact of returning to sport following anterior cruciate ligament reconstruction surgery. *Phys Ther Sport Off J Assoc Chart Physiother Sports Med*. 2008;9(1):9-15. doi:10.1016/j.ptsp.2007.09.003

26. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. *J Man Manip Ther*. 2009;17(3):163-170. doi:10.1179/jmt.2009.17.3.163

27. National Strength & Conditioning Association. *Essentials of Strength Training and Conditioning*. 4th ed. Human Kinetics; 2015.

28. Borg G. *Borg's Perceived Exertion and Pain Scales*. Human Kinetics; 1998.

29. Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ) – Short and Long Forms. Published online November 2005. https://sites.google.com/site/theipaq/scoring-protocol

30. Katz NP, Paillard FC, Ekman E. Determining the clinical importance of treatment benefits for interventions for painful orthopedic conditions. *J Orthop Surg*. 2015;10:24. doi:10.1186/s13018-014-0144-x

31. Nwachukwu BU, Chang B, Voleti PB, et al. Preoperative Short Form Health Survey Score Is Predictive of Return to Play and Minimal Clinically Important Difference at a Minimum 2-Year Follow-up After Anterior Cruciate Ligament Reconstruction. *Am J Sports Med*. 2017;45(12):2784-2790. doi:10.1177/0363546517714472

32. Nwachukwu BU, Sullivan SW, Rauck RC, et al. Patient-Reported Outcomes and Factors Associated with Achieving the Minimal Clinically Important Difference After ACL Reconstruction: Results at a Mean 7.7-Year Follow-up. *JB JS Open Access*. 2021;6(4):e21.00056. doi:10.2106/JBJS.OA.21.00056

33. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003;1:64. doi:10.1186/1477-7525-1-64

34. MARS Group. Predictors of clinical outcome following revision anterior cruciate ligament reconstruction. *J Orthop Res*. 2020;38(6):1191-1203. doi:10.1002/jor.24562

35. Zarzycki R, Arhos E, Failla M, Capin J, Smith AH, Snyder-Mackler L. Association of the Psychological Response to the ACL-SPORTS Training Program and Self-reported Function at 2 Years After Anterior Cruciate Ligament Reconstruction. *Am J Sports Med*. Published online October 8, 2021:03635465211045388. doi:10.1177/03635465211045388

36. Monticone M, Ambrosini E, Rocca B, Foti C, Ferrante S. Responsiveness and minimal clinically important changes for the Tampa Scale of Kinesiophobia after lumbar fusion during cognitive behavioral rehabilitation. *Eur J Phys Rehabil Med*. 2017;53(3):351-358. doi:10.23736/S1973-9087.16.04362-8

37. Stratford PW, Binkley J, Solomon P, Gill C, Finch E. Assessing change over time in patients with low back pain. *Phys Ther*. 1994;74(6):528-533. doi:10.1093/ptj/74.6.528

38. Noyes FR, Barber-Westin S, Sipes L. Blood Flow Restriction Training Can Improve Peak Torque Strength in Chronic Atrophic Postoperative Quadriceps and Hamstrings Muscles. *Arthrosc J Arthrosc Relat Surg Off Publ Arthrosc Assoc N Am Int Arthrosc Assoc*. Published online March 31, 2021. doi:10.1016/j.arthro.2021.03.040

39. Dempsey IJ, Norte GE, Hall M, et al. Relationship Between Physical Therapy Characteristics, Surgical Procedure, and Clinical Outcomes in Patients After ACL Reconstruction. *J Sport Rehabil*. 2019;28(2):171-179. doi:10.1123/jsr.2017-0176

40. Kahlenberg CA, Nwachukwu BU, Ferraro RA, Schairer WW, Steinhaus ME, Allen AA. How Are We Measuring Patient Satisfaction After Anterior Cruciate Ligament Reconstruction? *Orthop J Sports Med*. 2016;4(12):2325967116673971. doi:10.1177/2325967116673971

41. Ardern CL, Österberg A, Sonesson S, Gauffin H, Webster KE, Kvist J. Satisfaction With Knee Function After Primary Anterior Cruciate Ligament Reconstruction Is Associated With Self-Efficacy, Quality of Life, and Returning to the Preinjury Physical Activity. *Arthrosc J Arthrosc Relat Surg Off Publ Arthrosc Assoc N Am Int Arthrosc Assoc*. 2016;32(8):1631-1638.e3. doi:10.1016/j.arthro.2016.01.035

42. Sadeqi M, Klouche S, Bohu Y, Herman S, Lefevre N, Gerometta A. Progression of the Psychological ACL-RSI Score and Return to Sport After Anterior Cruciate Ligament Reconstruction: A Prospective 2-Year Follow-up Study From the French Prospective Anterior Cruciate Ligament Reconstruction Cohort Study (FAST). *Orthop J Sports Med*. 2018;6(12):2325967118812819. doi:10.1177/2325967118812819

43. Kong DH, Jung WS, Yang SJ, Kim JG, Park HY, Kim J. Effects of Neuromuscular Electrical Stimulation and Blood Flow Restriction in Rehabilitation after Anterior Cruciate Ligament Reconstruction. *Int J Environ Res Public Health*. 2022;19(22):15041. doi:10.3390/ijerph192215041

44. Vieira de Melo RF, Komatsu WR, Freitas MS de, Vieira de Melo ME, Cohen M. Comparison of Quadriceps and Hamstring Muscle Strength after Exercises with and without Blood Flow Restriction following Anterior Cruciate Ligament Surgery: A Randomized Controlled Trial. *J Rehabil Med*. 2022;54:jrm00337. doi:10.2340/jrm.v54.2550

45. Curran MT, Bedi A, Mendias CL, Wojtys EM, Kujawa MV, Palmieri-Smith RM. Blood Flow Restriction Training Applied With High-Intensity Exercise Does Not Improve Quadriceps Muscle Function After Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial. *Am J Sports Med*. 2020;48(4):825-837. doi:10.1177/0363546520904008

46. Agarwalla A, Puzzitiello RN, Liu JN, et al. Timeline for Maximal Subjective Outcome Improvement After Anterior Cruciate Ligament Reconstruction. *Am J Sports Med*. 2019;47(10):2501-2509. doi:10.1177/0363546518803365

47. Marok E, Soundy A. The effect of kinesiophobia on functional outcomes following anterior cruciate ligament reconstruction surgery: an integrated literature review. *Disabil Rehabil*. 2022;44(24):7378-7389. doi:10.1080/09638288.2021.1998665

48. Ardern CL, Taylor NF, Feller JA, Whitehead TS, Webster KE. Psychological responses matter in returning to preinjury level of sport after anterior cruciate ligament reconstruction surgery. *Am J Sports Med*. 2013;41(7):1549-1558. doi:10.1177/0363546513489284

49. Courtot L, Ferre F, Reina N, et al. Patient Participation During Anterior Cruciate Ligament Reconstruction Improves Comprehension, Satisfaction, and Functional Outcomes: A Simple Way to Improve Our Practices. *Orthop J Sports Med*. 2019;7(4):2325967119841089. doi:10.1177/2325967119841089

50. Paterno MV, Flynn K, Thomas S, Schmitt LC. Self-Reported Fear Predicts Functional Performance and Second ACL Injury After ACL Reconstruction and Return to Sport: A Pilot Study. *Sports Health*. 2018;10(3):228-233. doi:10.1177/1941738117745806

Tables

Table 3.1. Individual participant demographic information by group

Group	Participant (#)	Age (y)	Height (cm)	Mass (kg)	Graft (type)	TSS (m)	Tegner Score		Knee Satisfaction (Y, N)
							Pre	Post	
LL-BFRT	2	21.81	161.29	67.40	PT	10.08	7	7	Yes
	3	18.76	169.42	86.45	H	45.56	7	2	No
	4	18.61	165.10	63.14	Q	5.58	8	7	No
	7	18.68	166.37	59.69	PT	15.28	8	6	No
	14	39.72	172.08	70.21	Q	5.06	6	2	No
	Group Mean ± SD	23.52± 9.16	166.85 ±4.12	69.38± 10.35		16.31± 16.86	7.20± 0.84	4.80± 2.59	1 Y, 4 N
Control	1	18.55	158.75	65.04	Q	7.78	9	8	No
	9	28.60	175.26	73.94	PT	78.22	9	6	No
	10	21.46	171.45	84.46	H	99.74	9	6	Yes
	12	20.03	156.84	52.80	BEAR	46.75	9	3	Yes
	16	20.75	168.91	69.40	PT	7.66	9	5	No
	Group Mean ± SD	21.88± 3.91	166.24 ±8.06	69.13± 11.64		48.03±41.34	9.00± 0.00	5.60± 1.82	2 Y, 3 N
Mean Difference ± SE (p-value)		1.64 ± 4.45 (0.723)	0.61 ± 4.05 (0.884)	0.25 ± 6.97 (0.972)		-31.71 ± 19.97 (0.151)	-1.80± 0.37 (0.009)*	-0.80± 1.41 (0.587)	3 Y, 7 N

** Statistically significant at $p \leq 0.05$*

Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; TSS, time since surgery; Y, yes; N, no; SD, standard deviation; SE, standard error; PT, patellar tendon; H, hamstring; Q, quadriceps; BEAR, bridge-enhanced anterior cruciate ligament repair

Table 3.2. Weekly IPAQ physical activity level between groups

Visit	MET-min/week (Mean ± SD)		Mean Difference ± SE	p-value
	LL-BFRT	Control		
Baseline	4,573.80 ± 3,390.73	3,107.40 ± 2,567.30	1,466.40 ± 1,902.00	0.463
Week #1	4,361.60 ± 2,388.34	3,525.30 ± 2,957.91	836.30 ± 1,700.20	0.636
Week #2*	4,066.62 ± 2,466.83	2,571.00 ± 1,222.06	1,495.62 ± 1,248.04	0.270
Week #3	5,196.20 ± 3,006.98	2,306.00 ± 1,362.57	2,890.20 ± 1,476.38	0.086
Week #4	4,736.60 ± 2,680.21	2,447.10 ± 1,460.03	2,289.50 ± 1,364.93	0.132
Follow-up #1	4,964.00 ± 2,605.06	2,634.50 ± 1,408.15	2,329.50 ± 1,324.33	0.117
Follow-up #2	4,010.10 ± 1,898.07	3,040.50 ± 2,028.87	969.60 ± 1,242.49	0.458

**One participant in LL-BFRT group excluded from week 2 summary statistics*
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy; SD, standard deviation; SE, standard error

Table 3.3. Mean PROM sum scores by group and time

	Mean ± SD						
	Baseline			Follow-up #1		Follow-up #2	
PROM Variable	LL-BFRT	Control	p-value	LL-BFRT	Control	LL-BFRT	Control
ACL-RSI	55.30 ± 17.04	64.70 ± 16.79	0.406	76.06 ± 11.96	72.73 ± 16.38	81.36 ± 15.55	76.51 ± 12.31
TSK	38.80 ± 7.82	33.80 ± 4.82	0.258	31.40 ± 3.05	32.00 ± 2.74	29.60 ± 2.79	29.40 ± 3.51
IKDC	74.25 ± 14.25	79.31 ± 14.38	0.592	79.77 ± 7.52	80.23 ± 17.83	86.67 ± 7.56	79.77 ± 22.77
KOOS	83.45 ± 9.53	87.38 ± 10.13	0.545	90.59 ± 3.19	88.57 ± 10.36	92.50 ± 1.71	87.50 ± 13.24
Symptom	75.71 ± 13.46	74.29 ± 21.93	0.904	85.00 ± 4.66	77.86 ± 21.04	86.43 ± 2.99	75.00 ± 26.36
Pain	88.89 ± 7.86	89.44 ± 10.83	0.928	93.89 ± 3.62	88.89 ± 12.73	95.56 ± 2.48	86.11 ± 17.24
ADL	95.00 ± 6.63	97.94 ± 3.83	0.415	97.65 ± 1.31	97.94 ± 2.46	99.12 ± 0.80	97.06 ± 5.79
Sport	70.00 ± 26.69	78.00 ± 22.53	0.622	85.00 ± 9.35	79.00 ± 22.75	85.00 ± 9.35	84.00 ± 19.81
QoL	52.50 ± 14.39	72.50 ± 14.39	0.059	70.00 ± 10.27	78.75 ± 14.39	77.50 ± 12.18	76.25 ± 14.25
GRoC	-	-	-	5.20 ± 0.84	0.60 ± 1.34	6.00 ± 0.71	1.60 ± 2.61

Abbreviations: PROM, patient reported outcome measure; LL-BFRT, low load exercise with blood flow restriction therapy; SD, standard deviation; ACL-RSI, Anterior Cruciate Ligament – Return to Sport Index; TSK, Tampa Scale for Kinesiophobia; IKDC, International Knee Documentation Committee Subjective Knee Evaluation; KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QoL, quality of life; GRoC, Global Rating of Change scale

Table 3.4. Change Scores: PROM sum scores by group

	Mean ± SD					
	ΔFollow-up #1 – Baseline			ΔFollow-up #2 – Baseline		
PROM Variable	LL-BFRT	Control	Mean Difference	LL-BFRT	Control	Mean Difference
ACL-RSI	20.76 ± 22.48	8.03 ± 17.84	12.73 ± 12.83	26.06 ± 22.17	11.82 ± 18.84	14.24 ± 13.01
TSK	-7.40 ± 6.73	-1.80 ± 2.39	-5.60 ± 3.19	-9.20 ± 7.73	-4.40 ± 4.93	-4.80 ± 4.10
IKDC	5.52 ± 8.58	0.92 ± 5.35	4.60 ± 4.52	12.41 ± 7.85	0.46 ± 9.29	11.95 ± 5.44
KOOS	7.14 ± 6.48	1.19 ± 1.40	5.95 ± 2.96	9.05 ± 9.01	0.12 ± 5.78	8.93 ± 4.79
Symptom	9.29 ± 9.65	3.57 ± 5.05	5.71 ± 4.87	10.71 ± 15.57	0.71 ± 15.65	10.00 ± 9.87
Pain	5.00 ± 5.69	-0.56 ± 3.04	5.56 ± 2.89	6.67 ± 5.76	-3.33 ± 6.63	10.00 ± 3.93
ADL	2.65 ± 5.34	0.00 ± 2.08	2.65 ± 2.56	4.12 ± 6.19	-0.88 ± 1.97	5.00 ± 2.90
Sport	15.00 ± 18.71	1.00 ± 11.40	14.00 ± 9.80	15.00 ± 20.92	6.00 ± 16.73	9.00 ± 11.98
QoL	17.50 ± 9.27	6.25 ± 8.84	11.25 ± 5.73	25.00 ± 13.26	3.75 ± 5.59	21.25 ± 6.43
GRoC	5.20 ± 0.84	0.60 ± 1.34	4.60 ± 0.71	6.00 ± 0.71	1.60 ± 2.61	4.40 ± 1.21

Abbreviations: PROM, patient reported outcome measure; LL-BFRT, low load exercise with blood flow restriction therapy; SD, standard deviation; ACL-RSI, Anterior Cruciate Ligament – Return to Sport Index; TSK, Tampa Scale for Kinesiophobia; IKDC, International Knee Documentation Committee Subjective Knee Evaluation; KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QoL, quality of life; GRoC, Global Rating of Change scale

Table 3.5. Separate RM-ANOVAs: PROM change scores by group and time

PROM Variable	Source	F statistic	p-value	η^2_p
ACL-RSI	Time	4.19	0.075	0.34
	Time*Group	0.12	0.742	0.01
	Group	1.12	0.320	0.12
TSK	Time	6.25	0.037*	0.44
	Time*Group	0.21	0.662	0.03
	Group	2.12	0.183	0.21
IKDC	Time	5.35	0.049*	0.40
	Time*Group	6.99	0.030*	0.47
	Group	2.97	0.123	0.27
KOOS	Time	0.10	0.756	0.01
	Time*Group	1.32	0.284	0.14
	Group	3.91	0.083	0.33
Symptom	Time	0.06	0.807	0.01
	Time*Group	0.58	0.470	0.07
	Group	1.17	0.310	0.13
Pain	Time	0.13	0.731	0.02
	Time*Group	2.03	0.192	0.20
	Group	6.40	0.035*	0.44
ADL	Time	0.11	0.749	0.01
	Time*Group	1.75	0.222	0.18
	Group	2.18	0.178	0.21
Sport	Time	1.25	0.296	0.14
	Time*Group	1.25	0.296	0.14
	Group	1.15	0.314	0.13
QOL	Time	1.07	0.332	0.12
	Time*Group	4.27	0.073	0.35
	Group	8.45	0.020*	0.51
GRoC	Time	7.36	0.027*	0.48
	Time*Group	0.09	0.771	0.01
	Group	23.28	0.001*	0.74

** Statistically significant at $p \leq 0.05$*

Abbreviations: RM-ANOVA, repeated measures analysis of variance; PROM, patient reported outcome measure; ACL-RSI, Anterior Cruciate Ligament – Return to Sport Index; TSK, Tampa Scale for Kinesiophobia; IKDC, International Knee Documentation Committee Subjective Knee Evaluation; KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QoL, quality of life; GRoC, Global Rating of Change scale

Table 3.6. Pairwise Comparisons: Time by Group interaction

PROM Variable	Group	Comparison (Mean (SE)) ΔFollow-up #2 – Baseline		ΔFollow-up #1 – Baseline	Mean Difference (SE)	p-value	95% CI
IKDC	LL-BFRT	12.41 (3.85)	-	5.52 (3.20)	6.90 (1.97)	0.008*	2.36 – 11.43
	Control	0.46 (3.85)	-	0.92 (3.20)	-0.46 (1.97)	0.821	-5.00 – 4.08

** Statistically significant at $p \leq 0.05$*

Abbreviations: PROM, patient reported outcome measure; SE, standard error; CI, confidence interval; IKDC, International Knee Documentation Committee Subjective Knee Evaluation; LL-BFRT, low load exercise with blood flow restriction therapy

Table 3.7. Pairwise Comparisons: Group

PROM Variable	Comparison (Mean (SE)) LL-BFRT		Control	Mean Difference (SE)	p-value	95% CI
ACL-RSI	23.41 (9.00)	-	9.92 (9.00)	13.48 (12.73)	0.320	-15.87 – 42.84
TSK	-8.30 (2.52)	-	-3.10 (2.52)	-5.20 (3.57)	0.183	-13.43 – 3.03
IKDC	8.97 (3.40)	-	0.69 (3.40)	8.28 (4.80)	0.123	-2.80 – 19.36
KOOS	8.10 (2.66)	-	0.65 (2.66)	7.44 (3.76)	0.083	-1.24 – 16.12
Symptom	10.00 (5.13)	-	2.14 (5.13)	7.86 (7.25)	0.310	-8.87 – 24.58
Pain	5.83 (2.17)	-	-1.94 (2.17)	7.78 (3.07)	0.035*	0.69 – 14.87
ADL	3.38 (1.83)	-	-0.44 (1.83)	3.82 (2.59)	0.178	-2.15 – 9.80
Sport	15.00 (7.57)	-	3.50 (7.57)	11.50 (10.71)	0.314	-13.20 – 36.20
QoL	21.25 (3.95)	-	5.00 (3.95)	16.25 (5.59)	0.020*	3.36 – 29.14
GRoC	5.60 (0.66)	-	1.10 (0.66)	4.50 (0.93)	0.001*	2.35 – 6.65

** Statistically significant at $p \leq 0.05$*

Abbreviations: PROM, patient reported outcome measure; SE, standard error; CI, confidence interval; LL-BFRT, low load exercise with blood flow restriction therapy; ACL-RSI, Anterior Cruciate Ligament – Return to Sport Index; TSK, Tampa Scale for Kinesiophobia; IKDC, International Knee Documentation Committee Subjective Knee Evaluation; KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QoL, quality of life; GRoC, Global Rating of Change scale

Table 3.8. Pairwise Comparisons: Time

PROM Variable	Comparison (Mean (SE))			Mean Difference (SE)	p-value	95% CI
	ΔFollow-up #2 – Baseline		ΔFollow-up #1 – Baseline			
ACL-RSI	18.94 (6.51)	-	14.39 (6.42)	4.55 (2.22)	0.075	-0.58 – 9.67
TSK	-6.80 (2.05)	-	-4.60 (1.60)	-2.20 (0.88)	0.037*	-4.23 – -0.17
IKDC	6.44 (2.72)	-	3.22 (2.26)	3.22 (1.39)	0.049*	0.01 – 6.43
KOOS	4.58 (2.39)	-	4.17 (1.48)	0.42 (1.30)	0.756	-2.57 – 3.41
Symptom	5.71 (4.94)	-	6.43 (2.44)	-0.71 (2.82)	0.807	-7.23 – 5.80
Pain	1.67 (1.96)	-	2.22 (1.44)	-0.56 (1.56)	0.731	-4.15 – 3.04
ADL	1.62 (1.45)	-	1.32 (1.28)	0.29 (0.89)	0.749	-1.75 – 2.34
Sport	10.50 (5.99)	-	8.00 (4.90)	2.50 (2.24)	0.296	-2.66 – 7.66
QoL	14.38 (3.22)	-	11.88 (2.86)	2.50 (2.42)	0.332	-3.08 – 8.08
GRoC	3.80 (0.60)	-	2.90 (0.35)	0.90 (0.33)	0.027*	0.14 – 1.66

** Statistically significant at $p \leq 0.05$*

Abbreviations: PROM, patient reported outcome measure; SE, standard error; CI, confidence interval; ACL-RSI, Anterior Cruciate Ligament – Return to Sport Index; TSK, Tampa Scale for Kinesiophobia; IKDC, International Knee Documentation Committee Subjective Knee Evaluation; KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QoL, quality of life; GRoC, Global Rating of Change scale

Table 3.9. MCID Proportions

	Achieved MCID (*no.* / *total no. (%)*)			
	ΔFollow-up #1 – Baseline		ΔFollow-up #2 – Baseline	
Characteristic	LL-BFRT	Control	LL-BFRT	Control
ACL-RSI (≥ 10)	3/5 (60)	1/5 (20)	4/5 (80)	1/5 (20)
TSK (≥ 6)	2/5 (40)	0/5 (0)	4/5 (80)	3/5 (60)
IKDC (≥ 9)	2/5 (40)	0/5 (0)	3/5 (60)	1/5 (20)
KOOS (≥ 8)	2/5 (40)	0/5 (0)	2/5 (40)	0/5 (0)
Symptom	2/5 (40)	1/5 (20)	2/5 (40)	1/5 (20)
Pain	1/5 (20)	0/5 (0)	1/5 (20)	0/5 (0)
ADL	1/5 (20)	0/5 (0)	1/5 (20)	0/5 (0)
Sport	4/5 (80)	1/5 (20)	4/5 (80)	2/5 (40)
QoL	4/5 (80)	1/5 (20)	4/5 (80)	0/5 (0)
GRoC (≥ 5)	4/5 (80)	0/5 (0)	5/5 (100)	1/5 (20)

Abbreviations: MCID, minimally clinically important difference; LL-BFRT, low load exercise with blood flow restriction therapy; ACL-RSI, Anterior Cruciate Ligament – Return to Sport Index; TSK, Tampa Scale for Kinesiophobia; IKDC, International Knee Documentation Committee Subjective Knee Evaluation; KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QoL, quality of life, GRoC, Global Rating of Change scale

Table 3.10. Pearson correlations between changes in quadriceps strength and changes in PROMs

Torque Measure	Variable	Change	PROM									
			ACL-RSI	TSK	IKDC	KOOS	*Symptom*	*Pain*	*ADL*	*Sport*	*QoL*	GRoC
Peak Torque at 90 deg/s	Limb Symmetry Index (%)	ΔFollow-up #1 – Baseline	0.71* (0.021)	-0.70* (0.025)	0.63 (0.053)	0.61 (0.059)	0.52 (0.120)	0.71* (0.021)	0.38 (0.275)	0.40 (0.253)	0.44 (0.203)	0.71* (0.022)
		ΔFollow-up #2 – Baseline	0.68* (0.029)	-0.49 (0.151)	0.60 (0.066)	0.51 (0.136)	0.43 (0.211)	0.57 (0.084)	0.45 (0.195)	0.23 (0.532)	0.58 (0.078)	0.57 (0.084)
	Involved Limb Strength (Nm/kg)	ΔFollow-up #1 – Baseline	0.77** (0.009)	-0.69* (0.029)	0.65* (0.043)	0.67* (0.035)	0.64* (0.045)	0.70* (0.025)	0.39 (0.260)	0.45 (0.191)	0.47 (0.167)	0.74* (0.014)
		ΔFollow-up #2 – Baseline	0.74* (0.016)	-0.47 (0.171)	0.68* (0.035)	0.64* (0.046)	0.59 (0.072)	0.78** (0.008)	0.57 (0.088)	0.28 (0.434)	0.59 (0.071)	0.69* (0.028)

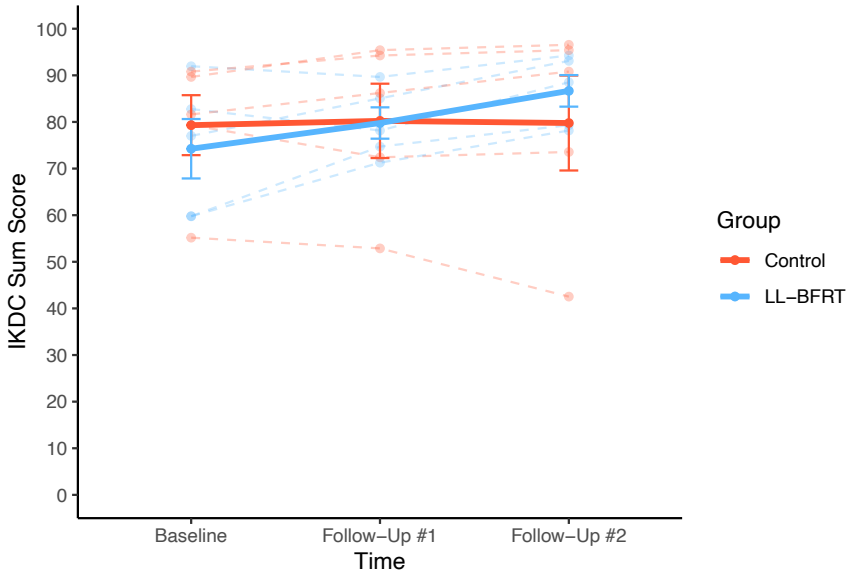
** Statistically significant at $p \leq 0.05$*

*** Statistically significant at $p \leq 0.01$*

Abbreviations: PROM, patient reported outcome measure; ACL-RSI, Anterior Cruciate Ligament – Return to Sport Index; TSK, Tampa Scale for Kinesiophobia; IKDC, International Knee Documentation Committee Subjective Knee Evaluation; KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QoL, quality of life; GRoC, Global Rating of Change scale

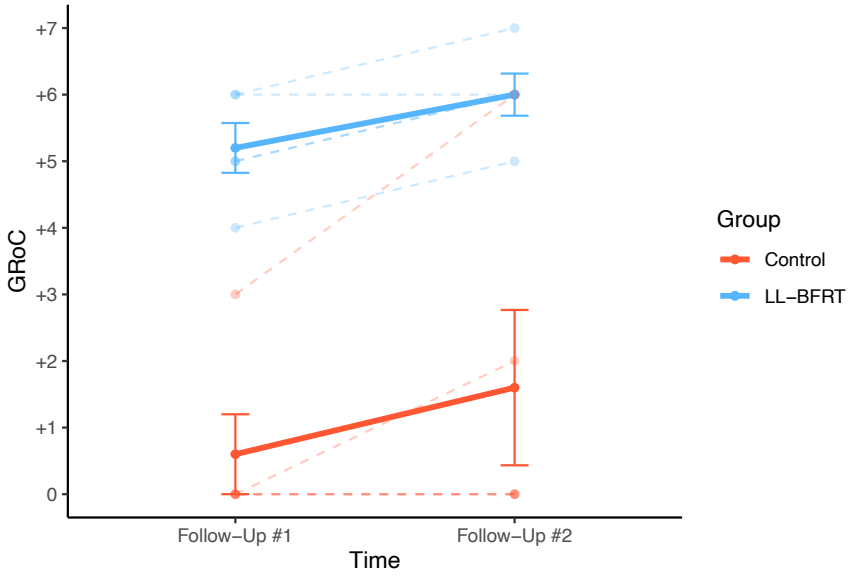
Figures

Figure 3.1. Changes in IKDC sum scores by group and time.



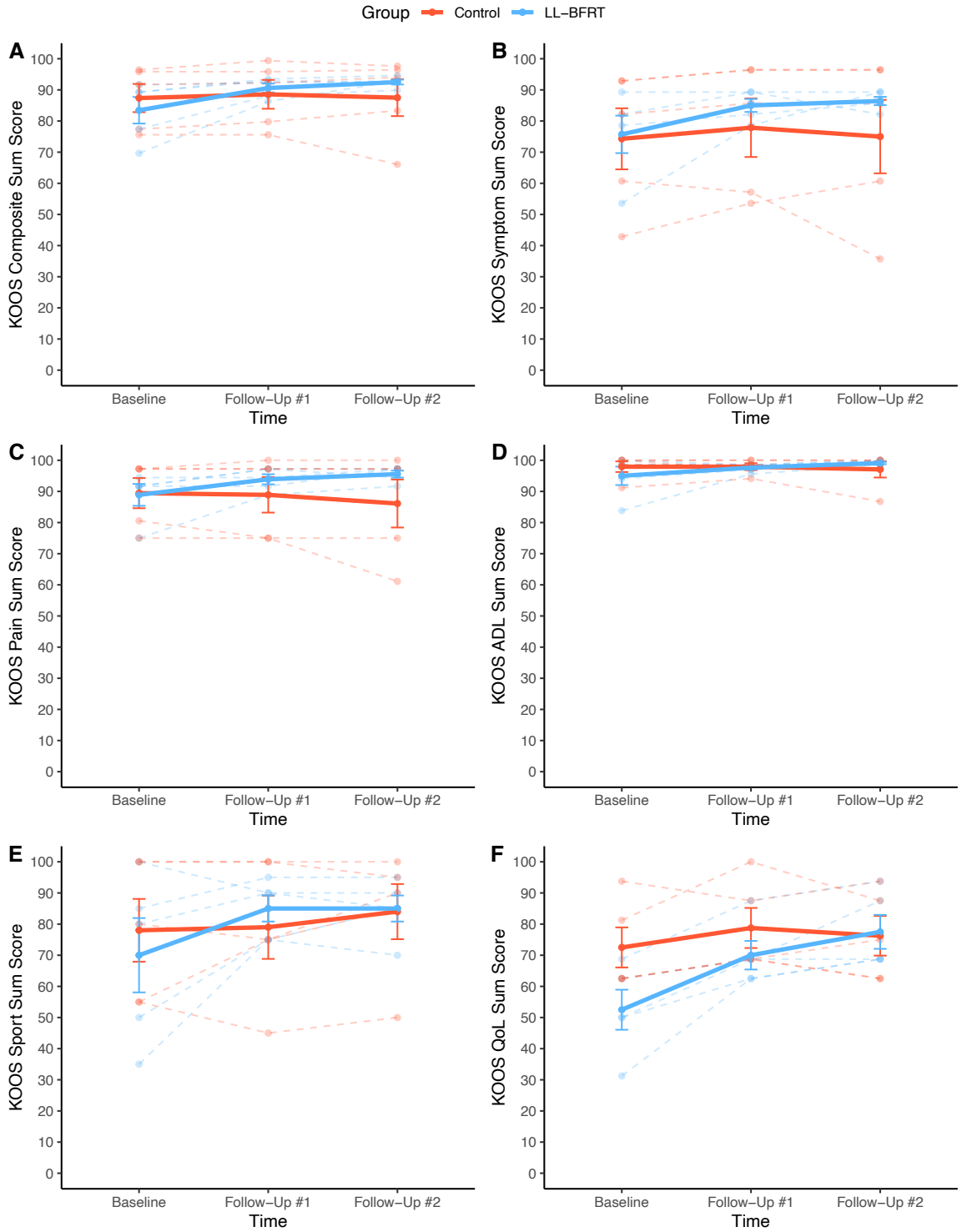
Abbreviations: IKDC, International Knee Documentation Committee Subjective Knee Evaluation; LL-BFRT, low load exercise with blood flow restriction therapy

Figure 3.2. Changes in GRoC by group and time.



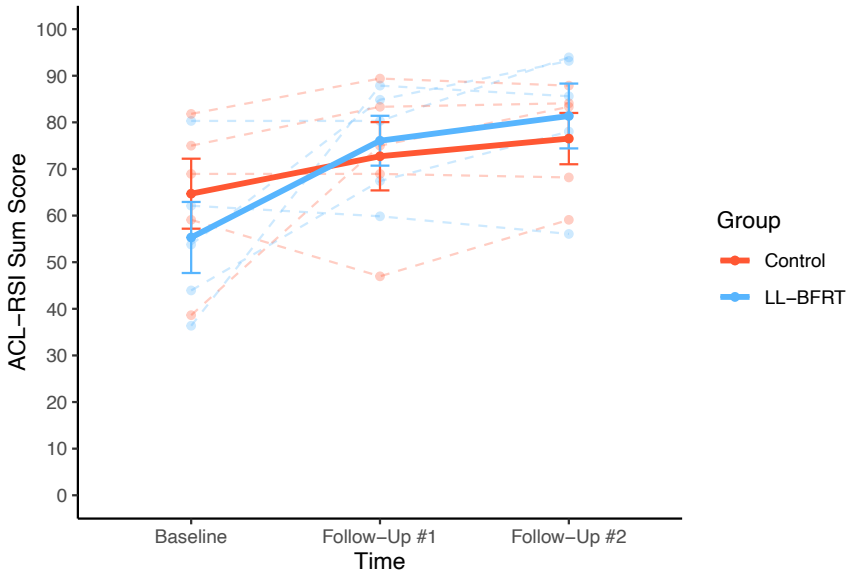
Abbreviations: GRoC, Global Rating of Change scale; LL-BFRT, low load exercise with blood flow restriction therapy

Figure 3.3. Changes in KOOS sum scores (A) composite, (B) symptom, (C) pain, (D) activities of daily living, (E) sport, (F) quality of life by group and time.



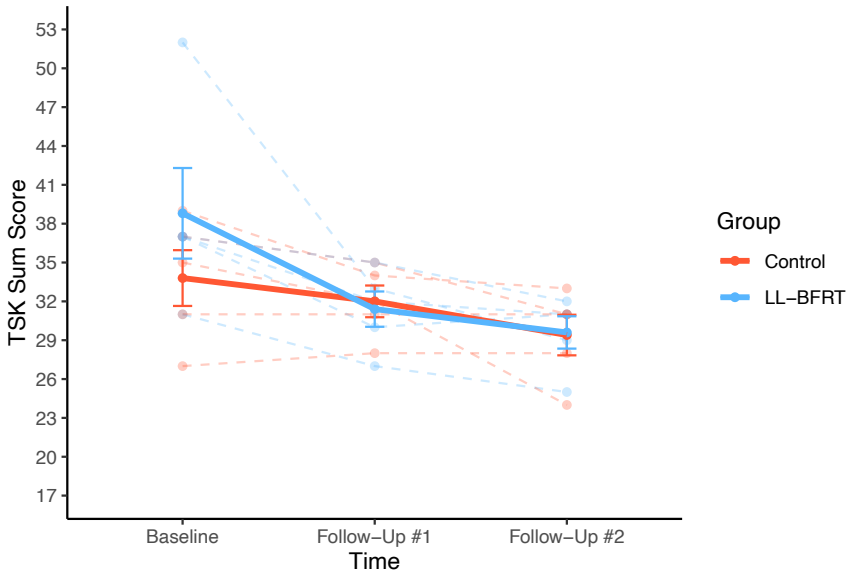
Abbreviations: KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QoL, quality of life; LL-BFRT, low load exercise with blood flow restriction therapy

Figure 3.4. Changes in ACL-RSI sum scores by group and time.



Abbreviations: ACL-RSI, Anterior Cruciate Ligament – Return to Sport Index; LL-BFRT, low load exercise with blood flow restriction therapy

Figure 3.5. Changes in TSK sum scores by group and time.



Abbreviations: TSK, Tampa Scale for Kinesiophobia; LL-BFRT, low load exercise with blood flow restriction therapy

APPENDIX A: THE PROBLEM

Statement of the Problem

This project aimed to address the underlying mechanisms and effects of low-load blood flow restriction therapy (LL-BFRT) in three ways: 1) Identifying the effects of LL-BFRT on motor unit recruitment and behavior of the vastus lateralis during exercise, 2) Examining the effects of a LL-BFRT intervention program on muscle function in patients post-anterior cruciate ligament reconstruction (ACLR) presenting with quadriceps strength deficits, and 3) Exploring the psychological effects of LL-BFRT in patients post-ACLR.

Manuscript I

Low-load exercise with blood flow restriction therapy (LL-BFRT) may offer clinicians a complementary therapeutic approach for achieving neuromuscular gains while mitigating the potentially harmful adverse events associated with increased joint stress during high load resistance exercise. LL-BFRT has been speculated to enhance muscle function by metabolically stimulating the early recruitment of high threshold motor units and type II (fast-twitch anaerobic) muscle fibers during exercise.[1,2] This recruitment has been suggested to lead to increases in muscle strength and hypertrophy, despite exercises producing low mechanical tension, by stimulating more muscle fibers hence causing a more widespread hypertrophic stimulus within the muscle.[2,3]

These changes in muscle activation and motor unit recruitment during LL-BFRT have been primarily quantified using general measures of surface electromyography (sEMG) such as EMG amplitude and integrated EMG.[4–7] However, due to the influence of factors such as motor unit synchronization and fatigue, we are unable to unambiguously assess changes at

the motor unit level using these indirect measurement techniques.[4–7] Utilization of novel sEMG technology with motor unit decomposition capabilities (i.e., Trigno Galileo Sensor) may allow for further investigation of the underlying mechanisms of LL-BFRT in a functional, real-time manner during submaximal exercise.

Manuscript II

Regaining full strength and limb symmetry of the quadriceps following ACLR is critical for successful recovery and reducing the risk of devastating, long-term health ramifications such as reinjury and knee osteoarthritis. Achieving side-to-side quadriceps strength deficits of 10% or less has been recommended as a criterion for physical activity clearance after ACLR.[8,9] However, despite the completion of traditional post-surgical rehabilitation programs, persistent quadriceps weakness continues to be a major limitation for many individuals following ACLR.[10,11] Reports have indicated surgical limb knee extensor strength deficits up to 30% compared to the non-surgical limb in patients six months post-surgery.[12]

Unfortunately, no true standard of care has been established for improving quadriceps strength deficits in patients failing to respond to these more traditional methods of rehabilitation. Exploring non-traditional therapeutic techniques may help to identify an alternative approach for addressing these strength limitations in patients post-ACLR. Recent research has suggested that LL-BFRT may be a viable treatment option for improving muscle function in patients following an ACLR.[13–18] However, additional investigation of the effects of LL-BFRT in patients with persistent quadriceps weakness after ACLR is warranted.

Manuscript III

Along with physical and social components, psychological characteristics are critical factors to consider when evaluating an individual's response to injury and readiness for unrestricted physical activity after ACL injury and surgical reconstruction. Subjective factors including fear of reinjury, unsatisfactory knee function, and lack of knee confidence have been identified as barriers for the return to physical activity and sport following ACLR.[19] Direct relationships have been identified between these psychological limitations and lingering quadriceps weakness in patients post-ACLR.[20,21] Exploring interventions that may address both the physical and psychological components of recovery could improve the overall rehabilitative process in this patient population. Recent studies have secondarily examined the effects of LL-BFRT for improving common patient reported outcomes measures in patients following knee surgery.[15] However, the overall psychological implications of LL-BFRT in patients with quadriceps strength deficits in the later stages of recovery following ACLR has not yet been fully investigated. Gaining a better understanding of the physiological and psychological responses related to LL-BFRT is critical for evaluating its overall clinical utility in an ACLR population.

Experimental Hypotheses

***Specific Aim I:** To determine the effects of LL-BFRT on motor unit recruitment and motor unit behavior compared to standard LL exercise without BFRT.*

Primary Hypothesis I: We hypothesize that the LL-BFRT condition will increase overall motor unit recruitment of the vastus lateralis compared to the LL condition.

Specific Aim II: ***To examine the effects of LL-BFRT on muscle strength and limb symmetry in patients with quadriceps strength deficits following ACLR compared to a control condition.***

Primary Hypothesis II: Those treated with LL-BFRT will experience improved quadriceps strength deficits compared to those to those exposed to a control condition.

Specific Aim III: ***To explore the effects of LL-BFRT on patient reported outcomes in patients with quadriceps strength deficits following ACLR compared to a control condition.***

Primary Hypothesis III: Individuals treated with LL-BFRT will experience improvements in kinesiophobia, subjective function, psychological readiness, and the overall condition of their injured limb compared to participants exposed to a control condition.

Project and Designs

I. Manuscript I

Motor Unit Recruitment During Low Load Exercise with Blood Flow Restriction Therapy

a. Research Question

- How does BFRT influence motor unit recruitment and behavior during low-load exercise compared to low-load exercise without BFRT?

b. Experimental Design

- Cross-Sectional Cross-Over Study

c. Independent Variables:

- Exercise condition (LL-BFRT vs. LL)
- Exercise set (Set 1-4 and a maximal isometric fatigue trial)

d. Dependent Variables:

- Number of motor units recruited
- Peak Motor Unit Action Potential Amplitude
- Average Motor Unit Action Potential Amplitude
- Peak Motor Unit Firing Rate
- Average Motor Unit Firing Rate
- Initial Motor Unit Firing Rate
- Terminal Motor Unit Firing Rate
- Rating of Perceived Exertion (RPE)

e. Inclusion

- Adults 18 years of age or older
- Score of 14 or more on the Godin Leisure-Time Exercise Questionnaire or a score of 5 or more on the Tegner Activity Scale
- Willingness and ability to comply with the scheduled visit and study procedures

f. Exclusion

- Lower extremity injury within the past 6 months
- Lower extremity surgery within the past 12 months
- History or current diagnosis of a metabolic, pulmonary, or cardiovascular disease (e.g., Peripheral Artery Disease and/or Peripheral Vascular Disease (PAD/PVD), diabetes, venous thromboembolism, deep vein

thrombosis, impaired circulation or peripheral vascular compromise, sickle cell anemia, and severe hypertension)

- Current use of anti-coagulant medication
- Current diagnosis of cancer
- Patient is pregnant
- Unable to provide informed consent

II. Manuscript II

Influence of Blood Flow Restriction Therapy on Quadriceps Weakness in Patients Post-Anterior Cruciate Ligament Reconstruction

a. Research Question

- Does the utilization of LL-BFRT improve quadriceps strength deficits in patients post-ACLR?

b. Experimental Design

- Randomized Pilot Study

c. Independent Variables:

- Group (LL-BFRT vs. True Control)

d. Dependent Variables:

- Involved Knee Extensor Strength (Nm/kg)
    - Isokinetic knee extension at 180 deg/s
    - Isokinetic knee extension at 90 deg/s
    - Isometric knee extension at 90 deg of knee flexion
- Knee Extensor Strength – Limb Symmetry Index (%)

- Isokinetic knee extension at 180 deg/s
- Isokinetic knee extension at 90 deg/s
- Isometric knee extension at 90 deg of knee flexion

e. Inclusion

- 15-64 years of age
- Diagnosis of unilateral ACLR
- 3 months or more post-ACLR
- Limb symmetry index (LSI) for isokinetic or isometric knee extension strength is < 80% (LSI = (ACLR / Contralateral) * 100)

f. Exclusion

- Graft failure
- Severe surgical complication
- Current or history of cardiovascular, metabolic, or neurological disorders or conditions (e.g., Peripheral Artery Disease and/or Peripheral Vascular Disease (PAD/PVD), diabetes, venous thromboembolism, deep vein thrombosis, impaired circulation or peripheral vascular compromise, sickle cell anemia, and severe hypertension)
- Current use of anti-coagulant medication
- Known pregnancy (per query)
- Malignancy diagnosis
- Serious infection near lower limb
- Muscular abnormalities

- Formal, structured experience with LL-BFRT during post-surgical ACLR physical therapy

III. Manuscript III

Psychological Responses to Blood Flow Restriction Therapy in Patients Following Anterior Cruciate Ligament Reconstruction

a. Research Question

- Does LL-BFRT improve patient-reported outcome measures in patients with quadriceps strength deficits following ACLR?
- *Secondary:* Is there a relationship between changes in quadriceps strength symmetry and changes in patient reported outcome measures?

b. Experimental Design

- Exploratory Pilot Study

c. Independent Variables:

- Group (LL-BFRT vs. Control)

d. Dependent Variables:

- Subjective Knee Function and Symptomology
    - International Knee Documentation Committee Subjective Knee Evaluation (IKDC)
    - Knee Injury and Osteoarthritis Outcome Score (KOOS)
- Psychological Readiness
    - Anterior Cruciate Ligament – Return to Sport Index (ACL-RSI)
- Fear of Movement and Reinjury

    - Tampa Scale for Kinesiophobia (TSK)
- Overall patient perception of involved limb
    - Global Rating of Change (GRoC)

e. Inclusion

- 15-64 years of age
- Diagnosis of unilateral ACLR
- 3 months or more post-ACLR
- Limb symmetry index (LSI) for isokinetic or isometric knee extension strength is < 80% (LSI = (ACLR / Contralateral) * 100)

f. Exclusion

- Graft failure
- Severe surgical complication
- Current or history of cardiovascular, metabolic, or neurological disorders or conditions (e.g., Peripheral Artery Disease and/or Peripheral Vascular Disease (PAD/PVD), diabetes, venous thromboembolism, deep vein thrombosis, impaired circulation or peripheral vascular compromise, sickle cell anemia, and severe hypertension)
- Current use of anti-coagulant medication
- Known pregnancy (per query)
- Malignancy diagnosis
- Serious infection near lower limb
- Muscular abnormalities

- Formal, structured experience with LL-BFRT during post-surgical ACLR physical therapy

Assumptions

- Participants were honest when answering all questions related to inclusion and exclusion criteria
- Participants exerted maximal effort during each baseline and follow-up strength assessment
- Participants gave their best effort during the LL-BFRT intervention program (if allocated to the LL-BFRT intervention group)
- Participants were honest when answering all patient reported outcome measures
- Participants allocated to the control group did not perform LL-BFRT while participating in the study
- Knee extension assessments were representative of maximal quadriceps strength
- Muscle activation assessed via sEMG was isolated to the vastus lateralis and was not influenced by cross-talk from surrounding musculature
- Participants did not take part in any strenuous activity within 24 hours of their scheduled study session (Manuscript I)
- Measurement tools were accurate and reliable

Delimitations

- Participation was limited by our predetermined inclusion and exclusion criteria
- All components of the project were completed at a single-site academic institution

- All participants were between 15 to 64 years of age
- Participants were recruited from the local university as well as the surrounding community and associated health system
- Participants were randomly allocated to their group assignment (Manuscript II/III)
- LL-BFRT exercise sessions were supervised by a single certified athletic trainer across the entire intervention timeframe
- Strength assessments were completed by a blinded assessor (Manuscript II)
- Torque output was normalized to a participant's body mass to allow for between subject comparisons (Manuscript II)
- Participants served as their own control for making comparisons (Manuscript I)
- Participants reported having no formal experience with LL-BFRT in their previous post-surgical rehabilitative program (Manuscript II/III)

Limitations

- For Manuscript II and III, our sample size was relatively small compared to the overall target population due to the pilot design of our study
- Our samples for each manuscript were primarily comprised of females (all females in Manuscript II/III)
- Due to methodological constraints in Manuscript I, we were unable to make direct comparisons to determine how an individual motor unit's behavioral characteristics may have changed across each set of exercise and condition

- For Manuscript I, we were unable evaluate motor unit recruitment thresholds as measures of torque output and muscle activation were not synchronized during each assessment
- For Manuscript II and III, participants enrolled in the study at varying stages in their recovery process as indicated by their time since surgery
- We were unable to determine what each participant may have experienced during their previous post-surgical rehabilitation program following their ACLR
- For Manuscript II, we were unable to determine the direct underlying cause of a participant's persistent quadriceps strength deficits
- For Manuscript III, the TSK has not been validated in an ACLR population
- One participant in the control group for Manuscript II/III received clearance for unrestricted physical activity midway through the intervention timeframe

Operational Definitions & Equations

1. Isokinetic strength – The amount of torque produced during a task where the velocity of movement is set at a certain speed.
2. Isometric strength – The amount of torque produced during a task where the joint maintains a stationary position.
3. Maximal Voluntary Isometric Contraction – The peak torque that can be generated voluntarily with the joint in a stationary position.
4. Limb Symmetry Index – The comparison of the involved limb (ACL-Reconstructed limb) to the uninvolved (Healthy) limb. The limb symmetry index (LSI) was calculated as: (Involved Limb/Uninvolved Limb) *100

5. Patient Reported Outcome Measure (PROM) – Subjective assessments that measure the influence of injury or illness on an individual's function, lifestyle, and well-being.
6. Persistent Muscle Weakness – Strength deficits that report following injury or surgery and that do not improve following prescribed treatments and rehabilitation.
7. Limb Occlusion Pressure (LOP) – Minimum amount of pressure needed to fully occlude the flow of arterial blood distal to the site of cuff application.[22]
8. Personalized Tourniquet Pressure (PTP) - An individualized amount of pressure determined by taking a percentage of an individual's total limb occlusion pressure.
9. Surface Electromyogram (sEMG) – The electrical signal generated by a muscle contraction as detected from the skin surface.[23]
10. Motor Unit – A group of skeletal muscle fibers innervated by a single alpha motor neuron.[23]
11. Motor Unit Action Potential (MUAP) – The electrical signal generated by a motor unit firing.[23]
12. Peak Firing Rate – The inverse of the max inter-pulse interval of all motor unit firing instances within the specified time interval. Each inter-pulse interval is a measure of the interval between adjacent motor unit firing instances.[23]
13. Average Firing Rate – The inverse of the average inter-pulse interval of all motor unit firing instances within the specified time interval. Each inter-pulse interval is a measure of the interval between adjacent motor unit firing instances.[23]
14. Peak MUAP Amplitude – The maximum across all channels of the maximum value of the rectified MUAP waveforms.[23]

15. Average MUAP Amplitude – The mean across all channels of the maximum value of the rectified MUAP waveforms.[23]

Innovation

Manuscript I

The implementation of BFRT during low resistance exercise has been suggested to elicit strength gains and muscular hypertrophy via altered recruitment of high threshold motor units. Until recently, this proposed physiological mechanism of LL-BFRT has been investigated using indirect measures of sEMG.[4–7] Unfortunately, these methods are unable to directly assess changes in muscle activation at the individual motor unit level. Utilizing novel, noninvasive sEMG technology with motor unit decomposition capabilities may counter these limitations and help to further elucidate the influence of BFRT on motor unit recruitment.[24]

The proposed study would provide preliminary evidence to support this proposed mechanism of LL-BFRT on motor unit recruitment and behavior in healthy, physically active individuals. By exploring the recruitment of motor units and their specific behavior characteristics such as the number of motor units recruited, peak and average firing rates, and peak and average action potential amplitudes, we can begin to examine how LL-BFRT may influence these factors during exercise.

Manuscript II

Rupture of the ACL is one of the most common knee-related injuries. In the United States, an estimated 250,000 ACL injuries are sustained per year with many patients electing

to undergo surgical reconstruction followed by postoperative physical therapy.[25] While the structure and components of traditional ACLR rehabilitation programs may vary, protocols typically focus on restoring knee function and increasing muscle strength in order to return patients to preinjury levels of physical activity and reduce the risk of subsequent injury. Despite the completion of traditional rehabilitation, persistent quadriceps weakness continues to be a major limitation and costly burden for many individuals following ACLR.[10,11]

Unfortunately, there is no true standard of care for patients that have failed to respond to traditional ACLR rehabilitation in terms of muscle weakness and atrophy. Non-traditional therapies, such as LL-BFRT, have been recently investigated as potential rehabilitative treatment techniques for improving muscle strength in patients post-ACLR. However, many of these studies have explored the implementation of LL-BFRT early on in the rehabilitative process (2 days to 18 weeks post-operatively).[13–18] The benefits of LL-BFRT for improving muscle strength deficits during the later phases of rehabilitation have yet to be substantially explored. This intervention study would provide evidence to support the utilization of LL-BFRT as complementary treatment approach for improving muscle strength deficits during the mid-to-late post-operative phases of rehabilitation in patients following ACLR.

Manuscript III

Although successful recovery after ACLR is considered to be multifactorial, identification of interventions that are able to address both the modifiable physical (i.e., strength and functional performance) and psychological risk factors (i.e., anxiety, psychological readiness, fear of reinjury, and subjective appraisal of knee function)

associated with poor recovery may improve the return to sport process and mitigate the risk of reinjury.[26,27]

While the physiological effects of LL-BFRT, including increased muscle strength and hypertrophy with reduced joint loading, have started to be examined,[28] the psychological impact of this treatment method has not been fully investigated. As BFRT drastically increases the perceived difficulty of low load exercises due to augmented exercise induced muscle fatigue, patients may report the exercise as more challenging and that they are getting stronger despite decreased loading and mechanical tension. Recent studies have secondarily examined the subjective outcomes associated with BFRT and have demonstrated conflicting results.[29–33] Findings associated with the proposed study would provide evidence to support the psychological benefits associated with LL-BFRT in patients with quadriceps strength deficits following ACLR and traditional post-surgical rehabilitation.

References

1. Fatela P, Mendonca GV, Veloso AP, Avela J, Mil-Homens P. Blood Flow Restriction Alters Motor Unit Behavior During Resistance Exercise. *Int J Sports Med*. 2019;40(9):555-562. doi:10.1055/a-0888-8816

2. Lorenz D, Bailey L, Wilk K, et al. Current Clinical Concepts: Blood Flow Restriction Training. *J Athl Train*. Published online January 22, 2021. doi:10.4085/418-20

3. Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. *Br J Sports Med*. 2017;51(13):1003-1011. doi:10.1136/bjsports-2016-097071

4. Centner C, Lauber B. A Systematic Review and Meta-Analysis on Neural Adaptations Following Blood Flow Restriction Training: What We Know and What We Don't Know. *Front Physiol*. 2020;11:887. doi:10.3389/fphys.2020.00887

5. Hedt C, McCulloch PC, Harris JD, Lambert BS. Blood Flow Restriction Enhances Rehabilitation and Return to Sport: The Paradox of Proximal Performance. *Arthrosc Sports Med Rehabil*. 2022;4(1):e51-e63. doi:10.1016/j.asmr.2021.09.024

6. de Queiros VS, de França IM, Trybulski R, et al. Myoelectric Activity and Fatigue in Low-Load Resistance Exercise With Different Pressure of Blood Flow Restriction: A Systematic Review and Meta-Analysis. *Front Physiol*. 2021;12. Accessed August 23, 2022. https://www.frontiersin.org/articles/10.3389/fphys.2021.786752

7. Cerqueira MS, Maciel DG, Barboza JAM, et al. Low-Load Blood-Flow Restriction Exercise to Failure and Nonfailure and Myoelectric Activity: A Meta-Analysis. *J Athl Train*. 2022;57(4):402-417. doi:10.4085/1062-6050-0603.20

8. Burgi CR, Peters S, Ardern CL, et al. Which criteria are used to clear patients to return to sport after primary ACL reconstruction? A scoping review. *Br J Sports Med*. 2019;53(18):1154-1161. doi:10.1136/bjsports-2018-099982

9. Schmitt LC, Paterno MV, Hewett TE. The impact of quadriceps femoris strength asymmetry on functional performance at return to sport following anterior cruciate ligament reconstruction. *J Orthop Sports Phys Ther*. 2012;42(9):750-759. doi:10.2519/jospt.2012.4194

10. Palmieri-Smith RM, Thomas AC, Wojtys EM. Maximizing quadriceps strength after ACL reconstruction. *Clin Sports Med*. 2008;27(3):405-424, vii-ix. doi:10.1016/j.csm.2008.02.001

11. Lepley LK. Deficits in Quadriceps Strength and Patient-Oriented Outcomes at Return to Activity After ACL Reconstruction: A Review of the Current Literature. *Sports Health*. 2015;7(3):231-238. doi:10.1177/1941738115578112

12. Bryant AL, Kelly J, Hohmann E. Neuromuscular adaptations and correlates of knee functionality following ACL reconstruction. *J Orthop Res Off Publ Orthop Res Soc*. 2008;26(1):126-135. doi:10.1002/jor.20472

13. Bobes Álvarez C, Issa-Khozouz Santamaría P, Fernández-Matías R, et al. Comparison of Blood Flow Restriction Training versus Non-Occlusive Training in Patients with Anterior Cruciate Ligament Reconstruction or Knee Osteoarthritis: A Systematic Review. *J Clin Med*. 2020;10(1):E68. doi:10.3390/jcm10010068

14. Caetano D, Oliveira C, Correia C, Barbosa P, Montes A, Carvalho P. Rehabilitation outcomes and parameters of blood flow restriction training in ACL injury: A scoping review. *Phys Ther Sport Off J Assoc Chart Physiother Sports Med*. 2021;49:129-137. doi:10.1016/j.ptsp.2021.01.015

15. Wengle L, Migliorini F, Leroux T, Chahal J, Theodoropoulos J, Betsch M. The Effects of Blood Flow Restriction in Patients Undergoing Knee Surgery: A Systematic Review and Meta-analysis. *Am J Sports Med*. Published online August 18, 2021:3635465211027296. doi:10.1177/03635465211027296

16. Koc BB, Truyens A, Heymans MJLF, Jansen EJP, Schotanus MGM. Effect of Low-Load Blood Flow Restriction Training After Anterior Cruciate Ligament Reconstruction: A

Systematic Review. *Int J Sports Phys Ther*. 2022;17(3):334-346. doi:10.26603/001c.33151

17. Charles D, White R, Reyes C, Palmer D. A SYSTEMATIC REVIEW OF THE EFFECTS OF BLOOD FLOW RESTRICTION TRAINING ON QUADRICEPS MUSCLE ATROPHY AND CIRCUMFERENCE POST ACL RECONSTRUCTION. *Int J Sports Phys Ther*. 2020;15(6):882-891. doi:10.26603/ijspt20200882

18. Colapietro M, Portnoff B, Miller SJ, Sebastianelli W, Vairo GL. Effects of Blood Flow Restriction Training on Clinical Outcomes for Patients with ACL Reconstruction: A Systematic Review. *Sports Health*. Published online February 8, 2022:19417381211070830. doi:10.1177/19417381211070834

19. Nwachukwu BU, Adjei J, Rauck RC, et al. How Much Do Psychological Factors Affect Lack of Return to Play After Anterior Cruciate Ligament Reconstruction? A Systematic Review. *Orthop J Sports Med*. 2019;7(5):2325967119845313. doi:10.1177/2325967119845313

20. Zwolski C, Schmitt LC, Quatman-Yates C, Thomas S, Hewett TE, Paterno MV. The influence of quadriceps strength asymmetry on patient-reported function at time of return to sport after anterior cruciate ligament reconstruction. *Am J Sports Med*. 2015;43(9):2242-2249. doi:10.1177/0363546515591258

21. Lepley AS, Pietrosimone B, Cormier ML. Quadriceps Function, Knee Pain, and Self-Reported Outcomes in Patients With Anterior Cruciate Ligament Reconstruction. *J Athl Train*. 2018;53(4):337-346. doi:10.4085/1062-6050-245-16

22. McEwen JA, Owens JG, Jeyasurya J. Why is it Crucial to Use Personalized Occlusion Pressures in Blood Flow Restriction (BFR) Rehabilitation? *J Med Biol Eng*. 2019;39(2):173-177. doi:10.1007/s40846-018-0397-7

23. NeuroMap Software User Guide. Published online April 23, 2019.

24. De Luca CJ, Adam A, Wotiz R, Gilmore LD, Nawab SH. Decomposition of surface EMG signals. *J Neurophysiol*. 2006;96(3):1646-1657. doi:10.1152/jn.00009.2006

25. Griffin LY, Albohm MJ, Arendt EA, et al. Understanding and preventing noncontact anterior cruciate ligament injuries: a review of the Hunt Valley II meeting, January 2005. *Am J Sports Med*. 2006;34(9):1512-1532. doi:10.1177/0363546506286866

26. Ardern CL. Anterior Cruciate Ligament Reconstruction—Not Exactly a One-Way Ticket Back to the Preinjury Level. *Sports Health*. 2015;7(3):224-230. doi:10.1177/1941738115578131

27. Ardern CL, Taylor NF, Feller JA, Webster KE. A systematic review of the psychological factors associated with returning to sport following injury. *Br J Sports Med*. 2013;47(17):1120-1126. doi:10.1136/bjsports-2012-091203

28. Ramme AJ, Rourke BJ, Larson CM, Bedi A. Ischemic Therapy in Musculoskeletal Medicine. *Am J Sports Med*. 2020;48(12):3112-3120. doi:10.1177/0363546520901539

29. Tennent DJ, Hylden CM, Johnson AE, Burns TC, Wilken JM, Owens JG. Blood Flow Restriction Training After Knee Arthroscopy: A Randomized Controlled Pilot Study. *Clin J Sport Med Off J Can Acad Sport Med*. 2017;27(3):245-252. doi:10.1097/JSM.0000000000000377

30. Hughes L, Rosenblatt B, Haddad F, et al. Comparing the Effectiveness of Blood Flow Restriction and Traditional Heavy Load Resistance Training in the Post-Surgery Rehabilitation of Anterior Cruciate Ligament Reconstruction Patients: A UK National Health Service Randomised Controlled Trial. *Sports Med Auckl NZ*. Published online July 12, 2019. doi:10.1007/s40279-019-01137-2

31. Curran MT, Bedi A, Mendias CL, Wojtys EM, Kujawa MV, Palmieri-Smith RM. Blood Flow Restriction Training Applied With High-Intensity Exercise Does Not Improve Quadriceps Muscle Function After Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial. *Am J Sports Med*. 2020;48(4):825-837. doi:10.1177/0363546520904008

32. Noyes FR, Barber-Westin S, Sipes L. Blood Flow Restriction Training Can Improve Peak Torque Strength in Chronic Atrophic Postoperative Quadriceps and Hamstrings Muscles. *Arthrosc J Arthrosc Relat Surg Off Publ Arthrosc Assoc N Am Int Arthrosc Assoc*. Published online March 31, 2021. doi:10.1016/j.arthro.2021.03.040

33. Kargaran A, Abedinpour A, Saadatmehr Z, Yaali R, Amani-Shalamzari S, Gahreman D. Effects of dual-task training with blood flow restriction on cognitive functions, muscle quality, and circulatory biomarkers in elderly women. *Physiol Behav*. 2021;239:113500. doi:10.1016/j.physbeh.2021.113500

APPENDIX B: LITERATURE REVIEW

The purpose of this literature review is to I: Review the neuromuscular system including motor unit characteristics and mechanisms of muscle growth and performance, II: Review the anterior cruciate ligament including its anatomy and surrounding musculature, injury epidemiology and risk factors, injury intervention, traditional post-surgical rehabilitation procedures, and common neuromuscular and psychological limitations after surgical reconstruction, III: Review the proposed mechanisms of blood flow restriction therapy and its potential benefits in patients following anterior cruciate ligament reconstruction.

Section I: Neuromuscular System

The neuromuscular system is comprised of two major organ systems: the muscular system and the nervous system. This intricate network of connections between extrafusal muscle fibers and alpha motor neurons allows for communication between the central nervous system, peripheral nervous system, and muscles to produce muscle contractions resulting in bodily movement. The specialized site of communication between the axon terminal of an alpha motor neuron, synaptic cleft, and motor end plate of a muscle fiber is known as the neuromuscular junction (NMJ).[1]

To initiate and terminate a muscle contraction, the following series of events must take place.[2] As an action potential (i.e., electrical stimuli) propagates from the cell body of an alpha motor neuron towards the axon terminal, a neurotransmitter, acetylcholine, is released into the synaptic cleft where it binds to acetylcholine-receptor membrane channels on the motor end plate. This binding allows for the action potential to transfer from the neuron to

the muscle fiber where it then travels along the sarcolemma, down various transverse-tubules (i.e., T-tubules) resulting in a release of calcium ions from the sarcoplasmic reticulum into the cytosol via gated calcium channels. This excitation-contraction coupling event is the primary mechanism for eliciting muscle fiber contraction. Calcium ions bind to troponin revealing active binding sites along actin filaments for myosin head attachment. Utilizing ATP, the interaction between actin and myosin (i.e., cross-bridge formation) produces sarcomere shortening creating tension within the muscle. Cycles of cross-bridge formation between actin and myosin are subject to continue as long as calcium ions and ATP are available within the cytosol. Once action potentials cease, calcium ions are removed from the cytosol via calcium ion pumps, troponin regains its initial position covering myosin binding sites, and myosin heads split ATP into ADP and phosphate resulting in recocking of the free myosin heads and muscle relaxation. The strength of a motor response is directly proportional to the action potential frequency and number of motor units stimulated.[2]

Motor Unit Characteristics

A motor unit, often considered the final common pathway,[3,4] is defined as an alpha motor neuron and all of the homogenous muscle fibers that it innervates. An early feline study by Burke et al.[5] described the identification and classification of motor units into three distinguishable categories: slow (S), fast-fatigue resistant (FR), and fast-fatigable (FF). This classification scheme is based on several motor unit characteristics such as their fatiguability, twitch response, and histochemical profile.[5–7] However, more recently, Heckman and Enoka[8] have suggested the continuous distribution of these characteristics in humans and have proposed the utilization of terminology based on a motor unit's recruitment threshold in

terms of force (i.e., low- and high-threshold motor units). Although several variations have been described, research has suggested that there are three primary types of skeletal muscle fibers (i.e., isoforms of the myosin heavy chain) that are innervated by alpha motor neurons in the human body: Type I, Type IIA, and Type IIX.[9] Muscle fibers innervated by a given alpha motor neuron are intermingled within a region of the muscle to allow for an even production of tension on the respective muscle tendon. Similar to that of motor units, muscle fibers are often referred to by their contractile characteristics and utilization of oxidative or glycolytic energy sources with Type I fibers referred to as slow oxidative, Type IIA fibers referred to as fast oxidative glycolytic, and Type IIX fibers referred to as fast glycolytic.[10,11] In general, Type I muscle fibers are typically associated with smaller alpha motor neurons with low force recruitment thresholds and present with small amplitude, long duration twitch responses and are capable of producing low-grade contractions for sustained periods of time.[11] Conversely, larger alpha motor neurons with higher force recruitment thresholds innervate Type IIA and Type IIX muscle fibers that have fast twitch responses and are capable of producing fast, high-grade contractions (Figure B1).[11]

A given muscle can contain hundreds of motor units that innervate up to thousands of muscle fibers. However, the distribution of motor unit and muscle fiber types within a muscle is largely dependent on the function of that muscle. For example, on average the human vastus lateralis

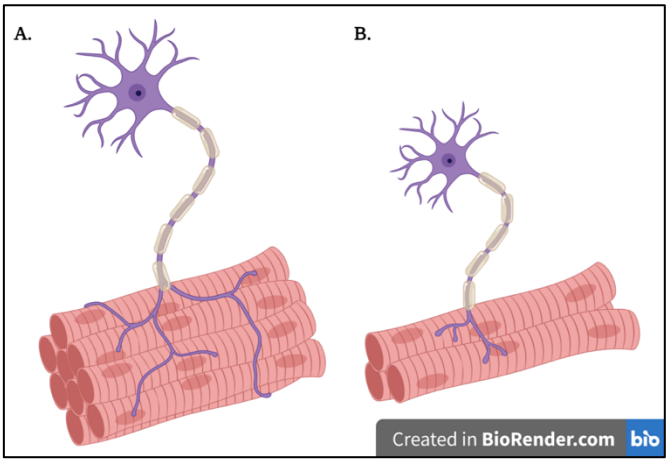


Figure B1. A. Large motor unit; B. Small motor unit

muscle is composed of 40% to 70% Type I muscle fibers, 20% to 30% Type IIA muscle fibers, and 7% to 30% Type IIX muscle fibers.[12–14] In general, muscles responsible for generating low forces and performing fine, precise movements (i.e., movement of the eyes and fingers) are commonly innervated by smaller motor units that possess low innervation ratios.[11] Whereas muscles that produce larger forces and perform more gross movements (i.e., jumping or kicking) tend to have higher innervation ratios.[11]

Additionally, the amount of force produced by a muscle can be modulated by two primary mechanisms: altering the number of active motor units or their firing rates.[15] When force production is initiated, smaller motor units with lower recruitment thresholds tend to be activated first followed by progressive activation of larger motor units with higher recruitment thresholds as force production increases.[16–18] This phenomenon is also known as the "Henneman Size Principle".[16–18] This orderly recruitment of motor units by size allows for smooth, graded muscle contractions that are dependent on the desired force output.[11] During sustained contractions, motor units with similar recruitment thresholds discharge on a rotating basis to allow for metabolic recovery thus minimizing the impact of neuromuscular fatigue.[19,20] In terms of firing rates, the relationship between motor unit recruitment thresholds and firing rates has been debated.[15] Traditionally, the notion that motor units with higher recruitment thresholds

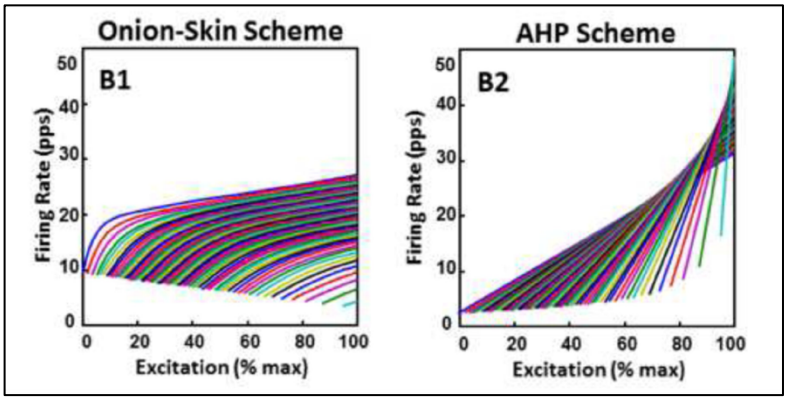


Figure B2. Simulated motor unit firing rate as a function of increasing input excitation to the motor neuron pool in the Onion-Skin (B1) and AHP (B2) scheme. (De Luca and Contessa, 2015)

have higher firing rates than motor units with lower recruitment thresholds has been commonly accepted.[15,21] This hypothesis suggests that alpha motor neurons with larger diameters present with shorter after-hyperpolarization periods and higher firing rates than alpha motor neurons with smaller diameters.[15,21] This linear relationship between recruitment threshold and firing rate has also been referred to as the "after-hyperpolarization" (AHP) scheme.[15,21] However, another phenomenon, commonly referred to as the "onion-skin" scheme,[22] suggests an inverse relationship between recruitment threshold and firing rate. In contrast, this scheme indicates that during voluntary, constant-force contractions motor units recruited early on display and maintain higher firing rates than motor units recruited later (Figure B2).[15]

Mechanisms of Muscle Growth and Performance

Muscle growth, or hypertrophy which is defined as an enlargement of a body part or muscle resulting from an increase in the size of its existing cells, occurs when protein synthesis exceeds protein breakdown generating a positive net protein balance.[23] In general, muscle hypertrophy can be achieved in two ways: an increase in muscle fiber diameter or an increase in muscle fiber length by adding additional sarcomeres in series along the myofibrils. Conversely, atrophy is the reduction in the size, tone, and power of a muscle due to disease or inactivity.[24] As the cross-sectional area of muscles increase, there is a proportional increase in muscular strength, or the ability of a muscle to produce a single bout of maximal force. There are three proposed mechanisms for stimulating exercise-induced muscle growth including mechanical tension, metabolic stress, and muscle damage.[25,26]

Mechanically induced tension is created when muscle fibers are either passively stretched (i.e., passive tension) or actively contracted (i.e., active tension) when resisting an external load. The combination of active and passive tension produced during eccentric muscle contractions may elicit an additive hypertrophic response generated by overall mechanical tension.[26] Evidence has demonstrated that mechanical stress is a primary determinant of muscle hypertrophy.[27,28] According to Wackerhage et al,[29] there are several evidence-based theories to support the relationship between mechanical stimuli and muscle growth. For example, reduced mechanical loading during periods of immobilization has been associated with muscle atrophy,[30] whereas mechanically overloaded muscles have demonstrated characteristics of hypertrophy.[28] However, when used in isolation mechanical tension has been shown to induce neural adaptations without associated muscle hypertrophy, therefore secondary mechanisms of metabolic stress and muscle damage are necessary for optimal muscular improvements.[31,32]

Metabolic stress due to metabolite accumulation is also considered to be an important secondary component of the exercise-induced hypertrophic response within muscles.[26] After performing exercise that relies on anaerobic glycolysis for ATP production, such as high load (HL) training, there is a subsequent production and accumulation of metabolites including lactate, hydrogen ions, and inorganic phosphate.[26,27] The abundance of these metabolites produced during glycolytic-based training generates metabolic stress and may act as an assistive mechanism for stimulating muscle growth. Similarly, the hypoxic environment produced during resistance training can augment this metabolite accumulation and further prompt the hypertrophic response. Hypertrophic adaptations resulting from metabolic stress have been associated with increased muscle fiber recruitment, elevated hormone and reactive

oxygen species production, altered myokines, and cellular swelling.[27,33–36] It has been suggested that exercise-induced muscle damage (EIMD), often resulting from unaccustomed exercise, may also contribute to muscle hypertrophy.[37] Ranging from indistinguishable microtrauma to compromised contractile components within muscle tissue, the severity of EIMD is dependent on several factors including exercise type, intensity, and duration.[38] Given the increased mechanical tension produced when performing exercise in a lengthened state, eccentric exercise has been proposed to have a greater contribution to EIMD compared to concentric and isometric-based exercises.[37,39,40] It has also been suggested that mechanically induced detachment of actin and myosin cross-bridges formations may be related to EIMD during eccentric exercise.[41] Currently, research has established that EIMD may be associated with factors related to muscle repair and regeneration such as inflammatory cell and insulin-like growth factor-1 signaling, satellite cell activity, and cellular swelling.[37] However, insufficient evidence has been established to confirm the causal relationship between muscle damage and hypertrophy.[37]

The capacity of a muscle to perform work via strength, power, and endurance is also known as muscle performance or fitness. When exercising to improve muscle performance via increases in muscle strength and size, initial increases in strength that are noted without increases in muscle size typically occur due to improved neuromuscular function.[24] As muscles are overloaded during exercise or weight training, additional motor units become activated and more efficient at transmitting action potentials resulting in stronger muscle contractions and greater force output. It has also been suggested that improvements in strength following resistance training may reverse in as little as 48 hours. Therefore, consistent exercise is required to prevent decrements in strength and atrophy. Strengthening

recommendation guidelines from the American College of Sports Medicine recommend the use of resistance training at 60-70% of the 1 repetition maximum (1RM) for novice individuals and 80% of the 1RM for experienced individuals to induce strength and hypertrophy responses.[42] Unfortunately, these loads are not well tolerated after injury, surgical intervention, or in elderly populations.

Section II: Anterior Cruciate Ligament Injury and Surgical Reconstruction

Anatomy

There are four primary ligamentous structures within the tibiofemoral joint that are responsible for reducing excessive motion about the joint: the anterior cruciate ligament (ACL), the posterior cruciate ligament (PCL), the medial collateral ligament (MCL), and the lateral collateral ligament (LCL) (Figure B3). The ACL is responsible for controlling and limiting excessive anterior translation of the tibia and extreme degrees of internal and external tibial rotation.[43] It has been suggested that the ACL is comprised of two primary bundles, the anteromedial bundle (AM) and the posterolateral bundle (PL), which have been named based on their insertion location on the tibia.[44] Each of these component bundles of the ACL have been found to originate on the posteromedial side of the lateral femoral condyle. According to Giuliani et al,[44] these bundles are largely composed of type I

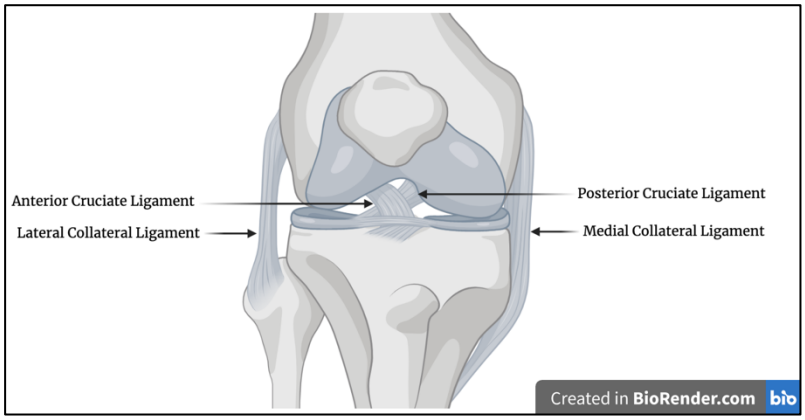


Figure B3. The four primary ligamentous structures of the tibiofemoral including the anterior cruciate ligament, posterior cruciate ligament, medial collateral ligament, and lateral collateral ligament.

collagen fibers that receive their primary blood supply from the middle genicular artery with secondary supply from the inferomedial and inferolateral genicular arteries.[44] The ACL also contains various types of mechanoreceptors including Ruffini corpuscles, Paccini corpuscles, Golgi organs, and free neural ends.[45] These mechanoreceptors allow the ACL to function not only as a mechanical restraint but also as a sensory organ that has protective proprioceptive and reflexive properties.[43]

In terms of biomechanics, when exposed to an anterior tibial load the in situ force in the PL bundle of the ACL is greatest in full knee extension (i.e., in this position the PL bundle is most taught).[46] When the knee moves into a flexed position the in situ force in the PL bundle decreases as the in situ force in the AM bundle increases. The in situ force in the AM bundle of the ACL is greatest between 60 and 90 degrees of knee flexion (i.e., throughout this range of motion the AM bundle is most taught).[46] However, it has been suggested that at varying angles of knee flexion the forces of the PL bundle are similar to those of the entire ACL.[47] Given this and the fact that most ACL injuries occur when the knee is in an extended position, it is important to consider the stability and function of the both the PL and AM bundles during surgical reconstruction of the ACL following injury.[43]

Surrounding Musculature

The tibiofemoral joint is comprised of two primary types of stabilizing structures, static (i.e., passive) stabilizers and dynamic (i.e., active) stabilizers. As described above, the ACL is considered to be one of the primary static stabilizers within the tibiofemoral joint and is responsible for limiting excessive anterior movement of the tibia. In contrast, the musculature surrounding the tibiofemoral joint acts to provide dynamic stabilization at the

joint. On the anterior aspect, the quadriceps muscle group including the rectus femoris, vastus medialis, vastus intermedius, and vastus lateralis attach to the tibial tuberosity via the quadriceps tendon, patella, and patellar tendon. During active contraction, these muscles act to perform knee extension resulting in anterior translation of the tibia on the femur. Additionally, the quadriceps muscles are innervated by the posterior motor division of the femoral nerve and receive their primary blood supply via the femoral artery with drainage into the femoral vein.[48]

Conversely, on the posterior aspect of tibiofemoral joint, the hamstring muscle group including the biceps femoris, semimembranosus, and semitendinosus insert onto the proximal tibia. This muscle group acts to perform knee flexion thus resisting anterior translation of the tibia. In terms of innervation, the short head of the biceps femoris is innervated by the common peroneal nerve whereas the long head of the biceps femoris, semimembranosus, and semitendinosus are innervated by the tibial nerve.[49] These muscles receive their primary blood supply from the perforating branches of the deep femoral artery and drain largely into the femoral vein.[49]

Epidemiology and Risk Factors

Sprain or rupture of the ACL is one of the most common, costly, and severe knee-related ligamentous injuries, especially among physically active individuals and athletes.[50] The incidence of ACL injury has increased from 33 cases per 100,000 in 1994 to nearly 60 cases per 100,000 in 2014.[51] Upwards of approximately 250,000 ACL injuries are sustained annually, accruing more than $2 billion in annual healthcare costs.[50,52,53] Furthermore, nearly 100,000 ACL reconstructions (ACLR) are performed per year to correct this injury and allow

patients to return to unrestricted participation in physical activity.[50,54] It is commonly accepted that the ACL is most vulnerable for injury when the tibia is rotated with the knee in an extended, valgus position. However, common mechanisms for noncontact ACL injury (i.e., injury that occurs when no direct contact is made with the knee) when the knee is in a valgus, internally or externally rotated, and extended position are rapid cutting when changing direction, landing, jumping, decelerating, and hyperextending the knee with a planted foot.[55] Although isolated ACL injury frequently occurs, concomitant injury of other supporting structures including the menisci, MCL, LCL, PCL, or joint capsule can result in rotary instabilities of the knee. Common symptoms associated with ACL injury are an audible or perceived pop within the knee, pain surrounding the knee joint, a sensation of "giving out" when ambulating, swelling, and reduced knee range of motion.[43]

Various intrinsic and extrinsic risk factors have been found to be associated with ACL injury. An intrinsic risk factor is an individualized personal, physical, or psychological characteristic that increases one's vulnerability to sustaining an ACL injury.[50,55] There are three major categories of intrinsic risk factors related to ACL injury: anatomical, hormonal, and neuromuscular.[56] Extrinsic risk factors are environmental features that are external to the individual (i.e., weather, playing surface, footwear), but also contribute to ACL injury suseptability.[57] A two-part review of the literature by Smith et al[57,58] highlighted and summarized several of these important risk factors for ACL injury including the female sex, increased body mass index, decreased femoral notch size, decreased depth of medial tibial plateau, increased slope of the tibia plateaus, excessive anterior-posterior knee laxity, altered proprioception and lower extremity biomechanics, history of ACL injury, genetic predisposition, phase of menstrual cycle, etc.

Injury Intervention

The primary goals after ACL injury are to restore the overall stability and function of the tibiofemoral joint, address psychological barriers associated with the return to physical activity, prevent subsequent knee injury, mitigate the factors influencing the onset of knee osteoarthritis, and improve short- and long-term quality of life.[59] Three main management options have been proposed by Filbay and Grindem[59] for the treatment of ACL injury: 1) conservative rehabilitation as the first-line treatment (followed by ACLR if the patient develops functional instability), 2) ACLR as the first line treatment followed by postsurgical rehabilitation, and 3) presurgical rehabilitation followed by ACLR and postsurgical rehabilitation. However, the decision between conservative management and surgical intervention following ACL injury is largely dependent on a patient's personal characteristics (i.e., comorbid medical conditions) and goals for physical activity after treatment. For individuals hoping to return to high-level physical activity or pre-injury level of sport participation following an ACL injury, surgical reconstruction is considered the gold standard for treatment.[51] Even though conservative treatment involving structured rehabilitation (i.e., strengthening of the surrounding musculature) has been shown to be an effective option for ACL management under certain circumstances,[60] the risks associated with ACL deficiencies such as meniscal and chondral injuries as well as symptomatic knee instability, especially within youth populations, may exceed the suggested benefits of this treatment approach.[51,61,62]

Many young, active individuals choose to undergo surgical reconstruction after sustaining an ACL injury. Reconstructive surgery requires the replacement or repair of the

ACL utilizing either an allograft (i.e., donor graft) or autograft. When deciding which graft type to utilize there are several important variables to consider including graft stability, muscle strength, function, return to activity status, overall patient satisfaction, associated complications, cost, and ultimately the physician's preference.[63] The most common types of allografts utilized during ACLR include the patellar tendon, achilles tendon, and tibialis tendon, whereas the most common autografts are the patellar tendon using the "bone-patellar tendon-bone" method, the hamstring tendon, and the quadriceps tendon.[51,63] While there are noted advantages and disadvantages each graft type,[51] research has demonstrated minimal differences between graft types in terms of functional outcomes measures (i.e., stability, strength, etc.), patient satisfaction, and rate of return to preinjury level of physical activity.[63,64]

Traditional Post-Surgical Rehabilitation Procedures

After sustaining an ACL injury, evidence-based rehabilitation completed before and or after surgical reconstruction of the ACL is crucial for a successful recovery process. Targeted interventions and rehabilitation exercises that are implemented prior to surgical intervention, also known as preoperative rehabilitation or "prehabiliation", are often utilized to improve function and range of motion of the knee, decrease pain and swelling, and increase strength of the lower extremity before surgery. Although the type of prehabiliation exercises and interventions prescribed may differ based on provider preferences, a review by Giesche et al highlighted similarities in current research-based exercise programs including 4-6 weeks of lower extremity open and closed chain strengthening exercises, neuromuscular function and control exercises, stretching, and range of motion exercises.[65]

Once ACL surgery is completed, it is commonly recommended that postoperative rehabilitation should begin immediately and continue for approximately 9 to 12 months.[66] However, a recent descriptive epidemiological study investigating the temporal utilization of supervised physical therapy visits after ACLR found that on average patients only had 16.90 ± 10.60 physical therapy visits after ACLR.[67] Additionally, of those that completed physical therapy visits after ACLR, 52% of their physical therapy visits were utilized in the first 6 weeks following surgery, 75% in the first 10 weeks following surgery, and 90% in the first 16 weeks following surgery (Figure B4).[67] This suggests that patients only receive approximately 10% of their allotted physical therapy visits between 4 and 12 months post-surgery.[67] While the factors influencing an individual's access to physical therapy may differ (i.e., insurance, cost, time, etc.), the results of this study are largely concerning given that patients often continue to suffer from persistent muscle weakness and undesirable biomechanical changes after they no longer have access to physical therapy in the later phases of rehabilitation when clearance for activity is often considered.[67]

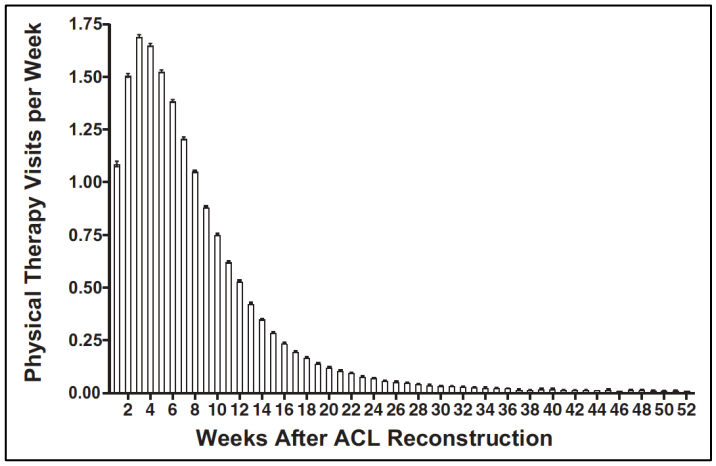


Figure B4. Mean number of physical therapy visits each week following ACLR (N = 10,411). Bars represent the mean number of visits per patient, and error bars represent the standard error of the mean. (Burroughs et al, 2021)

Rehabilitation following ACLR has shifted from relying on time-based protocols to criterion-based protocols that allow for individualized patient progression dictated by their ability to meet various clinical milestones. In a recent evidence statement, a multidisciplinary

group of ACL experts suggested utilization of 3 criterion-based phases of post-surgical rehabilitation: 1) impairment-based, 2) sport-specific training, and 3) return to play.[66] Similarly, evidence-based recommendations by Filbay and Grindem[59] suggest 5 rehabilitative phases with specific goals per phase as shown in Figure B5. Utilizing a criterion-based approach to rehabilitation progression ensures that patients do not exceed the functional or biological capacity of their surgically involved limb while also mitigating unnecessary delays in progress due to timing.[59]

Rehabilitation Phase	Main Goals
Preoperative phase (prehabiliation)	No knee joint effusion, full active and passive range of motion, 90% quadriceps strength symmetry
Acute phase	No knee joint effusion, full active and passive range of motion, straight leg raise without lag
Intermediate phase	Control of terminal knee extension in weight-bearing positions, 80% quadriceps strength symmetry, 80% hop test symmetry with adequate movement quality
Late phase	90% quadriceps strength symmetry, 90% hop test symmetry with adequate movement quality, maintain/build athletic confidence, progress sport-specific skills from closed skills with internal focus to open skills with external focus
Continued injury prevention phase	Maintain muscle strength and dynamic knee stability, manage load

Figure B5. ACL rehabilitation recommendations (adapted from Filbay and Grindem, 2019)

According to the University of Virginia Sports Medicine ACL Reconstruction Post-Operative Rehabilitation Protocol, in the earliest phase of post-operative rehabilitation (0-4 weeks post-op), interventions and exercises should focus on protecting the surgical graft, minimizing pain and swelling, and increasing knee range of motion. While exercises may vary based on surgical factors such as graft type, strengthening techniques in this phase may include exercises such as ankle pumps, quadriceps sets, heel slides, and straight leg raises. Transitioning into the next phase of rehabilitation (4-10 weeks

post-op), there should be increased focus on restoring normal gait, achieving and maintaining full knee range of motion, and improving proprioception and strength of the hip, quadriceps, hamstrings, and calf musculature. Common therapeutic activities may include closed kinetic chain strengthening exercises (i.e., squats, leg press, step ups, lunges, and wall sits), stationary biking, and balance exercises. In the next rehabilitative phase (10-16 weeks post-op), interventions should target achieving full knee range of motion, normal running mechanics, and strength approximately 70% of the individuals uninvolved lower extremity. Mechanisms for improving strength, endurance, and proprioception of the lower extremity in this phase may include open kinetic chain knee extensions (90-30 degrees), eccentrically-based exercises, advanced proprioceptive activities, and progressive strengthening exercises for the hips, quadriceps, hamstrings, and calves. In the following phase of rehabilitation (4-6 months post-op), patients should display symmetric performance of non-specific and sport specific agility drills, complete hop tests with 85% symmetry of the uninvolved limb, and have 85% strength of the quadriceps and hamstrings compared to the uninvolved limb. Physical therapy should target need-based progression of flexibility, strengthening, and agility programs, the initiation of plyometric exercises, and assessment of running mechanics. For the latest phase of rehabilitation (6+ months post-op), clinicians should determine the patient's readiness to return to physical activity or sport, prescribe maintenance programs for strength, endurance, and proprioception, and educate patients on any limitations or conditions they may face moving forward.

The decision to clear a patient for the return to physical activity after ACLR is based on three primary considerations: 1) physical readiness, 2) psychological readiness, and 3) biological healing (i.e., time since surgery).[59] To elucidate these factors, a battery of targeted

assessments should be utilized to evaluate an individual's readiness to return to activity following an ACLR. A scoping review of 209 studies, including over 22,000 participants, identified six domains for return to sport criteria following ACLR: 1) time, 2) strength, 3) hop testing, 4) clinical examination, 5) patient-reported outcome measures, and 6) performance-based criteria (Figure B6).[68] Eighty-five percent of the included studies reported time as a return to sport criterion with 72% indicating a time frame of 6 to 9 months post-surgery for clearance. Although assessment techniques varied, 41% of the included studies used isokinetic or isometric strength as a return to sport criterion with a majority requiring a limb symmetry index (i.e., [Involved ACL Limb/ Uninvolved Contralateral Limb]*100]) of greater than or equal to 85% or 90%. Similarly, at least one hop test was reported as a return to sport criterion in 14% of the included studies. Achieving at least 85% limb symmetry index during hop testing was required for clearance in 22 of these studies. Additionally, 12% of the 209 studies included patient-reported information such as patient reported outcome measures, subjective statements, or pain as return to sport criteria. However, in recent years the overall importance of psychological readiness in the return to sport assessment after ACLR has greatly increased.[69] It has been recommended that individuals achieve deficits of 10% or less prior to returning to sport following ACLR.[70,71]

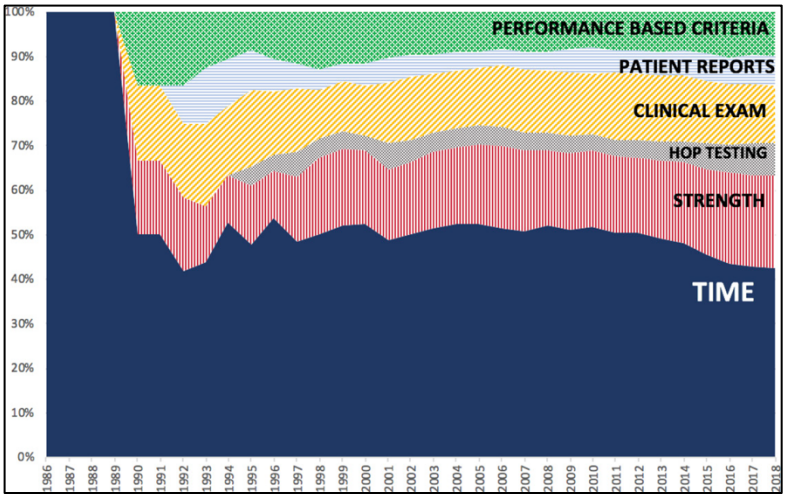


Figure B6. Relative proportion of return to sport criteria reported per year (Burgi et al, 2019)

Health-Related Consequences Following ACLR

Even with surgical and rehabilitative advancements, a systematic review of 48 studies including 5,570 individuals following ACLR reported that approximately 81% of those that suffer from an ACL injury will return to athletic activity, yet only 65% return to their preinjury level of sport participation.[72] Furthermore, for competitive athletes, only 55% reported returning back to their competitive level sport after surgical reconstruction. Individuals may not return to sport after sustaining ACL injury for various reasons including limb strength asymmetries, unrealistic expectations, fear of reinjury, and poor self-reported knee function.[73] The process of returning to physical activity and sport following ACLR can be affected by preoperative (e.g. rehabilitation, neuromuscular control, etc.), intraoperative (e.g. graft type), and postoperative (e.g. strength, neuromuscular control, psychological aspects, etc.) factors.[74] Given the multifactorial nature of the return to sport process, identifying and intervening on modifiable, physical (i.e., strength, neuromuscular control) and psychological risk factors (i.e., psychological readiness, fear of reinjury and movement, and subjective appraisal of knee function) may improve this process and reduce the risk of subsequent injury as well as the development of knee osteoarthritis.[30,75] Post-traumatic knee osteoarthritis is a debilitating condition suggested to affect more than 50% of those who have suffered from ACL injury.[76] Furthermore, a review indicated an increase in the rate of knee osteoarthritis after ACLR from 11% at 5 years post-surgery, to 21% at 10 years post-surgery, and up to 52% at 20 years post-surgery.[77] Similarly, the incidence rate of subsequent ACL injury to the reconstructed or contralateral limb has been shown to increase across time from 6% at 2 years post-surgery, to 12% at 5 years post-surgery, to 27% at 10 years post-surgery,

and to 31% at 15 years post-surgery.[78–81] It has been established that individuals who have undergone an ACLR are at a 15 times greater risk for subsequent ACL injury to either limb compared to individuals who have not previously suffered from an ACL injury.[82]

Neuromuscular Limitations

Despite the completion of traditional rehabilitation programs, persistent weakness and activation failure of the quadriceps are commonly reported in patients following injury to the tibiofemoral joint and ACL.[83] Atrophy and dysfunction of the quadriceps has been considered a primary modifiable factor contributing to the accelerated development of knee osteoarthritis[71,84] and altered knee biomechanics leading to an increased risk of subsequent ACL injury following a primary ACLR.[85] As previously stated, achieving side-to-side quadriceps strength deficits of 10% or less has been recommended as a criterion for physical activity clearance after ACLR.[68,70] However, a review of 37 studies by Lepley et al.[71] discovered that only 5 of the included studies met these clinical recommendations for side-to-side quadriceps strength deficits of 10% or less at 6 months post-surgery. Additionally, results of these 5 studies were inconclusive due to their heterogenous methodology.[71,86–90] On average, side-to-side quadriceps strength deficits of 23% ± 8% were reported with a range of 3%-40% at 6-months post-ACLR.[71] These strength deficits appeared to persist 12-months post-ACLR with only 9 of the included studies meeting the clinical recommendations for side-to-side quadriceps strength deficits.[71] Average side-to-side quadriceps strength deficits of 14% ± 6% with a range of 3%-28% were found in patients 12-months post-ACLR.[71] However, it is important to note that while it is acceptable to utilize limb symmetry index to

quantify strength-related and functional deficits of the ACL limb, it does not account for limb dominance or contralateral deficits often reported after ACLR.[71,91]

Unpublished data collected in the Exercise and Sports Injury Laboratory at the University of Virginia also demonstrate these concerning bilateral knee extension strength deficits in patients following ACLR (Figure B7). In a total sample of 1,150 patients, median side-to-side strength deficits of 37.65% and 28.03% were revealed during isokinetic knee extension tests at 90 deg/s occurring less than 6 months post-ACLR (n = 486) and 6 to 12 months post-ACLR (n = 664), respectively (Figure B7 A and B7 B). Results from isokinetic knee extension strength tests at 180 deg/s indicated median strength deficits of 30.78% for tests occurring less than 6 months post-ACLR and 22.46% for tests occurring 6 to 12 months post-ACLR (Figure B7 C and B7 D). Lastly, in terms of isometric knee extension strength at 90 degrees of knee flexion, tests occurring less than 6 months post-ACLR demonstrated median side-to-side strength deficits of 43.64% and 31.14% for tests occurring 6 to 12 months post-ACLR (Figure B7 E and B7 F). These results further exemplify the short- and long-term prevalence of persistent quadriceps weakness in this patient population.

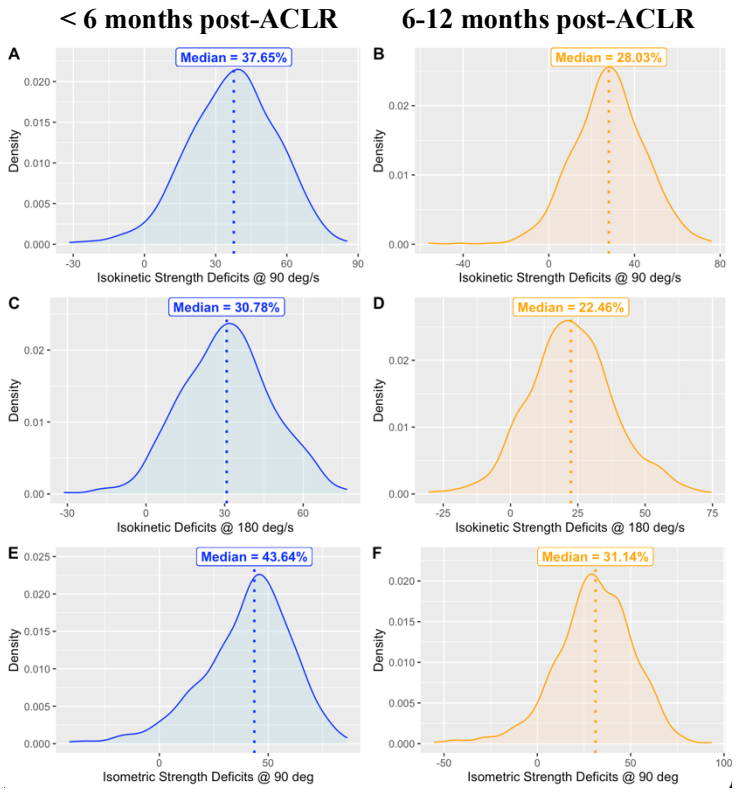


Figure B7. Median knee extension strength deficits.

Although the primary cause of persistent muscle weakness following ACLR remains elusive, several factors have been suggested to contribute to these lingering strength deficits including muscle atrophy,[92–94] incomplete or insufficient rehabilitation,[92] reduced motor unit output,[95] and quadriceps activation failure.[83,88] A recent clinical review highlighted numerous underlying mechanisms associated with muscle atrophy following traumatic joint injury such as neurophysiological alterations, muscle fiber-type transitions, intrinsic changes within muscle fibers, increased circulating factors of atrophy (i.e., MAFbx, MuRF1, and myostatin), increased inflammatory cytokines, and a reduction in satellite cells.[93] Neurological alterations (i.e., denervation and changes in afferent signaling, alpha motor neuron excitability, and the number of neuromuscular connections) following ACL injury have been suggested to negatively influence a muscle's ability to generate a contraction.[93] Similarly, these alterations in neural activity may result in an increase in the co-expression of fiber types where slow-twitch muscle fibers start to display characteristics commonly associated with fast-twitch muscle fibers.[93,96] Interventions to counter these unwarranted changes, and indirectly combat persistent muscle weakness, include electromagnetic stimulation (i.e., transcutaneous electrical nerve stimulation, neuromuscular electrical stimulation, electromyographic feedback),[97–99] eccentric exercise,[100] and more recently, blood flow restriction therapy.[93]

To monitor and quantify changes in neuromuscular control and motor unit activation of the quadriceps following ACL injury and surgical reconstruction, many studies have reported utilizing measures of surface electromyography (sEMG) during various functional assessments (i.e., jumping tasks, maximal strength tests, weight bearing exercises, etc.).[101–104] However, these more general measures of muscle activation, such as peak or mean EMG amplitude, provide indirect and nonspecific information regarding changes in behavior at the

individual motor unit level. In recent years, few studies have attempted to explain aspects of neural impairment associated with persistent muscle weakness following ACLR using more novel and complex techniques such as high-density sEMG (HDsEMG) and sEMG motor unit decomposition.[105–107] A study investigating muscle fiber conduction velocity (MFCV) of the vastus lateralis and vastus medialis muscles via HDsEMG in soccer players that had undergone an ACLR, found lower maximal voluntary isometric forces (-20.5%; $p < 0.05$), quadriceps cross-sectional areas (-12.7%), and MFCV peaks and slopes in the ACLR limb compared to the contralateral limb for both the vastus lateralis (-28.5% and -10.1%, respectively; $p < 0.001$) and vastus medialis (-22.6% and -8.1%, respectively; $p < 0.001$).[107] Authors suggest that these results may indicate potential impairments in the recruitment of high threshold motor units of the quadriceps muscles following ACLR.[107] In another study, Nuccio et al[105] found similar results when examining motor unit discharge patterns in the vastus lateralis and vastus medialis muscles in patients post-ACLR vs. controls (Figure B8). Using motor unit decomposition, this study also identified reduced motor unit discharge rates (21%; $p < 0.05$) and lower absolute motor unit

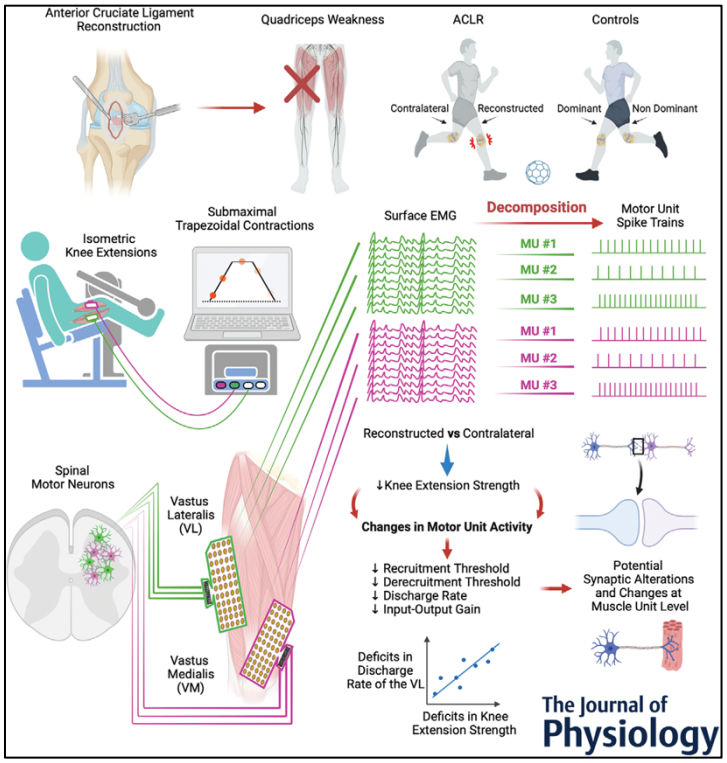


Figure B8. Relationship between changes in motor unit activity and knee extension strength following ACLR. (Nuccio et al, 2021)

recruitment (22%; $p < 0.05$) and derecruitment (22.5%; $p < 0.05$) thresholds for the quadriceps muscles of the reconstructed limb vs. the contralateral limb for individuals in the ACLR group.[105] A longitudinal study by Schilaty et al[106] also investigated the motor unit characteristics of the thigh musculature using EMG signal decomposition in patients after ACL injury, post-ACLR, and throughout rehabilitation up to 12-months post-surgery compared to healthy controls. Results of this study demonstrated smaller motor unit action potential peak-to-peak amplitudes (considered an indirect measure of motor unit size), lower quadriceps motor unit coding rates, and higher hamstring motor unit coding rates for participants in the ACL group compared to those in the healthy control group.[106] Due to a dearth of research investigating motor unit behavior of the quadriceps in patients post-ACLR, evidence to corroborate the findings of these select studies is limited. Nevertheless, the findings of each of these studies can be attributed to the decreased neural drive of the quadriceps muscles in patients post-ACLR despite completion of post-surgical rehabilitation, further suggesting the need for targeted intervention programs to overcome these persistent strength deficits.

Psychological Limitations

Although assessments regarding an individual's physical abilities (i.e., strength and functional performance) often dominate the return to sport evaluation, psychological characteristics are critical factors to consider when examining an individual's response to injury and readiness for the return to activity after ACL injury and surgical reconstruction. In a systematic review of 28 studies evaluating the available evidence regarding the psychological factors related to return to play after ACLR, there was only a 63.4% (n =

1,380/2175) rate of return to play in patients post-ACLR and 36.6% of those that did return to play could not perform at their pre-injury level of participation.[108] For patients that did not return to play (n = 795/2175), 64.7% (n = 514/795) reported a psychological reason for their lack of return to play including fear of reinjury (n = 394; 76.7%), lack of confidence in their reconstructed knee (n = 76; 14.8%), depression (n = 29; 5.6%), and lack of interest or motivation (n = 13; 2.5%).[108] An online survey of 304 patients that were one to 20 years post-ACLR, also found fear of re-injury to be the highest rating barrier for adherence to rehabilitation in patients post-ACLR.[109]

Common outcome measures used to assess these patient-reported variables include the International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Osteoarthritis and Outcome Score (KOOS), Anterior Cruciate Ligament Return to Sport Index, and the Tampa Scale of Kinesiophobia (TSK). Changes in subjectively reported symptoms, function, and sports activity after ACLR can be assessed using the IKDC Subjective Knee Form.[110] This 18 item questionnaire includes three primary domains: 1) symptoms (i.e., pain, stiffness, swelling, locking/catching, and giving way), 2) sports and daily activities, and 3) current knee function and knee function prior to injury.[110] Individual items are scored using an ordinal method with a possible total score range of 0-100, where a total score of 0 indicates high symptoms and low function and a total score of 100 indicates no symptoms and no limitations with daily or sporting activities.[111] The IKDC Subjective Knee Form has been shown to be both reliable and valid in patients post-ACLR.[111] The KOOS is often utilized to evaluate a patients' perception regarding their knee as well as any short-term and long-term knee-related problems.[111,112] This questionnaire includes 42 items across 5 subscales of pain, symptoms, activities of daily living, sport and recreation function,

and knee-related quality of life.[112] Each item is scored from 0-4 and each subscale is then separately scored from 0-100 based on the sum of its corresponding items, where 0 indicates extreme knee-related problems and 100 indicates no knee-related problems. This scale has demonstrated good validity and reliability in an ACLR population.[111,112] Emotions, confidence in performance, and risk appraisal associated with the return to sport after ACLR can be measured using the ACL-RSI. This tri-component questionnaire is comprised of 12 items with scores ranging from 1-10. Total scores in the form of percentages are calculated by adding the values of each individual item and calculating their relationship to 100. This scale has been shown to have acceptable reliability and validity.[113] Fear of pain, reinjury, and movement (i.e., kinesiophobia) can be quantified using the TSK.[114] Individual scores on the TSK range from 1-4 and total scores range from 17-68 with higher scores suggesting increased degrees of kinesiophobia.[114,115] Patients are considered to suffer from kinesiophobia if their total score is greater than 37.[116] However, the overall reliability and validity of the TSK in an ACLR population is still under investigation.

Given their significant contribution to the return to sport process, the relationship between quadriceps strength and patient reported outcome measures has started to be explored. It has been reported that individuals with IKDC scores greater than or equal to 90 are 3 times more likely to present with a limb symmetry index for quadriceps strength of 90% or greater.[117] However, quadriceps strength normalized to body mass has been suggested to be a stronger predictor of self-reported knee function when compared to limb symmetry index in an ACLR population.[118,119] A threshold of 3.0 Nm/kg was identified as a strong indicator of good patient reported outcomes post-ACLR.[119] However, this relationship may be dependent on an individual's time since surgery with patients under 2 years post-

ACLR demonstrating stronger relationships between measures of subjective function and normalized measures of muscle function than patients over 5 years post-ACLR.[120] Additionally, a study by Lepley et al[121] found significant associations between decreased quadriceps strength and lower self-reported knee function, psychological readiness to return to sport, and emotional response to injury in patients returning to unrestricted physical activity after ACLR. Similarly, significant associations between greater quadriceps strength symmetry and increased psychological readiness have been reported in female athletes that have sustained a noncontact ACL injury.[122] Self-reported fear has also been found to be associated with decreased quadriceps strength, where patients with greater fear were 6 times more likely to have quadriceps strength symmetry less than 90%, 4 times more likely to report lower levels of physical activity, and 7 times more likely to have a limb symmetry index of less than 95% for hopping.[123] Additionally, a study by Markström et al[124] indicated that individuals who report higher levels of fear also adopt altered, protective muscle activation patterns when compared to individuals that report lower levels of fear.

Section III: Blood Flow Restriction Therapy – Proposed Mechanisms and Benefits

Blood Flow Restriction Therapy

Blood flow restriction therapy (BFRT) may offer clinicians and researchers an alternative approach to traditional high intensity exercise for eliciting various neuromuscular improvements such as increased strength and hypertrophy. The development of BFRT dates back to 1966 when Dr. Yoshiaki Sato coined the term “KAATSU training”, meaning additional pressure, to characterize this novel technique.[125] This training protocol, more modernly known as BFRT, occlusion training, or ischemic training, involves the utilization

of a device such as a band, strap, or pneumatic cuff to apply an external circumferential pressure to a proximal extremity. This restrictive device acts to constrain the vascular passages to and from the distal musculature resulting in the complete occlusion of venous outflow and partial occlusion of arterial inflow, typically while performing low intensity (20-40% 1-repetition maximum) exercise.[126] Despite exercises being performed at submaximal levels, research has demonstrated similar muscular improvements when comparing outcomes associated with low-load BFRT exercise (LL-BFRT) to those achieved with traditional high load (HL) resistance exercise (>70% 1RM).[127,128] Similarly, when compared to standard low-load (LL) exercise, LL-BFRT demonstrates greater increases in muscle strength.[129] By altering load intensity, BFRT minimizes the amount of stress on targeted joints and surrounding tissues while still promoting increases in strength compared to HL exercise.[130] Therefore, this complementary approach to rehabilitation and strength training may be a viable option for healthy individuals,[127,131,132] older populations,[133] and load restricted patients (i.e., following severe sport-related injuries or surgical intervention).[129]

As previously stated, BFRT is performed by applying a pneumatic tourniquet cuff to the most proximal region of the upper or lower extremity of interest. It is recommended that the cuff is then inflated to an individualized pressure between 40% and 80% of an individual's limb occlusion pressure (LOP) based on patient tolerance.[134] LOP is the minimum amount of pressure required to completely occlude arterial blood flow distal to the applied cuff.[135] Historically, the most common method for obtaining LOP is Doppler ultrasound.[136] Unfortunately, this method of LOP measurement is neither cost nor time efficient and has varying accuracy depending on the experience of the clinician recording the measurement.[135] Modern surgical-grade (third-generation) tourniquet systems have allowed

for automatic determination of personalized tourniquet pressures (PTP, i.e., an individualized amount of pressure determined by taking a percentage of an individual's total LOP).[135] These surgical-grade systems, such as the Delfi PTSII system (Delfi Medical Vancouver, BC), have been shown to be safe, accurate, and reliable measures of LOP and PTP.[137] Regulation of PTP throughout the exercise prescription helps to mitigate the occurrence of adverse events following BFRT such as nerve and ischemic injury, and allows for standardization across BFRT protocols.[137,138] Although there is significant variation in exercise prescription protocols available for BFRT, recommendations for increasing muscle strength and hypertrophy using this technique include training frequency, load, restriction time, sets and repetitions, cuff size, PTP of LOP, rest periods, and execution speed.[134] However, the model for exercise prescription depends on the type of exercises being performed with BFRT such as resistance (BFRT-RE), aerobic (BFRT-AE), or no exercises/passive (P-BFRT) (Figure B9).[134]

Guideline	Recommendation		
	BFRT-RE	BFRT-AE	P-BFRT
Frequency	2-3 times per week (>3 weeks) 1-2 times per day (1-3 weeks)	2-3 times per week (>3 weeks) 1-2 times per day (1-3 weeks)	1-2 times per day
Load	20-40% 1RM	<50% VO2 max or HRR	
Total restriction time	5-10 minutes per exercise	5-20 minutes	5 minutes
Sets	2-4		3-5
Repetitions	30x15x15x15 (Or sets to failure)		
Interset rest	30-60 seconds (Cuff remains inflated)		3-5 minutes
LOP	40-80%	40-80%	Uncertain; 70-100%
Execution speed	1-2s		

Figure B9. Recommendation protocols for BFRT by exercise type (adapted from Patterson et al., 2019)

Proposed Mechanisms

Current research has shown that LL-BFRT has the potential to increase muscle strength, hypertrophy, and activation when high-load exercise may be contraindicated.[139–143] Unfortunately, the proposed mechanisms of BFRT have yet to be substantially supported. There has been speculation that BFRT works to enhance muscle function by three primary mechanisms: 1) intracellular swelling, 2) decreased oxygen availability, and 3) increased metabolite accumulation.[144–147] During prolonged occlusion due to tourniquet cuff application, it has been suggested that increased pooling of fluid distal to the cuff alters hydrostatic and osmotic pressure gradients thus driving fluid into and around muscles fibers (Figure B10).[147] This shift in pressure is suspected to inhibit protein catabolism while promoting protein synthesis.[147,148] Additionally, maintained vascular occlusion during BFRT drastically reduces oxygen availability to the working muscle.[144,149] The resulting hypoxic environment has been speculated to induce muscle fatigue, promote anabolic hormone signaling, and increase the production of reactive oxygen species.[144–147] When performing exercise under these ischemic conditions there is a suggested increase in metabolic stress due to metabolite accumulation (i.e., lactate, hydrogen ions, inorganic phosphate).[36,145,150] These factors, as well as a lowered intramuscular pH, may further stimulate group III and group IV afferent fibers leading to earlier neuromuscular

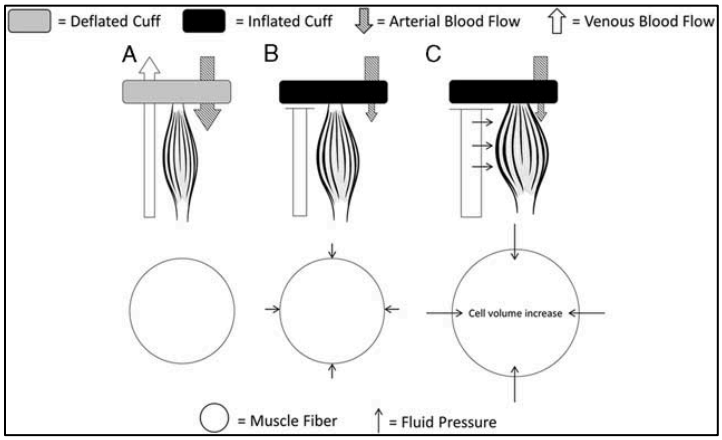


Figure B10. Influence of fluid pressure shifts during BFRT (Jessee et al, 2018)

fatigue of low threshold motor units and Type I muscle fibers (i.e., slow-twitch oxidative) (Figure B11).[144–147] This fatigued, hypoxic state and increased presence of metabolic byproducts has been suggested to promote the early recruitment of high threshold motor units and Type IIA and Type IIX muscle fibers during exercise in order to maintain the desired force output (Figure B12).[139,144] This altered recruitment can lead to increases in muscle strength and hypertrophy, despite exercises being completed under low mechanical tension, by activating more motor units and stimulating an increased number of muscle fibers causing a more widespread hypertrophic stimulus within the muscle.[129,144]

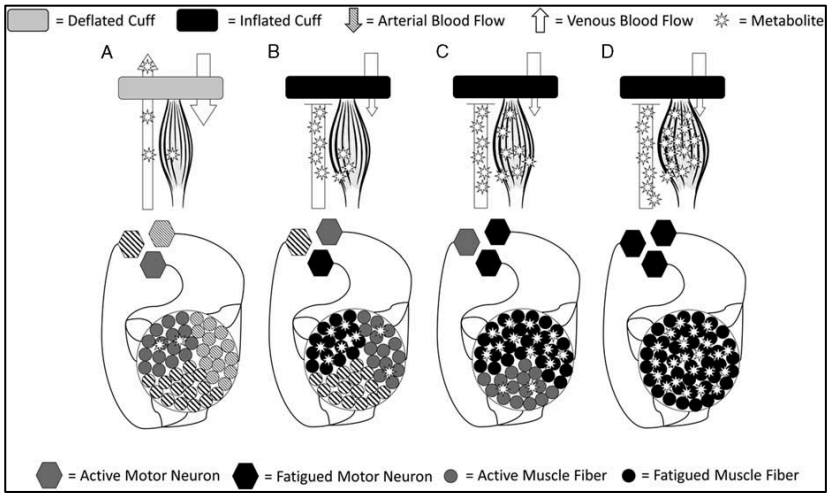


Figure B11. Increased metabolite accumulation and muscular fatigue as a result of prolonged vascular occlusion during BFRT. (Jessee et al, 2018)

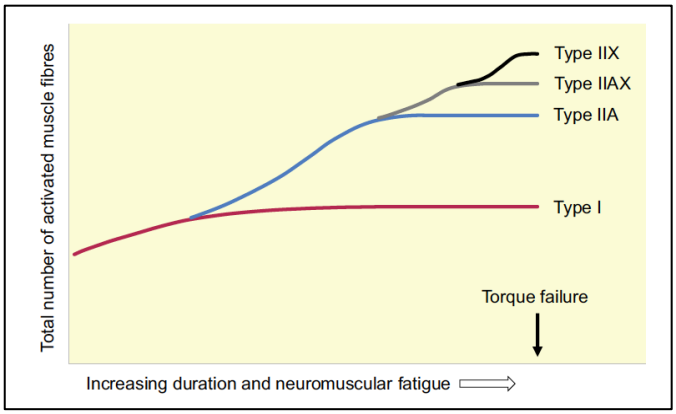


Figure B12. Suggested scheme of the successive and cumulative activation of type I, IIA, IIAX and IIX muscle fibers in LL-BFRT with increasing fatigue and duration. (Wernbom and Aagaard, 2020)

Changes in motor unit recruitment during BFRT have been primarily quantified using indirect measurement methods of sEMG (i.e., root mean squared (RMS), integrated EMG (iEMG), peak of the EMG signal (EMGpeak), EMG amplitude, and average EMG).[151–154] However, findings related to myoelectric activity during LL-BFRT compared to LL and HL

exercise without BFRT are mixed and likely due to methodological heterogeneity.[151,152,154] A systematic review and meta-analysis by Centner and Lauber[151] identified significant increases in muscle excitation during LL-BFRT compared to LL exercise without BFRT. However, these differences appear to be dependent on whether or not exercise is performed to volitional fatigue, where greater short-term increases in muscle excitability during LL-BFRT compared to LL exercise are observed only during non-fatiguing protocols.[154] No significant differences in muscle excitation were identified between LL-BFRT and LL exercise when exercise was performed to volitional failure.[154] Conversely, greater increases in muscle excitability have been observed during HL exercise compared with LL-BFRT during non-fatiguing and fatiguing protocols.[154]

However, the interpretation of the aforementioned results should be considered with caution as changes in sEMG cannot be directly associated with changes in motor unit behavior (i.e., recruitment, firing rates, etc.).[150] Factors such as muscle fiber potential, motor unit synchronization, and fatigue can all influence general measures of sEMG.[150,151] Given recent technological advancements, Fatela et al[139] utilized a noninvasive, high-density EMG sensor and decomposition algorithms to measure and characterize changes in individual motor unit behavior including motor unit recruitment thresholds, firing rates, and action potential amplitudes of the vastus lateralis before and after LL exercise with and without BFRT. Results of this study indicate greater decrements in the linear slope co-efficient of the regression line between motor unit recruitment threshold and firing rate as well as a shift towards higher firing rates and motor unit action potential amplitudes following LL-BFRT compared to LL exercise.[139] It has been suggested that these results demonstrate the early

recruitment of high threshold, low firing rate motor units as a result of LL-BFRT compared to LL exercise.[139,151]

Potential Benefits of BFRT During ACLR Rehabilitation

Although research has demonstrated positive findings associated with BFRT, few studies have examined the effects of BFRT on muscle function in patients that have sustained an ACL injury.[155–161] BFRT has been recently investigated as a prehabilitative[162–164] and rehabilitative[165–173] treatment technique for improving muscle strength deficits and atrophy after ACLR. However, the methodology and results of these studies are inconsistent regarding the overall benefits of LL-BFRT compared to high load exercise and control interventions in patients post-ACL injury.

Prehabilitatively, a study investigating the effects of 5 preoperative LL-BFRT sessions during the last 10 days before ACL surgery found no significant differences in postoperative rectus femoris muscle mass, isometric strength, or knee function compared to a sham preoperative LL-BFRT condition.[162] An additional study by Žargi et al[163] also examined the effects of 5 preoperative LL-BFRT sessions compared to a sham LL-BFRT condition, however these sessions occurred during the last 8 days prior to ACL surgery. Results indicated a positive effect of preoperative LL-BFRT on postoperative muscle endurance, activation, and perfusion of the quadriceps in patients following ACLR compared to a sham LL-BFRT condition.[163] However, this study also demonstrated significant deterioration of quadriceps muscle strength following ACLR in patients treated with preoperative LL-BFRT and those treated with sham LL-BFRT.[163] A more recent study by Kacin et al[164] examined the benefits of 9 preoperative LL-BFRT sessions on muscle size and

function of the quadriceps and hamstrings compared to a sham BFRT condition. Improvements in muscle cross-sectional area, isokinetic strength, and fatigue index of the knee extensors were significantly greater for patients treated with LL-BFRT compared sham BFRT.[164] Although improvements were noted, the effects of LL-BFRT on muscle strength and size of the hamstrings were much less pronounced.[164] Researchers have also investigated the efficacy of home-based prehabilitative BFRT compared to standard at-home prehabiliation in patients undergoing ACLR.[174] The results of this study demonstrated significant improvements in quadriceps peak force measurements for patients treated with and without BFRT.[174] However, when comparing quadriceps size, strength, and patient reported outcomes, no significant between group differences were found.[174] Collectively, the results of these studies suggest the need for additional research to determine the potential value of prehabilitative LL-BFRT for improving postoperative muscle strength and function in patients undergoing ACLR.

Several systematic reviews have also examined the available evidence on the use of postoperative BFRT for improving muscle strength and function in patients that have undergone ACL surgery.[155–158,160,161] One of the first studies to investigate the application of vascular occlusion for attenuating disuse atrophy of the knee extensor muscles in patients following ACLR included a sample of 16 individuals were allocated into either a control group or an experimental vascular occlusion group.[1] Individuals in the experimental group underwent 10 consecutive days of vascular occlusion between day 3 and day 13 post-surgery involving two sessions of occlusive stimulus per day consisting of 5 repetitions of vascular occlusion for 5 minutes each and 3 minutes of rest between each occlusive repetition.[165] The cross-sectional area of the knee extensors decreased to a significantly lesser extent in the

experimental group compared to the control group (9.4% ± 1.6% vs. 20.7% ± 2.2%, respectively).[165] However, in a study utilizing a similar design and methodology, no significant reductions in quadriceps cross-sectional area atrophy were reported for individuals treated with or without vascular occlusion.[167] A study by Ohta et al[166] examined the effects of LL-BFRT vs. standard low-load training on the size and strength of the quadriceps during the first 16 weeks post-ACLR. Compared to preoperative measurements, results of this study indicate significantly greater improvements in quadriceps cross-sectional area and less strength deficits for isokinetic knee extension at 60 deg/s, isokinetic knee extension at 180 deg/s, and isometric knee extension at 60 deg of knee flexion for those in the LL-BFRT group compared to the standard low-load training group.[166] When comparing LL-BFRT to HL resistance training, Hughes et al[170] found comparable increases in scaled 10 repetition maximum strength of the injured and uninjured limb following 16 sessions (2 sessions/week for 8 weeks) of unilateral leg press training. There were also significant increases in muscle thickness, pennation angle, and peak torque for knee extension and flexion at 60 deg/s, 150 deg/s, and 300 deg/s following both conditions with no group differences.[170] In contrast, Curran et al[172] investigated the efficacy of 16 sessions (2 sessions/week for 8 weeks) of high-load BFRT (HL-BFRT) for improving quadriceps muscle function in patients 10 weeks post-ACLR. The results of this study found no significant between group differences in quadriceps muscle strength, activation, or volume between HL-BFRT and traditional HL resistance training.[172]

While the aforementioned studies reported implementing BFRT between immediate post-surgery to 18 weeks post-surgery, one study did examine the effectiveness of a home-based BFRT program to improve quadriceps strength and size in patients 2 or more years

post-ACLR with lingering muscle deficits.[171] Participants completed 25 minutes of exercise under BFRT 5 times per week for 4 weeks.[171] Compared to baseline, muscle thickness of the rectus femoris and vastus lateralis as well as knee extensor strength symmetry increased by 11% ± 5%, 10% ± 6%, and 20% ± 14% (all $p < 0.01$).[171] Knee extensor strength symmetry increased from 88% ± 4% to 99% ± 5% from baseline to post-intervention which did not differ from uninjured controls.[171] The results of this study suggest BFRT may be a beneficial treatment option for improving long-term muscle strength deficits in patients post-ACLR.

Unfortunately, there is no true "standard of care" treatment for individuals failing to respond to traditional rehabilitation following knee surgery including ACLR. A study by Noyes et al[173] did investigate the effects of BFRT on quadriceps and hamstring deficits in patients failing to respond to rehabilitation after knee surgery. Results indicated that a majority of patients had significant improvements in both quadriceps and hamstring strength deficits of at least 10% following 9 sessions of BFRT and 20% following 18 sessions of BFRT.[173] However, this study did report small effect sizes and had a very diverse patient population including time since surgery, type of surgery, and degree of muscle strength deficits.[173] Therefore, it is still largely unknown how BFRT may affect muscle strength in patients with persistent muscle weakness following ACLR and the conclusion of traditional rehabilitation protocols.

Recent studies have secondarily examined the effects of BFRT on commonly used patient reported outcomes measures in individuals following knee surgery.[157] Tennent et al[175] explored both physical and subjective outcome measures following 12 sessions of supervised physical therapy with and without BFRT after knee arthroscopy. The results of this study found significant improvements for all subscales of the KOOS as well as the physical

component of the Veterans RAND 12-Item Health Survey (VR-12) in both the BFRT group and conventional therapy group.[175] However, significant improvements in the mental component of the VR-12 were only identified in the BFRT group.[175] Similarly, Hughes et al also found significantly greater increases in IDKC, Lower Extremity Function Scale (LEFS), Lysholm Knee-Scoring Scale (LKSS), and KOOS subscale scores following 8 weeks of BFRT compared to HL resistance training.[170] Conversely, Curran et al[172] did not find significant differences in IKDC change scores from preintervention to postintervention, and no group differences were found from preoperative to postintervention or preoperative to return to activity between HL-BFRT and traditional HL resistance training. Other studies have reported changes in more general subjective measures like rating of perceived exertion (RPE), pain, exercise effectiveness, and patient satisfaction which all may be influenced by augmented exercise induced muscle fatigue during BFRT. Two studies reported no significant differences in RPE between BFRT and HL resistance training in patients post-ACLR.[168,169] However, when compared to uninjured individuals, patients post-ACLR reported higher RPE during BFRT.[168] Patients have also reported lower levels of knee pain during and following BFRT compared to HL resistance training.[168,169] In contrast, muscle pain has been found to be significantly higher during exercise with BFRT compared to HL resistance training.[169] Noyes et al[173] found that 63% of individuals treated with BFRT after failing to respond to traditional post-surgical rehabilitation reported experiencing significantly better results than their previous rehabilitation program and had a mean patient satisfaction score of 8.9 out of 10. So, although BFRT may be effective for improving subjectively reported limitations, the overall psychological impact of BFRT in patients with lingering muscle weakness has not yet been fully investigated. All in all, gaining a better

understanding of the physiological and psychological responses to BFRT is critical for evaluating its various potential benefits in an ACLR population.

APPENDIX C: ADDITIONAL METHODS

Table C1. Summary of Protocol Procedures

i. University of Virginia Institutional Review Board Documentation (i.e., Protocol, Application, Consent, Data Security Plan, Recruitment)
    a. Manuscript I
        i. Protocol
        ii. Application
        iii. Consent
        iv. Data Security Plan
        v. Recruitment
    b. Manuscript II/III
        i. Protocol
        ii. Application
        iii. Consent
        iv. Data Security Plan
        v. Recruitment

ii. Questionnaires and Patient Reported Outcome Measures
    a. Modified Tegner Activity Scale
    b. Tegner Activity Scale
    c. Godin Leisure-Time Exercise Questionnaire
    d. International Physical Activity Questionnaire (IPAQ) Short Form
    e. Rating of Perceived Exertion
    f. International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form
    g. Knee Injury and Osteoarthritis Outcome Score (KOOS)
    h. Tampa Scale for Kinesiophobia
    i. Anterior Cruciate Ligament – Return to Sport Index
    j. Exercise Adherence Rating Scale (EARS)
    k. Global Rating of Change Scale

iii. Laboratory Measures
    a. Ultrasound Imaging
    b. Electromyographic Signaling (Trigno Galileo Sensor)
    c. Isokinetic and Isometric Torque

iv. Blood Flow Restriction Therapy Program Procedures
    a. Delfi Personalized Tourniquet System Setup
    b. Exercise Protocol

Table C2. University of Virginia Institutional Review Board Documentation

Table C2a. Manuscript I

i. Protocol

PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.
Answer/Response:

Blood flow restriction therapy offers clinicians and researchers an alternative therapeutic intervention for achieving neuromuscular gains while mitigating the potentially harmful adverse events associated with increased joint stress. This therapy requires the partial occlusion of muscular arterial inflow and complete occlusion of venous outflow during either anaerobic or aerobic-based exercise.[1] Blood flow restriction therapy utilizes low resistance exercise between 20% and 40% of an individual's 1-repetition maximum to achieve similar strength and hypertrophy gains to those acquired through high resistance exercise (i.e., 80% of an individual's 1-repetition maximum). By altering load intensity, blood flow restriction therapy minimizes the amount of stress on the affected joint and surrounding tissues. Therefore, this complementary approach to rehabilitation and strength training may be a viable treatment option for load restricted populations such as post-surgical patients, elderly individuals, and those recovering from severe sport-related injuries.

Current research has shown that low resistance exercise completed with blood flow restriction therapy has the potential to increase muscle strength, hypertrophy, and activation when high resistance exercise may be contraindicated.[2–6] Unfortunately, the proposed mechanisms of blood flow restriction therapy have yet to be substantially supported. Blood flow restriction therapy has been speculated to enhance muscle function by two primary mechanisms, decreased oxygen availability (i.e., hypoxia) and increased metabolite accumulation. [7–10] These factors, as well as a lowered intramuscular pH, may further stimulate group III and group IV afferent fibers leading to earlier neuromuscular fatigue of type I (i.e., slow-twitch oxidative) muscle fibers. [7–10] This fatigued, hypoxic state has been suggested to promote the early recruitment of high threshold motor units and type II (fast-twitch anaerobic) muscle fibers during exercise.[2,7] This recruitment can lead to increases in muscle strength and hypertrophy, despite exercises being completed under low resistance, by stimulating more muscle fibers causing a more widespread hypertrophic stimulus within the muscle.[7,11] Therefore, the utilization of blood flow restriction therapy may help elicit beneficial muscular adaptations with reduced joint stress.

Until recently, muscle activation during blood flow restriction therapy has been primarily quantified using surface electromyographic signaling. However, this general measurement of electrical currents has not provided specific information regarding individual motor unit activity during exercise.

A novel measurement technique using automatic decomposition of surface electromyographic signals has been introduced to counter this limitation.[12] The Trigno Galileo Sensor (Delsys Inc, Boston, MA) is a small, unobtrusive device that has been designed to measure not only surface electromyographic signals but also motor unit behavior, firing rates

and patterns, recruitment thresholds, and action potential amplitudes. The four-pin array sensor measures differential combinations of electrical signals that are then amplified, filtered, stored, and later decomposed using built-in software algorithms. Additional information regarding the decomposition algorithms and Artificial Intelligence framework can be found in a report by De Luca et al.[12] This innovative technology may allow researchers to further investigate the underlying mechanisms of blood flow restriction therapy in a functional and real-time manner.

For reference, another approved and on-going protocol at the University of Virginia (IRB# 21416) has been investigating the effects of blood flow restriction therapy on muscle function after traumatic femur fracture fixation surgery compared to standard physical therapy. Procedures including the application of the Delfi PTSII tourniquet system (Delfi Medical Vancouver, BC) during low resistance exercise can be further identified within their study protocol. Many of the associated risks with blood flow restriction therapy are higher in a post-surgical population, whereas our study will only include healthy participants free of common contraindications to tourniquet cuff application. The PTSII system and cuffs are FDA Class 1 devices, and are classified as "pneumatic tourniquets" typically used to restrict or occlude blood flow during surgery. The use of pneumatic tourniquets by qualified health care professionals in environments with lower risks than the surgical environment is an appropriate use, and no FDA clearance will be necessary for this study.

Objectives/Hypothesis

Answer/Response:

The primary objective of this study is to determine the effects of low resistance exercise with blood flow restriction on muscle activation and motor unit recruitment compared to standard low resistance exercise without blood flow restriction.

A secondary objective of this study is to examine the relationship between motor unit recruitment and muscle size and quality.

A third objective of this study is to evaluate and determine the responsiveness and precision of the Trigno Galileo Sensor for measuring motor unit behavior during various exercise activities including isometric exercise, isokinetic exercise, fatigue exercise, and functional exercise.

We hypothesize that when exercise is completed with blood flow restriction there will be an increase in overall motor unit recruitment and firing rates as well as a decrease in motor unit recruitment thresholds compared to exercise without blood flow restriction. We also hypothesize that there will be positive relationship between the number of motor units recruited and muscle size and quality in both exercise conditions.

Study Design: Biomedical

1. Will controls be used?
Answer/Response: No
►IF YES, explain the kind of controls to be used.
Answer/Response: N/A

2. What is the study design?
Answer/Response: Randomized Cross-Over Study

3. Does the study involve a placebo?
Answer/Response: No
►IF YES, provide a justification for the use of a placebo
Answer/Response: N/A

Human Participants

Ages: 18 years of age or older
Sex: Males and Females
Race: All

Subjects- see below
1. Provide target # of subjects (at all sites) needed to complete protocol.
Answer/Response: 40

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.
Answer/Response: 20% - We are over-estimating the expected attrition rate due to the technology being used for measuring muscle activity. This technology requires extensive skin preparation that if not done properly may hinder the quality of the data collected.

3. How many subjects will be enrolled at all sites?
Answer/Response: 48

4. How many subjects will sign a consent form under this UVA protocol?
Answer/Response: 48

Inclusion/Exclusion Criteria

1. List the criteria for inclusion
Answer/Response:
- Adults 18 years of age or older
- Score of 14 or more on the Godin Leisure-Time Exercise Questionnaire
- Score of 5 or more on the Tegner Activity Scale
- Willingness and ability to comply with the scheduled visit and study procedures.

2. List the criteria for exclusion
Answer/Response:
- Lower extremity injury within the past 6 months
- Lower extremity surgery within the past 12 months

- History or current diagnosis of a metabolic, pulmonary, or cardiovascular disease (such as Peripheral Artery Disease and/or Peripheral Vascular Disease (PAD/PVD), diabetes, venous thromboembolism, deep vein thrombosis, impaired circulation or peripheral vascular compromise, sickle cell anemia, and severe hypertension)
- Current use of anti-coagulant medication
- Current diagnosis of cancer
- Patient is pregnant
- Unable to provide informed consent

3. List any restrictions on use of other drugs or treatments.
Answer/Response:
- Supplements or medications with anti-coagulation properties

Statistical Considerations

1. Is stratification/randomization involved?
Answer/Response: Yes
►IF YES, describe the stratification/ randomization scheme.
Answer/Response: For the blood flow restriction session, participants will be randomly allocated to an exercise condition order. All participants will undergo both exercise conditions, however the exercise condition that they start with will be randomized. Exercise condition order will be predetermined using a random number generator. Randomization will not be blinded and only the study coordinator will have access to the randomization scheme.
►IF YES, who will generate the randomization scheme?
____ Sponsor
____ UVA Statistician. Insert name Answer/Response:
____ UVA Investigational Drug Service (IDS)
__x__ Other: Specify Answer/Response: The study coordinator

2. What are the statistical considerations for the protocol?
Answer/Response:
- **Overview and Study Objective**
  - The primary objective of this cross-over study is to determine the effects of low resistance exercise with blood flow restriction on muscle activation and motor unit recruitment compared to standard low resistance exercise without blood flow restriction.
  - A secondary objective of this study is to examine the relationship between motor unit recruitment and muscle size and quality.
  - A third objective of this study is to evaluate and determine the responsiveness and precision of the Trigno Galileo Sensor for measuring motor unit behavior during various exercise activities including isometric exercise, isokinetic exercise, fatigue exercise, and functional exercise.

- **Primary Endpoints (measurements to address the primary hypothesis)**
  - **Trigno Galileo Electromyography Sensor**
    - **Motor Unit Recruitment**
      - This is the total number of motor units detected during the test or exercise procedure. This measure will be used to assess differences in motor unit recruitment between exercise done with and without blood flow restriction. Paired t-tests will be used to compare differences in the mean number of motor units recruited between the two exercise conditions. Paired t-tests will also be used to compare differences in the mean number of motor units recruited between each type of exercise in the optional sub-study.
    - **Average Motor Unit Firing Rates**
      - This is the average firing rate of the motor unit which is calculated from the inverse of the average inter-pulse interval of all motor unit firing instances during the test or exercise procedure. This measure will be used to assess differences in average motor unit firing rates between exercise done with and without blood flow restriction. Paired t-tests will be used to compare differences in the average motor unit firing rates between the two exercise conditions. Paired t-tests will also be used to compare differences in the average motor unit firing rates between each type of exercise in the optional sub-study.
    - **Motor Unit Recruitment Thresholds**
      - This is the muscular voltage level at which the motor unit began firing. This measure will be used to assess differences in recruitment thresholds across various motor units between exercise done with and without blood flow restriction. Paired t-tests will be used to compare differences in recruitment thresholds between the two exercise conditions. Paired t-tests will also be used to compare differences in recruitment thresholds between each type of exercise in the optional sub-study.
    - **Peak Motor Unit Action Potential Amplitudes**
      - This is calculated as the maximum amplitude across all channels of the maximum value of the rectified motor unit action potential waveforms. This measure will be used to assess differences in motor unit action potential amplitudes between exercise done with and without blood flow restriction. Paired t-tests will be used to compare differences in peak motor unit action potential amplitudes between the two exercise conditions. Paired t-tests will also be used to compare differences in peak motor unit action potential amplitudes between each type of exercise in the optional sub-study.

- **Secondary Endpoints (measurements to assess the secondary hypothesis)**
  - **Diagnostic Ultrasound**
    - **Muscle Cross-Sectional Area**
      - The cross-sectional area of the vastus lateralis will be measured to represent the circumference (size) of the muscle at the measurement location. Ultrasound images will be taken at each 2cm mark from the medial aspect of the vastus lateralis to the lateral aspect of the vastus lateralis. The combination of these images will be used to assess the size of the vastus lateralis. The relationship between the size of the vastus lateralis and the number of motor units recruited will be determined using Pearson correlations.
    - **Muscle Thickness**
      - The thickness of the vastus lateralis will be measured using the distance between the superficial and deep fascial boarders of the vastus lateralis. The average distance of three diagnostic ultrasound images at the measurement location will be used for analysis. The relationship between the thickness of the vastus lateralis and the number of motor units recruited will be determined with Pearson correlations.
    - **Muscle Echogenicity**
      - The echogenicity of the vastus lateralis will be measured to represent the quality of the muscle. This variable is determined using a computer assisted grey-scale analysis feature of ultrasound images in ImageJ. The echogenicity of the vastus lateralis will be determined using the average echo intensity of the measurement location across each of the ultrasound images. The relationship between the echogenicity of the vastus lateralis and the number of motor units recruited will be determined with Pearson correlations.
    - **Subcutaneous Fat Tissue Thickness**
      - The subcutaneous fat tissue thickness of the measurement location will be assessed from the skin to the superficial fascia of the vastus lateralis. The relationship between the thickness of the subcutaneous fat tissue layer and the number of motor units recruited will be determined with Pearson correlations.
  - **Rating of Perceived Exertion**
    - This measure will be used to represent how hard a participant felt that he or she was working during each of the exercise procedures. Participant perceived difficulty of each exercise condition will be assessed using a Rating of Perceived Exertion Scale ranging from 0 (no effort) to 10

(maximal effort). Paired t-tests will be used to compare differences in rating of perceived exertion following each of the two exercise conditions.

3. Provide a justification for the sample size used in this protocol.
Answer/Response:
To determine the difference between two dependent means with two-tailed paired-samples t-tests, we performed an a-prior sample size estimation (Power = 0.95, Alpha = 0.05) using an estimated effect size (ES = 1.37) from the results of a previous study examining the effects of blood flow restriction on motor unit behavior of the vastus lateralis.[2]

- Cohen's d effect size (Pooled SD) = 1.37
- Alpha = 0.05
- Power = 0.95
- Sample size = 8

Although the sample size estimation suggested only needing 8 participants in order to obtain significant results, we want a more robust and generalizable sample. Therefore, taking into consideration the attrition rate and optional second visit for the sub-study with additional variables being measured, we set our sample size to 48 participants. Each visit of the study should have at least 24 participants completed to detect differences between groups and exercises, therefore given the optional nature of the second visit sub-study part of the study 48 participants will be enrolled.

- Attrition rate = 20% (40 * .20 = 8 participants)
  - Sample size = 48

4. What is your plan for primary variable analysis?
Answer/Response:
Motor Unit Recruitment

- BFR Visit: For each of the primary outcome variables (i.e., motor unit recruitment, motor unit firing rates, motor unit recruitment thresholds, and motor unit action potential amplitudes) paired t-tests will be used to compare the differences between exercise with blood flow restriction and exercise without blood flow restriction.
- Optional Second visit sub-study: For each of the primary outcome variables (i.e., motor unit recruitment, motor unit firing rates, motor unit recruitment thresholds, and motor unit action potential amplitudes) paired t-tests will be used to compare the differences between each type of exercise.

5. What is your plan for secondary variable analysis?
Answer/Response:
Muscle Size and Quality

- BFR Visit: Relationships between motor unit recruitment and muscle cross-sectional area, thickness, echogenicity, and subcutaneous fat tissue thickness will be determined using Pearson correlations.
- Optional Second Visit sub-study: Relationships between motor unit recruitment and muscle cross-sectional area, thickness, echogenicity, and subcutaneous fat tissue thickness will be determined using Pearson correlations.

Rating of Perceived Exertion

- BFR Visit: Paired t-tests will be used to compare the differences in rating of perceived exertion following each of the exercise conditions.

6. Have you been working with a statistician in designing this protocol?
Answer/Response: No

IF YES, what is their name?
Answer/Response: N/A

7. Will data from multiple sites be combined during analysis?
Answer/Response: No

7(a). Does the study involve randomization?
Answer/Response: N/A

IF YES, will randomization be done at each site or among sites?
Answer/Response: N/A

7(b). Has the sample size calculation considered the variation among sites?
Answer/Response: N/A

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?
Answer/Response: N/A

7(d). Is there a common protocol used in all sites?
Answer/Response: N/A

IF NO, how will differences among sites, such as those related to the implementation, inclusion criteria, patient characteristics, or other sites characteristics, be considered to assess the study results?
Answer/Response: N/A

Study Procedures-Biomedical Research

1. What will be done in this protocol?
Answer/Response:

Prior to participation, all participants will be required to answer screening questions (i.e., age, physical activity level, and brief medical history), however this data will not be collected. Eligible participants will then be scheduled for a session. Upon arrival for their session, participants will fill out a demographic questionnaire (i.e., age, sex, height, weight, and dominant leg) and two physical activity questionnaires (i.e., Tegner Activity

Scale and Godin Leisure-Time Exercise Questionnaire). Participants will be randomly allocated to receive each of the exercise conditions in a randomized order starting with either the blood flow restriction exercise condition or the standard low resistance exercise condition. Participants will be informed that the second visit of the study is optional. If participants opt to participate in the second visit sub-study part of the study, then a second visit will be scheduled for 1 week after the initial visit and demographics will only be collected at the beginning of their first visit.

BFR Visit:
Following the completion of the questionnaires, the research team will assess the cross-sectional area, thickness, and echogenicity of the participants vastus lateralis of their dominant leg using b-mode diagnostic ultrasound (i.e., ACUSON Freestyle, Siemens Medical Solutions, USA). Once these measurements are taken, the researchers will prepare two small sections of the skin for placement of noninvasive electromyography sensors (i.e., Trigno Galileo, Delsys Inc, Boston, MA). Skin preparation will include the shaving of any hair and dead skin cells as well as extensive cleaning of these sites with gauze and alcohol prep pads. After the sites are prepared, the researchers will secure the sensors to the skin using a non-adhesive wrapping to limit movement of the sensors. Participants will then be asked to sit still while the device is set up and their resting muscle activity is measured. The strength assessment device (i.e., Biodex Systems III Isokinetic Dynamometer, Biodex Medical Systems) will then be set up to the individual's settings including their knee range of motion. Next, the researchers will ask participants to perform 3 maximal knee extension and flexion contractions. One minute of rest will be provided after these contractions are completed. Participants will then begin their first exercise condition. The procedures for these exercise conditions are identical except the blood flow restriction condition will include the inflation of a Delfi PTSII tourniquet cuff (Delfi Medical Vancouver, BC). For this condition, the cuff will be calibrated and inflated to 60% of the individual's total limb occlusion pressure (the amount of pressure needed to completely stop blood from entering and leaving the limb). The cuff will remain inflated during all sets, repetitions, and rest periods until the blood flow restriction exercise condition is completed. The Delfi PTSII tourniquet system will have a built-in tourniquet deflation safety feature that will automatically deflate the cuff after 8 minutes.

Under each condition, participants will complete a total of 75 knee extension and knee flexion exercise repetitions and a single 30-second maximum knee extension contraction in a stationary position. Each exercise condition should take about 7.5 to 8 minutes to complete.

Condition 1 (WITHOUT blood flow restriction FIRST)

Participants will be asked to perform 30 repetitions of knee extension and knee flexion at 20% of their maximum strength. A 30 second rest will be provided following this set. Participants will then be asked to perform three sets of 15 knee extension and flexion repetitions at 20% of their maximum strength. A rest period of 30 seconds will be provided following each set. Lastly, participants will be asked to perform one 30-second maximal knee extension contraction in a stationary position. Participants will then receive a 5-minute rest period before they repeat these procedures WITH blood flow restriction. The study session will be complete after participants have completed their last 30-second maximum contraction of the second condition.

Condition 2 (WITH blood flow restriction FIRST)

The blood flow restriction cuff will be inflated to the predetermined pressure (60% of the individual's limb occlusion pressure). Participants will be asked to perform 30 repetitions of knee extension and knee flexion at 20% of their maximum strength. A 30 second rest will be provided following this set. Participants will then be asked to perform three sets of 15 knee extension and flexion repetitions at 20% of their maximum strength. A rest period of 30 seconds will be provided following each set. Lastly, participants will be asked to perform one 30-second maximal knee extension contraction in a stationary position. Participants will then receive a 5-minute rest period before they repeat these procedures WITHOUT blood flow restriction. The study session will be complete after participants have completed their last 30-second maximum contraction of the second condition.

Optional Second Visit Sub-Study:

Following the completion of the questionnaires, the research team will assess the cross-sectional area, thickness, and echogenicity of the participants vastus lateralis of their dominant leg using b-mode diagnostic ultrasound (i.e., ACUSON Freestyle, Siemens Medical Solutions, USA). Once these measurements are taken, the researchers will prepare two small sections of the skin for placement of noninvasive electromyography sensors (i.e., Trigno Galileo, Delsys Inc, Boston, MA). Skin preparation will include the shaving of any hair and dead skin cells as well as extensive cleaning of these sites with gauze and alcohol prep pads. After the sites are prepared, the researchers will secure the sensors to the skin using a non-adhesive wrapping to limit movement of the sensors. Participants will then be asked to sit still while the device is set up and their resting muscle activity is measured. The strength assessment device (i.e., Biodex Systems III Isokinetic Dynamometer, Biodex Medical Systems) will then be set up to the individual's settings including their knee range of motion. Participants will then begin their first type of exercise in a randomized order. Three minutes of rest will be provided following each type of exercise.

Exercise 1: Isometric Exercise
Researchers will ask participants to perform three 5 second knee extension contractions in a stationary position at 25%, 50%, 75%, and 100% of their maximal effort. The order of these contractions will be randomized. Thirty seconds of rest will be provided following each set of 3 contractions.

Exercise 2: Isokinetic Exercise
Researchers will ask participants to perform 3 knee extension and flexion contractions at 25%, 50%, 75%, and 100% of their maximal effort at 2 speeds (90 degrees per second and 180 degrees per second). The order of these contractions will be randomized. Thirty seconds of rest will be provided following each set of 3 contractions.

Exercise 3: Fatigue Exercise
Researchers will ask participants to perform one 30-second maximal knee extension contraction in a stationary position. Participants will be asked to kick out against the device as hard as they can for 30 seconds.

Exercise 4: Functional Exercise
Researchers will ask participants to stand on a forceplate mat with each limb on a separate side of the mat. The participant will then squat down to maximum depth and then will return to their standing position. The participant will perform three sets of three squats.

The study session will be complete after the end of their final type of exercise.

2. If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.
Answer/Response: N/A

Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.**
(e.g. study team will administer study drug/ study interventions, study drug inventory of dispensed and returned drug, diary etc.)
Answer/Response: The study team will oversee all testing and exercise procedures during the study session.

2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.**
(e.g. subject returns more than 20% of the study drug, subject misses 20% of study visits)

Answer/Response: The subject is unable to complete all study procedures including strength testing and both exercise condition protocols in the blood flow restriction session of the study.

Bibliography

1. Scott BR, Loenneke JP, Slattery KM, Dascombe BJ. Exercise with blood flow restriction: an updated evidence-based approach for enhanced muscular development. *Sports Med Auckl NZ*. 2015;45(3):313-325. doi:10.1007/s40279-014-0288-1
2. Fatela P, Mendonca GV, Veloso AP, Avela J, Mil-Homens P. Blood Flow Restriction Alters Motor Unit Behavior During Resistance Exercise. *Int J Sports Med*. 2019;40(9):555-562. doi:10.1055/a-0888-8816
3. Cook SB, Scott BR, Hayes KL, Murphy BG. Neuromuscular Adaptations to Low-Load Blood Flow Restricted Resistance Training. *J Sports Sci Med*. 2018;17(1):66-73.
4. Lauver JD, Cayot TE, Rotarius T, Scheuermann BW. The effect of eccentric exercise with blood flow restriction on neuromuscular activation, microvascular oxygenation, and the repeated bout effect. *Eur J Appl Physiol*. 2017;117(5):1005-1015. doi:10.1007/s00421-017-3589-x
5. Hammer SM, Alexander AM, Didier KD, Barstow TJ. Influence of blood flow occlusion on muscular recruitment and fatigue during maximal-effort small muscle-mass exercise. *J Physiol*. 2020;598(19):4293-4306. doi:10.1113/JP279925
6. Killinger B, Lauver JD, Donovan L, Goetschius J. The Effects of Blood Flow Restriction on Muscle Activation and Hypoxia in Individuals With Chronic Ankle Instability. *J Sport Rehabil*. 2020;29(5):633-639. doi:10.1123/jsr.2018-0416
7. Lorenz D, Bailey L, Wilk K, et al. Current Clinical Concepts: Blood Flow Restriction Training. *J Athl Train*. Published online January 22, 2021. doi:10.4085/418-20
8. Pearson SJ, Hussain SR. A review on the mechanisms of blood-flow restriction resistance training-induced muscle hypertrophy. *Sports Med Auckl NZ*. 2015;45(2):187-200. doi:10.1007/s40279-014-0264-9
9. Rossi FE, de Freitas MC, Zanchi NE, Lira FS, Cholewa JM. The Role of Inflammation and Immune Cells in Blood Flow Restriction Training Adaptation: A Review. *Front Physiol*. 2018;9. doi:10.3389/fphys.2018.01376
10. Jessee M, Mattocks K, Buckner S, et al. Mechanisms of Blood Flow Restriction: The New Testament. *Tech Orthop*. 2018;33(2):72-79. doi:10.1097/BTO.0000000000000252

HSR210058-Motor Unit Recruitment of the Vastus Lateralis During Blood Flow Restriction Exercise

11. Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. *Br J Sports Med*. 2017;51(13):1003-1011. doi:10.1136/bjsports-2016-097071
12. De Luca CJ, Adam A, Wotiz R, Gilmore LD, Nawab SH. Decomposition of surface EMG signals. *J Neurophysiol*. 2006;96(3):1646-1657. doi:10.1152/jn.00009.2006

ii. Application

RESEARCH APPLICATION

Will this study be conducted outside of UVA Health during the COVID-19 pandemic?

If YES, Describe all study-specific risk minimization procedures regarding COVID-19 that will or might be used that go above and beyond the baseline health and safety requirements of the University, UVA Health, Commonwealth of Virginia or off-site location policies (e.g. asking new screening questions before in-person interventions, special cleaning protocols, use of PPE, social distancing, etc.):
Answer/Response: Yes. Twenty-four hours prior to arriving for study participation, participants will be asked to fill out a COVID screening questionnaire. They will be asked to fill out the same questionnaire at the time of their arrival for study participation. Participants' temperatures will be checked with an infrared thermometer upon arrival for the study. This study will abide by all clinical research guidelines set forth by the VPR office. All lab equipment will be thoroughly cleaned before and after each participant visit. All research staff and participants will be required to wear face masks during in-person study visits. Researchers will also wear eye protection and gloves. No more than 3 people (two researchers and one participant) will be allowed in the laboratory space during the testing procedures. As part of the VPR plan, all researchers will submit asymptomatic tests once per week until recommendations change.

Investigators Experience

Answer/Response: The PI, Dr. Susan Saliba (PhD, ATC, PT), is a professor and co-director of the Exercise and Sports Injury (EaSIL) for musculoskeletal injury research at the University of Virginia. She has 18 years of clinical experience as both a physical therapist and athletic trainer. She also has extensive experience in conducting clinical trials and studies as well as experience in utilizing blood flow restriction therapy during patient care.

Investigator Agreement

Will the Investigator Agreement and Signatures be obtained in Clinical Research Connect? Answer/Response: Yes

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

1. I am not currently debarred by the US FDA from involvement in clinical research studies.

2. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
3. That if this study involves any funding or resources from an outside source or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
4. The protocol will abide by the ethical standards of The Belmont Report
5. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
6. That no personnel will have access to subjects in this protocol or their information until they have completed the human subject research protection on-line training through CITI and the IRB-HSR has been notified.
7. That all personnel working on this protocol will follow all Policies and Procedures of:
   - the UVA Human Research Protection Program (HRPP SOPS)
   - the IRB-HSR https://research.virginia.edu/irb-hsr
   - the School of Medicine Clinical Trials Office: http://www.medicalcenter.virginia.edu/intranet/cto/index.html
   - and any additional UVA requirements for conducting research.
8. I will ensure that all those personnel delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training, experience or credentialing to undertake those tasks.
9. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
10. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
11. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
12. That all subjects will give informed consent unless the requirement has been specifically waived by the IRB.
13. That unless written consent has been waived by the IRB all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
14. They will establish and maintain an open line of communication with research subjects within their responsibility.
15. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.

16. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
17. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
18. That any serious deviation from the protocol will be reported promptly to the Board in writing.
19. That any data breach will be reported to the IRB, the UVA Corporate Compliance and Privacy Office , UVA Police as applicable.
20. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
21. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.
22. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time. If the current PI leaves UVA permanently, a new PI will be assigned PRIOR to the departure of the current PI.
23. All study team members will have access to the current protocol and other applicable documents such as the IRB-HSR Application, consent forms and Investigator Brochures.
24. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept according to UVA Records Management policies.
25. No data/specimens may be taken from UVA without a signed Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at UVA. The agreement will delineate what copies of data, health information and/or specimens may be taken outside of UVA. It will also approve which HIPAA identifiers may be taken outside of UVA with the health information or specimens.
26. If any member of study team leaves UVA, they are STRONGLY ENCOURAGED to use Exit Checklist found on IRB-HSR website at https://provost.virginia.edu/system/files/documents/Faculty-Departure-Checklist-2015_508.pdf

IF THE IRB-HSR WILL BE THE IRB OF RECORD FOR MULTIPLE SITES IN A MULTISITE TRIAL, THE UVA PI AGREES TO CARRY OUT THE FOLLOWING RESPONSIBILITIES:

1. Ensure all UVA personnel designated as Conflict of Interest Investigators complete Reviewing IRB's financial interest disclosure requirements unless the UVA personnel will adhere to the UVA conflict of interest policies that are compliant with DHHS requirements.

2. Promptly provide the Principal Investigator at each site with:
   a. Current approved protocol and consent documents;
   b. Approved modifications, amendments or changes to research protocols; and
   c. Approval of continuing reviews and reviews of unanticipated problems;
3. Notify the Principal Investigator at each site of standards and guidelines for reporting any post approval events such as adverse events, subject injuries, unanticipated problems, and protocol violations. Collect reports from Principal Investigator at each site of any unanticipated problems, deviations, suspensions and terminations, non-compliance, subject complaints, and submit such reports to Reviewing IRB per reporting requirements.
4. Notify the Principal Investigator at each site promptly of any unanticipated problems involving risks to subjects or others as determined by the Reviewing IRB.
5. Collect required information from the Principal Investigator at each site necessary for completing continuing review submissions.
6. Notify the Principal Investigator at each site promptly about any lapses of approval. Forward to the IRB of Record any request from the Principal Investigator of a site for continuation of a specific research subject on a protocol during a lapsed period of approval.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Signatures

Principal Investigator

Principal Investigator Signature	Principal Investigator Name Printed	Date

Department Chair or Designee

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound.
4. He/she is not the Principal Investigator or a sub investigator on this protocol.

Department Chair or Designee Signature | Department Chair or Designee Name Printed | Date

Brief Summary/Abstract

Answer/Response: Recent research has demonstrated that low resistance exercise completed with blood flow restriction (BFR) therapy has the potential to increase muscle strength, hypertrophy, and activation in various pathologic and post-surgical populations when high resistance exercise may be contraindicated. Unfortunately, the proposed mechanisms of BFR therapy have yet to be substantially supported. One of these mechanisms suggests that tourniquet induced arterial and venous occlusion may promote the early recruitment of type II (fast-twitch anaerobic) muscle fibers. This recruitment can lead to increases in muscle strength and hypertrophy despite exercises being completed under low resistance. Therefore, the utilization of BFR therapy may result in a more widespread hypertrophic stimulus within the muscle and cause beneficial muscular adaptations with reduced joint stress. The purpose of this study will be to determine how low resistance exercise with BFR effects muscle activation and specific motor unit recruitment of the vastus lateralis compared to standard low resistance exercise without BFR. An additional purpose of this study is to evaluate and determine the responsiveness and precision of the novel EMG device (Trigno Galileo Sensor) for measuring motor unit behavior during various exercise activities including isometric (stationary) exercise, isokinetic (moving) exercise, fatigue exercise, and functional exercise. We hypothesize that when exercise is completed with BFR there will be an increase in motor unit recruitment and firing rates as well as a decrease in motor unit recruitment thresholds compared to exercise without BFR. We also hypothesize that there will be positive relationship between the number of motor units recruited and muscle size and quality in both exercise conditions.

Healthy participants recruited for this single session study will be screened for inclusion and exclusion criteria over the phone. Eligible participants will then be scheduled for participation. Upon arrival for their session, participants will be asked to fill out a consent form and questionnaires regarding their demographic information and physical activity level. The participants will then begin the BFR visit of the study. Initially, participants will be randomly allocated to an exercise condition order (i.e., BFR exercise first followed by standard low resistance exercise second or vice versa). Imaging of their vastus lateralis size will be assessed using diagnostic ultrasound at the distal 1/3 portion of their muscle. Muscle activity will be assessed during all strength testing and exercise procedures using a wireless

electromyography device. Participants will complete maximal isokinetic strength testing of their dominant knee using an isokinetic dynamometer (Biodex). The participants will then begin their first exercise procedure including 4 sets of low resistance isokinetic exercise and 1 set of maximal isometric exercise. Then after a 5-minute resting period, the participants will complete the same exercise procedures under the second exercise condition. Participants will also rate their level of perceived exertion following each exercise condition protocol. Additionally, participants will be asked to complete a second study session, which will be scheduled after the blood flow restriction session. Participants will have the choice to opt out of the second session if they prefer to only complete the initial blood flow restriction session.

For the optional visit of the study, participants will return 1 week after the initial study visit. Participants will have their vastus lateralis imaged using the same procedures as the BFR visit of the study. Participants will then begin their first of four types of exercise: 1) isometric, 2) isokinetic, 3) fatigue, 4) functional, in a randomized order. Three minutes of rest will be provided following each type of exercise. Isometric exercise includes participants performing 3 knee extension contractions in a stationary position at 25%, 50%, 75%, and 100% of their maximal effort. Isokinetic exercise includes participants performing 3 knee extension and flexion contractions at 25%, 50%, 75%, and 100% of their maximal effort at 2 fixed speeds (90 degrees per second and 180 degrees per second). Fatigue exercise involves participants performing a maximal isometric knee extension contraction for 30 seconds. Lastly, the functional exercise involves participants completing 9 body weight squats to the height of the participant sitting in a chair.

Paired t-tests will be used to compare the effects of exercise with BFR to exercise without BFR (differences in mean number of motor units recruited, firing rates, recruitment thresholds, action potential amplitudes, and rating of perceived exertion). Paired t-tests will also be used to compare the differences in each of the motor unit behavior variables between each type of exercise in the optional visit of the study. Cohen's d effect sizes and 95% confidence intervals will also be reported. To examine the relationship between motor unit recruitment and muscle size and quality, Pearson correlations will be calculated.

All devices being used in this study are being used per the approved indication from the FDA and are not being evaluated in this study for an additional indication.

Sponsor

1. **Explain the sponsorship for this study.**
   Answer/Response: N/A

Support Source

1. Describe what will be provided and by whom.
Answer/Response: N/A

Human Participants

1. **How many subjects will be enrolled in this study by the UVA site?** *(e.g. sign a UVA consent form)*
   Answer/Response: 48

2. **Will subjects be recruited or receive study interventions in a UVA patient care setting?**
   Answer/Response: No

If YES, all study team members must review the Guideline for Research in Patient Care Settings prior to the start of the study.

Recruitment

INFORMATION: * *The UVA HIPAA Covered Entity includes the following areas:*
UVA Health including the School of Medicine & the School of Nursing, the Sheila C. Johnson Center, the Exercise, Sports Injury Laboratory and the Exercise Physiology Laboratory and University Physicians Group (UPG)
Identifiable health info may also be shared with the following areas without tracking the disclosure as agreements are in place to protect the information:

- *VP Office of Research*
- *Nutrition Services (Morrison's)*
- *UVA Center for Survey Research*

How do you plan to identify potential subjects?

a.____ Electronic Medical Record Review or Report (can include EPIC Slicer Dicer, Clarity, Caboodle, and other EMR reporting tools) / EMR data copy from an enterprise research database (CDR-IRB-HSR# 10797, OR OMOP, TriNetX, i2b2, ACT IRB-HSR #20840:) / Database established for health care operations (departmental clinical database or UVA Enterprise Data Warehouse) / Quality Improvement Data (*e.g. Performance Improvement, Practice Improvement, Quality Improvement*).

b____ Review of a research data repository that was established to keep data to be used for future research such as a departmental research database or use of data from a separate current active research protocol.
IRB# _____

c. ____ Patients UVA health care provider supplies the UVA study team with the patients contact information without patients' knowledge.

d. ____ Patient obtains information about the study from their health care provider. The patient contacts the study team if interested in participating. (Health care provider may or may not also be the a member of the study team)

e. __x__ Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc.

f. _____ Potential subjects have previously signed a consent to have their name in a registry/database to be contacted for future studies of this type.
IRB# of registry/ database: _____

g. ____ Other: Specify Answer/Response:

If item # a, b or c is checked above and if this protocol involves the use of protected health information do you confirm the following to be true?

- The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the UVA covered entity.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

Answer/Response: N/A

1. **How will potential subjects be contacted?**
   a.____Direct contact of potential subjects by the study team via letter, phone, direct e-mail. Members of study team ARE NOT health care providers of patients. Information will not be collected from psychotherapy notes.

b.____Potential subjects will be approached while at UVA Hospital or Health Clinic by a person who is NOT a member of their health care team. Information will not be collected from psychotherapy notes.

c.____Direct contact of potential subjects by the study team by approaching in person at UVA or via letter, phone, direct e-mail. Members of study team contacting potential subjects ARE health care providers of patients.

d.___X_ Indirect contact (flyer, brochure, TV, broadcast emails, patient provided info about the study from their health care provider and either the patient contacts study team or gives their healthcare provider permission for the study team to contact them.)

e. ____ Potential subjects are not patients. The study does not include obtaining subjects health information. Subjects will be contacted directly via email, phone, letter or presentation in group setting with consent then obtained individually in a private setting.

3. Will any information be obtained from a potential subject during "prescreening"?
Answer/Response: Yes (inclusion/exclusion criteria and COVID screening)

IF YES, Will any of the questions involve health information?
Answer/Response: Yes

IF YES, will you collect HIPAA identifiers with the health information?
Answer/Response: No

IF YES, which HIPAA identifiers will be recorded?
Answer/Response:
Do you confirm that health information with HIPAA identifiers will not be shared outside of UVA until a consent form is signed or only shared in a de-identified manner?
Answer/Response: YES

2. Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?

Answer/Response: Yes

►IF YES, explain in detail what you will ask them to do.
Answer/Response: Participants will be asked to refrain from participating in strenuous physical activity 24 hours before participating in each visit of the study. However, a participant will not be excluded if they failed to do so.

3. How will the consenting process take place with either the prospective subject, the subject's legally authorized representative or parent/legal guardian of a minor (if applicable)?
Answer/Response: The study team will determine a participant's eligibility as soon as the participant reaches out about participating in the study. A copy of the consent form will be provided to eligible participants via email for them to review prior to their scheduled study session. Participants will be provided with information on the consent form regarding the study including the risks and benefits of participation and what to expect if they choose to participate. Each participant will be encouraged to ask any and all questions regarding the study and its procedures. Consent will be obtained by a member of the study team (specifically the study coordinator) when participants arrive at the Exercise and Sport Injury Laboratory for their study session. Study procedures will begin immediately after the participant consents to the study.

6. Will subjects sign a consent form for any part of the study?
Answer/Response: Yes

7. Will the study procedures be started the same day the subject is recruited for the study?
Answer/Response: No

►IF YES, explain in detail why the subject cannot be given more time to make a decision to consent.
Answer/Response: N/A

►IF YES, explain in detail what will be done to assure the potential subject has enough time to make an informed decision.
Answer/Response: N/A

8. Is there the potential to recruit a vulnerable population? (e.g. economically or educationally disadvantaged subjects, or other vulnerable subjects such as

students , employees, investigator is health care provider of potential subject, pregnant women, children or prisoners?
Answer/Response: Yes

IF YES, what protections are in place to protect the rights and welfare of these subjects so that any possible coercion or undue influence is eliminated?

Check all applicable options:

____ Consent will be obtained by the CRC rather than the Investigator

____ Subjects will be assured that their relationship with their UVA health care providers will not be affected if they decide not to participate

__x__ Subjects will be given all the time needed to make their decision, and will not be pressured for a quick decision. They will be encouraged to seek advice from friends and family before signing consent.

__x__ Employees will be reassured that their decision will not affect their job or benefits.

__x__ Students will be reassured that their decision will not affect their status as a student or their grades.

____ If minors are enrolled, parental permission will be obtained prior to explaining the study to a minor and the minor's assent will be obtained prior to initiation of study procedures.

____ all subjects, especially those who are educationally disadvantaged will be asked open ended questions to confirm that they understand the study.

___ Other Explain:

9. Do you need to perform a "dry run" of any procedure outlined in this protocol?
Answer/Response: No

9a. List the "dry run" procedure(s) that must be performed.

Answer/Response: N/A

9b. How many "subjects" will be recruited for "dry run" procedures?
Answer/Response: N/A

9c. Describe the recruitment procedures for those participating in the "dry run".
Answer/Response: N/A

9d. Will those participating in the "dry run" be compensated?
Answer/Response: N/A

9e. Who will pay for the cost of the "dry run" procedure(s)?
Answer/Response: N/A

10. Is the study regulated by the Department of Defense (DoD)?
Answer/Response: No

If YES, do you confirm the following protections will be in place for military research participants to minimize undue influence?
Answer/Response: N/A

- Officers are not permitted to influence the decision of their subordinates.
- Officers and senior non-commissioned officers may not be present at the time of recruitment.
- Officers and senior non-commissioned officers have a separate opportunity to participate.
- When recruitment involves a percentage of a unit, an independent ombudsman is present.

If YES, do you also confirm that the following procedures will be in place to require limitations on dual compensation?
Answer/Response: N/A

- Prohibit an individual from receiving pay of compensation for research during duty hours.
- An individual may be compensated for research if the participant is involved in the research when not on duty.
- Federal employees while on duty and non- federal persons may be compensated for blood draws for research up to $50 for each blood draw.

- Non-federal persons may be compensated for research participating other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.

11. Non-Monetary Retention Incentives
If subjects will be provided with non-monetary gifts or tokens of appreciation, such as totes, books, toys, or other such materials, the study team will submit a description and approximate retail value of the item to the IRB.

Study Procedures- Biomedical Research

1. Where will the study procedures be done?
Check One:
____ UVA Health facilities (In patient or outpatient)
If checked, verify all study team members have reviewed the "Research in Patient Care Settings Guidance"
__x__ UVA but not medical center facilities: LIST specific location
Answer/Response: Exercise and Sport Injury Laboratory (Memorial Gymnasium at UVA)
____ Other: List specific location Answer/Response:

2. If the study involves medical risk and study procedures will be done outside of the UVA Medical Center what is your plan to protect the subjects in case of a medical emergency?
____ *NA*

Check all applicable options:
_____ MD, RN, onsite during procedures
__x___ Individual trained in CPR on site during procedures
__x___ AED and Individual trained to use it onsite
__x___ Call 911
_____ Other: Describe Answer/Response:

3. List the procedures, in bullet form, that will be done for RESEARCH PURPOSES as stipulated in this protocol.

INSTRUCTIONS:
Examples: blood tests, EKG, x-rays, surveys, administration of investigational drug/device, randomization to one of two approved drugs
Do NOT list those procedures which are being ordered for clinical standard of care.
If ALL procedures are being done for the research study, simply write: ALL

Answer/Response:

- Participant Questionnaires (age, height, weight, dominant leg, physical activity level)
- BFR Visit:
  - Randomized exercise condition order
  - Diagnostic ultrasound assessment of thigh muscle
  - Muscle activity assessment of thigh muscle during exercise
  - Muscle strength testing
  - Exercise condition 1
  - Rating of perceived exertion questionnaire after exercise condition 1
  - Exercise condition 2
  - Rating of perceived exertion questionnaire after exercise condition 2
- Optional Second Visit Sub-study:
  - Diagnostic ultrasound assessment of thigh muscle
  - Muscle activity assessment of thigh muscle during exercise
  - Isometric exercise
  - Isokinetic exercise
  - Fatigue exercise
  - Functional exercise

4. Do you confirm that, except for blood draws through a peripheral site, that all invasive procedures will be performed by a licensed health care provider under the supervision of an MD?
Answer/Response: N/A – no invasive procedures

5. Will you be using data/specimens in this study that were collected previously, with the use of a research consent form, from another research study?
Answer/Response: No

IF YES, will the data/specimens be used in this study without a new consent from the original donor?
Answer/Response: N/A

IF YES, explain how the proposed use is consistent with the use planned in this study and submit a copy of the consent form used to collect the data/specimens.
Answer/Response: N/A

6. Will any of the procedures listed in item # 3 have the potential to identify an incidental finding?
Answer/Response: No

_____The examination(s) utilize(s) the same techniques, equipment, etc., that would be used if the subject were to have the examination(s) performed for clinical care.
Procedures, assessments, evaluations: _____

There exists the potential for the discovery of clinically significant incidental findings.
- The PI takes full responsibility for the identification of incidental findings:
- The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance.
- If an incidental finding is serious and emergent (e.g. mass on x-ray), the study team will inform the subject and contact the subject's health care provider.
- If applicable a follow-up letter describing the finding should be provided to the subject with instructions to either show the letter to their PC or if the subject has no PCP, the subject should be instructed to make an appointment at UVA or at the Free Clinic.

____This examination(s) utilizes non-standard/investigational, technique, equipment, etc. It is impossible to determine the significance of such results, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit.
Procedures, assessments, evaluations: _____

7. Do any of the procedures listed above, under question # 3, utilize any imaging procedures for RESEARCH PURPOSES?
Answer/Response: Yes – diagnostic ultrasound

►IF YES, check one of the following two options:

__x___This imaging research examination utilizes the same imaging techniques, equipment, scanning sequences that would be used, if the subject were to have the imaging performed for clinical care. There exists the potential for the discovery of clinically significant incidental findings.

►If checked, answer the following:

List procedures:
Answer/Response: With participants resting in a chair, the researchers will take cross-sectional area and thickness measures of the vastus lateralis using ultrasound to determine muscle size, thickness, and

echogenicity. Screen-shot images will be taken in perpendicular and parallel planes.

Will the images be read by a licensed radiologist and the reading placed in the subject's medical record?
Answer/Response: No

►IF NO: The PI takes full responsibility for the identification of incidental findings:
- The PI will have all incidental findings reviewed by a radiologist who will advise the PI regarding clinical significance.
- The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance.
- A follow-up letter describing the finding should be provided to the subject with instructions to either show the letter to their PC or if the subject has no PCP, the subject should be instructed to make an appointment at UVA or at the Free Clinic.

_____This imaging research examination utilizes non-standard/investigational imaging modality, techniques, equipment, scanning sequences, etc. It is impossible to determine the significance of such images, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit.
List procedures:
Answer/Response:

8. Will your study involve measures used to screen or assess for depression and/or suicidality for research purposes?
Answer/Response: No
NOTE: Answer this question YES and answer the questions below if any of the following apply:
1) *The protocol has a research purpose to study suicide, suicidal ideation, depression or trauma*
2) *The protocol has a research purpose to study traumatic life events that may evoke powerful emotion in participants;*
3) *The protocol includes **assessments** or tools (e.g. Surveys, exams, questionnaires, etc.) that can be used to screen or identify **depression (C-SSRS/BID/SCID, etc.) and/or suicidal ideation** (thoughts of suicide, either active or passive), plan (the means or mechanism) or intent (the expressed desire and willingness to act on the plan).*

a. Which research staff members will be qualified and available to provide a referral for further care or intervention if the subject's responses indicate this need?
Answer by position with study (e.g. PI, sub investigator etc. Do not include names in answer.
Answer/Response: N/A

b. Include specific guidelines for intervention or further assessment based on tools and rating scales used in this study. Include information regarding how soon information from a subject will be reviewed. *(e.g. Questionnaire(s) will be reviewed the same day they are administered/submitted. Based on score of xxx or response of X, subject will be assessed further by the PI for suicide risk or referred urgently to an ED, crisis center, or clinic immediately).*
Answer/Response: N/A

REMINDER: If your subjects will be patients at UVA Medical Center, you must adhere to **Medical Center Policy 0140 Judicial Treatment Order and 0197 Suicide Risk Assessment and Prevention.**

9. Will any data from this study be submitted to or held for inspection by the FDA?
NOTE: Publication is not equivalent to submission of data to the FDA.
Answer/Response: No

Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits which may accrue to society in general, as a result of this study?
Answer/Response: There are no direct benefits to participants for taking part in this study. However, the information gained by completing this study will help to identify a potential underlying mechanism of blood flow restriction therapy. This information may help inform future researchers and healthcare providers when implementing this treatment technique into their clinical practice. Results of the Optional Second Visit Sub-study will also help to determine the responsiveness and precision of the Trigno Galileo Sensor device for measuring muscle activity and motor unit behavior during various types of exercise.

2. Do the anticipated benefits justify asking subjects to undertake the risks?
Answer/Response: Yes

APPENDIX: Device Information: (Device being evaluated)

- **List name of device being evaluated.**
  Answer/Response: Trigno Galileo Sensor
- **Describe pertinent animal data that is available regarding the safety of this device.**
  Answer/Response: N/A
- **Describe pertinent human data that is available regarding the safety of this device.**
  Answer/Response: Although limited, the data regarding safety of this device is available. Delsys Inc. provides various research articles on the device safety and guarantees the safety, reliability, and performance of the equipment only if assembly, modifications and repairs are carried out by authorized technicians; the electrical installation complies with the appropriate requirements; and the equipment is used in accordance with the instructions for use. The environmentally sealed enclosure of the device protects the internal electronics from the ingress of liquids and other environmental elements and provides a high standard of user safety and durability.
- **Have there been any human deaths associated with this device?**
  Answer/Response: No
- **In how many humans has this device been used previously?**
  Answer/Response: Unknown amount.
- **If this protocol will be used in children describe any previous use of this device with children of a similar age range.**
  Answer/Response: N/A
- **Is this device implanted?**
  Answer/Response: No

  ►IF YES, is it removable?
  Answer/Response: N/A

  ►IF YES, explain the removal procedure, and describe any risk or cost to the subject.
  Answer/Response: N/A
- **Is this a post-marketing study?**
  Answer/Response: No

  ►IF YES, is the study required to be done by the FDA?

Answer/Response: N/A

- **Does this device have an IDE# from the FDA?**
  Answer/Response: No.
  Primary Device ID #: 00851679007223

  ►IF YES, list IDE #:
  Answer/Response:

  ►IF NO, check the applicable items in the table below:

IDE Exemption Criteria

X	A legally marketed device when used in accordance with its labeling
	A diagnostic device if it complies with the labeling requirements in §809.10(c) and if the testing: • is noninvasive; • does not require an invasive sampling procedure that presents significant risk; • does not by design or intention introduce energy into a subject; and • is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure; *Additional guidance for an in vitro diagnostic device studies can be found in "Regulating In Vitro Diagnostic Device (IVD) Studies."*
	Consumer preference testing, testing of a modification, or testing of a combination of devices if the device(s) are legally marketed device(s) [that is, the devices have an approved PMA, cleared Premarket Notification 510(k), or are exempt from 510(k)] AND if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
	A device intended solely for veterinary use;
	A device shipped solely for research with laboratory animals and contains the labeling "CAUTION – Device for investigational use in laboratory animals or other tests that do not involve human subjects."
	A custom device : According to 21CFR812.2(c) (7) a custom device as defined in 812.3(b) is exempt unless the device is being used to determine safety or effectiveness for commercial distribution. A custom device means a device that: (1) Necessarily deviates from devices generally available or from an applicable performance standard or premarket approval requirement in order to comply with the order of an individual physician or dentist;

	(2) Is not generally available to, or generally used by, other physicians or dentists; (3) Is not generally available in finished form for purchase or for dispensing upon prescription; (4) Is not offered for commercial distribution through labeling or advertising; and (5) Is intended for use by an individual patient named in the order of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice.
	NA- None of the items above apply- device determined to NOT be exempt from IDE regulations. *If applicable will submit any documentation from the sponsor regarding device risk determination (eg. significant risk vs. non-significant risk)*

►If you did not check any item in the preceding table complete the following item.

According to 21CFR812.3(m) a Significant Risk (SR) device study is one that presents a potential for serious risk to the health, safety, or welfare of a subject and Check all applicable items:

____ is intended as an implant; or
____ is used in supporting or sustaining human life; or
____ is for use of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
____ otherwise presents a potential for serious risk to the health, safety, or welfare of a subject

If this is the only item checked- answer the following questions:

- Is this a class I, II or III device?
  If you are not sure- See the FDA Device Advice for information to help you make this determination.
  Answer/Response:
- Is there a similar device on the market and if so what is the safety profile of that device?
  Answer/Response:
- What would be the risk to the subject if the device failed?
  Answer/Response:

- Is the device removable?
  Answer/Response:
  - If the device is removable list potential risks to subject from removing the device.
    INSTRUCTIONS: If the participant must undergo a procedure as part of the investigational study, e.g., a surgical procedure to implant the device, the IRB-HSR must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device. Include the risks of the procedure.
    Answer/Response:

____None of the options above apply. Device qualifies as a non-significant risk device.

IMPORTANT: If you checked this option the protocol will need to be reviewed by the full board to determine if the device is significant or non-significant risk. Please refer to full board submissions deadlines on the IRB-HSR.

INSTRUCTIONS: Additional information regarding devices may be found on the IRB-HSR Website under DEVICES

Data and Safety Monitoring Plan

1. Definition:

1.1 How will you define adverse events (AE)) for this study?

___x__An adverse event will be considered any undesirable sign, symptom or medical or psychological condition **even if the event is not considered to be related** to the investigational drug/device/intervention. Medical condition/diseases present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment/intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of an investigational device that adversely affects the rights, safety or welfare of subject s.

_____Will use definitions provided in the Protocol

_____Other: Specify Answer/Response:

1.2 How will you define serious adverse events?

__x___A serious adverse event will be considered any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

__x___Any serious psychological and emotional distress resulting from study participation (suggesting need for professional counseling or intervention).

_____Will use definitions provided in the Protocol

_____Other: Specify Answer/Response:

1.3 What is the definition of an unanticipated problem?

An unanticipated problem is any event, experience that meets ALL 3 criteria below:

- Is unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studies
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the subject or others at greater risk of harm than was previously known or recognized OR results in actual harm to the subject or others

1.4 What are the definitions of a protocol deviations and/or noncompliance?

A **protocol deviation** is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB-HSR prior to its initiation or implementation. Protocol deviations may be major or minor.

Noncompliance can be a protocol deviation OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. Noncompliance may be minor or sporadic, or it may be serious or continuing.

1.5 If pregnancy occurs how will this information be managed?

__x___ Adverse Event- will follow adverse event recording and reporting procedures outlined in section 3.

_____ Unanticipated Problems- will follow Unanticipated Problem recording and reporting procedures outlined in section 3.

_____ Other Specify Answer/Response:

1.6 What is the definition of a Protocol Exception?

__x___NA- No outside sponsor

_____Protocol has a sponsor or a Data & Safety Monitoring Board (DSMB) outside of UVA. Protocol exceptions are circumstances in which the investigator wishes to deviate from eligibility criteria or one or more of the specific procedures called for in a research plan. Unlike modifications that apply to all subsequent subjects in the research, a protocol/research plan exception only applies to a specific subject or group of subjects. Exceptions are planned, and the investigator gets approval from the sponsor ahead of time. Such a request should be rare and justified in terms of serving the best interests of the potential study participant.

1.7 What is the definition of a data breach?

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

2. Identified risks and plans to minimize risk

2.1 What risks are expected due to the intervention in this protocol?

Expected Risks related to study participation.	Frequency
Rare But Serious Risks of Blood Flow Restriction Therapy • Blood clot • Pulmonary embolism • Rhabdomyolysis	____Occurs frequently ____Occurs infrequently __x__Occurs rarely ____Frequency unknown
Less Likely Risks of Blood Flow Restriction Therapy • Bruising	____Occurs frequently __x__Occurs infrequently ____Occurs rarely ____Frequency unknown
Likely Risks of Blood Flow Restriction Therapy	__x__Occurs frequently ____Occurs infrequently

• Muscle discomfort or cramping • Difficulty completing the exercise • Soreness, numbness, or tingling in your leg • Light-headedness • Cold feeling in your leg	____Occurs rarely ____Frequency unknown
Risks of Low Load Exercise • Muscle discomfort • Muscle soreness	__x__Occurs frequently ____Occurs infrequently ____Occurs rarely ____Frequency unknown
Risks of Skin Preparation for Electromyography • Skin redness • Skin tenderness • Skin swelling	__x__Occurs frequently ____Occurs infrequently ____Occurs rarely ____Frequency unknown
Violation of subject's privacy and confidentiality	Minimized due to the requirements of the privacy plan in this protocol

2.2 List by bullet format a summary of safety tests/procedures/observations to be performed that will minimize risks to participants:

- To minimize all risks associated with blood flow restriction therapy, this study will only enroll healthy participants that are free of any contraindications associated with blood flow restriction. This will vastly mitigate the serious and less likely risks associated with blood flow restriction. Each of the likely risks of blood flow restriction therapy should go away after the cuff is deflated following the blood flow restriction exercise condition. Most side-effects of this condition are similar to that of standard strength training.

2.3 Under what criteria would an INDIVIDUAL SUBJECT'S study treatment or study participation be stopped or modified

__x___At subject, PI or sponsor's request

__x___Treatment would be stopped if the subject had a serious adverse event deemed related to study, or study drug will be increased if the subject tolerates dosing

_____Refer to the Protocol

2.4 Under what criteria would THE ENTIRE STUDY need to be stopped.

__x___Per IRB, PI, DSMB, or sponsor discretion

_____Refer to the Protocol

_____Other: Specify Answer/Response:

2.5 What are the criteria for breaking the blind/mask?
__x___NA – Not blinded/masked

_____Refer to the Protocol

_____Other: Specify Answer/Response:

2.6 **How will subject withdrawals/dropouts be reported to the IRB prior to study completion?**

__x___IRB-HSR continuation status form

_____Other: Specify Answer/Response:

3. Adverse Event / Unanticipated Problem Recording and Reporting

3.1 Will all adverse events, as defined in section 1.1, be collected/recorded? No
► IF NO, what criteria will be used?

__X___Only adverse events deemed related/possibly related to study

_____Only adverse events that are deemed serious

_____Only adverse events that are deemed related AND serious

_____If protocol requires oversight by Cancer Center DSMC and the protocol is Investigator Initiated- will use tables from the Cancer Center Protocol Review Committee (PRC) Requirements section to document what will be recorded.
_____Other: Specify Answer/Response:

3.2 How will adverse event data be collected/recorded? Check all that apply
__x___Paper AE forms/source documents

_____Spreadsheet: paper or electronic

_____Database Specify name/type of database Answer/Response:

3.3. How will AEs be classified/graded? Check all that apply
_____World Health Organization Criteria (WHO)

_____NCI Common Toxicity Criteria, Version 2.0/ NCI Common Terminology Criteria, Version 3.0

_____NCI CTCAE Version 4.0

_____Mild/Moderate/Severe

_X_ Serious/Not serious Required for all protocols

_____Will use classifications/ grades provided in the Protocol

_____Other: Specify Answer/Response:

3.4 What scale will the PI use when evaluating the relatedness of adverse events to the study participation? *Check all that apply:*

__x___The PI will determine the relationship of adverse events to the study using the following scale:

Related:	AE is clearly related to the intervention
Possibly related:	AE may be related to the intervention
Unrelated:	AE is clearly not related to intervention

_____Will use attribution scale provided in the Protocol

_____The PI will use an alternative attribution scale. Specify Answer/Response:

3.5 When will recording/reporting of adverse events/unanticipated problems begin?

_____After subject signs consent

__x___After subject begins study drug/ device placement/intervention /study-related procedure/specimen collection

_____Other: Specify Answer/Response:

3.6 When will the recording/reporting of adverse events/unanticipated problems end?
__x___ End of study drug/device/intervention/participation

_____30 days post study drug/device/intervention

_____Subject completes intervention and follow up period of protocol

_____Other: Specify Answer/Response:

_____See Protocol for additional information.

_____Two years past last exposure to Gadolinium ONLY if diagnosed with NSF/NSD.

3.7 How will Adverse Events, Unanticipated Problems, Protocol Deviations and Data Breaches be reported? Complete the table below to answer this question

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVA protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call
Internal, Serious, Unexpected Related adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online
Unanticipated Problems that are not adverse events or protocol deviations This might include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. Unanticipated Problem Report Form
Protocol Deviations/Noncompliance *The IRB-HSR only requires that MAJOR deviations be reported, unless otherwise required by your sponsor, if applicable.*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Deviation, Noncompliance and Protocol Exception Reporting Form Protocol Deviation Protocol Exception Reporting Form
Data Breach	The UVA Corporate Compliance and Privacy Office ITC: if breach involves electronic data	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVA Corporate Compliance and Privacy Office- Phone 924-2938 ITC: Information Security Incident Reporting procedure, https://security.virginia.edu/report-information-security-incident UVA Police-Phone- (434) 924-7166

	UVA Police if breach includes such things as stolen computers.		

Privacy Plan

The following procedures must be followed.

- The data will be secured per the Data Security Plan of this protocol.
- Only investigators for this study and clinicians caring for the patient will have access to data.
- UVA University Data Protection Standards will be followed.
- If identifiable data is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the University's Highly Sensitive Data Protection Standard for Individual-Use Electronic Devices or Media Additional requirements may be found in the University's Security of Network-Connected Devices Standard. If identifiable data is taken away from the UVA Health , Medical Center Policy # 0218 will be followed.
- Data will be securely removed from the server/drive, additional computer(s), and electronic media according to the University's Electronic Data Removal Standard.
- Data will be encrypted or removed if the electronic device is sent outside of UVA for repair according to the University's Electronic Data Removal Standard .
- If PHI will be faxed, researchers will follow the UVA Health Policy # 0194.
- If PHI will be emailed, researchers will follow the UVA Health Policy # 0193 and University Data Protection Standards (UDPS 3.0).
- Data may not be analyzed for any other study without additional IRB approval.
- If you are using patient information you must follow UVA Health Policy # 0021.
- Both data on paper and stored electronically will follow the University's Record Management policy and the Commonwealth statute regarding the Destruction of Public Records.

If you have a question or concerns about the required security standards contact InfoSec at it-security@virginia.edu

Summary of Requirements to Comply with UVA Health, Medical Center and University Policies and Guidance as noted above:

Highly Sensitive Data is:
-personal information that can lead to identity theft if exposed or
-data that reveals an individual's health condition and/or history of health services use.
Protected Health Information (PHI) a type of Highly Sensitive Data, is health information combined with certain HIPAA identifiers making the health information identifiable per HIPAA regulations
Sensitive Data is -any additional research data that is not publicly available
Identifiable Data under HIPAA regulations is considered to be *Highly Sensitive Data at UVA.*
A **Limited Data Set** (LDS) under HIPAA regulations is considered to be *Sensitive Data* at UVA. The only HIPAA identifiers associated with data: dates and or postal address information limited to town or city, state, and zip code.

Highly Sensitive Data (Identifiable Health Info per HIPAA)	**Sensitive Data (Limited Data Set and De-identified data per HIPAA)**
General Issues	*General Issues*
Discussions in private Do not share with those not on the study team or those who do not have a need to know.	Do not share with those not on the study team or those who do not have a need to know.
Password protect	Password protect
Physically secure (lock) hard copies at all times if not directly supervised. If not supervised hard copies must have double protection (e.g. lock on room OR cabinet AND in building requiring swipe card for entrance).	Physically secure (lock) hard copies at all times if not directly supervised.
For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.	For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.
Encrypt See Encryption Solutions Guidance *Files on UVA Health Network drives are automatically encrypted. If not stored there it is study teams responsibility to make sure data are encrypted.*	
If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVA Purchase order.	If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVA Purchase order.
Store files on a network drive specifically designated for storing this type of data, e.g. high-level security server/drives managed by Information Technology Services or the "F" and "O" managed by UVA Heath Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive such as the desktop of your computer (e.g. C drive) or to an individual Use Device*. May access via VPN	
Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract is in place.	Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract is in place.
If collected without consent/ HIPAA authorization will NOT be allowed to leave UVA HIPAA covered entity** unless disclosure is approved by the IRB and the disclosure is tracked in EPIC	If collected without consent/ HIPAA authorization will NOT be allowed to leave UVA HIPAA covered entity** unless disclosure is approved by the IRB and a contract is in place prior to sharing of data.

Highly Sensitive Data (Identifiable Health Info per HIPAA)	**Sensitive Data (Limited Data Set and De-identified data per HIPAA)**
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet) MUST consult with InfoSec or UVA Health Web Development Office: 434-243-6702 ▪ University Side: IT-Security@virginia.edu ▪ UVA Health: Web Development Center.	
May use: • Globus • Drop Box- UVA Health IT • Qualtrics Portal for HSD • Any additional programs identified by Information Security at ITS Web in the Software Gateway. UVA Health employees can also review Online Account Request to find additional options. May NOT use: • UVA Box • UVA Collab • Question Pro • non-UVA licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.	May use: • Globus • Drop Box- UVA Health IT • Qualtrics portal for MSD • UVA Box • UVA Collab • Any additional programs identified by Information Security at ITS Web in the Software Gateway. UVA Health employees can also review Online Account Request to find additional options. May NOT use • non-UVA licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.
The following vendors for handling communication with subjects are NOT allowed: • Google Voice • Facebook (including Messenger) • Linked In • Snapchat	The following vendors for handling communication with subjects are NOT allowed: • Google Voice • Facebook (including Messenger) • Linked In • Snapchat
Individual-Use Device	*Individual-Use Device*
Do not save to individual-use device* without annual written approval of your Department AND VP or Dean. If approval obtained, data must be password protected and encrypted.	
Do not save an email attachment containing HSD to an individual use device*. (e.g. smart phone)	

E Mail	*E Mail*
Do not share via email with Outlook Web/ or forward email using other email vendors like Gmail/ Yahoo	
Do not send via email on smart phone unless phone is set up by UVA Health	
Email may include name, medical record number or Social Security number only if sending email to or from a person with * HS in their email address. *NOTE: VPR & IRB staff do not meet this criteria!*	In addition to sharing LDS, may include initials if persons sending and receiving email works within the UVA HIPAA covered entity.**
FAX	*FAX*
Verify FAX number before faxing	Verify FAX number before faxing
Use Fax Cover Sheet with Confidentiality Statement	Use Fax Cover Sheet with Confidentiality Statement
Verify receiving fax machine is in a restricted access area	Verify receiving fax machine is in a restricted access area
Verify intended recipient is clearly indicated	Verify intended recipient is clearly indicated
Recipient is alerted to the pending transmission and is available to pick it up immediately	Recipient is alerted to the pending transmission and is available to pick it up immediately
TEXT	*TEXT*
Not acceptable.	Only acceptable if using a University contracted phone or with approval from Information Security.
LOST OR STOLEN RESEARCH DATA	LOST OR STOLEN RESEARCH DATA
Must report in accordance with the protocol and in accordance with the Reporting an Information Security Incident Procedure Any data breach must also be reported to the IRB of Record if the report meets the criteria of an Unanticipated Problem.	Must report in accordance with the protocol and in accordance with the Reporting an Information Security Incident Procedure Any data breach must also be reported to the IRB of Record if the report meets the criteria of an Unanticipated Problem.

** Individual Use Device – examples include smart phone, CD, flash (thumb) drive, laptop, C drive of your computer,*
*** At UVA this includes the following areas:, the UVA Health including the School of Medicine & the School of Nursing, the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory and the Exercise Physiology Laboratory.*
Identifiable health info may also be shared with the following areas without tracking the disclosure as agreements are in place to protect the information:

- *VP Office of Research*
- *Nutrition Services (Morrison's)*
- *UVA Center for Survey Research*

Informed Consent
Unless waived by the IRB, subjects will be fully informed of the:

- purpose of the study,
- reasonably anticipated benefits,
- potential risks or discomfort participation in the study may entail,
- and any alternative treatments.

They will also be informed that their

- consent is voluntary and that they may withdraw their consent to participate at any time, and
- (if applicable) choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease.

The consent documents used to obtain informed consent of the subject must be approved by the IRB prior to use. Any written materials (consent/ short form) will be provided to the potential subject in a language they can read understand. The subjects will be given sufficient time to read the consent form and have the opportunity to ask questions.. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled. After this explanation and before entry into the study, consent should be appropriately recorded. Subjects will be given a copy of the signed consent/ short form.

Institutional Review Board (IRB)
No subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment.
Any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.

Investigator Responsibilities
The investigator is responsible for ensuring that the study is performed in accordance with the protocol and applicable local, state and federal regulatory requirements including ICH guidelines on Good Clinical Practice (GCP-E-6).

Studies with a Certificate of Confidentiality
If a study has a Certificate of Confidentiality (automatic for any study funded in whole or in part by the federal government that collects *identifiable sensitive information**) researchers:

- May not disclose or provide, in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such

disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or

- May not disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.
- May disclose information only when:
  - Required by federal, state, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to state and local health departments), excluding instances of disclosure in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding.
  - Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual.
  - Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
  - Made for the purposes of other scientific research that is in compliance with applicable federal regulations governing the protection of human subjects in research.

* The term "*identifiable, sensitive information*" means information about an individual that is gathered or used during the course of biomedical, behavioral, clinical, or other research, where the following may occur:

- An individual is identified; or
- For which there is at least a very small risk, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

Taping/Photography

1. Will participants be recorded on audiotape?
Answer/Response: NO

▶ IF YES, answer the following questions.

1a. What steps will be taken to protect the privacy of the subjects?
Answer/Response:

1b. What data will be captured from the audiotapes?
Answer/Response:

1c. When will data from the tapes be transcribed?
Answer/Response:

1d. When will the audiotapes be destroyed?
Answer/Response:

2. Will participants be photographed or recorded on videotape?
Answer/Response: YES

▶ IF YES, answer the following questions.

2a. Will their faces be shown?
Answer/Response: No

2b. What steps will be taken to protect the privacy of the subjects?
Answer/Response: Ultrasound images are unidentifiable which will ensure that the privacy of each subject is maintained. These images will only be used for measurement purposes and no one outside of the study team will view them.

2c. What data will be captured from the photo or videotape that could not be obtained in other ways?
Answer/Response: These ultrasound images will capture the muscle architecture including the muscle size, muscle thickness, muscle echogenicity, and subcutaneous fat tissue thickness. Collection of these measures would not be possible without utilizing diagnostic ultrasound or a more invasive MRI.

2d. How is this data critical to this research?
Answer/Response: This data will allow researchers to assess the relationships between muscle size, thickness, echogenicity, and fat tissue

thickness with muscle activity and motor unit behavior. Without this data these associations can not be determined.

2e. When will data from the tapes be transcribed?
Answer/Response: These unidentifiable images will be transferred from the ultrasound device to a secure desktop computer using a flash drive. Once on the computer, the images will be measured using a measurement application (ImageJ).

2f. When will the tapes be destroyed?
Answer/Response: The images will be deleted from the ultrasound device after they have been successfully transferred to the desktop computer using a flash drive. The images will also be deleted from the flash drive after they have been saved to the desktop computer. At the end of the study, the images will be transferred to a high security server (es3) and permanently deleted from the desktop computer.

2g. Will participants be photographed, recorded or videotaped without their knowledge?
INSTRUCTIONS: IF YES, include a post-experiment release form offering the participants the option of having their tape erased.
Answer/Response: NO

3. If a subject withdraws from the study how will you withdraw them from the audiotape, videotape or photograph?
Answer/Response: If a subject withdraws from the study, all images captured using the diagnostic ultrasound device will be permanently deleted from the ultrasound device, as well as the flash drive and desktop computer if the images had been transferred prior to subject withdrawal.

iii. Consent

Consent of an Adult to Be in a Research Study

In this form "you" means a person 18 years of age or older who is being asked to volunteer to participate in this study.

Participant's Name_____

Principal Investigator:	Susan Saliba, Ph.D, M.P.T., ATC Department of Kinesiology PO Box 400407 Charlottesville, VA, 22908 P: 434-243-4033

What is the purpose of this form?

This form will provide you with information about this research study. You do not have to be in the study if you do not want to. You should have all your questions answered before you agree to be in this study.

Please read this form carefully. If you want to be in the study, you will need to sign this form. You will be given a copy of this form.

Who is funding this study?

This study is not funded.

Key Information About This Research Study

You are being asked to take part in a research study. You do not have to take part in this study. If you decide not to participate in this study, there will be no impact on your medical care. Participation in research is voluntary, and you may quit at any time.

- **What are the main reasons you may want to join this study?**
  - You are a healthy adult that would like to help inform future research and help determine the underlying mechanisms of blood flow restriction therapy. Blood flow restriction therapy involves the application of an inflatable cuff (similar to a blood pressure cuff) to an arm or leg in order to partially and temporarily stop blood from entering and leaving a muscle during exercise. Typically, increases in muscle strength and size can only be achieved when exercising under high loads such as 80% of an individual's maximum strength. However, blood flow restriction therapy has been used to increase muscle strength and size using low loads (15-30% of an individual's maximal strength) in populations that are unable to exercise using high loads. This therapy allows individuals to achieve these gains without increased stress and muscle damage that often results from high load exercise.

  - Your participation in this study may also help to evaluate the usage of a novel device for measuring muscle activity and motor unit behavior during various types of exercise.
- **What are the main reasons you may not want to join this study?**
  - You may not want to make the time or travel commitment required to participate.
  - You will be asked to refrain from participating in strenuous exercise 24 hours prior to participating in the study.
  - You will need to have the hair shaved and the top layer of skin removed from two small areas of your thigh
- **What is the research question the study is trying to answer?**
  - The purpose of this research is to determine the differences in thigh muscle activity during low load exercise with blood flow restriction compared to low load exercise without blood flow restriction. This study also aims to evaluate and determine the responsiveness and precision of a device for measuring changes in muscle activity and motor unit behavior during various types of exercise.
- **What information about you is being collected as part of this research?**
  - Age, sex, height, weight, and dominant leg
  - Physical activity level
  - Rating of perceived exertion
  - Muscle activity, muscle size, muscle quality, subcutaneous fat tissue thickness, and muscle strength.
- **What are the types of activities will you do in this research?**
  - Questionnaires, diagnostic ultrasound assessment, muscle strength assessment, and two sets of exercise; will be wearing a tourniquet around your thigh during one set of exercise.
- **What impact will participating in this research have on you outside of the research?**
  - Participating in this study will have no impact on you outside of the study. Following completion of the study session, you may have slight muscle discomfort or soreness similar to traditional strength training.

You are being asked to take part in a research study. You do not have to take part in this study. You should only agree to take part in this study after reading this consent form and discussing it with the study team.
You may also discuss this with your family, friends, health care providers or others before you make a decision.

What will you have to do if you take part in this study?
Full details of all the procedures are found later in this form.

If you take part in this study, you will initially participate in a blood flow restriction exercise session. For the blood flow restriction session, you will:

- Come to the Exercise and Sport Injury Lab in Memorial Gymnasium at the University of Virginia for a study session.
- Answer questions regarding your age, height, weight, dominant leg, and physical activity level as well as your perceived level of difficulty during the study exercises.
- Have your thigh muscle imaged with diagnostic ultrasound.
- Have the activity of your thigh muscle assessed with surface electromyography.
- Complete maximal strength assessments.
- Take part in two exercise protocols, one with low resistance and one with low resistance under blood flow restriction.
- Rate your level of perceived exertion following each exercise condition.

The session will take about 45 minutes to an hour to complete.

You will also be provided with the opportunity to participate in an optional second study visit. If you choose to take part in the second study visit you will:

- Return to the Exercise and Sport Injury Lab one week after your first study visit.
- Have your thigh muscle imaged with diagnostic ultrasound.
- Have the activity of your thigh muscle assessed with surface electromyography.
- Take part in four types of exercise: stationary exercise, moving/dynamic exercise, fatigue exercise, and functional exercise.

What is the difference between being in this study and getting usual care?
All activities being done in this study are being done for only for the purposes of this research study.

What will happen if you are in the study?

If you agree to be in this study, you will sign this consent form before any study related procedures take place.

STUDY PROCEDURES
You will come into the Exercise and Sport Injury Laboratory at UVA. You will also be asked to arrive to the session in or with shorts. For this session you will complete testing with and without blood flow restriction. Additionally, you will be asked to complete a second session, which can be scheduled after the blood flow restriction session. You will have the choice to opt out of the second session if you prefer to only complete the initial blood flow restriction session.

Blood Flow Restriction Visit:
For the blood flow restriction arm of the study the following steps will take place.

You will be randomly assigned (like the flip of a coin) to undergo the exercise conditions in a certain order (for example: with blood flow restriction first, then without blood flow restriction second). You have an equal chance of being assigned to either intervention order. You cannot

choose to which order you are assigned. Whatever condition is not completed first will be completed following the initial condition.

1. Following the completion of the questionnaires, the researchers will loosely apply a deflated blood flow restriction tourniquet cuff and skin protection sleeve to the upper thigh of your dominant leg.
2. You will be asked to sit and rest comfortably in the chair portion of a strength assessment device.
3. The researchers will then measure the length of your leg and assess the size of one of your thigh muscles using diagnostic ultrasound.
4. Once these measurements are taken the researchers will prepare two small sections of your skin for placement of electromyography sensors. Skin preparation will include the shaving of any hair and dead skin cells as well as extensive cleaning of these sites with gauze and alcohol prep pads.
5. After the sites are prepared, the researchers will secure the sensors to the skin using a non-adhesive wrapping to limit movement of the sensors.
6. You will then be asked to sit still while the device is set up and your resting muscle activity is measured.
7. The strength assessment device will then be set up to your individual settings including your knee range of motion.
8. Next, the researchers will measure the maximal strength of your thigh muscles. To do this the researchers ask you to perform 3 maximal contractions. For these contractions you will be asked to kick your leg out against the device as hard and as fast as you can and then pull your leg in against the device as hard and as fast as you can. You will perform the three contractions back-to-back. One minute of rest will be provided after these contractions are completed.
9. You will then begin your first exercise condition. The procedures for these exercise conditions are identical except the blood flow restriction condition will include the inflation of a tourniquet cuff. For this condition, the cuff will be calibrated and inflated to 60% of your total limb occlusion pressure (the amount of pressure needed to completely stop blood from entering and leaving your limb). The cuff will remain inflated during all sets, repetitions, and rest periods until the blood flow restriction exercise condition is completed. However, the cuff will remain inflated for no more than 8 minutes.

Exercise condition procedures:
Under each condition, you will complete a total of 75 low load exercises where you will be asked to kick your leg out against the device (knee extension) and pull your leg in against the device (knee flexion) at 20% of your maximum strength. Following these repetitions, you will be asked to perform a single 30-second maximal contraction in a stationary position. For this contraction you will be asked to kick out against the device as hard as you can and hold it for 30 seconds. The device will not move during this contraction. Each exercise condition should take about 7.5 to 8 minutes to complete. Following the completion of each exercise condition, you

will be asked to fill out a short questionnaire that will ask you to rate your level of perceived exertion during the previously completed exercise procedure.

Condition 1 (WITHOUT blood flow restriction FIRST, WITH blood flow restriction SECOND):
1. You will be asked to perform 30 repetitions of knee extension and knee flexion at 20% of your maximum strength that was initially assessed.
2. You will receive a 30 second rest following this set.
3. You will be asked to perform a first set of 15 repetitions of knee extension and knee flexion at 20% of your maximum strength that was initially assessed.
4. You will receive a 30 second rest following this set.
5. You will be asked to perform a second set of 15 repetitions of knee extension and knee flexion at 20% of your maximum strength that was initially assessed.
6. You will receive a 30 second rest following this set.
7. You will be asked to perform a final set of 15 repetitions of knee extension and knee flexion at 20% of your maximum strength that was initially assessed.
8. You will receive a 30 second rest following this set.
9. Lastly, you will be asked to perform one 30-second maximal knee extension contraction in a stationary position.
10. You will then receive a 5-minute rest period before you repeat these procedures WITH blood flow restriction.

Condition 2 (WITH blood flow restriction FIRST, WITHOUT blood flow restriction SECOND):
1. The blood flow restriction cuff will be inflated to your predetermined pressure.
2. You will be asked to perform 30 repetitions of knee extension and knee flexion at 20% of your maximum strength that was initially assessed.
3. You will receive a 30 second rest following this set.
4. You will be asked to perform a first set of 15 repetitions of knee extension and knee flexion at 20% of your maximum strength that was initially assessed.
5. You will receive a 30 second rest following this set.
6. You will be asked to perform a second set of 15 repetitions of knee extension and knee flexion at 20% of your maximum strength that was initially assessed.
7. You will receive a 30 second rest following this set.
8. You will be asked to perform a final set of 15 repetitions of knee extension and knee flexion at 20% of your maximum strength that was initially assessed.
9. You will receive a 30 second rest following this set.
10. Lastly, you will be asked to perform one 30-second maximal knee extension contraction in a stationary position.
11. You will then receive a 5-minute rest period before you repeat these procedures WITHOUT blood flow restriction.

Optional Second Visit:
The optional part of the study will follow these steps.
1. Following the completion of the questionnaires, you will be asked to sit and rest comfortably in the chair portion of a strength assessment device.
2. The researchers will then measure the length of your leg and assess the size of one of your thigh muscles using diagnostic ultrasound.
3. Once these measurements are taken the researchers will prepare two small sections of your skin for placement of electromyography sensors. Skin preparation will include the shaving of any hair and dead skin cells as well as extensive cleaning of these sites with gauze and alcohol prep pads.
4. After the sites are prepared, the researchers will secure the sensors to the skin using a non-adhesive wrapping to limit movement of the sensors.
5. You will then be asked to sit still while the device is set up and your resting muscle activity is measured.
6. The strength assessment device will then be set up to your individual settings including your knee range of motion.
7. Next, you will begin your first type of exercise being either stationary muscle contractions, dynamic muscle contractions, a fatigue contraction, or a functional squatting exercise. The order in which you complete these exercises will be random.
8. For the stationary muscle contractions, you will be asked to kick out against the device 3 times at 25%, 50%, 75%, and 100% of your maximal effort. Each contraction will be held for 5 seconds. The order of these contractions will be random. A three-minute rest will be provided after your last 3 contractions are completed.
9. For the moving muscle contractions, you will be asked to kick out and pull in against the device 3 times at 25%, 50%, 75%, and 100% of your maximal effort at 2 fixed speeds (a slower speed and a faster speed). The order of these contractions will be random. A three-minute rest will be provided after your last 3 contractions are completed.
10. For the fatigue contraction, you will be asked to kick out against the device as hard as you can for 30 seconds. A three-minute rest will be provided after you complete the contraction.
11. For the functional squatting exercise, you will be asked to perform 9 body weight squats to the height of you sitting in a chair. A three-minute rest will be provided after you complete the last squat.

WHAT ARE YOUR RESPONSIBILITIES IN THE STUDY?
You have certain responsibilities to help ensure your safety.

These responsibilities are listed below:
- You must come to the study visit.
- You must be completely truthful about your health information and history.
- Follow all instructions given.
- You should tell the study staff about any changes in your health or the way you feel.

If you want to know about the results before the study is done:
During the study your study leader will let you know of any test results that may be important to your health. The final results of the research will not be known until all the information from everyone is combined and reviewed. At that time, you can ask for more information about the study results.

What are the risks of being in this study?

Risks and side effects related to low-load exercise
You may feel some muscle discomfort or soreness during or after the lower extremity exercise. The risks from the exercise are the same as any participating physical therapy or strength training session. Your session will be done under the supervision of a specially trained athletic trainer or physical therapist, to be sure that you are doing the exercises correctly. Some people may experience mild soreness the next day, however this should not last more than a day or two.

Risks and side effects related to the use of the blood flow restriction inflated cuff include:

Likely
- Muscle discomfort or cramping
- Difficulty completing the exercise
- Soreness, numbness, or tingling in your leg
- Light-headedness
- Cold feeling in your leg

*** These feelings go away when the cuff is deflated.

Less Likely
- Bruising

*** This side effect will be limited given the short length of time the tourniquet cuff is inflated.

Rare but serious
- Blood clot
- Pulmonary embolism
- Rhabdomyolysis

*** However, in a healthy adult these risks are extremely rare. You will be carefully monitored during your participation in this study and would be referred for prompt treatment should any of these problems take place.

Risks of skin preparation for electromyography:
When preparing skin for electromyography measurement, there may be some discomfort and sensitivity during the abrasion and cleaning process. The prepared skin may be red and tender after the sensors are removed and participants will be instructed to keep the skin well

moisturized after the study is completed. Participants may notice slight redness and swelling of the application sites for a few days following the study.

Other unexpected risks:
You may have side effects that we do not expect or know to watch for now. Call the study leader if you have any symptoms or problems.

Could you be helped by being in this study?
You will not benefit from being in this study. However, the information researchers get from this study may help others in the future.

What are your other choices if you do not join this study?
The only choice is not to be in this study.

Will you be paid for being in this study?
You will not get any money for being in this study.

Will being in this study cost you any money?
All of the procedures in this study will be provided at no cost to you or your health insurance. You will be responsible for the cost of travel to come to the study visit and for any parking costs.

What if you are hurt in this study?
If you are hurt as a result of being in this study, there are no plans to pay you for medical expenses, lost wages, disability, or discomfort. The charges for any medical treatment you receive will be billed to your insurance. You will be responsible for any amount your insurance does not cover. You do not give up any legal rights, such as seeking compensation for injury, by signing this form.

What happens if you leave the study early?
You can change your mind about being in the study any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services you can normally get at the University of Virginia. Even if you do not change your mind, the study leader can take you out of the study. If you decide to stop being in the study, we will ask you to notify the study leader.

How will your personal information be shared?
The UVA researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you can continue to receive regular medical care at UVA.

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, age, sex, height, weight, and physical activity level.
- Muscle activity, muscle size, muscle quality, subcutaneous fat tissue thickness, and muscle strength.
- Rating of perceived exertion after each exercise condition.

Who will see your private information?

- The researchers to make sure they can conduct the study the right way, observe the effects of the study and understand its results
- People or groups that oversee the study to make sure it is done correctly
- Insurance companies or other organizations that may need the information in order to pay your medical bills or other costs of your participation in the study
- Tax reporting offices (if you are paid for being in the study)
- People who evaluate study results, which can include sponsors and other companies that make the drug or device being studied, researchers at other sites conducting the same study, and government agencies that provide oversight such as the Food and Drug Administration (FDA) if the study is regulated by the FDA.
- If you tell us that someone is hurting you, or that you might hurt yourself or someone else, the law may require us to let people in authority know so they can protect you and others.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

Information obtained from you during this study may be used in future research. Your information may be shared with other researchers inside or outside of the University of Virginia. They will not be sent with information that could identify you such as name, address or phone number.

What if you sign the form but then decide you don't want your private information shared?

You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form and return it to the researchers. Then you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation.

Please contact the Principal Investigator listed earlier in this form to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- 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: Susan Saliba
Address: Department of Kinesiology
Memorial Gym 201
PO Box 400407
Charlottesville, VA 22904
Telephone: (434)243-4033

What if you have a concern about this study?

You may also report a concern about this study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research
PO Box 800483
Charlottesville, Virginia 22908 Telephone: 434-924-9634

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the UVA Study Tracking Number (at the bottom of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

You may also report a concern anonymously by calling the UVA Compliance Hotline phone number at 1-800-235-8700.

Optional Second Visit:

You do not have to participate in the second study visit to complete the first visit in the main part of this study. You can tell us your choice by placing your initials in one of the options below:

Please indicate your choice by placing your initials below:

_____YES I would like to complete the second study visit.

_____NO I am not interested in completing the second study visit.

Signatures

What does your signature mean?

Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you have received this information and all your questions have been answered. If you sign the form it means that you agree to join the study. You will receive a copy of this signed document.

Consent From Adult

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

Person Obtaining Consent

By signing below you confirm that you have fully explained this study to the potential subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

_____	_____	_____
PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT (PRINT)	DATE

Signature of Impartial Witness

If this consent form is read to the subject because the subject is blind or illiterate, an impartial witness not affiliated with the research or study doctor must be present for the consenting process and sign the following statement. The subject may place an X on the Participant Signature line above.

I agree the information in this informed consent form was presented orally in my presence to the **identified individual(s)** who has had the opportunity to ask any questions he/she had about the study. I also agree that the **identified individual(s)** freely gave their informed consent to participate in this trial.

_____	_____	_____
IMPARTIAL WITNESS (SIGNATURE)	IMPARTIAL WITNESS (PRINT)	DATE

iv. Data Security Plan

UNIVERSITY of VIRGINIA

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DATA SECURITY PLAN

WF SUMMARY DETAILS	
Version Date:	*February 19, 2021*
Workflow Name:	*HSR210058-MUR During BFR*
Proposal Org / Dept. No.	*31200 CU-KINE Kinesiology*
Principal Investigator:	*Susan Saliba - saf8u*
DSP Submitted by:	*sls4fe*
Protocol File Uploaded to Study Documents:	*Yes*

HIPAA IDENTIFIER OPTIONS

OPTIONS	OPTION SELECTED	HOW STORED
Note: You will refer to this list throughout the document.	If the identifier is not listed, it is not applicable.	Options include: ▪ Original source data collection (receive, collect, or record at UVA) ▪ Store long term at UVA ▪ Send or transmit outside of UVA ▪ Not Applicable
1. Name	*1. Name - Highly Sensitive Data*	*Original source data collection:* *- Subject names will only be collected on the paper consent form which will be stored in a locked filing cabinet in a locked office (Memorial Gym 222). Memorial Gym requires 24-hour swipe access to enter the building when unattended.* *- Subject names will not be collected on any other devices or questionnaires. Randomized subject numbers will be used to save subject data in an unidentifiable manner.*
2a. Postal address includes street and/or PO Box, and town or city, state, and zip code		
2b. Postal address that includes only town or city, state, and/or zip code		
3. All date elements (except year) for dates related to an individual, e.g. service date		
4. Telephone numbers		
5. Fax numbers		
6. Electronic mail addresses		
7. Social Security number		
8. Medical Record number		
9. Health plan beneficiary numbers		
10. Account numbers		
11. Certificate/license numbers		
12. Vehicle identifiers and serial numbers, including license plate numbers		
13. Device identifiers and serial numbers		
14. Web Universal Resource Locators (URLs)		
15. Internet Protocol (IP) address numbers		
16. Biometric identifiers, including finger and voice prints		
17. Full face photographic images and any comparable images		
18. Other unique number, characteristic, code related to an individual, e.g. initials		

COLLECTION & STORAGE OF HUMAN SUBJECT RESEARCH DATA

A) Paper Documents

OPTIONS	SELECTED
Storage location	*Appropriate UVa location:* *- Paper documents including the consent form and paper questionnaires (if not collected electronically) will be stored in a locked filing cabinet in a locked office (Memorial Gym 222). Memorial Gym requires 24-hour swipe access to enter the building when unattended.* *- If collected electronically on an iPad, questionnaires will be directly answered on UVA RedCap and no data will be collected or stored onto the iPad device. The iPad will only be used to link to the questionnaires for subjects to fill out.*
Other: (Please describe)	

*Appropriate UVA locations include one or more of the following:

- Kept in a locked office in a building with 24-hour swipe locks when unattended
- Kept in a locked file cabinet in a locked room when unattended
- Kept in an office where study are personnel present in room at all times located in a building with 24-hour swipe locks or a room with a lock when unattended
- Behind two locked doors when unattended

B) Emailed to other UVA Personnel

OPTIONS	SELECTED
Research data emailed to UVA personnel, but with no HIPAA identifiers except dates. -or/and- Email only to and from UVA personnel with *HS in the Global Address List	
Other Email Characteristics: (Please describe)	

C) Electronic Medical Record (EPIC)

OPTIONS	SELECTED
Data will be collected in EPIC as part of routine care or as part of medical center encounters during the research study.	*Not Applicable*

D) UVA-approved eCRF or Clinical Trials Management System

LIST	USED / SELECTED
hstsdatalab.hscs.virginia.edu	
hstsdsmpogapp.hscs.virginia.edu	
musicvpn01.med.virginia.edu	
OnCore (oncore.med.virginia.edu)	
Redcap-int.hscs.virginia.edu	*Redcap-int.hscs.virginia.edu* - UVA RedCap will be used to fill out and collect subject questionnaires (demographics, Tegner, Godin, RPE). An iPad will be used to link to the questionnaires on RedCap. No data will be collected or stored onto the iPad.
https://reveal.studymanager.com/	
Forte EDC : https://uva-edc.forteresearchapps.com/	
I acknowledge that ANY electronic use devices used to connect to any servers/websites checked above are supported by UVA Health IT	Yes

E) UVA Servers & Websites

LIST	USED / SELECTED
domatlas.eservices.virginia.edu	
dom-titan.eservices.virginia.edu	
Elson1.studenthealth.virginia.edu	
es3.eservices.virginia.edu	es3.eservices.virginia.edu - The es3 server will be used for long-term storage of the data collected in this study. Data will be transferred from a desktop computer to this server at the end of the study. After the data has been transferred to the server it will be permanently deleted from the secure desktop computer.
gcroserver.itc.virginia.edu	
\\HSCS-ss7	
\\HSCS-ss8	
\\HSCS-ss9	
\\HSCS-ss10	
\\HSCS-ss11	
\\HSCS-ss12	
\\HSCS-ss13	
\\hscs-share1\	
\\hscs-share2\	
\\hscs-share3\	
\\redshare\	
upgusers.hscs.virginia.edu	
Ivy Secure Computing Platform/ Ivy Secure Cloud/Ivy Cloud	
School of Nursing SECURE NET	
UVA HIT DropBox/Sookasa	
UVA Qualtrics HSD survey tool: https://virginiahsd.co1.qualtrics.com/ControlPanel/	

F) Web-based or Cloud Format (not listed above)

LIST	USED / SELECTED
Data will be collected and/or stored in UVA Box or UVA-Collab	*No*
If you are using other web-based or cloud servers please describe:	
Check the HIPAA identifiers stored on UVA Box or Collab	

INDIVIDUAL USE DEVICES

Current list of individual use device choices available for use:

- No Individual Use Devices will be used
- Flash (thumb) drive
- External drive

- CD or DVD
- Desktop Computer
- Laptop
- Tablet
- Smart phone
- Camera
- Video recorder
- Audio recorder
- Biometric recording device
- Fitness Trackers
- Other

G) Individual use devices	Desktop Computer	Biodex	Diagnostic Ultrasound	iPad	Flash Drive
If you selected "Other" above, please identify the device type:	A secure university desktop computer will be used to collect data from the Trigno sensor and store data from the Trigno sensor, Biodex and diagnostic ultrasound device.	The Biodex device will be used to collect data on strength measures.	The diagnostic ultrasound device will be used to collect images of the vastus lateralis muscle.	An iPad will be used to link participants to questionnaires on RedCap.	A flash drive will be used to transfer data from the Biodex and images from the diagnostic ultrasound to the secure desktop computer.
Please describe your process for collecting, storing and/or transmitting data on the Individual Use Devices you selected in earlier steps (phones, flash drives, CDs, etc.):	Data from the Trigno sensor is directly collected and stored on the secure desktop computer. The sensor itself does not have any storing capabilities. Data from the Trigno sensor will be transferred to a high security server at the end of the study and deleted from the desktop computer. Data from the Biodex and diagnostic ultrasound devices will be transferred from those devices to the secure desktop computer using a flash drive. All data (Trigno, Biodex, Ultrasound) will be stored on the desktop computer until it is transferred to a secure server at the end of the study.	Data collected on the Biodex will be stored onto the Biodex device during the participant's visit. At the completion of the visit, the strength data collected from this device will be transferred from the Biodex to the desktop computer using a flash drive. The data will be permanently deleted from the Biodex after they have been successfully transferred to the desktop computer. This data will be stored on the desktop computer until it is transferred to a secure server at the end of the study.	Images collected on the diagnostic ultrasound device will be stored onto the ultrasound device during the participant's visit. At the completion of the visit, the images will be transferred from the ultrasound device to the desktop computer using a flash drive. The images will be permanently deleted from the ultrasound device after they have been successfully transferred to the desktop computer. The images will be stored on the desktop computer until they are measured and transferred to a secure server at the end of the study.	An iPad will be used to link to the questionnaires on RedCap. Each questionnaire (demographics, Tegner, Godin, and RPE) will be directly filled out, collected, and stored onto *Redcap-int.hscs.virginia.edu* using an iPad. No data will be stored on the iPad itself.	A flash drive will be used to transfer data from the Biodex and images from the diagnostic ultrasound to the desktop computer. Once the files are transferred from the flash drive to the desktop computer, they will be permanently deleted from the flash drive as well as the Biodex and ultrasound devices.
Check the HIPAA Identifiers stored with the data on this device (e.g. such as full-face picture or video):	No HIPAA identifiers will be stored on this device. Subject names will only be collected on the consent form and will be stored in a locked filing cabinet in a locked office (Memorial Gym 222).	No HIPAA identifiers will be stored on this device. Subject names will only be collected on the consent form and will be stored in a locked filing cabinet in a locked office (Memorial Gym 222).	No HIPAA identifiers will be stored on this device. Subject names will only be collected on the consent form and will be stored in a locked filing cabinet in a locked office (Memorial Gym 222).	No HIPAA identifiers will be stored on this device. Subject names will only be collected on the consent form and will be stored in a locked filing cabinet in a locked office (Memorial Gym 222).	No HIPAA identifiers will be stored on this device. Subject names will only be collected on the consent form and will be stored in a locked filing cabinet in a locked office (Memorial Gym 222).
Describe any backups made of the data stored on the device. Please include the location & method of data transfer:	N/A	N/A	N/A	N/A	N/A
How long will the data remain on the individual-use device before being transferred?	After the data from the Biodex and images from the diagnostic ultrasound are transferred to the desktop computer, the data will remain on the secure desktop computer until they are transferred to a high security server. The data from the Trigno sensor that was directly collected and stored onto the desktop computer will also remain on the secured computer until it is transferred to a high security server. All data from the Biodex, ultrasound, and Trigno sensor will remain on the secure desktop computer until the end of the study.	Data collected directly on the Biodex will remain on the Biodex until the end of the participant's visit. At the end of the visit, the researchers will transfer the data from the Biodex to the secure desktop computer where it will be stored until the end of the study. Data collected onto this device will be deleted after it has been transferred to the desktop computer.	Images collected directly onto the ultrasound device will remain on the ultrasound device until the end of the participant's visit. At the end of the visit, the researchers will transfer the images from the ultrasound to the secure desktop computer where they will be stored until the end of the study. Images collected onto the ultrasound will be deleted after they have been transferred to the desktop computer.	No data will be stored onto the iPad at any time. The iPad will only be used to access RedCap for participants to fill out the study questionnaires.	Data from the Biodex and images from the ultrasound will only remain on the flash drive until they have been successfully transferred to the desktop computer. This transfer will take place at the end of each participant visit. After the data has been transferred to the desktop computer it will be permanently deleted from the flash drive.
After the information is transferred elsewhere, will you securely delete all the data from this device?	Yes. After data has been successfully transferred to the es3 server at the end of the study, it will be permanently deleted from the secure desktop computer.	Yes. After data has been successfully transferred to the secure desktop computer, the data will be permanently deleted from the Biodex.	Yes. After the images have been successfully transferred to the secure desktop computer, the images will be permanently deleted from the ultrasound device.	Data will not be stored onto, or transferred from, the iPad.	Yes. After the data from the Biodex and images from the ultrasound have been successfully transferred to the secure desktop computer, the data and images will be permanently deleted from the flash drive.
Will anyone other than the study team or sponsor/CRO have access to data on this device?	No. The data on this device can only be accessed through the study coordinators private UVA account on the computer. No other individuals will be able to access the information.	No. The data on the Biodex will be deleted from the device at the end of the participant visit after it has been transferred. No other individuals will have access to this data.	No. The images on the ultrasound will be deleted from the device at the end of the participant visit after it has been transferred. No other individuals will have access to these images.	No. Data will not be stored on this device.	No. The data from the Biodex and images from the ultrasound will only remain on the device until they are transferred to the desktop computer. After they have been transferred to the computer, they will be permanently deleted from the flash drive. No other individuals will have access to this data on the flash drive.
If yes, describe					
Other storage alternatives that were considered and the reasons they are unworkable	No other alternatives were considered.	No other alternatives were considered.	No other alternatives were considered.	No other alternatives were considered.	No other alternatives were considered.
The justification for storage of these data on this individual use device is:	The desktop computer is a secure UVA computer that is supported by UVA IT. It is stored in a locked lab in Memorial Gym and only the study team will have access to the data on this device. Data from the Trigno sensor, Biodex, and ultrasound will only be accessible on the study coordinator's UVA computer account. The data from these devices will be stored in a private folder in the user's Documents section of computer. The data stored on this device will not contain the subject's name or other identifiable information. All files will be saved under a randomized subject number. The data will remain stored on this secure computer until it is transferred to a high security server at the end of the study.	Data will only remain stored on the Biodex until the end of the participant's visit. The data will be deleted from the device after it has been transferred to the secure desktop computer.	Images will only remain stored on the ultrasound device until the end of the participant's visit. The data will be deleted from the device after it has been transferred to the secure desktop computer.	No data will be stored on the iPad.	Data from the Biodex and images from the ultrasound will only be stored temporarily on the flash drive until they have been transferred from the flash drive to the secure desktop computer. The files will be deleted from the flash drive after they have been transferred.

TRANSMISSION & STORAGE OF THE HUMAN SUBJECT RESEARCH DATA OUTSIDE OF UVA

QUESTION	
Will data be transmitted to a sponsor or a colleague at another institution?	*No*
Data will be emailed to non-UVA personnel via HSC secure email	*No*
I acknowledge that ANY electronic individual use devices used to connect to any servers/websites listed below are supported by UVA Health System IT. (CRO)	Yes
Check the HIPAA Identifiers stored by the Sponsor or CRO	
If sharing data with anyone outside of UVA, do you confirm that you will obtain a contract with them via the School of Medicine Grants and Contracts Office or the Office of Sponsored Programs (OSP)?	
Data will be sent and stored in an encrypted fashion (e.g. will only be shared and via Secure FX, Secure FTP, HTTPS, PGP) and the server/drive is configured to store data regulated by HIPAA	
Name (URL) of website (e.g. http://remote.sponsor.com/project name)	
Paper documents will shipped using trackable method.	*NA, paper documents will not be shipped*

QUESTION	
Data encrypted on an individual use device and shipped using trackable method. Password to the encrypted data transmitted separately.	*NA, data will not be shipped on an individual use device*
Data faxed to a receiving machine in a restricted-access location. The intended recipient is clearly indicated, alerted to the pending transmission and available to pick up immediately.	*NA, data will not be faxed*

DATA SENSITIVITY

When paired with health information, any of the below data elements are considered Highly Sensitive Data by UVA's Data Protection policy (https://uvapolicy.virginia.edu/policy/IRM-003). Please note that Social Security Numbers, Driver's license numbers, passport numbers, financial account numbers, and credit card numbers are considered Highly Sensitive Data regardless of whether or not they are paired with health information.

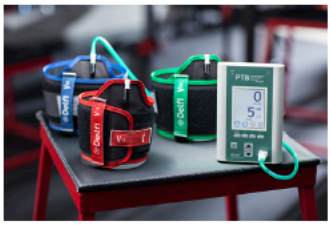
1. Name
2. Postal address, other than town or city, state, and zip code (e.g. street name or GPS information.)
3. Telephone numbers
4. Fax numbers
5. Electronic mail addresses
6. Social Security Numbers
7. Medical Record Numbers
8. Health plan beneficiary numbers
9. Account numbers (e.g. bank numbers, credit card numbers, hospital bill account number)
10. Certificate/license numbers (e.g. passport number, driver's license number, medical board license number)
11. Vehicle identifiers and serial numbers, including license plate numbers
12. Device identifiers and serial numbers
13. Web Universal Resource Locators (URLs)
14. Internet Protocol (IP) address numbers
15. Biometric identifiers, including finger and voice prints
16. Full face photographic images and any comparable images

DATA SECURITY STUDY TEAM

NOTES

v. Recruitment

ARE YOU INTERESTED IN HOW BLOOD FLOW RESTRICTION AFFECTS YOUR MUSCLES DURING EXERCISE?



The Exercise and Sport Injury Laboratory is seeking healthy adults (ages 18 or older) for participation in a research study.

- The purpose of this research study is to investigate the effects of blood flow restriction on muscle activity during low resistance exercise.
- This study will require:
  - 1 laboratory session to assess demographic information as well as muscle size, quality, strength, and activity.

The visit will be conducted in the Exercise and Sport Injury Laboratory at the University of Virginia.
The laboratory session will last approximately 1 hour.

Personal Protective Equipment and Screening Measures will be taken to protect your health and ensure your safety.

For more information, please contact:

Stephanie Stephens
sls4fe@virginia.edu

or call the Exercise and Sport Injury Laboratory:
434-924-6184

***IRB-HSR:** 16390* ***Principal Investigator:** Dr. Susan Saliba*

Table C2b. Manuscript II/III

i. Protocol

PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.

Answer/Response: Reduced engagement in physical activity, impaired quality of life, risk of reinjury, and lingering strength deficits are common, and potentially costly, concerns for many individuals following anterior cruciate ligament (ACL) injury and surgical reconstruction.[1,2] Despite completing postsurgical rehabilitation and receiving clearance for physical activity, reports have indicated surgical limb knee extensor strength deficits up to 30% compared to the non-surgical limb six months post-surgery.[3] An important factor influencing persistent muscle weakness and atrophy after ACLR is arthrogenic muscle inhibition (AMI).[4] Quadriceps activation failure (QAF) and AMI describe the neural inhibition of the quadriceps alpha-motoneuron pool following knee joint injury despite a lack of nerve damage.[4,5] Various therapeutic interventions such as cryotherapy, exercise, neuromuscular electrical stimulation, transcutaneous electrical nerve stimulation, vibration, ultrasound, transcranial magnetic stimulation, and taping and bracing have been investigated in an attempt to alter quadriceps motor unit excitability by targeting different aspects of the nervous system.[4] However, a recent review by Sonnery-Cottet et al only demonstrated moderate-quality evidence for cryotherapy and physical exercises at improving AMI after ACLR.[4]

Regaining full strength and limb symmetry following ACLR is critical for successful recovery and reducing the risk of devastating, long-term ramifications. Prolonged decreases in strength and atrophy of the quadriceps and hamstrings resulting from impaired muscle function may also contribute to early degeneration of the articular surfaces with the knee. Post-traumatic knee osteoarthritis (OA) is a debilitating condition suggested to affect more than 50% of those who have suffered from ACL injury.[6] Furthermore, a review indicated an increase in the rate of OA after ACLR from 11% at 5 years to 21% at 10 years and up to 52% at 20 years post-surgery.[7] By identifying the effect of ACL injury, surgical intervention, and various therapeutic rehabilitation techniques on specific motor unit behavior, researchers can continue to explore the vast impact of ACL injury on muscle function, quality of life, and long-term health outcomes.

Strengthening recommendation guidelines from the American College of Sports Medicine recommend the use of resistance training at 60-70% of 1 repetition maximum (1RM) for novice individuals and 80% 1RM for experienced individuals to induce strength and hypertrophy responses.[8] Unfortunately, these loads are not well tolerated after injury and surgical interventions or in elderly populations. Blood flow restriction therapy (BFRT) offers clinicians and researchers an alternative therapeutic intervention for achieving neuromuscular gains while mitigating the potentially harmful adverse events associated with increased joint stress. This therapy requires the partial occlusion

of muscular arterial inflow and complete occlusion of venous outflow during either anaerobic or aerobic-based exercise.[9] Blood flow restriction therapy utilizes low resistance exercise between 20% and 40% of an individual's one-repetition maximum (1RM) to achieve similar strength and hypertrophy gains to those acquired through high resistance exercise (i.e., 80% of an individual's 1RM). By altering load intensity, blood flow restriction therapy minimizes the amount of stress on the affected joint and surrounding tissues. Therefore, this complementary approach to rehabilitation and strength training may be a viable treatment option for load restricted populations such as post-surgical patients, elderly individuals, and those recovering from severe sport-related injuries.

Current research has shown that low resistance exercise completed with blood flow restriction therapy has the potential to increase muscle strength, hypertrophy, and activation when high resistance exercise may be contraindicated.[10–14] Unfortunately, the proposed mechanisms of blood flow restriction therapy have yet to be substantially supported. Blood flow restriction therapy has been speculated to enhance muscle function by two primary mechanisms, decreased oxygen availability (i.e., hypoxia) and increased metabolite accumulation. [15–18] These factors, as well as a lowered intramuscular pH, may further stimulate group III and group IV afferent fibers leading to earlier neuromuscular fatigue of type I (i.e., slow-twitch oxidative) muscle fibers. [15–18] This fatigued, hypoxic state has been suggested to promote the early recruitment of high threshold motor units and type II (fast-twitch anaerobic) muscle fibers during exercise.[10,15] This recruitment can lead to increases in muscle strength and hypertrophy, despite exercises being completed under low resistance, by stimulating more muscle fibers causing a more widespread hypertrophic stimulus within the muscle.[15,19] Therefore, the utilization of blood flow restriction therapy may help elicit beneficial muscular adaptations with reduced joint stress.

Another important aspect of injury, therapeutic intervention, and recovery is psychological readiness. Following ACL injury and reconstruction, impaired subjective function and well-being have been suggested to be associated with suboptimal recovery, lack of return to play, and an increased risk of reinjury. Although successful recovery after ACL is considered to be multifactorial, identification and intervention on modifiable physical and psychological risk factors (i.e., anxiety, psychological readiness, fear of reinjury, and subjective appraisal of knee function) may improve the return to sport process and mitigate the risk of reinjury.[20,21] While the physiological effects of low-load blood flow restriction therapy, including increased muscle strength and hypertrophy and reduced joint loading, have started to be examined,[22] the psychological impact of this treatment method has not yet been fully investigated. As blood flow restriction drastically increases the perceived difficulty of low load exercises due to augmented exercise induced muscle fatigue, patients may report the exercise as more challenging and that they are getting stronger despite decreased loads and mechanical tension. Recent studies have secondarily examined the subjective outcomes associated with blood flow restriction and have demonstrated conflicting results.[23–27] It is possible

that this alternative rehabilitative method may help individuals overcome lingering psychological and physical complications following ACLR. Hence, gaining a better understanding of the physical and psychological responses to blood flow restriction therapy in patients with lingering strength deficits is critical for evaluating the various potential benefits of this treatment method and identifying its overall clinical utility during the return to sport process following ACL injury.

Objectives/Hypothesis

a. Answer/Response: The primary aim of this study is to examine the effects of BFRT on muscle strength, hypertrophy, and psychological recovery in patients with persistent muscle weakness following ACLR. Our primary hypothesis is that those treated with BFRT will experience improved quadriceps strength deficits, hypertrophy, and psychological recovery. Additionally, participants treated with BFRT will experience altered motor unit behavior including increased motor unit recruitment of high threshold, low firing rate motor units during maximal strength testing.

Study Design: Biomedical

1. Will controls be used?
Answer/Response: Yes

▶ IF YES, explain the kind of controls to be used.
Answer/Response: Controls in this study will be individuals with persistent muscle weakness after ACLR that are not treated with BFRT. Instead, these individuals will not receive any additional treatment as this is the standard of care within this population. However, these participants will have their weekly physical activity assessed during the intervention timeframe via online surveys.

2. What is the study design?
Answer/Response: Randomized control study

3. Does the study involve a placebo?
Answer/Response: There is a control group not undergoing BFRT.

Human Participants

Ages: _15-64 years of age___
Sex: _Males and Females__
Race: _All___

Subjects- see below
1. Provide target # of subjects (at all sites) needed to complete protocol.
Answer/Response: 24

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.
Answer/Response: 10%

3. How many subjects will be enrolled at all sites?
Answer/Response: 28

4. How many subjects will sign a consent form under this UVA protocol?
Answer/Response: 28

Inclusion/Exclusion Criteria

1. List the criteria for inclusion
Answer/Response:

- 15-64 years of age
- Diagnosis of unilateral ACLR
- 3 months or more post-ACLR
- Limb symmetry index (LSI) for isokinetic or isometric knee extension strength is < 80% (LSI = (ACLR / Contralateral) * 100)

2. List the criteria for exclusion
Answer/Response:

- Graft failure
- Surgical complication
- Current or history of cardiovascular, metabolic, or neurological disorders or conditions (such as Peripheral Artery Disease and/or Peripheral Vascular Disease (PAD/PVD), diabetes, venous thromboembolism, deep vein thrombosis, impaired circulation or peripheral vascular compromise, sickle cell anemia, and severe hypertension)
- Current use of anti-coagulant medication
- Known pregnancy (per query)
- Malignancy diagnosis
- Serious infection near lower limb
- Muscular abnormalities
- Experience with BFRT during post-surgical ACLR physical therapy

3. List any restrictions on use of other drugs or treatments.
Answer/Response: Supplements or medications with anti-coagulation properties

Statistical Considerations

1. Is stratification/randomization involved?
Answer/Response: Yes

►IF YES, describe the stratification/ randomization scheme.
Answer/Response: Participants will be randomly allocated to either the control group or the BFRT intervention group. Group randomization will be predetermined using a random number generator. Randomization will not be blinded and only the study coordinator will have access to the randomization scheme.

►IF YES, who will generate the randomization scheme?
_____ Sponsor
_____ UVA Statistician. Insert name Answer/Response:
_____ UVA Investigational Drug Service (IDS)
__x__ Other: Specify Answer/Response: The study coordinator

2. What are the statistical considerations for the protocol?
Answer/Response: The primary intended analysis will compare changes in bilateral isokinetic and isometric strength via a multimode dynamometer between two groups: BFRT and control. Psychological recovery will be assessed using several patient reported outcome measures. Muscle morphological characteristics will be assessed using a b-mode ultrasound system. Motor unit behavior will be assessed using a surface EMG device. All measures will be compared between groups before and after their designated intervention period using separate two by three ANOVAs. Separate two by three ANCOVAs with baseline values as a covariate will be used to assess changes in patient reported outcome measures. Cohen's d effect sizes will be calculated for these points to evaluate clinical meaningfulness. For all analyses alpha will be set *a priori* to 0.05.

3. Provide a justification for the sample size used in this protocol.
Answer/Response: Using G*Power Version 3.1, the sample size was based on the between-group effect size for muscle strength with BFRT and low load (Hughes 2017) or high load resistance training (Lixandrão 2017). To achieve a power of 95% at an alpha level of 0.05 a total of 24 patients (12 per group) are required to detect meaningful between group changes for improvements in strength. Considering a withdrawal rate of 10%, a total of 28 subjects will be recruited for this study.

4. What is your plan for primary variable analysis?
Answer/Response: We will utilize separate two by three ANOVAs to evaluate the differences in strength, hypertrophy, and motor unit behavior between groups. We will use separate two by three ANCOVAs with baseline values as a covariate to analyze differences in patient reported outcome measures between groups. The difference in the relationship between changes in strength and patient reported outcomes between groups will be analyzed using Pearson correlations.

5. What is your plan for secondary variable analysis?
Answer/Response: N/A

6. Have you been working with a statistician in designing this protocol?
Answer/Response: No

7. Will data from multiple sites be combined during analysis?
Answer/Response: No

Study Procedures-Biomedical Research

1. What will be done in this protocol?
Answer/Response:

1. RECRUITMENT/ELIGIBILITY:
Participants will be indirectly recruited via a study flyer or study information sheet that is shared by researchers in the Exercise and Sport Injury Lab at the University of Virginia and orthopedic surgeons referring patients for Lower Extremity Assessment Protocols at the University of Virginia. In response to this flyer or information sheet, participants will be prompted to reach out to the research team to gain additional information regarding the study and to determine their potential eligibility. A participant's eligibility will be determined by examining their demographics, surgical information and strength values from their Lower Extremity Assessment Protocol report via electronic medical record review, and additional screening information regarding potential contraindications to blood flow restriction therapy. Eligible participants will be provided with a copy of the informed consent to review prior to their scheduled baseline session.

2. BASELINE/FAMILIARIZATION SESSION:
Upon arrival for the baseline session of the study, participants and or parents will provide electronic informed consent using REDcap prior to starting the study procedures. If one of the parents is unable to attend the baseline session, their electronic informed consent will be remotely obtained prior to the baseline session via REDcap. Following informed consent, participants will be randomly allocated into either the control group or the BFRT intervention group.

Patient Reported Outcomes: Questionnaires; about 10 minutes in total (Both groups)
Participants will then fill out patient reported outcome measures to evaluate their subjective function, fear of movement/reinjury, psychological readiness, and level of physical activity. Information from the following questionnaires will be collected from each subject:

- General health history
- Injury history and goals

- International Knee Documentation Committee Subjective Knee Joint Evaluation (IKDC)[25]
- Tegner Activity Sclae[27]
- International Physical Activity Questionnaire (IPAQ) Short Form
- Knee Injury and Osteoarthritis Outcome Score (KOOS)
- Tampa Scale for Kinesiophobia (TSK)
- Anterior Cruciate Ligament – Return to Sport Index (ACL-RSI)
- Exercise Adherence Rating Scale (EARS)
- Global Rating of Change (GRoC)

Ultrasound Assessment and Girth; about 10 minutes in total (Both groups)
Muscle size, thickness, and echogenicity of the participants quadriceps will be assessed in their injured and non-injured limb using b-mode ultrasound (i.e., ACUSON Freestyle, Siemens Medical Solutions, USA). Limb length and thigh girth will be assessed using a tape measure at 6cm and 16cm above the superior pole of the patella, bilaterally.

Motor Unit Behavior Assessment; about 5 minutes in total (Both groups)
Surface EMG (Trigno Galileo Sensor, Delsys) will be applied to the participants quadriceps to measure motor unit behavior during isokinetic and isometric strength testing. The skin will be prepped for electrode placement by shaving off any hair and dead skin cells as well as extensive cleaning of these sites with gauze and alcohol prep pads. After the sites are prepared, the researchers will secure the sensors to the skin using a non-adhesive wrapping to limit movement of the sensors.

Isokinetic Strength Assessment; about 5 minutes in total (Both groups)

- Participants will be secured to a chair (Biodex System 3 Dynamometer) with their hips flexed to 90 degrees and the involved knee flexed to 90 degrees.
- Participants' waist and ankle will be secured to the chair with Velcro straps and their arms will be crossed over their chest.
- Participants' feet will be secured to a padded restraint, which is connected to a device designed to measure how much force you can produce (Biodex).
- Participants will be asked to "practice" prior to testing at each speed. This will entail performing up to 5 repetitions at a self-selected pace.
- Testing will begin at a rate of 90°/second speed of resistance in the knee flexion/ extension movement pattern. Participants will perform 1 trial of 8 repetitions and will have 30 seconds to recover between trials. This task will then be repeated at 180°/second.

Isometric Strength Assessment; about 5 minutes in total (Both groups)

- Isometric strength will be assessed by an isometric dynamometer (Biodex, System 3) in knee extension at 90 degrees of knee flexion.
- Participants will be seated in a chair with handles on each side. Both legs will be tested, but measurements will start with the non-injured side.
- One 30 second maximal trial of knee extension and flexion will be recorded for each leg. Participants will rest for 2 minutes between each trial.
- Maximum voluntary isometric contraction (MVIC) in knee extension and knee flexion will be measured, and used to show participants their produced force during an isometric contraction.

One-Repetition Maximum; about 30 minutes in total (BFRT group only)
Participants allocated into the BFRT intervention group will then have their 1 repetition maximum (1RM) predicted for each exercise in the BFRT intervention program.

- 1RM will be predicted by assessing an individual's 5 repetition maximum (5RM) per exercise following a modified version of the National Strength and Conditioning Association's 1RM testing protocol and 1RM estimation table.
- The table below describes these procedures in detail.

1RM Determination via 5RM — NSCA Testing Protocol

1	5-minute warm-up on stationary bike
2	2-minute Rest
3	5 repetitions at self-selected weight (Exercise specific warm-up)
4	2-minute Rest
5	10-20% load increase — 5 repetitions at conservative, near maximal load
6	2-minute Rest
7	10-20% load increase — 5 repetitions at estimated maximal load
8	2-minute Rest
9	If step 7 was successful = 10-20% load increase and REPEAT 7 If step 7 was unsuccessful = 5-10% load decrease and REPEAT 7
10	2-minute Rest
11	Repeat step 9 until only 5 repetitions can be completed with proper form
12	Calculate 1RM *5-rep weight / 0.87 = Estimated 1RM*

BFRT Intervention Familiarization; about 10 minutes in total (BFRT group only)
Participants allocated into the BFRT intervention group will then practice the BFRT exercise protocol.

- With the Delfi PTSII tourniquet cuff (Delfi Medical Vancouver, BC) applied and inflated to 60% of the individual's total limb occlusion pressure (the amount of pressure needed to completely stop blood from entering and leaving the limb), participants will practice 5-10 repetitions of each exercise at a low percentage of their predicted 1RM.
- Special attention will be given to the rate of exercise execution and patient form.

3. BFRT INTERVENTION SESSIONS; about 1 hour per session (BFRT group only):
Following the baseline assessment session, participants in the BFRT group will take part in 2 physical therapy sessions per week for 4 weeks (8 sessions total).

- These sessions will include the performance of 5 lower extremity exercises at a low percentage of the individuals 1RM with BFR applied at 60% of an individual's total limb occlusion pressure.
- Prior to starting the exercise session, participants will perform a 5-minute warm-up on a stationary bike and perform stretching of their lower extremities.
- Five single leg exercises will be performed on injured limb only in the following order: knee extension, hamstring curl, hip abduction, hip extension, and leg press.
- The blood flow restriction cuff will be inflated to the predetermined pressure (60% of the individual's limb occlusion pressure). The cuff will remain inflated for all sets, repetitions, and interset rest periods. The cuff will only be deflated between exercise types.
- Four sets of each exercise will be performed (set 1: 30 repetitions, set 2-4: 15 repetitions).
- Thirty seconds of rest will be provided between each exercise set and 2 minutes of rest will be provided between each exercise type.
- Participants will be asked to rate their level of perceived exertion following each exercise type.
- Each week, the weight applied during each exercise will be modified based on your tolerance and performance.

Weekly Physical Activity Assessment; about 5 minutes per week (Both groups):

- Participants in both groups will complete a general online physical activity questionnaire (i.e., IPAQ) at the end of each week during the intervention timeframe to assess their amount of participation in physical activity outside of the scheduled study sessions. Access to these online questionnaires on REDCap will be sent out to participants weekly via email.

4. FOLLOW-UP SESSION #1 (Both groups):
After the completion of the intervention period, participants in the BFRT group and control group will return for an initial follow-up session. The participant's patient

reported outcome measures, ultrasound, motor unit behavior, and strength will be reassessed using the same protocols as described in the baseline assessment.

5. FOLLOW-UP SESSION #2 (Both groups):
Participants will return for a second, final follow-up session one month after their initial follow-up session. The participant's patient reported outcome measures, ultrasound, motor unit behavior, and strength will be reassessed using the same protocols as described in the baseline assessment.

2. If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.
Answer/Response: Following the completion of this study, participants will be instructed to return to their typical activities of daily living. No transition is necessary following the intervention program.

Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.**
Answer/Response: The study team will administer the BFRT intervention to ensure compliance of the study procedures. For monitoring compliance of those in the control group, participant's physical activity outside of the study will also be assessed via a questionnaire at the end of each week within the intervention period.

2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.**
Answer/Response: A subject will be considered non-compliant if they do not attend all BFRT intervention sessions.

Bibliography

1. Keays SL, Bullock-Saxton JE, Newcombe P, Keays AC. The relationship between knee strength and functional stability before and after anterior cruciate ligament reconstruction. *J Orthop Res Off Publ Orthop Res Soc*. 2003;21(2):231-237. doi:10.1016/S0736-0266(02)00160-2

2. Agarwal S, Jain H, Raichandani K, Godara J, Choudhary S. Early Quadriceps Wasting after Anterior Cruciate Ligament Reconstruction in Young Adults: A Prospective Study. *J Clin Diagn Res*. 2021;15. doi:10.7860/JCDR/2021/47254.14769

3. Bryant AL, Kelly J, Hohmann E. Neuromuscular adaptations and correlates of knee functionality following ACL reconstruction. *J Orthop Res Off Publ Orthop Res Soc*. 2008;26(1):126-135. doi:10.1002/jor.20472

4. Sonnery-Cottet B, Saithna A, Quelard B, et al. Arthrogenic muscle inhibition after ACL reconstruction: a scoping review of the efficacy of interventions. *Br J Sports Med*. 2019;53(5):289-298. doi:10.1136/bjsports-2017-098401

5. Hopkins JT, Ingersoll CD. Arthrogenic Muscle inhibition: A Limiting Factor in Joint Rehabilitation. *J Sport Rehabil*. 2000;9(2):135-159. doi:10.1123/jsr.9.2.135

6. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am J Sports Med*. 2007;35(10):1756-1769. doi:10.1177/0363546507307396

7. Cinque ME, Dornan GJ, Chahla J, Moatshe G, LaPrade RF. High Rates of Osteoarthritis Develop After Anterior Cruciate Ligament Surgery: An Analysis of 4108 Patients. *Am J Sports Med*. 2018;46(8):2011-2019. doi:10.1177/0363546517730072

8. Progression Models in Resistance Training for Healthy Adults. *Med Sci Sports Exerc*. 2009;41(3):687-708. doi:10.1249/MSS.0b013e3181915670

9. Scott BR, Loenneke JP, Slattery KM, Dascombe BJ. Exercise with blood flow restriction: an updated evidence-based approach for enhanced muscular development. *Sports Med Auckl NZ*. 2015;45(3):313-325. doi:10.1007/s40279-014-0288-1

10. Fatela P, Mendonca GV, Veloso AP, Avela J, Mil-Homens P. Blood Flow Restriction Alters Motor Unit Behavior During Resistance Exercise. *Int J Sports Med*. 2019;40(9):555-562. doi:10.1055/a-0888-8816

11. Cook SB, Scott BR, Hayes KL, Murphy BG. Neuromuscular Adaptations to Low-Load Blood Flow Restricted Resistance Training. *J Sports Sci Med*. 2018;17(1):66-73.

12. Lauver JD, Cayot TE, Rotarius T, Scheuermann BW. The effect of eccentric exercise with blood flow restriction on neuromuscular activation, microvascular oxygenation, and the repeated bout effect. *Eur J Appl Physiol*. 2017;117(5):1005-1015. doi:10.1007/s00421-017-3589-x

13. Hammer SM, Alexander AM, Didier KD, Barstow TJ. Influence of blood flow occlusion on muscular recruitment and fatigue during maximal-effort small muscle-mass exercise. *J Physiol*. 2020;598(19):4293-4306. doi:10.1113/JP279925

14. Killinger B, Lauver JD, Donovan L, Goetschius J. The Effects of Blood Flow Restriction on Muscle Activation and Hypoxia in Individuals With Chronic Ankle Instability. *J Sport Rehabil*. 2020;29(5):633-639. doi:10.1123/jsr.2018-0416

15. Lorenz D, Bailey L, Wilk K, et al. Current Clinical Concepts: Blood Flow Restriction Training. *J Athl Train*. Published online January 22, 2021. doi:10.4085/418-20

16. Pearson SJ, Hussain SR. A review on the mechanisms of blood-flow restriction resistance training-induced muscle hypertrophy. *Sports Med Auckl NZ*. 2015;45(2):187-200. doi:10.1007/s40279-014-0264-9

17. Rossi FE, de Freitas MC, Zanchi NE, Lira FS, Cholewa JM. The Role of Inflammation and Immune Cells in Blood Flow Restriction Training Adaptation: A Review. *Front Physiol*. 2018;9. doi:10.3389/fphys.2018.01376

18. Jessee M, Mattocks K, Buckner S, et al. Mechanisms of Blood Flow Restriction: The New Testament. *Tech Orthop*. 2018;33(2):72-79. doi:10.1097/BTO.0000000000000252

19. Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. *Br J Sports Med*. 2017;51(13):1003-1011. doi:10.1136/bjsports-2016-097071

20. Ardern CL. Anterior Cruciate Ligament Reconstruction—Not Exactly a One-Way Ticket Back to the Preinjury Level. *Sports Health*. 2015;7(3):224-230. doi:10.1177/1941738115578131

21. Ardern CL, Taylor NF, Feller JA, Webster KE. A systematic review of the psychological factors associated with returning to sport following injury. *Br J Sports Med*. 2013;47(17):1120-1126. doi:10.1136/bjsports-2012-091203

22. Ramme AJ, Rourke BJ, Larson CM, Bedi A. Ischemic Therapy in Musculoskeletal Medicine. *Am J Sports Med*. 2020;48(12):3112-3120. doi:10.1177/0363546520901539

23. Tennent DJ, Hylden CM, Johnson AE, Burns TC, Wilken JM, Owens JG. Blood Flow Restriction Training After Knee Arthroscopy: A Randomized Controlled Pilot Study. *Clin J Sport Med Off J Can Acad Sport Med*. 2017;27(3):245-252. doi:10.1097/JSM.0000000000000377

24. Hughes L, Rosenblatt B, Haddad F, et al. Comparing the Effectiveness of Blood Flow Restriction and Traditional Heavy Load Resistance Training in the Post-Surgery Rehabilitation of Anterior Cruciate Ligament Reconstruction Patients: A UK National Health Service Randomised Controlled Trial. *Sports Med Auckl NZ*. Published online July 12, 2019. doi:10.1007/s40279-019-01137-2

25. Curran MT, Bedi A, Mendias CL, Wojtys EM, Kujawa MV, Palmieri-Smith RM. Blood Flow Restriction Training Applied With High-Intensity Exercise Does Not Improve Quadriceps Muscle Function After Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial. *Am J Sports Med*. 2020;48(4):825-837. doi:10.1177/0363546520904008

26. Noyes FR, Barber-Westin S, Sipes L. Blood Flow Restriction Training Can Improve Peak Torque Strength in Chronic Atrophic Postoperative Quadriceps and Hamstrings Muscles.

Arthrosc J Arthrosc Relat Surg Off Publ Arthrosc Assoc N Am Int Arthrosc Assoc. Published online March 31, 2021. doi:10.1016/j.arthro.2021.03.040

27. Kargaran A, Abedinpour A, Saadatmehr Z, Yaali R, Amani-Shalamzari S, Gahreman D. Effects of dual-task training with blood flow restriction on cognitive functions, muscle quality, and circulatory biomarkers in elderly women. *Physiol Behav*. 2021;239:113500. doi:10.1016/j.physbeh.2021.113500

ii. Application

RESEARCH APPLICATION

Will this study be conducted outside of UVA Health during the COVID-19 pandemic?

Answer/Response: Yes. This study will abide by all clinical research guidelines set forth by the VPR office. All lab equipment will be thoroughly cleaned before and after each participant visit. All research staff and participants will be required to wear face masks during in-person study visits.

Investigators Experience

The PI, Dr. Susan Saliba (PhD, ATC, PT), is a professor and co-director of the Exercise and Sports Injury (EaSIL) for musculoskeletal injury research at the University of Virginia. She has 18 years of clinical experience as both a physical therapist and athletic trainer. She also has extensive experience in conducting clinical trials and studies as well as experience in utilizing blood flow restriction therapy during patient care.

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

a. I am not currently debarred by the US FDA from involvement in clinical research studies.
b. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
c. That if this study involves any funding or resources from an outside source or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
d. The protocol will abide by the ethical standards of The Belmont Report
e. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
f. That no personnel will have access to subjects in this protocol or their information until they have completed the human subject research protection on-line training through CITI and the IRB-HSR has been notified.
g. That all personnel working on this protocol will follow all Policies and Procedures of:
   - the UVA Human Research Protection Program (HRPP SOPS)
   - the IRB-HSR https://research.virginia.edu/irb-hsr
   - the School of Medicine Clinical Trials Office: http://www.medicalcenter.virginia.edu/intranet/cto/index.html
   - and any additional UVA requirements for conducting research.
h. I will ensure that all those personnel delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training, experience or credentialing to undertake those tasks.
i. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.

j. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
k. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
l. That all subjects will give informed consent unless the requirement has been specifically waived by the IRB.
m. That unless written consent has been waived by the IRB all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
n. They will establish and maintain an open line of communication with research subjects within their responsibility.
o. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
p. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
q. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
r. That any serious deviation from the protocol will be reported promptly to the Board in writing.
s. That any data breach will be reported to the IRB, the UVA Corporate Compliance and Privacy Office , UVA Police as applicable.
t. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
u. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.
v. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time. If the current PI leaves UVA permanently, a new PI will be assigned PRIOR to the departure of the current PI.
w. All study team members will have access to the current protocol and other applicable documents such as the IRB-HSR Application, consent forms and Investigator Brochures.
x. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept according to UVA Records Management policies.
y. No data/specimens may be taken from UVA without a signed Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at UVA. The agreement will delineate what copies of data, health information and/or specimens may be taken outside of UVA. It will also approve which HIPAA identifiers may be taken outside of UVA with the health information or specimens.
z. If any member of study team leaves UVA, they are STRONGLY ENCOURAGED to use Exit Checklist found on IRB-HSR website at https://provost.virginia.edu/system/files/documents/Faculty-Departure-Checklist-2015_508.pdf

IF THE IRB-HSR WILL BE THE IRB OF RECORD FOR MULTIPLE SITES IN A MULTISITE TRIAL, THE UVA PI AGREES TO CARRY OUT THE FOLLOWING RESPONSIBILITIES:

1. Ensure all UVA personnel designated as Conflict of Interest Investigators complete Reviewing IRB's financial interest disclosure requirements unless the UVA personnel will adhere to the UVA conflict of interest policies that are compliant with DHHS requirements.
2. Promptly provide the Principal Investigator at each site with:
   a. Current approved protocol and consent documents;

   b. Approved modifications, amendments or changes to research protocols; and
   c. Approval of continuing reviews and reviews of unanticipated problems;
3. Notify the Principal Investigator at each site of standards and guidelines for reporting any post approval events such as adverse events, subject injuries, unanticipated problems, and protocol violations. Collect reports from Principal Investigator at each site of any unanticipated problems, deviations, suspensions and terminations, non-compliance, subject complaints, and submit such reports to Reviewing IRB per reporting requirements.
4. Notify the Principal Investigator at each site promptly of any unanticipated problems involving risks to subjects or others as determined by the Reviewing IRB.
5. Collect required information from the Principal Investigator at each site necessary for completing continuing review submissions.
6. Notify the Principal Investigator at each site promptly about any lapses of approval. Forward to the IRB of Record any request from the Principal Investigator of a site for continuation of a specific research subject on a protocol during a lapsed period of approval.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Signatures

Principal Investigator

Principal Investigator Signature	Principal Investigator Name Printed	Date

Department Chair or Designee

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound.
4. He/she is not the Principal Investigator or a sub investigator on this protocol.

Department Chair or Designee Signature	Department Chair or Designee Name Printed	Date

Brief Summary/Abstract

Persistent muscle weakness is a common and concerning issue for many individuals following anterior cruciate ligament injury and surgical reconstruction (ACLR). Strength deficits are reported to persist even after the completion of traditional rehabilitation programs and the return to unrestricted physical activity. Regaining full strength and limb symmetry following ACLR is critical for successful recovery and reducing the risk of devastating, long-term physical and psychological ramifications. Blood flow restriction therapy (BFRT) may offer clinicians and researchers an alternative therapeutic approach for achieving neuromuscular strength gains in ACLR patients that have failed to respond to traditional rehabilitation techniques. Therefore, the primary aim of this study is to examine the effects of BFRT on muscle strength, hypertrophy, and psychological recovery in patients with persistent muscle weakness following ACLR. Our primary hypothesis is that those treated with BFRT will experience improved quadriceps strength deficits, hypertrophy, and psychological recovery. Additionally, participants treated with BFRT will experience altered motor unit behavior including increased motor unit recruitment of high threshold, low firing rate motor units during maximal strength testing.

Individuals at least 3 months post-ACLR with a limb symmetry index of less than 80% for peak torque during knee extension will be recruited for this study. Eligible participants will be randomly allocated into one of two groups: control or BFRT. Both groups will report for a baseline assessment of knee strength, motor unit behavior, ultrasound imaging, and patient reported outcome measures. Individuals in the BFRT group will also undergo five-repetition maximum (5RM) testing to predict their one-repetition maximum (1RM) and practice the BFRT intervention protocol. Following the baseline assessment session, participants in the BFRT group will take part in 2 physical therapy sessions per week for 4 weeks. These sessions will include the performance of 5 single leg lower extremity exercises (i.e., knee extension, hamstring curls, hip abduction, hip extension, and leg press) with BFR applied at 60% of an individual's total limb occlusion pressure. Each exercise will involve 75 low intensity repetitions divided into four sets (30 x 15 x 15 x15) at a low percentage of an individual's 1RM. At the end of each exercise participants will rate their level of perceived exertion during each type of exercise. Exercise intensity will be increased or decreased for the following session based on the participants performance and tolerance. Throughout the 1-month intervention timeframe, participants in both groups will fill out weekly assessments of his or her physical activity outside of the study. After the conclusion of the 1-month BFRT program (8 sessions), both groups will return for a follow-up assessment of their knee strength, motor unit behavior, ultrasound imaging, and patient reported outcome measures. An additional follow-up assessment will be scheduled for 1 month after the initial follow-up assessment and the same outcome measures will be evaluated. Separate two by three ANOVA will be utilized to evaluate the differences in strength deficits, hypertrophy, and motor unit behavior between groups. Patient reported outcome measures will be analyzed using separate two by three ANCOVA with baseline values utilized as a covariate. The difference in the relationship between changes in strength and patient reported outcomes between groups will be analyzed using Pearson correlations. Cohen's d effect sizes, 95% confidence intervals, and p-values will also be reported. All devices being used in this study are being used per the approved indication from the FDA and are not being evaluated in this study for an additional indication.

Sponsor

1. **Explain the sponsorship for this study.**
   Answer/Response: N/A

Support Source

1. Describe what will be provided and by whom.
Answer/Response: N/A

Human Participants

1. How many subjects will be enrolled in this study by the UVA site? *(e.g. sign a UVA consent form)*
Answer/Response: 28

2. Will subjects be recruited or receive study interventions in a UVA patient care setting?
Answer/Response: No

Participation of Children

1. Explain why this research topic is relevant to children.
Answer/Response: ACL injury has becoming increasingly more popular in young, athletic populations. Many of these young individuals wishing to return to physical activity or sport choose to undergo an ACLR and subsequently have the potential to suffer from persistent muscle weakness. By including children in this research study, we will be able to further identify the benefits of BFRT on persistent muscle weakness after ACLR and generalize our findings to young, athletic populations.

2. Is the knowledge being sought in this study already available for children or is it currently being acquired through another ongoing study?
Answer/Response: No other studies have directly investigated the benefits of BFRT on persistent muscle weakness in children. However, a previous research study was conducted looking at the effects of BFRT vs. high load resistance training in a population of children between the ages of 14 and 18 (Curran 2020). No adverse events or complications were reported.

3. Provide data that is available in adults in order that the IRB may judge the potential risk in children. If there is no adult data available, provide reasons why not. If this information is available in a sponsor's protocol, you may reference the section # here and not duplicate the information.
Answer/Response: According to a systematic review by Minniti et al in 2020, blood flow restriction therapy appears to be a safe strengthening technique for individuals with knee related musculoskeletal disorders. Of the 19 studies included in this review, 168 participants were exposed to blood flow restriction therapy with 10 experiencing an adverse event, 3 of which were considered rare. Of the 154 control participants in this review, 4 experienced a common adverse event. The results of this review indicate minimal risk associated with using blood flow restriction therapy for treating adults and adolescents with musculoskeletal disorders.

4. Is the potential subject population likely to include wards of the state or children who are more at risk for becoming a ward of the state?

INSTRUCTIONS:

- There are provisions in the research regulations that pertain to the participation of children who are considered wards of the state. A "ward," in this context signifies any child who has been adjudged dependent by a court and who is under the care or custody of a public official or agency,

which may include foster children, or any child under the control of the Department of Social Services in the state of Virginia. An incarcerated youth is a child who is in penal custody or otherwise detained within the criminal justice system. These children are often under the care of the Department of Youth Services and some may also be wards of the state. Recruiting a ward of the state for research may be a very infrequent or unlikely event. It is important that these children not be discriminated against with regards to enrollment in research especially if the research offers a potential for benefit. However, their enrollment requires additional IRB determinations including the IRB appointing an advocate. Therefore, you are asked to consider the possibility of enrolling a ward of the state based upon eligibility criteria and the population of your study.

- If the study will enroll subjects from patients at UVA, this question MUST be answered YES

▶IF YES: If the caregiver is someone other than the person providing permission for the child to participate, the study team may wish to consider the use of an additional form for them. (example: a child is in foster care however the biological parent has not lost legal custody and provides their permission for the child to participate, but the foster parent will be the person involved in driving the child to their study visits. This form might address things such as who will receive the compensation for driving the child to the visits- the foster parent or the biological parent).

▶IF YES and if neither of the items 4a or 4b listed below is answered YES, children who are wards of the state must be excluded from this protocol. Add "wards of state" as an additional exclusion criteria.

Answer/Response: Yes

4a. Is the research is this protocol related to the child's status as a ward of the state?
Answer/Response: No

4b. Is the research to be conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards?

INSTRUCTIONS

- If this study will be done at UVA, answer this question YES.
- An applicable time to answer this question NO would be if the research is being done in children who are in foster care where a majority of the children involved would likely be wards of state.
- If you answered YES to # 4 and YES to EITHER 4a or 4b you may NOT exclude children who are wards of state.
- If you answered YES to # 4 and you answered NO to both 4 a or 4b you must exclude children who are wards of the state from the protocol- Add " Wards of State" as an exclusion criteria.

Answer/Response: Yes

4c. Are you aware of the following requirement?
If the consent form contains a signature line for both parents the study team will notify the IRB immediately, if at any time during the course of the research, it becomes known that a potential subject is a ward of the state or that a child already enrolled in this protocol becomes a ward of the state.
Answer/Response: Yes

5. Does this study involve a placebo arm?
Answer/Response: There is a control group not undergoing BFRT.

6. Will UVA researchers conduct the study outside the state of Virginia?
Answer/Response: No

Recruitment

INFORMATION: ** The UVA HIPAA Covered Entity includes the following areas:*
UVA Health including the School of Medicine & the School of Nursing, the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory and the Exercise Physiology Core Laboratory and University Physicians Group (UPG)
Identifiable health info may also be shared with the following areas without tracking the disclosure as agreements are in place to protect the information:

- *VP Office of Research*
- *Nutrition Services (Morrison's)*
- *UVA Center for Survey Research*

1. How do you plan to identify potential subjects?

a. __x__ Electronic Medical Record Review or Report (can include EPIC Slicer Dicer, Clarity, Caboodle, and other EMR reporting tools) / EMR data copy from an enterprise research database (CDR-IRB-HSR# 10797, OR OMOP, TriNetX, i2b2, ACT IRB-HSR #20840:) / Database established for health care operations (departmental clinical database or UVA Enterprise Data Warehouse) / Quality Improvement Data (*e.g. Performance Improvement, Practice Improvement, Quality Improvement*).

DHHS:
Pre 2018 Common Rule: Study team requests Waiver of Consent to identify prospective subjects.
2018 Common Rule: Allowed under Preparatory to Research if the investigator will identify subjects through oral or written communication with prospective subject or LAR OR the investigator will obtain identifiable private information or bio-specimens by accessing records or stored identifiable bio-specimens.

HIPAA: Allowed under Preparatory to Research if PHI to be accessed.

IMPORTANT
Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVA HIPAA covered entity; which means they meet one of the following criteria:
--a UVA student working in the UVA HIPAA Covered Entity*
--a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*
--a volunteer approved by the School of Medicine

b. _ Review of a research data repository that was established to keep data to be used for future research such as a departmental research database or use of data from a separate current active research protocol.

The research repository or study from which you are finding potential subjects must also have an IRB protocol approval. If this item is checked, enter the IRB # below.

c. ____ Patients UVA health care provider supplies the UVA study team with the patients contact information without patients' knowledge.

DHHS:
Pre 2018 Common Rule: Study team requests Waiver of Consent to identify prospective subjects.
2018 Common Rule: Allowed under Preparatory to Research if the investigator will identify subjects through oral or written communication with prospective subject or LAR OR the investigator will obtain identifiable private information or bio-specimens by accessing records or stored identifiable bio-specimens.

HIPAA: Allowed under Preparatory to Research if PHI will be shared by the health care provider.

IMPORTANT
Keep in mind that PHI may only be given to individuals who work under the UVA HIPAA covered entity; which means they meet one of the following criteria:
--a UVA student working in the UVA HIPAA Covered Entity*
--a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*
--a volunteer approved by the School of Medicine

d. __x__ Patient obtains information about the study from their health care provider. The patient contacts the study team if interested in participating. (Health care provider may or may not also be a member of the study team)

DHHS: NA
HIPAA: Allowed under Health Care Operations

If this choice is checked, check 3d-INDIRECT CONTACT below.

e. __x__ Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc.

If this choice is checked, check 3d- INDIRECT CONTACT below.
DHHS & HIPAA: NA

f. _____ Potential subjects have previously signed a consent to have their name in a registry/database to be contacted for future studies of this type.
IRB# of registry/ database: _____

g. ____ Other: Specify Answer/Response:

If item # a, b or c is checked above and if this protocol involves the use of protected health information do you confirm the following to be true?
- The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the UVA covered entity.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

Answer/Response: Yes

2. **How will potential subjects be contacted?**

To "contact" a potential subject, refer to the initial contact you plan to take to reach a potential subject to determine if they would be interested in participating in your study. This may include direct contact by such methods as by letter, phone, email or in-person or indirect contact such as the use of flyers, radio ads etc.

If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being contacted by the given method.

Check the methods below you plan to utilize:

a. Direct contact of potential subjects by the study team via letter, phone, direct e-mail. Members of study team ARE NOT health care providers of patients. Information will not be collected from psychotherapy notes.

Note: Letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.

Pre 2018 Common Rule:

DHHS/HIPAA: Study team requests a Waiver of Consent and Waiver of HIPAA Authorization to contact potential subjects.

2018 Common Rule:
DHHS:
Allowed under Preparatory to Research if the investigator will identify subjects through oral or written communication with prospective subject or LAR OR the investigator will obtain identifiable private information or bio-specimens by accessing records or stored identifiable bio-specimens.
HIPAA: Study team requests a Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:
Keep in mind that if PHI was collected during the identification phase that contact with potential subjects may only be performed by individuals who work under the UVA HIPAA covered entity; which means they meet one of the following criteria:
- a UVA student working in the UVA HIPAA Covered Entity*
- a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*
- a volunteer approved by the School of Medicine

b. ____Potential subjects will be approached while at UVA Hospital or Health Clinic by a person who is NOT a member of their health care team. Information will not be collected from psychotherapy notes.

Pre 2018 Common Rule:
DHHS/HIPAA: Study team requests a Waiver of Consent and Waiver of HIPAA Authorization to contact potential subjects.

2018 Common Rule:
DHHS:
Allowed under Preparatory to Research if the investigator will identify subjects through oral or written communication with prospective subject or LAR OR the investigator will obtain identifiable private information or bio-specimens by accessing records or stored identifiable bio-specimens.
HIPAA: Study team requests a Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:

Keep in mind that contacting individuals in a clinical setting may only be performed by individuals who work under the UVA HIPAA covered entity; which means they meet one of the following criteria:
a UVA student working in the UVA HIPAA Covered Entity*
a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*

You should share the following information with the potential subject:
- Your name
- Who you are: physician, nurse etc... at the University of Virginia.
- Why you want to speak with them
- Ask if you have their permission to explain the study to them
- If asked about how you obtained their information. use one of the following as an option for response.
  - DO NOT USE THIS RESPONSE UNLESS YOU HAVE OBTAINED PERMISSION FROM THEIR UVA PHYSICIAN: Your doctor, Dr. insert name wanted you to be aware of this research study and gave us permission to contact you.
  - We obtained your information from your medical records at UVA.
  - Federal regulations allow UVA Healt to release your information to researchers at UVA, so that we may contact you regarding studies you may be interested in participating. We want to assure you that we will keep your information confidential.
- IF THE PERSON SEEMS ANGRY, HESITANT OR UPSET, THANK THEM FOR THEIR TIME AND DO NOT ENROLL THEM IN THE STUDY. YOU MAY ALSO REFER THEM TO THE IRB-HSR AT 924-9634.

c. ____Direct contact of potential subjects by the study team by approaching in person at UVA or via letter, phone, direct e-mail. Members of study team contacting potential subjects ARE health care providers of patients.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.

Pre 2018 Common Rule:
DHHS: Study team requests a Waiver of Consent to contact potential subjects.
HIPAA: Allowed under Health Care Operations.

2018 Common Rule:
DHHS:
Allowed under Preparatory to Research if the investigator will identify subjects through oral or written communication with prospective subject or LAR OR the

investigator will obtain identifiable private information or bio-specimens by accessing records or stored identifiable bio-specimens.
HIPAA: Allowed under Health Care Operations.

d. __x__ Indirect contact (flyer, brochure, TV, broadcast emails, patient provided info about the study from their health care provider and either the patient contacts study team or gives their healthcare provider permission for the study team to contact them.)

DO NOT UNCHECK THIS BOX EVEN IF YOU DO NOT INTEND TO USE THIS RECRUITMENT METHOD AT THIS TIME.
The indirect method used (flyer, brochure, TV, broadcast emails) must be approved by the IRB prior to use. The IRB does not need to review any type of script to use when the potential subject responds to the indirect method.

DHHS & HIPAA: NA

e. ____ Potential subjects are not patients. The study does not include obtaining subjects health information. Subjects will be contacted directly via email, phone, letter or presentation in group setting with consent then obtained individually in a private setting.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.

When entering a classroom to recruit students and conduct research, e.g., administer a survey, investigators must do so at the end of the class period to allow non- participating students the option of leaving the classroom, thereby alleviating pressure to participate.

Pre 2018 Common Rule:
DHHS: Study team requests a Waiver of Consent to contact potential subjects.
HIPAA: NA

2018 Common Rule:
DHHS:
Allowed under Preparatory to Research if the investigator will identify subjects through oral or written communication with prospective subject or LAR OR the investigator will obtain identifiable private information or bio-specimens by accessing records or stored identifiable bio-specimens.
HIPAA: NA

3. **Will any information be obtained from a potential subject during "prescreening"?**

> **Pre-screening** for IRB purposes is the term used to describe activities PRIOR to obtaining Informed Consent and may not include any research procedures.
>
> The activities may involve pre-screening of potential subjects over the telephone or in person to determine their initial eligibility for, and, interest in a study and is a common strategy in the recruitment process.
>
> **Questions appropriate for pre-screening address the specific** inclusion/exclusion criteria for the study and other issues of suitability, for example, an individual's ability to come to the research site multiple times.
>
> It is NOT appropriate at this point in the process (i.e. prior to obtaining informed consent/enrollment) to gather information that is not directly related to assessing eligibility and suitability (e.g. obtaining complete medical histories, obtaining blood specimens for lab tests).

An additional telephone script is not required, for this pre-screening process, in addition to any scripts required under Recruitment question # 2.
Answer/Response: Yes

> F YES, submit any documents that will be used to collect pre-screening information so that the IRB may confirm what questions will be asked.
> NOTE: To comply with HIPAA regulations only the minimum necessary information may be collected at this time. This means that only questions pertaining to the Inclusion and Exclusion Criteria may be asked.

> IF YES,
> DHHS:
>
> Pre 2018 Common Rule: Study team requests a Waiver of Documentation of Consent for Pre-screening questions.
>
> 2018 Common Rule: No waiver of documentation of consent required per 45CFR46.116 (g).
> *45CFR46.116(g) an IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subjects legally authorized representative if either of the following conditions are met:*
> *1. The investigator will obtain information through oral or written communication with the prospective subject or LAR or*
> *2. The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.*
>
> *HIPPA:*
> HIPAA does not apply if:
> –no PHI is collected or
> –if PHI is collected from a potential subject by an individual from a department that is not part of the HIPAA covered entity.

> HIPAA does apply if the collection occurs by individuals* who work in a department that is part of the HIPAA covered entity.
>
> In this case the collection will be covered under Health Care Operations/
>
> These individuals are those that meet one of the following criteria:
> –a UVA student working in the UVA HIPAA Covered Entity*
> –a faculty or staff member in an appointment in the UVA HIPAA Covered Entity*
> –a volunteer approved by the School of Medicine

IF YES, Will any of the questions involve health information?
Answer/Response: Yes

IF YES, will you collect HIPAA identifiers with the health information?
Answer/Response: Yes

IF YES, which HIPAA identifiers will be recorded?
Answer/Response: Name, email, phone number, date of birth
Do you confirm that health information with HIPAA identifiers will not be shared outside of UVA until a consent form is signed or only shared in a de-identified manner?
Answer/Response: Yes

4. **Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?**

> For example: come to the first visit fasting, stop taking medications that may be an exclusion criteria, change diet, etc. As this is still part of pre-screening one is not allowed to gather information that is not directly related to inclusion/exclusion criteria or other issues of suitability (e.g. is person able to come to UVA for multiple visits)
>
> NOTE:
> Only those members of the study team with a DEA# (license to prescribe drugs) are allowed to determine if a potential subject may be asked/informed to stop taking a drug which is an exclusion criteria.
> It is recommended that the potential subject notify their health care provider if they plan to stop a prescription drug.

Answer/Response: No

5. **How will the consenting process take place with either the prospective subject, the subject's legally authorized representative or parent/legal guardian of a minor (if applicable)?**
Answer/Response: Participants will be indirectly recruited via a study flyer or study information sheet that is shared by researchers in the Exercise and Sport Injury Lab at the University of Virginia and orthopedic surgeons referring patients for Lower Extremity Assessment Protocols

at the University of Virginia. In response to this flyer or information sheet, potential participants and or parents will be prompted to reach out to the research team to gain additional information regarding the study and to determine their potential eligibility. A participant's eligibility will be determined by examining their demographics, surgical information and strength values from their Lower Extremity Assessment Protocol report via electronic medical record review, and additional screening information regarding potential contraindications to blood flow restriction therapy. A copy of the consent form will be provided to eligible potential participants and or parents via email for them to review prior to their scheduled study session. Potential participants and or parents will be provided with information on the consent form regarding the study including the risks and benefits of participation and what to expect if they choose to participate. Each potential participants and or parents will be encouraged to ask any and all questions regarding the study and its procedures. A member of the research team will then assess both subject and parental understanding of the study. Electronic informed consent will be obtained using REDcap by a member of the study team in a quiet private location, when potential participants and or parents arrive at the Exercise and Sport Injury Laboratory for their initial study session. When participants are under the age of 18, parental consent will be obtained prior to approaching the minor for consent. If one of the parents is unable to attend the baseline session, their electronic informed consent will be remotely obtained prior to the baseline session via REDcap. Study procedures will begin immediately after the potential participant and or parents signs consent. A copy of the signed consent will be given to the participant/parent.

6. **Will subjects sign a consent form for any part of the study?**
Answer/Response: Yes

7. **Will the study procedures be started the same day the subject is recruited for the study?**
Answer/Response: No

►IF YES, explain in detail why the subject cannot be given more time to make a decision to consent.
Answer/Response:

►IF YES, explain in detail what will be done to assure the potential subject has enough time to make an informed decision.
Answer/Response:

8. **Is there the potential to recruit a vulnerable population? (e.g. economically or educationally disadvantaged subjects, or other vulnerable subjects such as students, employees, investigator is health care provider of potential subject, pregnant women, children or prisoners?**

> **INSTRUCTIONS:** If you will be recruiting patients from UVA Health, you must answer this question YES as UVA Health cares for patients who are economically disadvantaged.

Answer/Response: Yes

IF YES, what protections are in place to protect the rights and welfare of these subjects so that any possible coercion or undue influence is eliminated?
Check all applicable options:

____ Consent will be obtained by the CRC rather than the Investigator

__x__ Subjects will be assured that their relationship with their UVA health care providers will not be affected if they decide not to participate

__x__ Subjects will be given all the time needed to make their decision, and will not be pressured for a quick decision. They will be encouraged to seek advice from friends and family before signing consent.

__x__ Employees will be reassured that their decision will not affect their job or benefits.

__x__ Students will be reassured that their decision will not affect their status as a student or their grades.

__x__ If minors are enrolled, parental permission will be obtained prior to explaining the study to a minor and the minor's assent will be obtained prior to initiation of study procedures.

__x__ all subjects, especially those who are educationally disadvantaged will be asked open ended questions to confirm that they understand the study.

___ Other Explain:

9. **Do you need to perform a "dry run" of any procedure outlined in this protocol?**
Answer/Response: No

10. **Is the study regulated by the Department of Defense (DoD)?**
Answer/Response: No

11. **Non-Monetary Retention Incentives**
If subjects will be provided with non-monetary gifts or tokens of appreciation, such as totes, books, toys, or other such materials, the study team will submit a description and approximate retail value of the item to the IRB.

Study Procedures- Biomedical Research

1. Where will the study procedures be done?
Check One:
____ UVA Health facilities (In patient or outpatient)

If checked, verify all study team members have reviewed the "Research in Patient Care Settings Guidance"

____ UVA Community Health Culpeper Hospital
____ UVA Community Health Haymarket Hospital
____ UVA Community Health Prince William Hospital
__x__ UVA but not UVA Health: Exercise and Sport Injury Laboratory (550 Brandon Ave, Room 329)
____ Non UVA Location: List specific location Answer/Response:

2. If the study involves medical risk and study procedures will be done outside of the UVA Medical Center what is your plan to protect the subjects in case of a medical emergency?
____ *NA*

Check all applicable options:
_____ MD, RN, onsite during procedures
__x___ Individual trained in CPR on site during procedures
__x___ AED and Individual trained to use it onsite
__x___ Call 911
_____ Other: Describe Answer/Response:

3. List the procedures, in bullet form, that will be done for RESEARCH PURPOSES as stipulated in this protocol.
Answer/Response: ALL

4. Do you confirm that, except for blood draws through a peripheral site, that all invasive procedures will be performed by a licensed health care provider under the supervision of an MD?
Answer/Response: N/A – no invasive procedures

5. Will you be using data/specimens in this study that were collected previously, with the use of a research consent form, from another research study?
Answer/Response: Yes

IF YES, will the data/specimens be used in this study without a new consent from the original donor?
Answer/Response: No

6. Will any of the procedures listed in item # 3 have the potential to identify an incidental finding?
Answer/Response: No

INSTRUCTIONS: This includes ALL procedures, assessments and evaluations that are being done for RESEARCH PURPOSES that may or may not be considered investigational.
Examples: MRI/CT/PET/CXR shows possible tumor, Blood collected and analyzed using an investigational assay and results show possibility of leukemia

►IF YES, check one of the following two options and list the applicable procedures, assessments or evaluations below.

7. Do any of the procedures listed above, under question # 3, utilize any imaging procedures for RESEARCH PURPOSES?
Answer/Response: Yes – diagnostic ultrasound

__x___ This imaging research examination utilizes the same imaging techniques, equipment, scanning sequences that would be used, if the subject were to have the imaging performed for clinical care. There exists the potential for the discovery of clinically significant incidental findings.
List procedures:
Answer/Response: With participants resting, the researchers will take cross-sectional area and thickness measures of the quadriceps using ultrasound to determine muscle size, thickness, and echogenicity. Screen-shot images will be taken in perpendicular and parallel planes.

Will the images be read by a licensed radiologist and the reading placed in the subject's medical record?
Answer/Response: No

►IF NO: The PI takes full responsibility for the identification of incidental findings:
- The PI will have all incidental findings reviewed by a radiologist who will advise the PI regarding clinical significance.
- The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance.
- A follow-up letter describing the finding should be provided to the subject with instructions to either show the letter to their PC or if the subject has no PCP, the subject should be instructed to make an appointment at UVA or at the Free Clinic.

_____This imaging research examination utilizes non-standard/investigational imaging modality, techniques, equipment, scanning sequences, etc. It is impossible to determine the significance of such images, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit.
List procedures:
Answer/Response: N/A

8. Will your study involve measures used to screen or assess for depression and/or suicidality for research purposes?
Answer/Response: No

9. Will any data from this study be submitted to or held for inspection by the FDA?
NOTE: Publication is not equivalent to submission of data to the FDA.
Answer/Response: No

Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits which may accrue to society in general, as a result of this study?
Answer/Response: After participating in this study, participants treated with BFRT may experience significant improvements in muscle strength, hypertrophy, and psychological factors associated with their ACLR recovery process. In the long-term, these benefits may increase an individual's activity level while reducing an individual's likelihood of reinjury after ACLR and decrease their risk of developing secondary conditions such as knee osteoarthritis. The information from this study may help inform future researchers and healthcare providers about the benefits of implementing BFRT into their clinical practice following ACLR.

2. Do the anticipated benefits justify asking subjects to undertake the risks?
Answer/Response: Yes, the anticipated benefits of this study do outweigh the potential risks associated with participation. Participants treated with blood flow restriction therapy in this study may experience significant increases in their physical and psychological recovery process following ACLR, which may improve their current and future health status. Given that the risks associated with this study are similar to that of traditional high load resistance training which is often completed by this patient population, we feel as though the potential benefits of this study do justify the risks.

Data and Safety Monitoring Plan

1. Definition:

1.1 How will you define adverse events (AE)) for this study?

__x___ An adverse event will be considered any undesirable sign, symptom or medical or psychological condition **even if the event is not considered to be related** to the investigational drug/device/intervention. Medical condition/diseases present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment/intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of an investigational device that adversely affects the rights, safety or welfare of subject s.

_____Will use definitions provided in the Protocol

_____Other: Specify Answer/Response:

1.2 How will you define serious adverse events?

__x___ A serious adverse event will be considered any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

__x___ Any serious psychological and emotional distress resulting from study participation (suggesting need for professional counseling or intervention).

_____Will use definitions provided in the Protocol

_____Other: Specify Answer/Response:

1.3 What is the definition of an unanticipated problem?

An unanticipated problem is any event, experience that meets ALL 3 criteria below:
- Is unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studies
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the subject or others at greater risk of harm than was previously known or recognized OR results in actual harm to the subject or others

1.4 What are the definitions of a protocol deviations and/or noncompliance?
A **protocol deviation** is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB-HSR prior to its initiation or implementation. Protocol deviations may be major or minor.

Noncompliance can be a protocol deviation OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. Noncompliance may be minor or sporadic, or it may be serious or continuing.

1.5 If pregnancy occurs how will this information be managed?
__x___ Adverse Event- will follow adverse event recording and reporting procedures outlined in section 3.

_____ Unanticipated Problems- will follow Unanticipated Problem recording and reporting procedures outlined in section 3.

_____ Other Specify Answer/Response:

1.6 What is the definition of a Protocol Exception?
__x___ NA- No outside sponsor

_____Protocol has a sponsor or a Data & Safety Monitoring Board (DSMB) outside of UVA. Protocol exceptions are circumstances in which the investigator wishes to deviate from eligibility criteria or one or more of the specific procedures called for in a research plan. Unlike modifications that apply to all subsequent subjects in the research, a protocol/research plan exception only applies to a specific subject or group of subjects. Exceptions are planned, and the investigator gets

approval from the sponsor ahead of time. Such a request should be rare and justified in terms of serving the best interests of the potential study participant.

1.7 What is the definition of a data breach?
A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

2. Identified risks and plans to minimize risk

2.1 What risks are expected due to the intervention in this protocol?

Expected Risks related to study participation.	Frequency
Rare But Serious Risks of Blood Flow Restriction Therapy • Blood clot • Pulmonary embolism • Rhabdomyolysis	____Occurs frequently ____Occurs infrequently __x__ Occurs rarely ____Frequency unknown
Less Likely Risks of Blood Flow Restriction Therapy • Bruising	____Occurs frequently __x__ Occurs infrequently ____Occurs rarely ____Frequency unknown
Likely Risks of Blood Flow Restriction Therapy • Muscle discomfort or cramping • Difficulty completing the exercise • Soreness, numbness, or tingling in your leg • Light-headedness • Cold feeling in your leg	__x__ Occurs frequently ____Occurs infrequently ____Occurs rarely ____Frequency unknown
Risks of Skin Preparation for Electromyography • Skin redness • Skin tenderness • Skin swelling	__x__ Occurs frequently ____Occurs infrequently ____Occurs rarely ____Frequency unknown
Violation of subject's privacy and confidentiality	Minimized due to the requirements of the privacy plan in this protocol

2.2 List by bullet format a summary of safety tests/procedures/observations to be performed that will minimize risks to participants:

- To minimize all risks associated with blood flow restriction therapy, this study will only enroll participants that are free of any contraindications associated with blood flow restriction. This will vastly

mitigate the serious and less likely risks associated with blood flow restriction. Each of the likely risks of blood flow restriction therapy should go away after the cuff is deflated following the blood flow restriction exercise. Most side-effects of this condition are similar to that of standard strength training.

- Subjects will be asked to confirm pregnancy status.

2.3 Under what criteria would an INDIVIDUAL SUBJECT'S study treatment or study participation be stopped or modified

__x___ At subject, PI or sponsor's request

__x___ Treatment would be stopped if the subject had a serious adverse event deemed related to study, or study drug will be increased if the subject tolerates dosing

_____Refer to the Protocol

2.4 Under what criteria would THE ENTIRE STUDY need to be stopped.
__x___ Per IRB, PI, DSMB, or sponsor discretion

_____Refer to the Protocol

_____Other: Specify Answer/Response:

2.5 What are the criteria for breaking the blind/mask?
__x___ NA – Not blinded/masked

_____Refer to the Protocol

_____Other: Specify Answer/Response:

2.6 How will subject withdrawals/dropouts be reported to the IRB prior to study completion?
__x___ IRB-HSR continuation status form

_____Other: Specify Answer/Response:

3. Adverse Event / Unanticipated Problem Recording and Reporting

3.1 Will all adverse events, as defined in section 1.1, be collected/recorded? No
►IF NO, what criteria will be used?

__x___ Only adverse events deemed related/possibly related to study
_____Only adverse events that are deemed serious
_____Only adverse events that are deemed related AND serious

_____If protocol requires oversight by Cancer Center DSMC and the protocol is Investigator Initiated- will use tables from the Cancer Center Protocol Review Committee (PRC) Requirements section to document what will be recorded.
_____Other: Specify Answer/Response:

3.2 How will adverse event data be collected/recorded? Check all that apply
__x___ Paper AE forms/source documents
_____Spreadsheet: paper or electronic
_____Database Specify name/type of database Answer/Response:

3.3. How will AEs be classified/graded? Check all that apply
_____World Health Organization Criteria (WHO)
_____NCI Common Toxicity Criteria, Version 2.0/ NCI Common Terminology Criteria, Version 3.0
_____NCI CTCAE Version 4.0
_____Mild/Moderate/Severe
_X_ Serious/Not serious Required for all protocols
_____Will use classifications/ grades provided in the Protocol
_____Other: Specify Answer/Response:

3.4 What scale will the PI use when evaluating the relatedness of adverse events to the study participation? *Check all that apply.*

__x___ The PI will determine the relationship of adverse events to the study using the following scale:

Related: AE is clearly related to the intervention
Possibly related: AE may be related to the intervention
Unrelated: AE is clearly not related to intervention

_____Will use attribution scale provided in the Protocol

_____The PI will use an alternative attribution scale. Specify Answer/Response:

3.5 When will recording/reporting of adverse events/unanticipated problems begin?

_____After subject signs consent
__x___ After subject begins study drug/ device placement/intervention /study-related procedure/specimen collection
_____Other: Specify Answer/Response:

3.6 When will the recording/reporting of adverse events/unanticipated problems end?
__x___ End of study drug/device/intervention/participation
_____30 days post study drug/device/intervention
_____Subject completes intervention and follow up period of protocol
_____Other: Specify Answer/Response:
_____See Protocol for additional information.
_____Two years past last exposure to Gadolinium ONLY if diagnosed with NSF/NSD.

3.7 How will Adverse Events, Unanticipated Problems, Protocol Deviations and Data Breaches be reported? Complete the table below to answer this question

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVA protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call
Internal, Serious, related-possibly related, Unexpected adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online
Unanticipated Problems that are not adverse events or protocol deviations This might include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. Unanticipated Problem Report Form
Protocol Deviations/Noncompliance *The IRB-HSR only requires that MAJOR deviations be reported, unless otherwise required by your sponsor, if applicable.* **OR** **Protocol Exceptions** *See definition- only allowed if there is a commercial sponsor*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Deviation, Noncompliance and Protocol Exception Reporting Form Protocol Deviation Protocol Exception Reporting Form

or a DSMB that has granted the protocol exception.			
Data Breach	The UVA Corporate Compliance and Privacy Office ITC: if breach involves electronic data UVA Police if breach includes such things as stolen computers.	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVA Corporate Compliance and Privacy Office- Phone 924-2938 ITC: Information Security Incident Reporting procedure, https://security.virginia.edu/report-information-security-incident UVA Police-Phone- (434) 924-7166

4. How will the endpoint data be collected/recorded. Check all that apply

_____Protocol specific case report forms

_____Source documents

__x___ Database: UVA REDCap

_____Other: Specify Answer/Response:

5. Data and Safety Oversight Responsibility

5.1. Who is responsible for overseeing safety data for this study?

__x___ No additional oversight body other than PI at UVA Skip question 5.2

_____The UVA Cancer Center Data and Safety Monitoring Committee

_____Medical Monitor

_____DSMB/ DSMC

_____Research Monitor: Insert Name Answer/Response:

_____Other: Specify Answer/Response:

5.2. What is the composition of the reviewing body and how is it affiliated with the sponsor? n/a

_____Information may be found in the UVA Cancer Center Institutional DSMP

_____ Collaborative Site Analysis Study- see CSAS section of this DSMP

_____ Other- Specify Answer/Response:

5.3. What items will be included in the aggregate review conducted by the PI?

_____ NA- PI is not the overall person overseeing the safety data for this study.

__x___All adverse events

__x___Unanticipated Problems

__x___Protocol deviations/Issues of noncompliance

_____Audit results

_____Application of dose finding escalation/de-escalation rules

_____Application of study designed stopping/decision rules

__x___Early withdrawals

__x___Whether the study accrual pattern warrants continuation/action

__x___Endpoint data

_____Other: Specify Answer/Response:

5.4 How often will aggregate review occur?

_____ NA- PI is not the overall person overseeing the safety data for this study.

_____Per Enrollment/Events

__x___Annually

_____Semi-Annually

_____Quarterly

_____Monthly

_____Other: Specify Answer/Response:

5.5. How often will a report, regarding the outcome of the review by the DSMB/DSMC, be sent to the UVA PI? n/a

_____ NA- PI is not the overall person overseeing the safety data for this study.

_____Per Enrollment/Events

_____Annually

_____Semi-Annually

_____Quarterly

_____Monthly

_____Other: Specify Answer/Response:

5.6. How will a report of the information discussed in question 5.4 OR 5.5 be submitted to the IRB?

_x____Part of IRB-HSR continuation status form

_____Separate report from DSMB/DSMC or UVA PI

_____ Other: Specify Answer/Response: N/A

Privacy Plan

The following procedures must be followed.

- The data will be secured per the Data Security Plan of this protocol.
- Only investigators for this study and clinicians caring for the patient will have access to data.
- UVA University Data Protection Standards will be followed.
- If identifiable data is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the University's Highly Sensitive Data Protection Standard for Individual-Use Electronic Devices or Media Additional requirements may be found in the University's Security of Network-Connected Devices Standard. If identifiable data is taken away from the UVA Health , Medical Center Policy # 0218 will be followed.
- Data will be securely removed from the server/drive, additional computer(s), and electronic media according to the University's Electronic Data Removal Standard.
- Data will be encrypted or removed if the electronic device is sent outside of UVA for repair according to the University's Electronic Data Removal Standard .
- If PHI will be faxed, researchers will follow the UVA Health Policy # 0194.
- If PHI will be emailed, researchers will follow the UVA Health Policy # 0193 and University Data Protection Standards (UDPS 3.0).
- Data may not be analyzed for any other study without additional IRB approval.
- If you are using patient information you must follow UVA Health Policy # 0021.
- Both data on paper and stored electronically will follow the University's Record Management policy and the Commonwealth statute regarding the Destruction of Public Records.

If you have a question or concerns about the required security standards contact InfoSec at ir-security@virginia.edu

Summary of Requirements to Comply with UVA Health, Medical Center and University Policies and Guidance as noted above:

Highly Sensitive Data is:
-personal information that can lead to identity theft if exposed or
-data that reveals an individual's health condition and/or history of health services use.

Protected Health Information (PHI) a type of Highly Sensitive Data, is health information combined with certain HIPAA identifiers making the health information identifiable per HIPAA regulations
Sensitive Data is -any additional research data that is not publicly available
Identifiable Data under HIPAA regulations is considered to be *Highly Sensitive Data at UVA.*
A **Limited Data Set** (LDS) under HIPAA regulations is considered to be *Sensitive Data* at UVA. The only HIPAA identifiers associated with data: dates and or postal address information limited to town or city, state, and zip code.

Highly Sensitive Data (Identifiable Health Info per HIPAA)	Sensitive Data (Limited Data Set and De-identified data per HIPAA)
General Issues	*General Issues*
Discussions in private Do not share with those not on the study team or those who do not have a need to know.	Do not share with those not on the study team or those who do not have a need to know.
Password protect	Password protect
Physically secure (lock) hard copies at all times if not directly supervised. If not supervised hard copies must have double protection (e.g. lock on room OR cabinet AND in building requiring swipe card for entrance).	Physically secure (lock) hard copies at all times if not directly supervised.
For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.	For electronic documents turn off File Sharing; turn on firewalls; use up to date antivirus and antispyware; delete data securely.
Encrypt See Encryption Solutions Guidance *Files on UVA Health Network drives are automatically encrypted. If not stored there it is study teams responsibility to make sure data are encrypted.*	
If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVA Purchase order.	If device sent out for service or repair, encrypt or remove data AND contract for repair using a UVA Purchase order.
Store files on a network drive specifically designated for storing this type of data, e.g. high-level security server/drives managed by Information Technology Services or the "F" and "O" managed by UVA Heath Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive such as the desktop of your computer (e.g. C drive) or to an individual Use Device*. May access via VPN	
Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract is in place.	Do not share with sponsor or other outside group before consent is obtained or the IRB has granted appropriate approvals and contract is in place.
If collected without consent/ HIPAA authorization will NOT be allowed to leave UVA HIPAA covered entity** unless disclosure is approved by the IRB and the disclosure is tracked in EPIC	If collected without consent/ HIPAA authorization will NOT be allowed to leave UVA HIPAA covered entity** unless disclosure is approved by the IRB and a contract is in place prior to sharing of data.

Highly Sensitive Data (Identifiable Health Info per HIPAA)	Sensitive Data (Limited Data Set and De-identified data per HIPAA)
Electronic Data Collection & Sharing	*Electronic Data Collection & Sharing*
(e.g. smart phone app, electronic consent using tablet) MUST consult with InfoSec or UVA Health Web Development Office: 434-243-6702 ▪ University Side: IT-Security@virginia.edu ▪ UVA Health: Web Development Center.	
May use: • Globus • Drop Box- UVA Health IT • Qualtrics Portal for HSD • Any additional programs identified by Information Security at ITS Web in the Software Gateway. UVA Health employees can also review Online Account Request to find additional options. May NOT use: • UVA Box • UVA Collab • Question Pro • non-UVA licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.	May use: • Globus • Drop Box- UVA Health IT • Qualtrics portal for MSD • UVA Box • UVA Collab • Any additional programs identified by Information Security at ITS Web in the Software Gateway. UVA Health employees can also review Online Account Request to find additional options. May NOT use • non-UVA licensed cloud providers, such as Dropbox, Google Drive, SkyDrive, Survey Monkey, etc.
The following vendors for handling communication with subjects are NOT allowed: • Google Voice • Facebook (including Messenger) • Linked In • Snapchat	The following vendors for handling communication with subjects are NOT allowed: • Google Voice • Facebook (including Messenger) • Linked In • Snapchat
Individual-Use Device	*Individual-Use Device*
Do not save to individual-use device* without annual written approval of your Department AND VP or Dean. If approval obtained, data must be password protected and encrypted.	
Do not save an email attachment containing HSD to an individual use device*. (e.g. smart phone)	

E Mail	*E Mail*
Do not share via email with Outlook Web/ or forward email using other email vendors like Gmail/ Yahoo	
Do not send via email on smart phone unless phone is set up by UVA Health	
Email may include name, medical record number or Social Security number only if sending email to or from a person with * HS in their email address. *NOTE: VPR & IRB staff do not meet this criteria!*	In addition to sharing LDS, may include initials if persons sending and receiving email works within the UVA HIPAA covered entity.**
FAX	*FAX*
Verify FAX number before faxing	Verify FAX number before faxing
Use Fax Cover Sheet with Confidentiality Statement	Use Fax Cover Sheet with Confidentiality Statement
Verify receiving fax machine is in a restricted access area	Verify receiving fax machine is in a restricted access area
Verify intended recipient is clearly indicated	Verify intended recipient is clearly indicated
Recipient is alerted to the pending transmission and is available to pick it up immediately	Recipient is alerted to the pending transmission and is available to pick it up immediately
TEXT	*TEXT*
Not acceptable.	Only acceptable if using a University contracted phone or with approval from Information Security.
LOST OR STOLEN RESEARCH DATA	LOST OR STOLEN RESEARCH DATA
Must report in accordance with the protocol and in accordance with the Reporting an Information Security Incident Procedure Any data breach must also be reported to the IRB of Record if the report meets the criteria of an Unanticipated Problem.	Must report in accordance with the protocol and in accordance with the Reporting an Information Security Incident Procedure Any data breach must also be reported to the IRB of Record if the report meets the criteria of an Unanticipated Problem.

** Individual Use Device – examples include smart phone, CD, flash (thumb) drive, laptop, C drive of your computer,*
*** At UVA this includes the following areas:, the UVA Health including the School of Medicine & the School of Nursing, the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory and the Exercise Physiology Laboratory.*
Identifiable health info may also be shared with the following areas without tracking the disclosure as agreements are in place to protect the information:

- *VP Office of Research*
- *Nutrition Services (Morrison's)*
- *UVA Center for Survey Research*

Legal/Regulatory/Ethical Considerations

Recruitment
The following procedures will be followed:

- Finders fees will not be paid to an individual as they are not allowed by UVA Policy.
- All recruitment materials will be approved by the IRB-HSR prior to use. They will be submitted to the IRB after the IRB-HSR has assigned an IRB-HSR # to the protocol.
- Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.

Retention Incentives
Any item used by the sponsor/ study team to provide incentive to a subject to remain in the study, other than compensation identified in the Payment section, will be submitted to the IRB for review prior to use. The IRB-HSR will provide the study team with a Receipt Acknowledgement for their records. Retention incentive items are such things as water bottles, small tote bags, birthday cards etc. Cash and gift cards are not allowed as retention incentives.

Clinical Privileges
The following procedures will be followed:

- Investigators who are members of the clinical staff at the University of Virginia Medical Center must have the appropriate credentials and been granted clinical privileges to perform specific clinical procedures whether those procedures are experimental or standard.
- The IRB cannot grant clinical privileges.
- Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.
- Personnel on this protocol will have the appropriate credentials and clinical privileges in place before performing any procedures required by this protocol.
- Contact the Clinical Staff Office- 924-9055 or 924-8778 for further information.

Sharing of Data/Specimens
Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have "permission" to share data/ specimens outside of UVA other than for a grant application and or publication. This "permission" may come in the form of a contract with the sponsor or a transfer agreement with others. An agreement/ contract is needed to share the
data outside of UVA even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

- No data will be shared outside of UVA, beyond using data for a grant application and or publication, without a signed agreement /contract approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.
- No specimens will be shared outside of UVA without a signed agreement/contract approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.

Prisoners
If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study,

the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.
For additional information see the OHRP website at http://www.hhs.gov/ohrp/policy/populations/index.html

Compensation in Case of Injury
If a subject requests compensation for an injury, the study team should notify the IRB-HSR (924-9634/924-2620) the UVA Health Patient Relations Department (924-8315). As a proactive courtesy, the study team may also notify UVA Health Patient Safety and Risk Management (924-5595).

On request, the study team should provide the UVA Risk Management Office with the following information/documents:

- Subject Name and Medical Record Number
- Research medical records
- Research consent form
- Adverse event report to IRB
- Any letter from IRB to OHRP

Subject Complaints
During a research study, the study team may receive complaints from a subject. If the study team is uncertain how to respond to a complaint, or is unable to resolve it with the subject, the study team may contact the IRB-HSR (924-9634/924-2620), the UVA Health Patient Relations Department (924-8315).

Request for Research Records from Search Warrant or Subpoena
If the study team receives a request for research records from a search warrant or subpoena, they should notify UVA Health Information Services at 924-5136. It is important to notify them if information from the study is protected by a Certificate of Confidentiality.

Informed Consent
Unless waived by the IRB, subjects will be fully informed of the:

- purpose of the study,
- reasonably anticipated benefits,
- potential risks or discomfort participation in the study may entail,
- and any alternative treatments.

They will also be informed that their

- consent is voluntary and that they may withdraw their consent to participate at any time, and
- (if applicable) choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease.

The consent documents used to obtain informed consent of the subject must be approved by the IRB prior to use. Any written materials (consent/ short form) will be provided to the potential subject in a language they can read understand. The subjects will be given sufficient time to read the consent form and have the opportunity to ask questions.. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled. After this explanation and before entry into the study, consent should be appropriately recorded. Subjects will be given a copy of the signed consent/ short form.

Institutional Review Board (IRB)
No subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment.
Any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.

Investigator Responsibilities
The investigator is responsible for ensuring that the study is performed in accordance with the protocol and applicable local, state and federal regulatory requirements including ICH guidelines on Good Clinical Practice (GCP-E-6).

Studies with a Certificate of Confidentiality
If a study has a Certificate of Confidentiality (automatic for any study funded in whole or in part by the federal government that collects *identifiable sensitive information*[4]) researchers:

- May not disclose or provide, in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- May not disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.
- May disclose information only when:
  - Required by federal, state, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to state and local health departments), excluding instances of disclosure in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding.
  - Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual.
  - Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
  - Made for the purposes of other scientific research that is in compliance with applicable federal regulations governing the protection of human subjects in research.

[4] The term "*identifiable, sensitive information*" means information about an individual that is gathered or used during the course of biomedical, behavioral, clinical, or other research, where the following may occur:

- An individual is identified; or

- For which there is at least a very small risk, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

iii. Consent

Consent of an Adult to Be in a Research Study

In this form "you" means a person 18 years of age or older who is being asked to volunteer to participate in this study.

Parents' or Guardians' Permission for Your Child to Be in a Research Study

Agreement of a Child (15-17 years of age) to Be in a Research Study

In this form "you" means the child in the study *and* the parent or guardian.

- ✓ If you are the parent or guardian, you are being asked to give permission for your child to be in this study.
- ✓ If you are the child, you are being asked if you agree to be in this study.

In this form "we" means the researchers and staff involved in running this study at the University of Virginia.

Participant's Name_____

Principal Investigator:	Susan Saliba, Ph.D, M.P.T., ATC Department of Kinesiology PO Box 400407 Charlottesville, VA, 22908 Telephone: 434-243-4033

What is the purpose of this form?

This form will provide you with information about this research study. You do not have to be in the study if you do not want to. You should have all your questions answered before you agree to be in this study. Please read this form carefully. If you want to be in the study, you will need to sign this form. You will be given a copy of this form.

Who is funding this study?

There will be no funding for this study.

Key Information About This Research Study

You should only agree to take part in this study after reading this consent form and discussing it with the study team. You may also discuss this with your family, friends, health care providers or others before you make a decision.

What problem is this study trying to solve?

Persistent muscle weakness continues to be a problem for many individuals after anterior cruciate ligament reconstruction (ACLR) surgery even after the completion of traditional physical therapy programs. This study is going to investigate the potential benefits of an alternative treatment technique, blood flow restriction

therapy (BFRT), for gaining muscle strength after ACLR. You are being asked to take part in this study because you currently have muscle weakness in your ACLR leg compared to your healthy, uninjured leg.

Why would you want to take part in this study?

You might like to take part in this study because previous research has shown that BFRT can be an effective method for increasing muscle strength in various patient populations including those who have undergone ACLR surgery. The information gained by doing this study may not only help your lingering muscle weakness, but it may also help others in the future.

Why would you NOT want to take part in this study?

You might not want to take part in this study because of the time and travel expenses required to attend each study session. Additionally, the study will require you to have your leg hair and dead skin cells removed from two small areas of your thighs for measurement purposes.

What will I have to do if I take part in this study?

Full details of all the procedures are found later in this form.

If you choose to participate in this study, you will sign this consent form before any study related procedures take place.

- Come to the Exercise and Sport Injury Lab at the University of Virginia for an initial baseline study session.
  - Answer questions regarding your demographics (i.e., age, sex, height, weight, etc.) , general health history, knee function, physical activity, etc.
  - Be randomly assigned to one of two groups: BFRT or control.
  - Have your thigh muscles imaged with ultrasound.
  - Have the length and circumference of your thigh measured with a tape measure.
  - Have the activity of your thigh muscles assessed with surface electromyography during moving and static strength testing.
  - Complete maximal strength assessments for 5 exercises (BFRT group only).
  - Practice BFRT exercise procedures (BFRT group only).
- If you are in the BFRT group you will attend 8 physical therapy sessions (2 sessions per week for 4 weeks) with blood flow restriction including 75 repetitions of 5 exercises at a low load resistance.
- Complete weekly physical activity questionnaires regarding your participation in physical activity outside of this study (Both groups).
- Complete two additional follow up sessions with the same assessments as the initial baseline session (Both groups).

What is the difference between being in this study and getting usual care?

If you take part in this study, the following things will be done differently than if you do not take part in this study:

- You will potentially receive 8 additional supervised physical therapy sessions involving BFRT.

All activities in this study are being done for only for the purposes of this research study.

What other treatments may I receive if I decide to not take part in this study?

While no alternative treatments will be provided to you by the members of this research team if you choose not to take part in this study, you may choose to participate in the following under the supervision of your healthcare provider:

- Attend additional physical therapy
- Participate in supervised or unsupervised high load strength training
- Continue your typical activities of daily living, sport, or home-based exercise program

You are being asked to be in this study, because you are at least 3 months post-ACLR and are continuing to have weakness of your quadriceps following your knee surgery. Up to ***28*** people will be in this study at UVA.

How long will this study take?

Your participation in this study will require 3 in-person study visits for those in the control group or 11 in-person study visits for those in the BFRT group over a 2-month period of time. Each visit will last about 1-1.5 hours. You will also be asked to remotely fill out a weekly physical activity questionnaire at the end of each week during the intervention timeframe (4 weeks total) which will take approximately 5 minutes of your time each week.

What will happen if you are in the study?

STUDY PROCEDURES

SCREENING

If you agree to participate, you will sign this consent form before any study related procedures take place. Before you can start in the study, there will be a screening period. You will have tests and procedures during this time to make sure you are eligible and it is safe for you to participate. These include the following:

- Medical History as it relates to your ACLR surgery via electronic medical record review
- Results of strength assessment during your Lower Extremity Assessment Protocol (LEAP) via electronic medical record review
- Your response to pre-screening questions regarding potential contraindications to blood flow restriction therapy.
- If you are pregnant you may not participate in this study. You will be asked if you are pregnant.

If you are eligible and interested in participation, an initial baseline session will be scheduled.

1. **BASELINE/FAMILIARIZATION SESSION (will take approximately 1.5 hours to complete):**
   Upon arrival for the baseline session of the study, you will provide informed consent prior to starting the study procedures. Following informed consent, you will be randomly allocated into either the control group or the BFRT intervention group. You have an equal chance of being assigned to either

group. Neither you nor your doctor can choose which treatment you are assigned. Pre-screening information will be saved following your consent for this study.

GROUP 1: BFRT intervention (will participate in a baseline session, attend 2 BFRT intervention sessions per week for 4 weeks, fill out weekly activity questionnaires, and participate in two follow-up sessions.
GROUP 2: Control (will participate in a baseline session, fill out weekly activity questionnaires, and participate in two follow-up sessions)

Patient Reported Outcomes: Questionnaires; about 10 minutes in total (Both groups)

You will complete several questionnaires. These questionnaires ask about:

- Demographic and general health information
- Injury history and goals
- How you are feeling
- Your lifestyle habits
- Physical activity level
- Daily activities
- Your perceived leg function
- Your pain during daily activities
- Your fear of reinjury/movement
- Physical therapy

You will be asked to complete these questionnaires in-person before starting the intervention and two times following the completion of the intervention period.

Ultrasound Assessment and Girth; about 10 minutes in total (Both groups)

Your muscle size, thickness, and quality will be assessed in your injured and non-injured limb using ultrasound. Your leg length and thigh girth will be assessed using a tape measure at 6cm and 16cm above your knee, bilaterally.

Motor Unit Behavior Assessment; about 5 minutes in total (Both groups)

Noninvasive, surface electromyographic (EMG) devices, which measure electrical signals sent to your muscles, will be applied to your quadriceps to measure motor unit behavior during strength testing. Your skin will be prepped for electrode placement by shaving off any hair and dead skin cells as well as extensive cleaning of these sites with gauze and alcohol prep pads. After the sites are prepared, the researchers will secure the sensors to the skin using a non-adhesive wrapping to limit movement of the sensors.

Isokinetic Strength Assessment; about 5 minutes in total (Both groups)

This test measures the force you produce with your leg.

- You will be asked to sit in a stationary chair with your knees bent at 90 degrees (a right angle).

- Your hips will be secured with Velcro straps. Your ankle will be secured to a padded strap below the chair. This strap is connected to a device which will measure how much force you can produce.
- You will be asked to kick out and pull back your leg 8 times. This will be repeated at two different levels of resistance.
- You will be asked to complete this trial as fast as you can.
- You will be asked to complete one trial at each level of resistance.
- This will be performed on both legs.

Isometric Strength Assessment; about 5 minutes in total (Both groups)
This test will measure the force you are producing with your leg.

- You will be seated in a stationary chair. The chair has handles on each side.
- Your hips will be secured with Velcro straps. Your ankle will be secured to a padded strap below the chair. This strap is connected to a device designed to measure how much force you can produce.
- You will then be asked to kick out at your maximum effort and hold your leg out for 30 seconds. We will ask you to try to keep the same amount of force for as long as you can.
- You will then be asked to pull back at your maximum effort and hold your leg in for 30 seconds. We will ask you to try to keep the same amount of force for as long as you can.
- This will be performed on both legs.

One-Repetition Maximum; about 30 minutes in total (BFRT group only)

- For those in the BFRT group, the maximum amount of weight you can resist with proper form during each exercise will then be predicted by determining your 5-repetition maximum.
  - You will start by performing a 5-minute warm-up followed by 2 minutes of rest.
  - You will then perform 5 repetitions of the exercise at a self-selected weight followed by 2 minutes of rest.
  - We will then increase your load by 10-20% and you will perform another 5 repetitions at this estimated maximal load followed by 2 minutes of rest.
  - If you successfully perform the previous 5 repetitions, we will increase your load by an additional 10-20%. If you fail to perform the previous 5 repetitions with proper form, we will decrease your load by 5-10%.
  - You will repeat the previous 2 steps until only 5 repetitions can be completed with proper form.
  - Your one repetition maximum will be predicted.
- These steps will be repeated for all 5 exercises.

BFRT Intervention Familiarization; about 10 minutes in total (BFRT group only)
If you are allocated into the BFRT group, you will then practice the BFRT exercise protocol.

- With the Delfi PTSII tourniquet cuff (Delfi Medical Vancouver, BC) applied and inflated to 60% of your total limb occlusion pressure (the amount of pressure needed to

completely stop blood from entering and leaving the limb), you will practice 5-10 repetitions of each exercise at a low percentage of your predicted one repetition maximum.

- Special attention will be given to the rate of exercise execution and your form.

2. BFRT INTERVENTION SESSIONS (each will take 1-1.5 hours to complete) (BFRT group only):
Following the baseline assessment session, if you are in the BFRT group you will take part in 2 physical therapy sessions per week for 4 weeks (8 sessions total).

- These sessions will include the performance of 5 lower extremity exercises at a low percentage of your maximal strength with BFR applied at 60% of your total limb occlusion pressure.
- Prior to starting the exercise session, you will perform a 5-minute warm-up on a stationary bike and perform stretching of your lower extremities.
- Five single leg exercises will be performed on your injured limb only in the following order: knee extension, hamstring curl, hip abduction, hip extension, and leg press.
- The blood flow restriction cuff will be inflated to the predetermined pressure (60% of your limb occlusion pressure) during each exercise. The cuff will remain inflated for all sets, repetitions, and interset rest periods. The cuff will only be deflated between exercise types.
- Four sets of each exercise will be performed (set 1: 30 repetitions, set 2-4: 15 repetitions).
- Thirty seconds of rest will be provided between each exercise set and 2 minutes of rest with cuff deflation will be provided between each exercise type.
- You will be asked to rate your level of perceived exertion (or how difficult it was) following each exercise type from 0 (i.e., no effort) to 10 (i.e., maximal effort).
- Each week, the weight applied during each exercise will be modified based on your tolerance and performance.

- **Weekly Physical Activity Assessment (will take about 5 minutes to complete) (Both groups):**
  - At the end of each week during the intervention timeframe, you will be asked to fill out an online physical activity questionnaire that will assess the amount of physical activity you completed outside of the study for the past 7 days. The questionnaire will be emailed to you.

3. FOLLOW-UP SESSION #1 (will take approximately 1 hour to complete) (Both groups):
After the completion of the intervention period, you will return for an initial follow-up session. Your patient reported outcome measures, ultrasound, motor unit behavior, and strength will be reassessed using the same protocols as described in the baseline assessment.

4. FOLLOW-UP SESSION #2 (will take approximately 1 hour to complete) (Both groups):
You will return for a second, final follow-up session one month after your initial follow-up session. Your patient reported outcome measures, ultrasound, motor unit behavior, and strength will be reassessed using the same protocols as described in the baseline assessment.

Study Schedule Table

	Eligibility	Baseline Visit (Both groups)	BFRT Visit 1	BFRT Visit 2	BFRT Visit 3	BFRT Visit 4	BFRT Visit 5	BFRT Visit 6	BFRT Visit 7	BFRT Visit 8	Follow-up #1 (Both groups)	Follow-up #2 (Both groups)
Study Week	0	0	1	1	2	2	3	3	4	4	5	8
Informed Consent		x										
Review study eligibility	x											
Questionnaires		x									x	x
Ultrasound		x									x	x
EMG		x									x	x
Strength testing		x									x	x
Physical therapy			x (BFRT group only)	x (BFRT group only)	x (BFRT group only)	x (BFRT group only)	x (BFRT group only)	x (BFRT group only)	x (BFRT group only)	x (BFRT group only)		
Weekly Physical Activity Questionnaire		x		x (Both groups)		x (Both groups)		x (Both groups)		x (Both groups)	x	x

Regardless of which group you are in, you will complete an online physical activity questionnaire once per week during the intervention timeframe of this study.

What are your/and your parent/legal guardian's responsibilities in the study?

You and your parent/legal guardian have certain responsibilities to help ensure your safety.
These responsibilities are listed below:

- Your parent/legal guardian must bring you to each study visit.
- You and your parent/legal guardian must be completely truthful about your health history.
- Follow all instructions given.
- You or your parent/legal guardian should tell the study doctor or study staff about any changes in your health or the way you feel.
- Answer all of the study-related questions completely.
- Inform the study doctor or study staff as soon as possible if you have to take any new medications, including anything prescribed by a doctor or those that you can buy without a prescription (over-the-counter), including herbal supplements and vitamins.

If you want to know about the results before the study is done:

During the study your study leader will let you know of any test results that may be important to your health. In addition, as the research moves forward, your study leader will keep you informed of any new findings that may be important for your health or may help you decide if you want to continue in the study. The final

results of the research will not be known until all the information from everyone is combined and reviewed. At that time, you can ask for more information about the study results.

What are the risks of being in this study?

Risks and side effects related to the use of the blood flow restriction inflated cuff include:

Likely

- Muscle discomfort or cramping
- Difficulty completing the exercise
- Soreness, numbness, or tingling in your leg
- Light-headedness
- Cold feeling in your leg

*** These feelings go away when the cuff is deflated.

Less Likely

- Bruising

*** This side effect will be limited given the short length of time the tourniquet cuff is inflated.

Rare but serious

- Blood clot
- Pulmonary embolism
- Rhabdomyolysis

*** However, in a healthy individual these risks are extremely rare. You will be carefully monitored during your participation in this study and would be referred for prompt treatment should any of these problems take place.

Risks of skin preparation for electromyography:
When preparing skin for electromyography measurement, there may be some discomfort and sensitivity during the abrasion and cleaning process. The prepared skin may be red and tender after the sensors are removed and participants will be instructed to keep the skin well moisturized after the study is completed. Participants may notice slight redness and swelling of the application sites for a few days following the study.

Other unexpected risks:
You may have side effects that we do not expect or know to watch for now. Call the study leader if you have any symptoms or problems.

Could you be helped by being in this study?

You may or may not benefit from being in this study. Possible benefits include: increased muscle strength and subjective function. In addition, information researchers get from this study may help others in the future.

What are your other choices if you do not join this study?

You do not have to be in this study to be treated for your illness or condition. You can get the usual treatment even if you choose not to be in this study. The usual treatment would include continuing to be followed and treated with traditional rehabilitation as prescribed by your treating physician.

If you are an employee of UVA your job will not be affected if you decide not to participate in this study.
If you are a student at UVA, your grades will not be affected if you decide not to participate in this study.

Will you be paid for being in this study?

You will not get any money for being in this study.

Will being in this study cost you any money?

All of the procedures in this study will be provided at no cost to you or your health insurance. You will be responsible for the cost of travel to come to any study visit and for any parking costs.

What if you are hurt in this study?

You do not give up any legal rights, such as seeking compensation for injury, by signing this form. If you feel you have been injured as a result of this study, you may contact the Principal Investigator or the IRB (phone numbers are located near the end of this form). If you are hurt as a result of being in this study, there are no plans to pay you for medical expenses, lost wages, disability, or discomfort. The charges for any medical treatment you receive will be billed to your insurance. You will be responsible for any amount your insurance does not cover.

What happens if you leave the study early?

You can change your mind about being in the study any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services you can normally get at the University of Virginia.

Even if you do not change your mind, the study leader (***Dr. Susan Saliba***) can take you out of the study. Some of the reasons for doing so may include:

b) Your injury gets worse
c) The side effects of the study procedures are too dangerous for you
d) New information shows BFRT will not work or is not safe for you
e) You do not follow instructions

How will your personal information be shared?

The UVA researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you can continue to receive regular medical care at UVA.

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, address and date of birth
- Social Security number ONLY IF you are being paid to be in this study
- Your health information if required for this study. This may include a review of your medical records and test results from before, during and after the study from any of your doctors or health care providers. This may include mental health care records, substance abuse records, and/or HIV/AIDS records.

Who will see your private information?

- The researchers to make sure they can conduct the study the right way, observe the effects of the study and understand its results
- People or groups that oversee the study to make sure it is done correctly
- The sponsor(s) of this study, and the people or groups it hires to help perform or review this research
- Insurance companies or other organizations that may need the information in order to pay your medical bills or other costs of your participation in the study
- Tax reporting offices (if you are paid for being in the study)
- People who evaluate study results, which can include sponsors and other companies that make the drug or device being studied, researchers at other sites conducting the same study, and government agencies that provide oversight such as the Food and Drug Administration (FDA) if the study is regulated by the FDA.
- If you tell us that someone is hurting you, or that you might hurt yourself or someone else, the law may require us to let people in authority know so they can protect you and others.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

What if you sign the form but then decide you don't want your private information shared?

You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form or complete the "Leaving the Study Early" part of this form and return it to the researchers. Then you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation.

Please contact the Principal Investigator listed earlier in this form to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- 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:	Susan Saliba, PhD, PT, ATC
Address:	Department of Kinesiology PO Box 400407 Charlottesville, VA 22904
Telephone:	(434)243-4033

What if you have a concern about this study?

You may also report a concern about this study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research
PO Box 800483
Charlottesville, Virginia 22908

Telephone: 434)-924-2620

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the UVA Study Tracking Number (at the bottom of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

You may also report a concern anonymously by calling the UVA Compliance Hotline phone number at 1-800-235-8700.

Would you like the study team to communicate with you by email or text message?
If you choose to communicate with the study team by unsecure email (email that is not encrypted) or text message to your personal phone, there is some risk that your health information could be read or accessed by someone else while the information is sent or saved by your email or phone provider.

Your personal email or phone provider may also share or release your information because they do not have to follow the privacy laws that UVA follows. Sometimes email and phone providers release information to marketing companies for use in direct advertising. If you choose to communicate by email or text messaging, UVA cannot control this potential loss of privacy but we want to tell you about this possible risk.

You do not have to agree to communicate with the study team by email or text message to be in this study. If you agree to texting or emailing, the study team will collect your phone and /or email address from you that you would like them to use to contact you. Please note, if you agree to text messaging, charges may apply depending on your data/text plan with your phone provider.

Signatures

What does your signature mean?
Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you have received this information and all your questions have been answered. If you sign the form, it means that you agree to join the study. You will receive a copy of this signed document.

Consent From Adult

PARTICIPANT	PARTICIPANT	DATE

(SIGNATURE) (PRINT)
To be completed by participant if 18 years of age or older.

Person Obtaining Consent
By signing below, you confirm that you have fully explained this study to the potential subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT(PRINT)	DATE

Assent from Child
Consent from the parent/guardian MUST be obtained before approaching the child for their assent.

PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

Person Obtaining Assent of the Child (less than 18 years of age)
Consent from the parent/guardian MUST be obtained before approaching the child for their assent.

By signing below, you confirm that the study has been explained to the child (less than 18 years of age), all questions have been answered and the child has voluntarily agreed to participate.

PERSON OBTAINING ASSENT (SIGNATURE)	PERSON OBTAINING ASSENT (PRINT)	DATE

Parental/ Guardian Permission
By signing below, you confirm you have the legal authority to sign for this child.

PARENT/GUARDIAN (SIGNATURE)	PARENT/GUARDIAN (PRINT NAME)	DATE
PARENT/GUARDIAN (SIGNATURE)	PARENT/GUARDIAN (PRINT NAME)	DATE

If you are unable to obtain parental permission from both parents/guardians, explain why not:

Person Obtaining Parental/Guardian Permission
By signing below, you confirm that you have fully explained this study to the parent/guardian, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

PERSON OBTAINING PARENTAL/ GUARDIAN PERMISSION (SIGNATURE)	PERSON OBTAINING PARENTAL/GUARDIAN PERMISSION (PRINT NAME)	DATE

Leaving the Study Early

Signatures should be obtained in this section if the subject decides to leave the study early.

If you leave the study early the study leader will keep the data collected about you up until the time you leave the study to help determine the results of the study.

Check one option below:

____ I am withdrawing my consent from the intervention or treatment part of this study but agree to continue to have follow up information about me collected by the study team.
The follow up information will be collected by:

- Two in-person follow up visits. Each visit will consist of measuring muscle size, muscle strength, motor unit behavior, and patient reported function.

____ I am withdrawing my consent for this study. No additional information may be collected about me including follow up information from my medical records.

Consent From Adult

PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

Person Obtaining Consent
By signing below you confirm that you have fully explained the implications of withdrawing from the study to the subject and have answered all their questions.

PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT(PRINT)	DATE

Parental/ Guardian Permission
By signing below you confirm you have the legal authority to sign for this child.

PARENT/GUARDIAN (SIGNATURE)	PARENT/GUARDIAN (PRINT NAME)	DATE

Person Obtaining Consent
By signing below you confirm that you have fully explained the implications of withdrawing from the study to the subject and have answered all their questions.

PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT(PRINT)	DATE

iv. Data Security Plan

UNIVERSITY of VIRGINIA

Cronnect

DATA SECURITY PLAN

WF SUMMARY DETAILS	
Version Date:	*January 14, 2022*
Workflow Name:	*HSR210507-BFRT and ACLR*
Proposal Org./ Dept. No.	*31200 CU-KINE Kinesiology*
Principal Investigator:	*Susan Saliba - saf8u*
DSP Submitted by:	*sls4fe*
Protocol File Uploaded to Study Documents:	*Yes*

HIPAA IDENTIFIER OPTIONS

OPTIONS	OPTION SELECTED	HOW STORED
Note: You will refer to this list throughout the document.	If the identifier is not listed, it is not applicable.	Options include: • Original source data collection (receive, collect, or record at UVA) • Store long term at UVA • Send or transmit outside of UVA • Not Applicable
1. Name	*1. Name - Highly Sensitive Data*	*Original source data collection, Store long term at UVa*
2a. Postal address includes street and/or PO Box, and town or city, state, and zip code		
2b. Postal address that includes only town or city, state, and/or zip code		
3. All date elements (except year) for dates related to an individual, e.g. service date		
4. Telephone numbers	*4. Telephone numbers - Highly Sensitive Data*	*Original source data collection, Store long term at UVa*
5. Fax numbers		
6. Electronic mail addresses	*6. Electronic mail addresses - Highly Sensitive Data*	*Original source data collection, Store long term at UVa*
7. Social Security number		
8. Medical Record number		
9. Health plan beneficiary numbers		
10. Account numbers		
11. Certificate/license numbers		
12. Vehicle identifiers and serial numbers, including license plate numbers		
13. Device identifiers and serial numbers		
14. Web Universal Resource Locators (URLs)		
15. Internet Protocol (IP) address numbers		
16. Biometric identifiers, including finger and voice prints		
17. Full face photographic images and any comparable images		
18. Other unique number, characteristic, code related to an individual, e.g. initials		

COLLECTION & STORAGE OF HUMAN SUBJECT RESEARCH DATA

A) PAPER DOCUMENTS

OPTIONS	SELECTED
Storage location	
Other: (Please describe)	*No paper documentation will be collected.*

*Appropriate UVA locations include one or more of the following:

- Kept in a locked office in a building with 24-hour swipe locks when unattended
- Kept in a locked file cabinet in a locked room when unattended
- Kept in an office where study are personnel present in room at all times located in a building with 24-hour swipe locks or a room with a lock when unattended
- Behind two locked doors when unattended

B) EMAILED TO OTHER UVA PERSONNEL

OPTIONS	SELECTED
Research data emailed to UVA personnel, but with no HIPAA identifiers except dates. -or/and- Email only to and from UVA personnel with *HS in the Global Address List	
Other Email Characteristics: (Please describe)	

C) ELECTRONIC MEDICAL RECORD (EPIC)

OPTIONS	SELECTED
Data will be collected in EPIC as part of routine care or as part of medical center encounters during the research study.	*Not Applicable*

D) UVA-APPROVED eCRF OR CLINICAL TRIALS MANAGEMENT SYSTEM

LIST	USED / SELECTED
hstsdsmpogapp.hscs.virginia.edu	
OnCore (oncore.med.virginia.edu)	
Redcap-int.hscs.virginia.edu	*Redcap-int.hscs.virginia.edu*
https://reveal.studymanager.com/	
Advarra: https://uva-edc.forteresearchapps.com/	
IT Security Team Lead CISSP|HCISPP|CEH|ITIL	
I acknowledge that ANY electronic use devices used to connect to any servers/websites checked above are supported by UVA Health IT	Yes

E) UVA SERVERS & WEBSITES

LIST	USED / SELECTED
domatlas.eservices.virginia.edu	
dom-titan.eservices.virginia.edu	
Elson1.studenthealth.virginia.edu	
es3.eservices.virginia.edu	*es3.eservices.virginia.edu*
gcrcserver.itc.virginia.edu	
\\HSCS-ss7	
\\HSCS-ss8	
\\HSCS-ss9	
\\HSCS-ss10	
\\HSCS-ss11	
\\HSCS-ss12	
\\HSCS-ss13	
\\hscs-share1\	
\\hscs-share2\	
\\hscs-share3\	
\\redshare\	
upgusers.hscs.virginia.edu	
Ivy Secure Computing Platform/ Ivy Secure Cloud/Ivy Cloud	
School of Nursing SECURE NET	
UVA HIT DropBox/Sookasa	
UVA Qualtrics HSD survey tool: https://virginiahsd.co1.qualtrics.com/ControlPanel/	

F) WEB-BASED OR CLOUD FORMAT (NOT LISTED ABOVE)

LIST	USED / SELECTED
Data will be collected and/or stored in UVA Box or UVA-Collab	*No*
If you are using other web-based or cloud servers please describe:	
Check the HIPAA identifiers stored on UVA Box or Collab	

INDIVIDUAL USE DEVICES

Current list of individual use device choices available for use:

- No Individual Use Devices will be used
- Flash (thumb) drive
- External drive
- CD or DVD
- Desktop Computer
- Laptop
- Tablet
- Smart phone
- Camera
- Video recorder
- Audio recorder
- Biometric recording device
- Fitness Trackers
- Other

G) Individual use devices	Desktop Computer
If you selected "Other" above, please identify the device type:	
Please describe your process for collecting, storing and/or transmitting data on the Individual Use Devices you selected in earlier steps (phones, flash drives, CDs, etc.):	Data from the Trigno sensor is directly collected and stored on the secure desktop computer that is owned by the Department of Kinesiology at the University of Virginia and managed by the Educational Technologies Office. The sensor itself does not have any storing capabilities. Data from the Trigno sensor will be transferred to a high security server at the end of the study and deleted from the desktop computer. Data from the Biodex and diagnostic ultrasound devices will be transferred from those devices to the secure desktop computer using a flash drive. All data (Trigno, Biodex, Ultrasound) will be transferred REDCap for data management

	and loaded to a secure server at the end of the study. Once transferred to REDCap, all data on the secure desktop computer will be permanently deleted.
Check the HIPAA identifiers stored with the data on this device (e.g. such as full-face picture or video):	No HIPAA identifiers will be recorded as part of this research
Describe any backups made of the data stored on the device. Please include the location & method of data transfer:	N/A
How long will the data remain on the individual-use device before being transferred?	After the data from the Biodex and images from the diagnostic ultrasound are transferred to the desktop computer, the data will remain on the secure desktop computer until they are transferred to REDCap and stored on a high security server. The data from the Trigno sensor that was directly collected and stored onto the desktop computer will also remain on the secured computer until it is transferred to a high security server. All data from the Biodex, ultrasound, and Trigno sensor will remain on the secure desktop computer until the end of the study.
After the information is transferred elsewhere, will you securely delete all the data from this device?	Yes
Will anyone other than the study team or sponsor/CRO have access to data on this device?	No
If yes, describe	
Other storage alternatives that were considered and the reasons they are unworkable	No other alternatives were considered.
The justification for storage of these data on this individual use device is:	The desktop computer is a secure UVA computer that is supported by UVA IT. It is stored in a locked lab in the Student Health and Wellness Building and only the study team will have access to the data on this device. Data from the Trigno sensor, Biodex, and ultrasound will only be accessible on the study coordinator's UVA computer account. The data from these devices will be stored in a private folder in the user's Documents section of computer. The data stored on this device will not contain the subject's name or other identifiable information. All files will be saved under a randomized subject number. The data will remain stored on this secure computer until it is transferred to a high security server at the end of the study.

G) Individual use devices	**Other**
If you selected "Other" above, please identify the device type:	Biodex
Please describe your process for collecting, storing and/or transmitting data on the Individual Use Devices you selected in earlier steps (phones, flash drives, CDs, etc.):	Data collected on the Biodex will be stored onto the Biodex device during the participant's visit. At the completion of the visit, the strength data collected from this device will be transferred from the Biodex to the desktop computer using a flash drive. The data will be permanently deleted from the

	Biodex after they have been successfully transferred to the desktop computer and onto REDCap. This data will be stored on REDCap until it is transferred to a secure server at the end of the study.
Check the HIPAA identifiers stored with the data on this device (e.g. such as full-face picture or video):	No HIPAA identifiers will be recorded as part of this research
Describe any backups made of the data stored on the device. Please include the location & method of data transfer:	N/A
How long will the data remain on the individual-use device before being transferred?	Data collected directly on the Biodex will remain on the Biodex until the end of the participant's visit. At the end of the visit, the researchers will transfer the data from the Biodex to the secure desktop computer where it will be uploaded onto REDCap and stored until the end of the study where it will then be stored on the secure server. Data collected onto this device will be deleted after it has been transferred to the desktop computer.
After the information is transferred elsewhere, will you securely delete all the data from this device?	Yes
Will anyone other than the study team or sponsor/CRO have access to data on this device?	No
If yes, describe	
Other storage alternatives that were considered and the reasons they are unworkable	No other alternatives were considered.
The justification for storage of these data on this individual use device is:	Data will only remain stored on the Biodex until the end of the participant's visit. The data will be deleted from the device after it has been transferred to the secure desktop computer.
G) Individual use devices	**Laptop**
If you selected "Other" above, please identify the device type:	
Please describe your process for collecting, storing and/or transmitting data on the Individual Use Devices you selected in earlier steps (phones, flash drives, CDs, etc.):	Participants will utilize the laptop that is owned by the Department of Kinesiology at the University of Virginia and managed by the Educational Technologies Office in order to fill out consent and all questionnaires associated with this study directly onto REDCap. Study investigators may also utilize this laptop to access REDCap for data collection purposes. No information will be stored onto this laptop.
Check the HIPAA identifiers stored with the data on this device (e.g. such as full-face picture or video):	No HIPAA identifiers will be recorded as part of this research
Describe any backups made of the data stored on the device. Please include the location & method of data transfer:	N/A
How long will the data remain on the individual-use device before being transferred?	Data will not be stored onto this device.
After the information is transferred elsewhere, will you securely delete all the data from this device?	Yes

Will anyone other than the study team or sponsor/CRO have access to data on this device?	No
If yes, describe	
Other storage alternatives that were considered and the reasons they are unworkable	No other alternatives were considered.
The justification for storage of these data on this individual use device is:	This laptop is a secure UVA laptop computer that is supported by UVA IT. It is stored in a locked lab in the Student Health and Wellness Building. No data will be stored on this device, it will only be used to access REDCap and the secure server.
G) Individual use devices	**Other**
If you selected "Other" above, please identify the device type:	Diagnostic Ultrasound
Please describe your process for collecting, storing and/or transmitting data on the Individual Use Devices you selected in earlier steps (phones, flash drives, CDs, etc.):	Images collected on the diagnostic ultrasound device will be stored onto the ultrasound device during the participant's visit. At the completion of the visit, the images will be transferred from the ultrasound device to the desktop computer using a flash drive. The images will be permanently deleted from the ultrasound device after they have been successfully transferred to the desktop computer. The images will be stored on the desktop computer until they are measured and transferred to a secure server at the end of the study.
Check the HIPAA identifiers stored with the data on this device (e.g. such as full-face picture or video):	No HIPAA identifiers will be recorded as part of this research
Describe any backups made of the data stored on the device. Please include the location & method of data transfer:	N/A
How long will the data remain on the individual-use device before being transferred?	Images collected directly onto the ultrasound device will remain on the ultrasound device until the end of the participant's visit. At the end of the visit, the researchers will transfer the images from the ultrasound to the secure desktop computer where they will be stored until the end of the study. Images collected onto the ultrasound will be deleted after they have been transferred to the desktop computer.
After the information is transferred elsewhere, will you securely delete all the data from this device?	Yes
Will anyone other than the study team or sponsor/CRO have access to data on this device?	No
If yes, describe	
Other storage alternatives that were considered and the reasons they are unworkable	No other alternatives were considered.
The justification for storage of these data on this individual use device is:	Images will only remain stored on the ultrasound device until the end of the participant's visit. The data will be deleted from the device after it has been transferred to the secure desktop computer.
G) Individual use devices	**Tablet**
If you selected "Other" above, please identify the device type:	

Please describe your process for collecting, storing and/or transmitting data on the Individual Use Devices you selected in earlier steps (phones, flash drives, CDs, etc.):	An iPad will be used to access data collection documents on RedCap. Each document will be directly filled out, collected, and stored onto Redcap-int.hscs.virginia.edu using an iPad. No data will be stored on the iPad itself.
Check the HIPAA identifiers stored with the data on this device (e.g. such as full-face picture or video):	No HIPAA identifiers will be recorded as part of this research
Describe any backups made of the data stored on the device. Please include the location & method of data transfer:	N/A
How long will the data remain on the individual-use device before being transferred?	Data will not be stored onto this device.
After the information is transferred elsewhere, will you securely delete all the data from this device?	Yes
Will anyone other than the study team or sponsor/CRO have access to data on this device?	No
If yes, describe	
Other storage alternatives that were considered and the reasons they are unworkable	No alternatives were considered.
The justification for storage of these data on this individual use device is:	No data will be stored on the iPad.
G) Individual use devices	**Flash (thumb) drive**
If you selected "Other" above, please identify the device type:	
Please describe your process for collecting, storing and/or transmitting data on the Individual Use Devices you selected in earlier steps (phones, flash drives, CDs, etc.):	An encrypted flash drive will be used to transfer data from the Biodex and images from the diagnostic ultrasound to the desktop computer. Once the files are transferred from the flash drive to the desktop computer, they will be permanently deleted from the flash drive as well as the Biodex and ultrasound devices.
Check the HIPAA identifiers stored with the data on this device (e.g. such as full-face picture or video):	No HIPAA identifiers will be recorded as part of this research
Describe any backups made of the data stored on the device. Please include the location & method of data transfer:	N/A
How long will the data remain on the individual-use device before being transferred?	Data from the Biodex and images from the ultrasound will only remain on the flash drive until they have been successfully transferred to the desktop computer. This transfer will take place at the end of each participant visit. After the data has been transferred to the desktop computer it will be permanently deleted from the flash drive.
After the information is transferred elsewhere, will you securely delete all the data from this device?	Yes
Will anyone other than the study team or sponsor/CRO have access to data on this device?	No
If yes, describe	
Other storage alternatives that were considered and the reasons they are unworkable	No other alternatives were considered.

The justification for storage of these data on this individual use device is:	Data from the Biodex and images from the ultrasound will only be stored temporarily on the flash drive until they have been transferred from the flash drive to the secure desktop computer. The files will be deleted from the flash drive after they have been transferred.

TRANSMISSION & STORAGE OF THE HUMAN SUBJECT RESEARCH DATA OUTSIDE OF UVA

QUESTION	
Will data be transmitted to a sponsor or a colleague at another institution?	*No*
Data will be emailed to non-UVA personnel via HSC secure email	*No*
I acknowledge that ANY electronic individual use devices used to connect to any servers/websites listed below are supported by UVA Health System IT. (CRO)	*Yes*
Check the HIPAA Identifiers stored by the Sponsor or CRO	*No HIPAA identifiers will be recorded as part of this research*
If sharing data with anyone outside of UVA, do you confirm that you will obtain a contract with them via the School of Medicine Grants and Contracts Office or the Office of Sponsored Programs (OSP)?	*No*
Data will be sent and stored in an encrypted fashion (e.g. will only be shared and via Secure FX, Secure FTP, HTTPS, PGP) and the server/drive is configured to store data regulated by HIPAA	*No*
Name (URL) of website (e.g. http://remote.sponsor.com/project name)	
Paper documents will shipped using trackable method.	*NA, paper documents will not be shipped*
Data encrypted on an individual use device and shipped using trackable method. Password to the encrypted data transmitted separately.	*NA, data will not be shipped on an individual use device*
Data faxed to a receiving machine in a restricted-access location. The intended recipient is clearly indicated, alerted to the pending transmission and available to pick up immediately.	*NA, data will not be faxed*

DATA SENSITIVITY

When paired with health information, any of the below data elements are considered Highly Sensitive Data by UVA's Data Protection policy (https://uvapolicy.virginia.edu/policy/IRM-003). Please note that Social Security Numbers, Driver's license numbers, passport numbers, financial account numbers, and credit card numbers are considered Highly Sensitive Data regardless of whether or not they are paired with health information.

1. **Name**
2. **Postal address, other than town or city, state, and zip code (e.g. street name or GPS information.)**
3. **Telephone numbers**
4. **Fax numbers**
5. **Electronic mail addresses**
6. **Social Security Numbers**
7. **Medical Record Numbers**
8. **Health plan beneficiary numbers**
9. **Account numbers (e.g. bank numbers, credit card numbers, hospital bill account number)**
10. **Certificate/license numbers (e.g. passport number, driver's license number, medical board license number)**
11. **Vehicle identifiers and serial numbers, including license plate numbers**
12. **Device identifiers and serial numbers**
13. **Web Universal Resource Locators (URLs)**
14. **Internet Protocol (IP) address numbers**
15. **Biometric identifiers, including finger and voice prints**
16. **Full face photographic images and any comparable images**

DATA SECURITY STUDY TEAM

NOTES

UVA Health Information Security Review

The data protection measures and privacy plan as described in this data security document (named: "Untitled attachment 00014_Approval262022.docx") are compliant with UVA data protection standards and guidelines and are approved by UVA Health Information Security (UVA Health InfoSec).

Please remember that data security and compliance with federal and state laws and University policies require continuous vigilance.

Date: 1/26/2022

SN #:

UVA Health InfoSec

Michael Gray mag2z@hscmail.mcc.virginia.edu

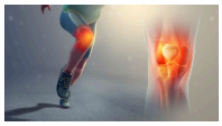
Desk Phone: 4348253126

Senior IT Security Analyst

UVA Health InfoSec at the 2211 Hydraulic Road, Charlottesville, VA 22901

v. Recruitment

HAVE YOU HAD ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION (ACLR) AND ARE EXPERIENCING LINGERING MUSCLE WEAKNESSES?



The Exercise and Sport Injury Laboratory is seeking individuals between 15 and 64 years of age that are having muscle weakness following an ACLR for participation in a research study.

- The purpose of this research study is to investigate the effects of blood flow restriction therapy on muscle strength deficits in patients post-ACLR compared to a control condition.
- This study will require:
  - A baseline assessment of muscle strength and patient reported questionnaires.
    - Randomization into one of two groups: blood flow restriction therapy vs. control
  - Participants in the blood flow restriction therapy group will meet 2 times per week for 4 weeks of treatment. Each session will take approximately an hour and consist of 5 lower extremity exercises with blood flow restriction therapy.
    - Participants in both groups will receive weekly online physical activity questionnaires to assess their amount of participation in physical activity outside of the study.
  - Two follow-up assessments: 1) within one week of completing the intervention program, 2) one month after completing the intervention program

The visits will be conducted in the Exercise and Sport Injury Laboratory at the University of Virginia.

For more information, please contact:

Stephanie Stephens
sls4fe@virginia.edu

or call the Exercise and Sport Injury Laboratory:
434-924-6184

UVA Study Tracking #: *HSR210507* **Principal Investigator:** *Dr. Susan Saliba*

HAVE YOU HAD ACL SURGERY?

We're recruiting research participants between 15-64 years of age!

For more information, please contact:

Stephanie Stephens
sls4fe@virginia.edu
434-924-6184

Study Location: Exercise and Sport Injury Lab
UVA Study Tracking #: HSR210507
Principal Investigator: Dr. Susan Saliba

UNIVERSITY OF VIRGINIA EXERCISE & SPORT INJURY LAB

The purpose of this study is to investigate the effects of blood flow restriction therapy (BFRT) on muscle strength in patients post-ACLR.

Study Requirements:

1) Baseline assessment (1-1.5 hour)
   - Strength testing
   - Questionnaires

2) Random group assignment
   - BFRT group vs. Control group

3) BFRT program *(*BFRT Group Only*)*
   - 2 sessions of BFRT per week for 4 weeks (1 hour each)

4) Weekly online physical activity questionnaires (5 min each)

5) Follow-up assessments (30-45 min)
   1. One week post-intervention
   2. One month post-intervention

Table C3. Questionnaire and Patient Reported Outcome Measures

Table C3a. Modified Tegner Activity Scale

Modified Tegner Activity Level Scale

Please indicate in the space below the HIGHEST level of activity that you CURRENTLY participate in.

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, etc.
Level 8	Competitive sports- racquetball, squash or badminton, track and field athletics (jumping, etc.), downhill skiing, etc.
Level 7	Competitive sports- tennis, running, motorcars speedway, handball Recreational sports- soccer, football, rugby, bandy, ice hockey, basketball, squash, racquetball, running, MTB, dancing, etc.
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 backpack or hike
Level 1	Work- sedentary (secretarial, etc.)
Level 0	Sick leave or disability pension because of lower extremity problems

Table C3b. Tegner Activity Scale

TEGNER ACTIVITY 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.), downhill 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 backpack or hike
Level 1	Work – sedentary (secretarial, etc.)
Level 0	Sick leave or disability pension because of knee problems

Table C3c. Godin Leisure-Time Exercise Questionnaire

Godin Leisure-Time Exercise Questionnaire

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

	Times Per Week
a) STRENUOUS EXERCISE (HEART BEATS RAPIDLY) (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long-distance bicycling)	_____
b) MODERATE EXERCISE (NOT EXHAUSTING) (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____
c) MILD EXERCISE (MINIMAL EFFORT) (e.g., yoga, archery, fishing from riverbank, bowling, horseshoes, golf, snow-mobiling, easy walking)	_____

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

OFTEN SOMETIMES NEVER/RARELY

* Weekly leisure activity score = (9 × Strenuous) + (5 × Moderate) + (3 × Light)
* Active = ≥ 24, Moderately Active = 23 to 14, Insufficiently Active = < 14

Version Date 2-18-21

Table C3d. International Physical Activity Questionnaire (IPAQ) Short Form

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

Table C3e. Rating of Perceived Exertion (RPE)

0	No Effort
1	Extremely Easy
2	
3	Easy
4	
5	Somewhat Hard
6	
7	Hard
8	
9	Very Hard
10	Maximal Effort

Post- Blood flow Restriction Exercise RPE: _____

Post Low Resistance Exercise RPE:

Table C3f. International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form

2000 IKDC SUBJECTIVE KNEE EVALUATION FORM

Name: First Last **Date:**

Physician: **Date of Injury:**

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

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:

	0	1	2	3	4	5	6	7	8	9	10	
Couldn't perform daily activities	○	○	○	○	○	○	○	○	○	○	○	No limitation in daily activities

CURRENT FUNCTION OF YOUR KNEE:

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

0 IKDC Score

Print Form

Submit

Table C3g. Knee Injury and Osteoarthritis Outcome Score (KOOS)

Koos Knee Survey

Please complete the survey below.

Thank you!

1) Date of Visit _____

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

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

2) S1. Do you have swelling in your knee?
- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Often
- ◯ Always

3) S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?
- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Often
- ◯ Always

4) S3. Does your knee catch or hang up when moving?
- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Often
- ◯ Always

5) S4. Can you straighten your knee fully?
- ◯ Always
- ◯ Often
- ◯ Sometimes
- ◯ Rarely
- ◯ Never

6) S5. Can you bend your knee fully?
- ◯ Always
- ◯ Often
- ◯ Sometimes
- ◯ Rarely
- ◯ Never

Stiffness

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

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

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

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

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

Pain

9) P1. How often do you experience knee pain?

- ◯ Never
- ◯ Monthly
- ◯ Weekly
- ◯ Daily
- ◯ Always

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

10) P2. Twisting/pivoting on your knee

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

11) P3. Straightening knee fully

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

12) P4. Bending knee fully

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

13) P5. Walking on flat surface

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

14) P6. Going up or down stairs

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

15) P7. At night while in bed

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

16) P8. Sitting or lying

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

17) P9. Standing upright

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

Function, daily living

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

18) A1. Descending stairs

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

19) A2. Ascending stairs

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

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

20) A3. Rising from sitting

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

21) A4. Standing

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

22) A5. Bending to floor/pick up an object

- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

23)	A6. Walking on flat surface	◯ None ◯ Mild ◯ Moderate ◯ Severe ◯ Extreme
24)	A7. Getting in/out of car	◯ None ◯ Mild ◯ Moderate ◯ Severe ◯ Extreme
25)	A8. Going shopping	◯ None ◯ Mild ◯ Moderate ◯ Severe ◯ Extreme
26)	A9. Putting on socks/stockings	◯ None ◯ Mild ◯ Moderate ◯ Severe ◯ Extreme
27)	A10. Rising from bed	◯ None ◯ Mild ◯ Moderate ◯ Severe ◯ Extreme
28)	A11. Taking off socks/stockings	◯ None ◯ Mild ◯ Moderate ◯ Severe ◯ Extreme
29)	A12. Lying in bed (turning over, maintaining knee position)	◯ None ◯ Mild ◯ Moderate ◯ Severe ◯ Extreme
30)	A13. Getting in/out of bath	◯ None ◯ Mild ◯ Moderate ◯ Severe ◯ Extreme
31)	A14. Sitting	◯ None ◯ Mild ◯ Moderate ◯ Severe ◯ Extreme
32)	A15. Getting on/off toilet	◯ None ◯ Mild ◯ Moderate ◯ Severe ◯ Extreme

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

33) A16. Heavy domestic duties (movign heavy boxes, scrubbing floors, etc)
- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

34) A17. Light domestic duties (cooking, dusting, etc)
- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

Function, sports and recreational activities

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

35) SP1. Squatting
- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

36) SP2. Running
- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

37) SP3. Jumping
- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

38) SP4. Twisting/pivoting on your injured knee
- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

39) SP5. Kneeling
- ◯ None
- ◯ Mild
- ◯ Moderate
- ◯ Severe
- ◯ Extreme

	Quality of Life	
40)	Q1. How often are you aware of your knee problem?	◯ Never ◯ Monthly ◯ Weekly ◯ Daily ◯ Constantly
41)	Q2. Have you modified your life style to avoid potentially damaging activities to your knee?	◯ Not at all ◯ Mildly ◯ Moderately ◯ Severely ◯ Totally
42)	Q3. How much are you troubled with lack of confidence in your knee?	◯ Not at all ◯ Mildly ◯ Moderately ◯ Severely ◯ Totally
43)	Q4. In general, how much difficulty do you have with your knee?	◯ None ◯ Mild ◯ Moderate ◯ Severe ◯ Extreme
44)	KOOS Symptom Score	_____
45)	KOOS Pain Score	_____
46)	KOOS ADL Score	_____
47)	KOOS Sport Score	_____
48)	KOOS QOL Score	_____
49)	Composite Score	_____ (Just used for Dr. Report)

Table C3h. Tampa Scale for Kinesiophobia (TSK)

TAMPA SCALE FOR KINESIOPHOBIA

	CIRCLE THE NUMBER THAT BEST DESCRIBES YOUR BELIEF FOR EACH STATEMENT BELOW:	STRONGLY DISAGREE	DISAGREE	AGREE	STRONGLY AGREE
1	I'm afraid that I might injure myself if I exercise	1	2	3	4
2	If I were to try to overcome it, my pain would increase	1	2	3	4
3	My body is telling me I have something dangerously wrong	1	2	3	4
4	My pain would probably be relieved if I were to exercise	1	2	3	4
5	People aren't taking my medical condition seriously enough	1	2	3	4
6	My accident has put my body at risk for the rest of my life	1	2	3	4
7	Pain always means I have injured my body	1	2	3	4
8	Just because something aggravates my pain does not mean it is dangerous	1	2	3	4
9	I am afraid that I might injure myself accidentally	1	2	3	4
10	Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening	1	2	3	4
11	I wouldn't have this much pain if there weren't something potentially dangerous going on in my body	1	2	3	4
12	Although my condition is painful, I would be better off if I were physically active	1	2	3	4
13	Pain lets me know when to stop exercising so that I don't injure myself	1	2	3	4
14	It's really not safe for a person with a condition like mine to be physically active	1	2	3	4
15	I can't do all the things normal people do because it's too easy for me to get injured	1	2	3	4
16	Even though something is causing me a lot of pain, I don't think it's actually dangerous	1	2	3	4
17	No one should have to exercise when he/she is in pain	1	2	3	4

Table C3i. Anterior Cruciate Ligament – Return to Sport Index (ACL-RSI)

Acl Rsi

Please complete the survey below.

Thank you!

1) Date of Visit

_____

2) Are you confident that you can perform at your previous level of sport participation?
(0 indicates "Not at all confident" 100 indicates "Fully confident")

○ 0 ○ 10 ○ 20 ○ 30 ○ 40 ○ 50 ○ 60 ○ 70 ○ 80 ○ 90 ○ 100

3) Do you think you are likely to re-injure your knee by participating in your sport?
(0 indicates "Extremely likely" 100 indicates "Not likely at all")

○ 0 ○ 10 ○ 20 ○ 30 ○ 40 ○ 50 ○ 60 ○ 70 ○ 80 ○ 90 ○ 100

4) Are you nervous about playing your sport?
(0 indicates "Extremely nervous" 100 indicates "Not nervous at all")

○ 0 ○ 10 ○ 20 ○ 30 ○ 40 ○ 50 ○ 60 ○ 70 ○ 80 ○ 90 ○ 100

5) Are you confident that your knee will not give way by playing your sport?
(0 indicates "Not at all confident" 100 indicates "Fully confident")

○ 0 ○ 10 ○ 20 ○ 30 ○ 40 ○ 50 ○ 60 ○ 70 ○ 80 ○ 90 ○ 100

6) Are you confident that you could play your sport without concern for your knee?
(0 indicates "Not at all confident" 100 indicates "Fully confident")

○ 0 ○ 10 ○ 20 ○ 30 ○ 40 ○ 50 ○ 60 ○ 70 ○ 80 ○ 90 ○ 100

7) Do you find it frustrating to have to consider your knee with respect to your sport?
(0 indicates "Extremely frustrating" 100 indicates "Not at all frustrating")

○ 0 ○ 10 ○ 20 ○ 30 ○ 40 ○ 50 ○ 60 ○ 70 ○ 80 ○ 90 ○ 100

8) Are you fearful of re-injuring your knee by playing your sport?
(0 indicates "Extremely fearful" 100 indicates "No fear at all")

○ 0 ○ 10 ○ 20 ○ 30 ○ 40 ○ 50 ○ 60 ○ 70 ○ 80 ○ 90 ○ 100

9) Are you confident about your knee holding up under pressure?
(0 indicates "Not at all confident" 100 indicates "Fully confident")

◯ 0 ◯ 10 ◯ 20 ◯ 30 ◯ 40 ◯ 50 ◯ 60 ◯ 70 ◯ 80 ◯ 90 ◯ 100

10) Are you afraid of accidentally injuring your knee by playing your sport?
(0 indicates "Extremely afraid" 100 indicates "Not at all afraid")

◯ 0 ◯ 10 ◯ 20 ◯ 30 ◯ 40 ◯ 50 ◯ 60 ◯ 70 ◯ 80 ◯ 90 ◯ 100

11) Do thoughts of having to go through surgery and rehabilitation prevent you from playing your sport?
(0 indicates "All of the time" 100 indicates "None of the time")

◯ 0 ◯ 10 ◯ 20 ◯ 30 ◯ 40 ◯ 50 ◯ 60 ◯ 70 ◯ 80 ◯ 90 ◯ 100

12) Are you confident about your ability to perform well at your sport?
(0 indicates "Not at all confident" 100 indicates "Fully confident")

◯ 0 ◯ 10 ◯ 20 ◯ 30 ◯ 40 ◯ 50 ◯ 60 ◯ 70 ◯ 80 ◯ 90 ◯ 100

13) Do you feel relaxed about playing your sport?
(0 indicates "Not at all relaxed" 100 indicates "Fully relaxed")

◯ 0 ◯ 10 ◯ 20 ◯ 30 ◯ 40 ◯ 50 ◯ 60 ◯ 70 ◯ 80 ◯ 90 ◯ 100

14) ACL-RSI Score

_____

Table C3j. Exercise Adherence Rating Scale (EARS)

Ears

Please complete the survey below.

Thank you!

Date of Visit	_____
Exercise Adherance Rating Score	
Did you perform any exercise specifically for your knee after your surgery?	◯ Yes ◯ No
Are you currently attending physical therapy in a formal clinic setting?	◯ Yes ◯ No
How many times per weeks are you attending?	◯ 1 time per week ◯ 2 times per week ◯ 3+ times per week ◯ 1-2 times per month
When did you stop attending physical therapy?	_____
Are you currently attending formal exercise classes and training sessions with any of the following healthcare providers: Fitness Trainers / Instructors Athletic Trainer Strength / Conditioning Coaches Other	◯ Yes ◯ No
Which type of healthcare provider are you seeing?	☐ Fitness Trainers / Instructors ☐ Athletic Trainer ☐ Strength / Conditioning Coaches ☐ Other
If Other please list:	_____
When did you start training sessions with this provider?	_____
How many times per week are you attending?	◯ 1 time per week ◯ 2 times per week ◯ 3+ times per week ◯ 1-2 times per month

Healthcare providers normally recommend that people do exercises and/or activities to improve their quality of life and manage their condition. People often find their own way of doing their exercises/activities. We would like you to tell us how you do yours.

What exercise/activity have you been asked to do?	☐ Group exercise sessions ☐ Individualized exercises to do at home, as recommended by a healthcare professional ☐ Strength training / circuit training with body weight, free weight or machine weight ☐ Walking/Running/Biking/Elliptical/Other aerobic exercises ☐ Exercises requiring jumping or hopping on two legs or one leg or running /cutting activities required to play sport ☐ Staying active in your daily life
Please rank from 1 to 6 all that apply. 1 being most frequent to 6 least frequently performed. If you do not perform a task described below, just leave it blank. __ Group exercise sessions __ Individualized exercises to do at home, as recommended by a healthcare professional __ Strength training / circuit training with body weight, free weight or machine weight __ Walking/Running/Biking/Elliptical/Other aerobic exercises __ Exercises requiring jumping or hopping on two legs or one leg or running /cutting activities required to play sport __ Staying active in your daily life Example Answer Format: 1 strength training, 2 Group exercise, 3 Staying active in your daily life, etc.	_____ (1 being most frequent to 6 least frequently performed)
If you have been going to physical therapy, performing exercises at home, or seeing another healthcare provider, which of the following exercises have you been doing?	☐ Knee Extensions on a machine or with weights ☐ Exercises such as squats, step ups, lunges ☐ Exercises requiring jumping or hopping on two legs or one leg, or running and cutting activities as required when playing sports
Knee Extensions: If Yes: when did you start?	_____
Knee Extensions: Are you still doing them?	◯ Yes ◯ No
Knee Extensions: How many times per week?	_____
Exercises such as squats, step ups, lunges: If Yes: when did you start?	_____

Exercises such as squats, step ups, lunges: Are you still doing them?	◯ Yes ◯ No
Exercises such as squats, step ups, lunges: How many times per week?	_____
Exercises requiring jumping or hopping on two legs or one leg, or running and cutting activities as required when playing sport: If Yes: when did you start?	_____
Exercises requiring jumping or hopping on two legs or one leg, or running and cutting activities as required when playing sports: Are you still doing them?	◯ Yes ◯ No
Exercises requiring jumping or hopping on two legs or one leg, or running and cutting activities as required when playing sports. How many times per week?	_____
How often have you been asked to do these exercies and/or activities?	◯ Every day ◯ 4 to 6 days a week ◯ 2 to 3 days a week ◯ 1 day a week ◯ Less than this ◯ Other
Other (Fill in): ____	_____
For how long have you been asked to continue doing these exercises and/or activities?	◯ Ongoing ◯ For a fixed duration ◯ Other
For a fixed duration (please specify): _____	_____
Other (please state): _____	_____
How often are you doing these exercies and/or activities?	◯ Every day ◯ 4 to 6 days a week ◯ 2 to 3 days a week ◯ 1 day a week ◯ Not at all
Have you stopped doing your exercises/activites?	◯ Yes ◯ No

If you have stopped doing your exercises/activities, when did you stop?	_____
Why did you stop?	_____
I do my exercises as often as recommended	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Disagree
I forget to do my exercises	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Disagree
I do less exercise than recommended by my healthcare professional	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Disagree
I fit my exercises into my regular routine	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Disagree
I don't get around to doing my exercises	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Disagree
I do most, or all, of my exercises	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Disagree
For each of the following 10 statements, please tick the box which best describes why you do or don't do your recommended exercises/activities.	
I don't have time to do my exercises	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Completely Disagree
Other commitments prevent me from doing my exercises	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Completely Disagree

I don't do my exercises when I am tired	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Completely Disagree
I feel confident about doing my exercises	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Completely Disagree
My family and friends encourage me to do my exercises	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Completely Disagree
I do my exercises to improve my health	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Completely Disagree
I do my exercises because I enjoy them	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Completely Disagree
I adjust the way I do my exercises to suit myself	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Completely Disagree
I stop exercising when my pain is worse	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Completely Disagree
I'm not sure how to do my exercises	◯ Completely Agree ◯ Somewhat Agree ◯ Neutral ◯ Somewhat Disagree ◯ Completely Disagree
EARS Section B Score:	_____
EARS Section C Score:	_____

Table C3k. Global Rating of Change Scale

Global Rating of Change

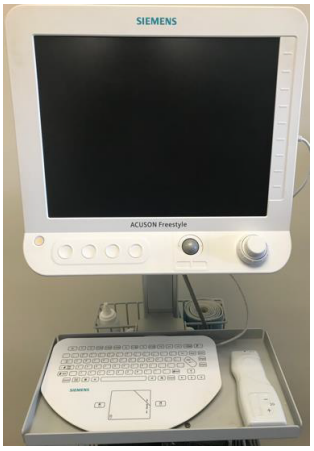
With respect to your ACL injury, please rate the overall condition of your injured limb from the time that you began this study until now. (Select one)

(+7) A very great deal better		(-7) A very great deal worse
(+6) A great deal better		(-6) A great deal worse
(+5) Quite a bit better		(-5) Quite a bit worse
(+4) Moderately better	About the same	(-4) Moderately worse
(+3) Somewhat better	(0)	(-3) Somewhat worse
(+2) A little bit better		(-2) A little bit worse
(+1) A tiny bit better		(-1) A tiny bit worse

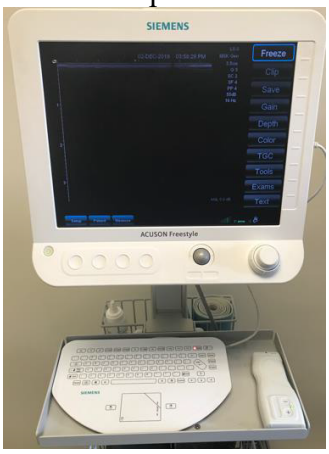
Table C4. Laboratory Measures

Table C4a. Ultrasound Imaging

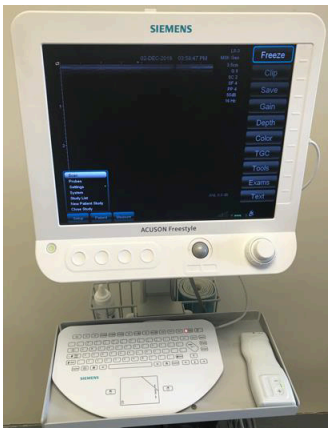
1. Ultrasound System Setup
    a. On Siemens Acuson Freestyle ultrasound unit monitor, press the power button on the left side of the lower panel.
    b. Once blank scanning screen appears (after startup of system), remove the 8-3MHz linear transducer from the holding area on the back of the monitor.
    c. Insert a battery pack into the back of the linear transducer and power on with two fingers pressed simultaneously on the + and – buttons on the transducer. An auditory chiming sound will ring as the transducer powers on.
    d. Check that Bluetooth is operating with a battery indicator on the lower right of the screen with a "P" for probe.



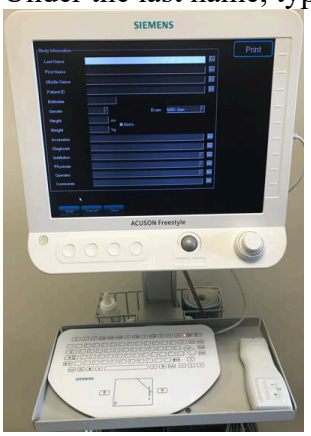
2. New Participant File Setup
    a. Press "Setup" tab on bottom of screen.



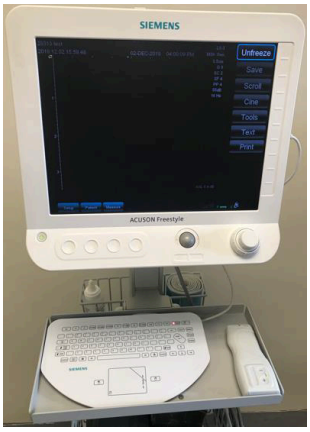
    b. Press "New Patient Study" on the setup menu.



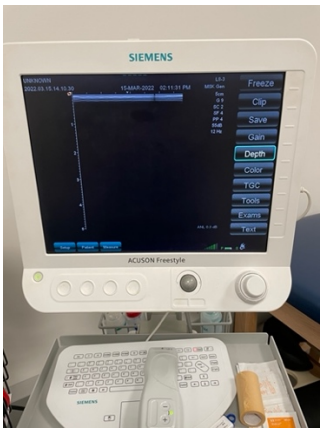
c. Under the last name, type “Subject#” and press save.



d. Select the “Scan” button and the unit is ready for ultrasound image collection.

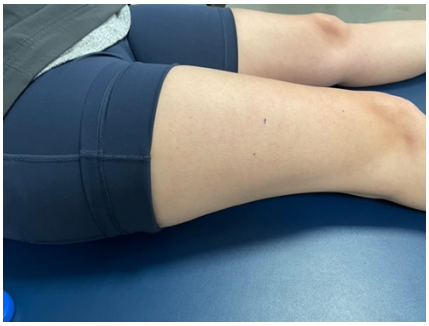


e. Select the “Depth” button and increase depth to 5-6cm.

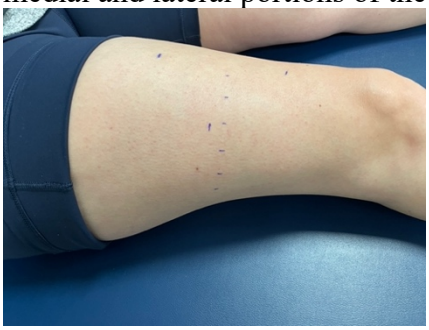


f. Ensure that the correctly named file appears in the top left-hand corner of the screen prior to saving the first image.

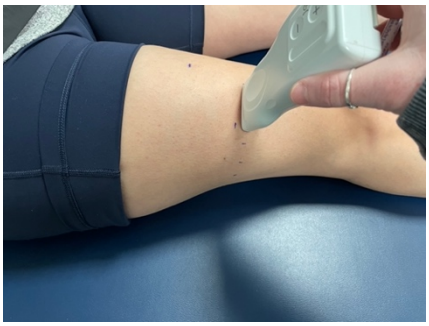
3. Vastus Lateralis Reference Location
    a. Place patient in a supine position on a treatment table.
    b. Measure the distance from the greater trochanter of the femur to the superior-lateral pole of the patella, and mark the distal 1/3 of this distance as the reference location.



4. Vastus Lateralis Cross-Sectional Area
    a. Transversely mark the skin every 2cm from the reference location towards the medial and lateral portions of the thigh (5-6 marks total).

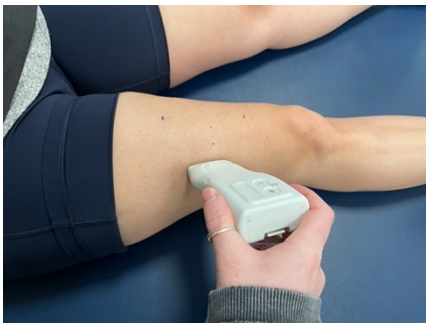


    b. Place ultrasound gel on the ultrasound transducer and over the transverse marks.
    c. Align the superior edge of the ultrasound transducer with the lateral side of each mark and capture images sequentially in a medial to lateral direction.



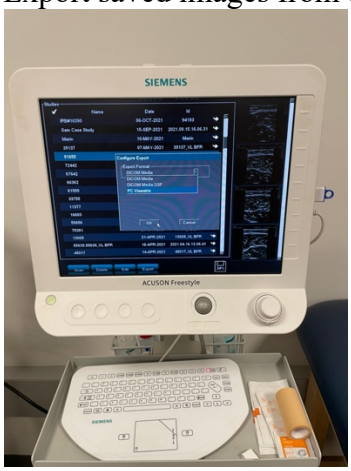
d. Save each image by pressing the “Save” button.
e. Once saved, subsequent images can be taken.

5. Vastus Lateralis Thickness
    a. Place ultrasound gel on the ultrasound transducer and over the reference location.
    b. Place the linear transducer parallel to muscle fiber orientation at the marked reference location.



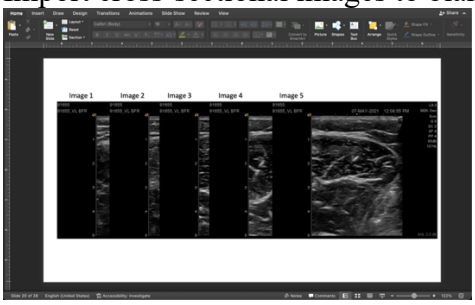
    c. Save each image by pressing the “Save” button.
    d. Once saved, subsequent images can be taken.

6. Cross-Sectional Area Image Reconstruction
    a. Export saved images from the Siemens Acuson Freestyle ultrasound unit.



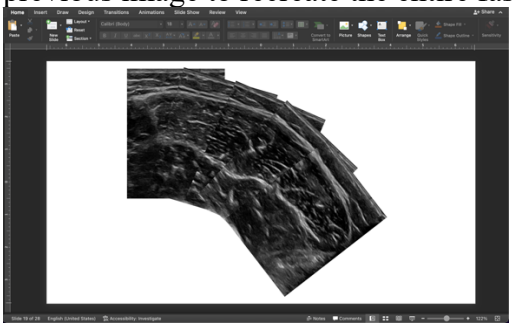
    b. Open Microsoft PowerPoint application.

c. Import cross-sectional images to blank PowerPoint slide.



d. Crop each cross-sectional image to remove borders.

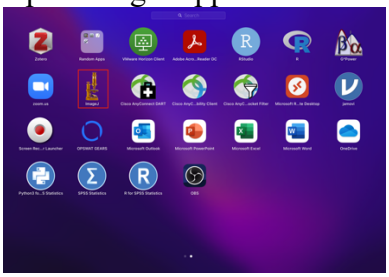
e. Starting with the most medial image, rotate and align the fascial border of the previous image to recreate the entire fascial border of the vastus lateralis.



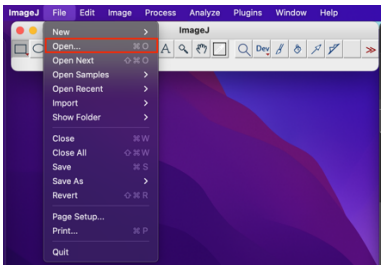
f. Group aligned images and save as new image.

7. Image Processing

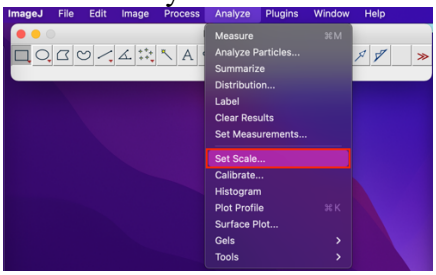
a. Open ImageJ application.



b. Select “File” tab and “Open”.

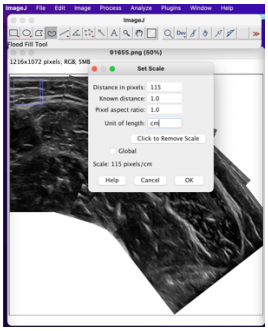


c. Select “Analyze” tab and “Set Scale”.



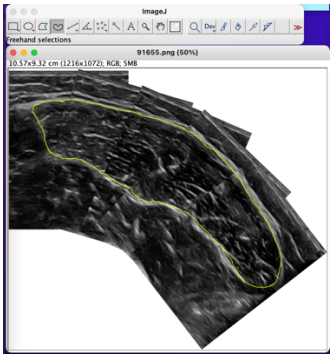
i. Set scale based on known distance in pixels.
   1. 6cm depth: 1cm → 95 pixels
   2. 5cm depth: 1cm → 115 pixels
   3. Known distance = 1.0, pixel aspect ratio = 1.0, unit of length = cm

ii. Select “OK”.



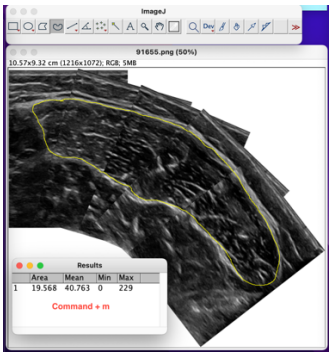
d. Select Segment tool on main toolbar to measure thickness image, or select Freehand tool on main toolbar to measure cross-sectional area image.

e. Measure image (i.e., outline fascial border to measure cross-sectional area or select distance between fascial borders to measure muscle thickness).



f. Once the image is measured, click command + M.

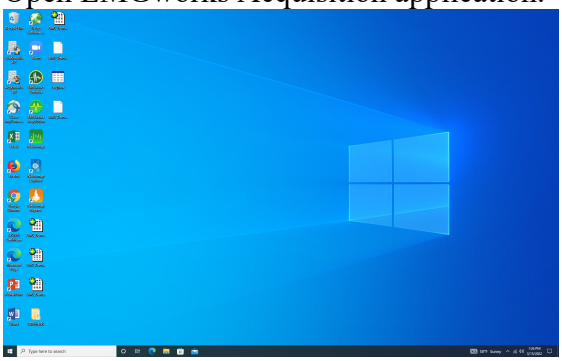
g. Measurement window will appear with area, max, min, length, etc.



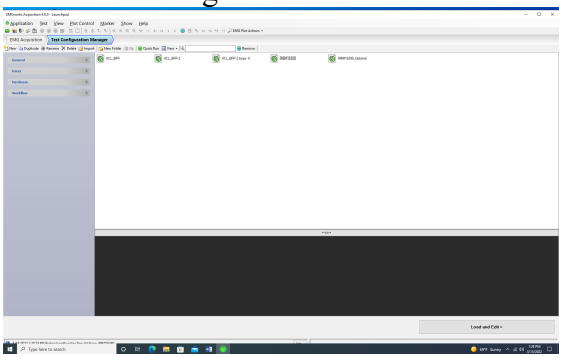
h. Screenshot measured image with the results window, and save as new image with "_m" following the previous image name.
i. Open next image and repeat.

Table C4b. Electromyographic Signaling (Trigno Galileo Sensor)

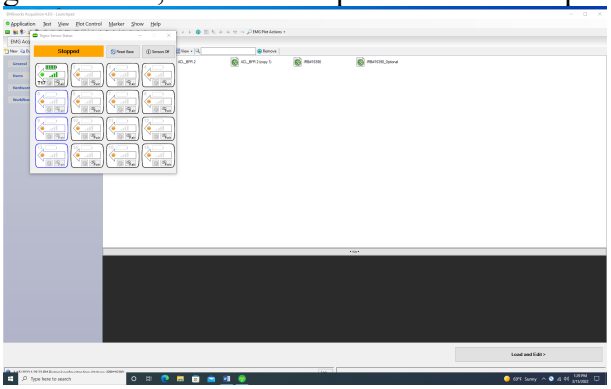
1. EMGworks Acquisition Setup
    a. Open EMGworks Acquisition application.



    b. Select the configuration file.

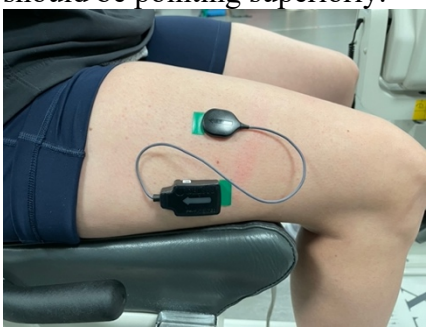


    c. To power on the sensors, take the Galileo sensors out of the base station and while the LED arrow is illuminated touch magnet to top of sensor along the white arrow.
    d. Select “Trigno Control Utility” button”.
    e. Select “Pair” for sensor one, touch the magnet to the top of the senor along the green arrow, and confirm pair on the desktop. Repeat this step for sensor two.

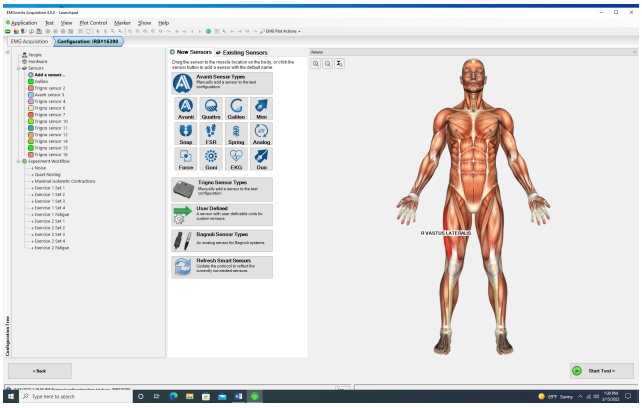


    f. Once each sensor is powered on and paired it can be secured to the prepared measurement location.
    g. For active head electrode placement, apply adhesives and align the black arrow on the posterior side of the electrode with muscle fiber orientation over the prepared measurement location. The black arrow should be pointing superiorly towards the origin of the muscle.

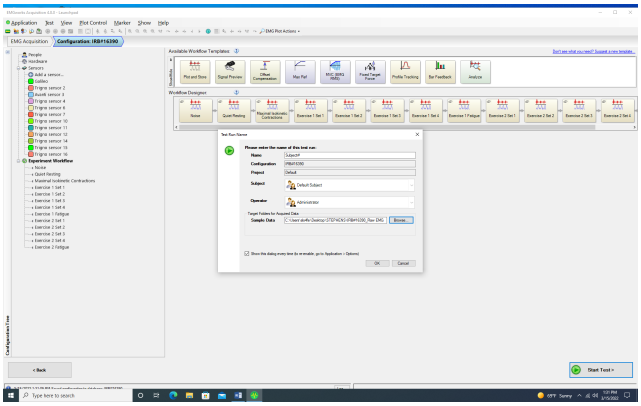
h. For reference body electrode placement, apply adhesives and align the blinking green arrow over the iliotibial band (inactive tissue). The green arrow should be pointing superiorly.



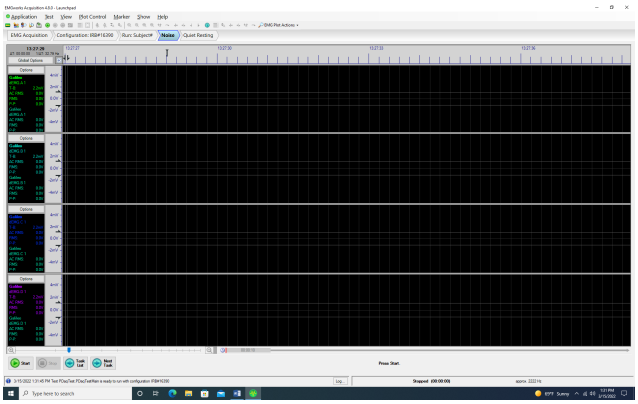
2. EMG Data Collection
   a. Select the green “Start” button in the lower right corner of the application window.



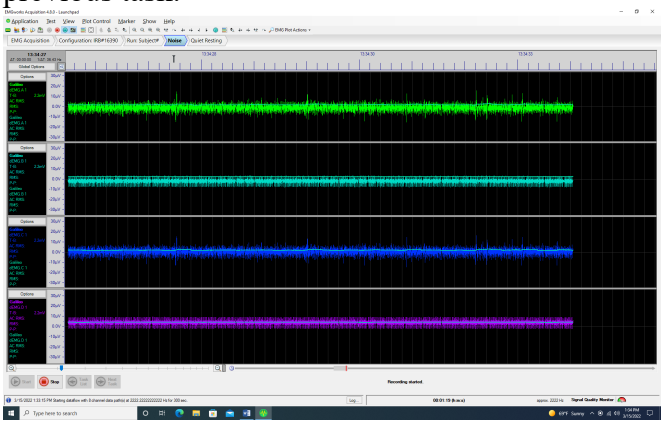
   b. Enter the patient ID# and set file path.
   c. Select “Start Test”.



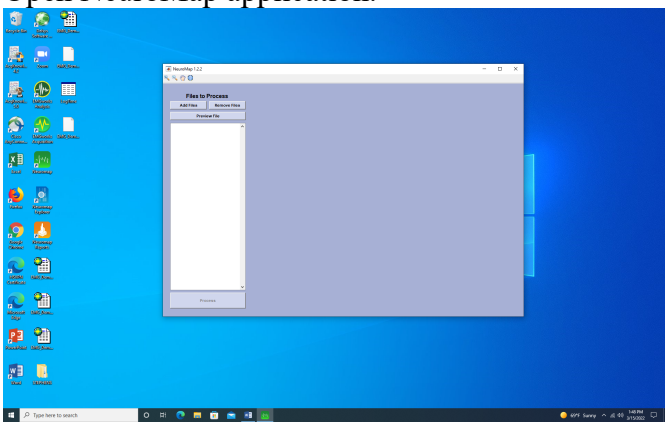
   d. Select and hold the y-axis and press F5 on the key to zoom in on the graphs (F6 to zoom out).
   e. Select “Start” to begin preset trial.



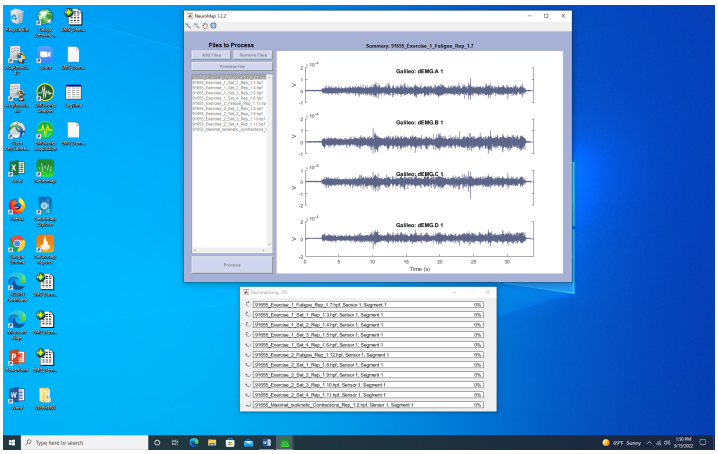
f. Select “Next Task” to advance to next task or select “Start” again to repeat the previous task.



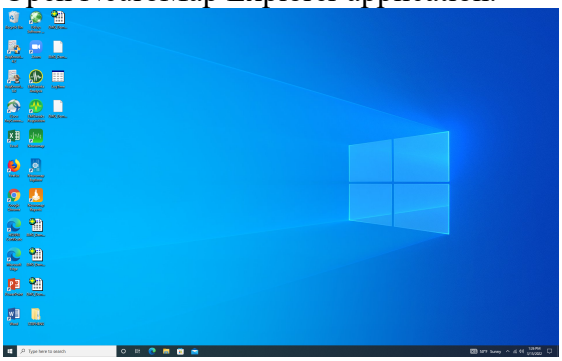
3. EMG Data Decomposition
    a. Ensure “Sleep Mode” is disabled on the PC.
    b. Open NeuroMap application.



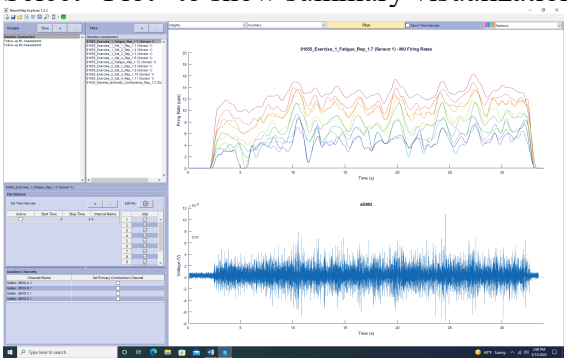
    c. Select “Add Files”.
    d. Select files to decompose.
    e. Select “Process”.



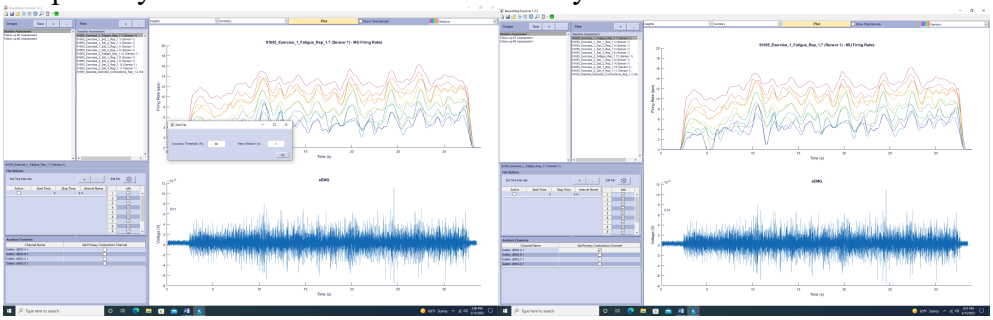
4. EMG Decomposed Data Visualization and Exportation
    a. Open NeuroMap Explorer application.



    b. Select “+” to open decomposed files.
    c. Select “Plot” to show summary visualization.



    d. Set primary contraction channel and accuracy threshold.



    e. Select “Export” button to export decomposed data as text files.

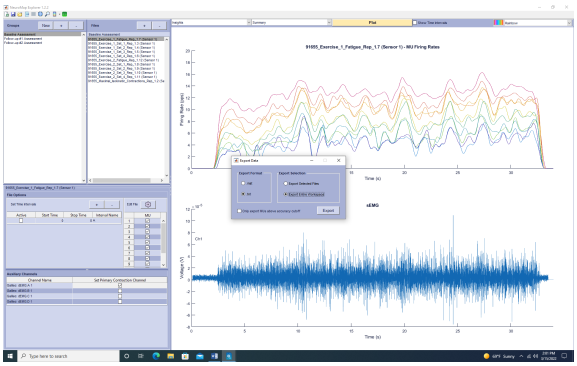
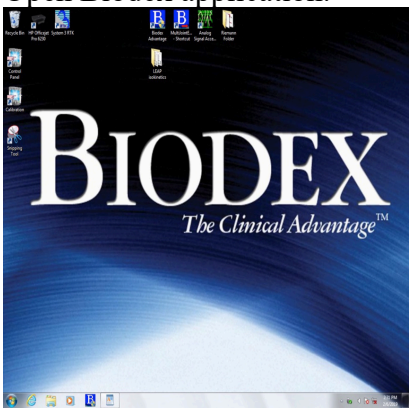

Export Data
sEMG

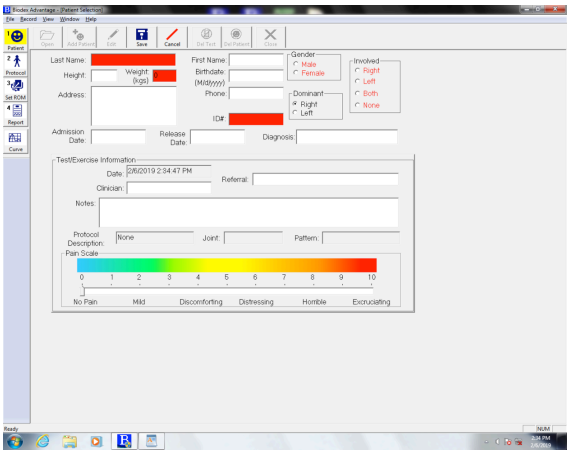
Table C4c. Isokinetic and Isometric Torque

1. Biodex Setup
    a. Turn on Biodex.
    b. Wait for Biodex calibration to occur.
    c. Position the back of the chair to 80 degrees.
    d. Attach limb being assessed.

2. Computer Setup
    a. Open Biodex application.



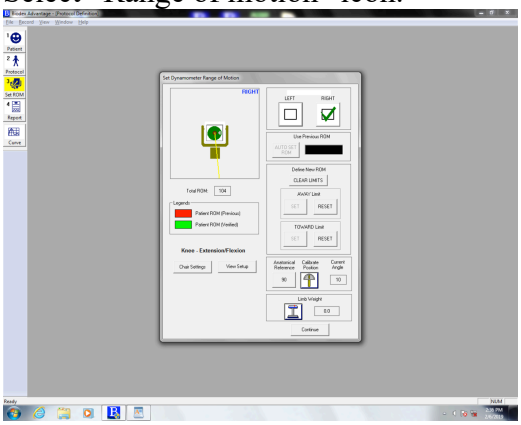
    b. Select “Patient” icon.



    c. Enter in patient demographics.
    d. Select “Protocol” icon.
        i. Select preestablished protocol based on the desired strength assessment.
            1. Manuscript 1 Protocols:
                a. Isokinetic Unilateral→ Knee→ CON/CON: TEST: 120/120 (VL_BFR_Max)
                b. Isokinetic Unilateral→ Knee→ CON/CON: TEST: 120/120, 120/120, 120/120, 120/120 (VL_BFR_Exercise)
                c. Isometric Unilateral→ Knee→ AWAY: TEST: 90 (VL_BFR_Fatigue)
            2. Manuscript 2 Protocols:

a. Isokinetic Unilateral→ Knee→ CON/CON: TEST: 90/90, 180/180 (LEAP_Isokinetic_90_180)

e. Select “Range of motion” icon.

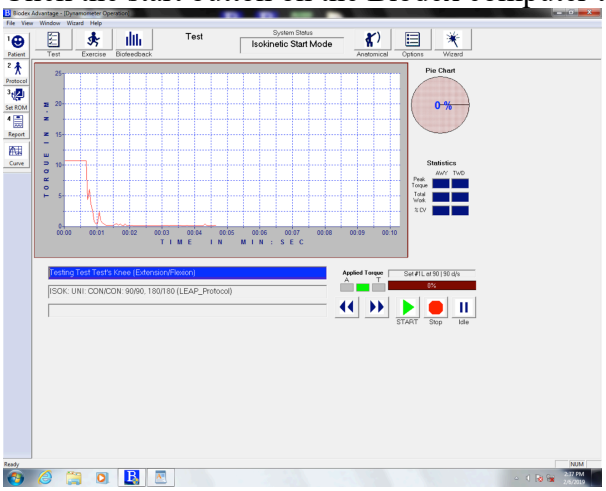


i. Select the appropriate side “Left” / “Right”.
ii. Click “Define New Range” | “Clear”.
iii. Attach magnetic goniometer to the arm of the limb attachment.
iv. Extend the patient’s knee to 0 degrees of extension | Press “Hold” button.
v. Select “Away” on Biodex computer | Press “Hold” button.
vi. Flex the patient’s knee to 70 degrees of flexion | Press “Hold” button.
vii. Select “Towards” on the Biodex computer | Press “Hold” button.
viii. Place the patient’s knee in 90 degrees of flexion (Neutral) | Press “Hold” button.
ix. Select “Position” on the Biodex computer | Press “Hold” button.
x. Extend the patient’s knee to 0 degrees of extension | Press “Hold” button.
xi. Ask the patient to relax their leg.
xii. Select “limb weight” on the Biodex computer.
xiii. Select “Continue” on the Biodex computer.
xiv. Select “Start” on the Biodex computer to begin testing.

3. Patient Preparation
   a. Position the Patient in the Biodex Chair.
   b. Move the back of the chair so that ~5 cm of the patient’s thigh overhang the edge of the chair.
   c. Move chair forward/backward so that the lateral epicondyle aligns with the axis of rotation of the Biodex.
   d. Move chair up/down so that the lateral epicondyle aligns with the axis of rotation of the Biodex.
   e. Flex patient’s knees to 90 degrees.
   f. Restrain the patient with the lap belt and strap distal shank (2 cm above lateral malleolus) to Biodex attachment.
   g. Provide instructions for proper testing procedures:
      i. “Sit up straight with your back against the backrest”
      ii. “Cross your arms across your chest”

iii. “Do not rotate or arch or back”

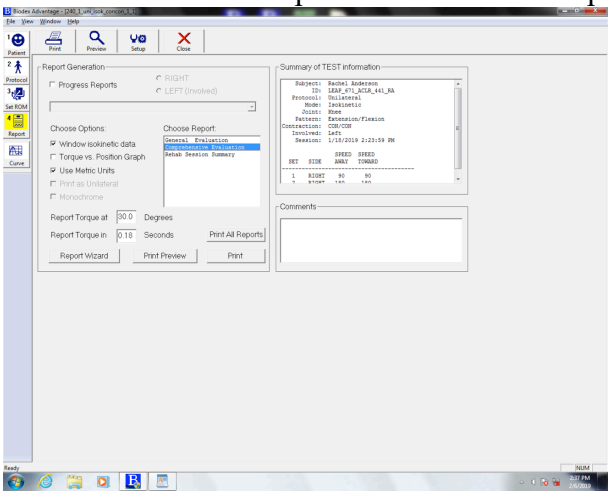
4. Data Collection
    a. Click the start button on the Biodex computer to initiate the assessment.



    b. Manuscript I:
        i. Isokinetic maximal trial:
            1. Inform the patient to perform as many practice trials as necessary until they are familiar with the task.
            2. Patient will perform 3 maximal repetitions at 120 deg/sec.
            3. Select Continue button on the screen.
        ii. Isokinetic submaximal exercise:
            1. Inform the patient to perform as many practice trials as necessary until they are familiar with the task.
            2. Patient will perform 30 repetitions at 20% of their maximal effort and 120 deg/sec.
            3. Patient will rest for 30 seconds.
            4. Patient will perform 15 repetitions at 20% of their maximal effort and 120 deg/sec.
            5. Patient will rest for 30 seconds.
            6. Patient will perform 15 repetitions at 20% of their maximal effort and 120 deg/sec.
            7. Patient will rest for 30 seconds.
            8. Patient will perform 15 repetitions at 20% of their maximal effort and 120 deg/sec.
            9. Select Continue button on the screen.
        iii. Isometric maximal trial:
            1. Patient will perform one maximal isometric knee extension contraction for 30 seconds.
            2. Select Continue button on the screen.
        iv. Repeat isokinetic submaximal exercise and isometric maximal trial under second exercise condition.

c. Manuscript II:
    i. Start with uninvolved limb.
    ii. Inform the patient to perform as many practice trials as necessary until they are familiar with the task.
    iii. Patient will perform 8 repetitions at 90 deg/sec.
    iv. Patient will rest for 30 seconds.
    v. Inform the patient to perform as many practice trials as necessary until they are familiar with the task.
    vi. Patient will perform 8 repetitions at 180 deg/sec.
    vii. Select Continue button on the screen.
    viii. Patient will perform one maximal isometric knee extension contraction for 30 seconds.
    ix. Patient will rest for one minute.
    x. Patient will perform one maximal isometric knee flexion contraction for 30 seconds.
    xi. Select Continue button on the screen.
    xii. Repeat isokinetic and isometric strength testing on involved limb.

5. Data Processing
    a. After each assessment protocol select the “Report” Icon.



    b. Under options, select “Window Isokinetic Data” and “Use Metric Units”.
    c. Under Choose Report, select “Comprehensive Evaluation”.
    d. Select “Print”.
    e. Save as PDF in appropriate folder.

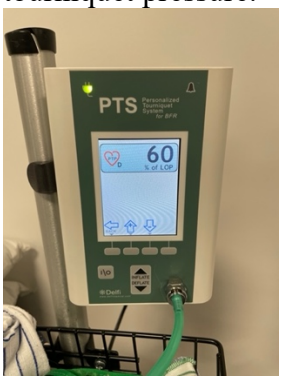
Table C5. Blood Flow Restriction Therapy Program Procedures

Table C5a. Delfi Personalized Tourniquet System

1. System Setup
    a. Turn on Delfi Personalized Tourniquet System.
    b. Allow device to complete self-test and calibration check.

    c. Select the “Settings” gear icon.

    d. Set limb occlusion pressure to 60% of the participant’s personalized tourniquet pressure.



    e. Press “Inflate” (i.e., upward facing arrow) button to begin occlusion.

Table C5b. Exercise Protocol

1. Knee Extension
    a. Patient will be positioned on N-K Exercise Table with hips and knees flexed to 90 degrees.

    b. Patient will extend their involved knee through their full knee range of motion at a controlled pace of 2 seconds into extension and 2 seconds into flexion.

2. Hamstring Curl
    a. Patient will be positioned on N-K Exercise Table with hips flexed to 90 degrees and involved knee starting in full knee extension.

    b. Patient will flex their knee through their full knee range of motion at a controlled pace of 2 seconds into flexion and 2 seconds into extension.

3. Standing Hip Extension
    a. Patient in standing position with weight around lower leg above the ankle and their hands on their hips or wall for stabilization.

    b. Patient will maintain an upright position with full knee extension (no trunk movement).
    c. Patient will extend their involved limb through their full hip extension range of motion at a controlled pace of 2 seconds into extension and 2 seconds into flexion.

4. Standing Hip Abduction
    a. Patient in standing position with weight around lower leg above the ankle, ipsilateral hand on hip, contralateral hand on hip or wall for stabilization.

b. Patient will maintain an upright position with full knee extension (no trunk movement).
c. Patient will abduct their involved limb through their full hip abduction range of motion at a controlled pace of 2 seconds into abduction and 2 seconds into adduction.

5. Leg Press
    a. Patients will be positioned on a Total Gym with an incline of 30 degrees.
    b. Patients will start with their hips flexed to approximately 90 degrees, their involved limb positioned at the midline of the foot plate, and their uninvolved limb positioned on the back rest.

c. Keeping their head and back against the back rest, patients will push up into knee extension of their involved limb and then lower back down into the starting position at a controlled pace of 2 seconds into flexion and 2 seconds into extension.

d. Patients will avoid locking knees into full extension and valgus collapse.

APPENDIX D: ADDITIONAL RESULTS

Manuscript I

Table D1.1. Descriptive statistics: motor unit behavior characteristics by condition and set

		Mean ± SD (n = 25)	
	Exercise set	LL-BFRT	LL
# Motor Units/ AVG Torque ([NMU/(Nm/kg)])	Set 1	34.68 ± 14.51	33.99 ± 13.72
	Set 2	21.50 ± 11.17	17.17 ± 8.07
	Set 3	21.31 ± 10.91	18.78 ± 9.33
	Set 4	21.95 ± 11.73	18.10 ± 10.31
	Isometric Fatigue	10.70 ± 3.42*	6.58 ± 1.89*
Peak MUAP (μV)	Set 1	79.54 ± 50.03	77.74 ± 71.98
	Set 2	91.09 ± 70.99	73.22 ± 59.62
	Set 3	93.01 ± 89.58	66.56 ± 53.03
	Set 4	88.16 ± 83.89	68.84 ± 49.32
	Isometric Fatigue	124.24 ± 97.58*	194.02 ± 170.36*
Average MUAP (μV)	Set 1	63.31 ± 39.30	60.58 ± 52.70
	Set 2	70.94 ± 53.33	57.61 ± 44.41
	Set 3	72.27 ± 68.07	52.75 ± 40.78
	Set 4	67.11 ± 60.49	53.95 ± 38.31
	Isometric Fatigue	96.02 ± 73.10*	150.87 ± 123.17*
Peak firing rate (pps)	Set 1	14.06 ± 2.75	13.54 ± 2.91
	Set 2	12.48 ± 3.06	11.89 ± 2.63
	Set 3	12.51 ± 2.53	12.18 ± 2.30
	Set 4	12.90 ± 2.83	11.77 ± 2.39
	Isometric Fatigue	17.77 ± 3.14*	19.21 ± 2.52*
Average firing rate (pps)	Set 1	4.60 ± 1.27	4.51 ± 1.22
	Set 2	3.99 ± 1.26	3.89 ± 0.98
	Set 3	4.00 ± 1.19	4.07 ± 0.81
	Set 4	4.19 ± 1.20	3.97 ± 1.04
	Isometric Fatigue	10.67 ± 2.43*	13.15 ± 1.89*
Initial firing rate (pps)	Set 1	4.99 ± 1.38	5.37 ± 1.54
	Set 2	4.56 ± 1.27	4.59 ± 1.21
	Set 3	4.50 ± 1.02	4.85 ± 1.31
	Set 4	4.38 ± 1.18	4.65 ± 0.95
	Isometric Fatigue	4.09 ± 1.68*	4.86 ± 1.44*
Terminal firing rate (pps)	Set 1	6.03 ± 1.52	5.96 ± 1.43
	Set 2	6.01 ± 1.36	5.41 ± 1.44
	Set 3	5.54 ± 1.41	5.68 ± 1.30
	Set 4	6.33 ± 1.54	5.81 ± 1.51
	Isometric Fatigue	6.42 ± 1.05*	6.61 ± 0.98*

* Calculated based on a full sample size of n = 28

Table D1.2. Pearson correlations: motor unit recruitment and morphological characteristics

	Variable	CSA	Thickness	Echogenicity	SATT
Accurate number of motor units recruited	Set 1	0.07 0.625	-0.19 0.169	-0.10 0.462	-0.39 0.003
	Set 2	0.11 0.423	-0.04 0.748	-0.04 0.752	-0.44 <0.001
	Set 3	0.11 0.400	-0.07 0.595	-0.04 0.791	-0.56 <0.001
	Set 4	-0.05 0.708	-0.20 0.137	-0.09 0.505	-0.41 0.002
	Isometric trail	-0.20 0.135	-0.16 0.253	0.12 0.363	-0.07 0.626

Manuscript II

Table D2.1. Additional participant demographic information

Group	Participant (#)	MOI	Contact vs. Noncontact	Dominant Limb	Surgical Limb	Meniscal Involvement	Primary ACLR	Returned to Preinjury Level of Activity		Knee Satisfaction	Currently in Formal PT
								Current	Intending		
LL-BFRT	2	Quidditch	Noncontact	Right	Right	Yes	Yes	Yes	-	Yes	No
	3	Swimming	Noncontact	Right	Left	Yes	Yes	No	Yes	No	No
	4	Field Hockey	Noncontact	Right	Left	Yes	Yes	No	Yes	No	Yes, 1 time per week
	7	Lacrosse	Noncontact	Right	Left	No	Yes	Yes	-	No	No
	14	Skiing	Noncontact	Right	Left	No	Yes	No	Yes	No	Yes, 2 times per week
Control	1	Gymnastics	Noncontact	Right	Left	No	Yes	Yes	-	No	No
	9	Soccer	Noncontact	Right	Left	No	Yes	Yes	-	No	No
	10	Gymnastics	Noncontact	Right	Right	No	Yes	Yes	-	Yes	No
	12	Soccer	Noncontact	Right	Left	Yes	No	No	No	Yes	No
	16	Ultimate Frisbee	Noncontact	Right	Left	Yes	Yes	No	Yes	No	Yes, 1 time per week

Table D2.2. Participant goals following ACL injury and surgical reconstruction

Group	Participant (#)	What are your overall goals in regard to your ACL injury and surgical reconstruction?
LL-BFRT	2	"Full participation/contact during club quidditch"
	3	"Reduce knee pain"
	4	"Full recovery and return to sport"
	7	"I want to feel symmetrical and have equal strength in both of my legs"
	14	"Return to sport - skiing, mountain biking, pickleball"
Control	1	"I would like to return to my high level of activity without pain occurring"
	9	"Regain strength balance"
	10	"Return to full participation in gymnastics (previously), and as much full range of motion and stability as possible"
	12	"Enjoy typical daily activities without pain"
	16	"Return to play after passing return to sport testing"

Table D2.3. Qualifying LSI metrics

Group	Participant (#)	Peak Torque for 90 deg/s	Average Peak Torque for 90 deg/s	Peak Torque for 180 deg/s	Average Peak Torque for 180 deg/s	Peak Torque for Isometric
LL-BFRT	2	x	x			
	3				x	x
	4	x	x	x	x	x
	7	x	x			x
	14	x	x	x	x	x
Control	1	x	x	x	x	x
	9	x	x			
	10					x
	12					x
	16	x	x	x	x	x
Total		7	7	4	5	8

Table D2.4. Individual normalized isokinetic knee extension torque and LSI at 90 deg/s

Group	Participant	Time	Peak Torque (Nm/kg)			Average Peak Torque (Nm/kg)		
			INV	UNINV	LSI (%)	INV	UNINV	LSI (%)
LL-BFRT	2	1	1.64	2.15	76.19	1.57	1.97	79.55
		2	1.86	2.19	85.15	1.76	2.00	88.13
		3	1.86	2.32	80.20	1.75	2.17	80.92
	3	1	1.22	1.46	83.02	1.06	1.24	85.74
		2	1.96	1.53	127.82	1.79	1.44	124.42
		3	1.69	1.54	109.44	1.61	1.43	112.77
	4	1	1.40	2.84	49.22	1.26	2.76	45.58
		2	1.56	2.71	57.56	1.46	2.59	56.42
		3	1.78	2.95	60.32	1.62	2.78	58.30
	7	1	1.53	2.32	65.94	1.37	2.11	64.89
		2	2.27	1.89	120.05	2.16	1.74	124.23
		3	2.01	1.93	104.43	1.89	1.70	111.32
	14	1	0.79	1.92	41.08	0.73	1.73	42.30
		2	1.04	1.95	53.32	0.90	1.72	52.48
		3	0.83	2.08	39.97	0.78	1.97	39.61
Control	1	1	1.13	1.67	67.56	1.02	1.49	68.49
		2	1.24	1.79	69.28	1.17	1.64	71.62
		3	1.22	1.81	67.74	1.15	1.65	69.52
	9	1	1.70	2.13	79.85	1.58	1.99	79.32
		2	1.49	2.07	71.82	1.42	1.94	73.17
		3	1.45	1.95	74.34	1.37	1.80	75.79
	10	1	1.62	1.75	92.24	1.49	1.52	98.13
		2	1.65	1.74	94.78	1.50	1.67	90.01
		3	1.63	1.86	87.56	1.48	1.71	86.38
	12	1	1.96	1.98	99.14	1.82	1.78	102.34
		2	2.05	2.06	99.27	1.86	1.89	98.40
		3	2.07	1.96	105.30	1.68	1.69	99.77
	16	1	1.65	2.32	71.07	1.54	2.22	69.48
		2	1.86	2.41	77.24	1.79	2.16	82.82
		3	1.74	2.44	71.18	1.62	2.26	71.73

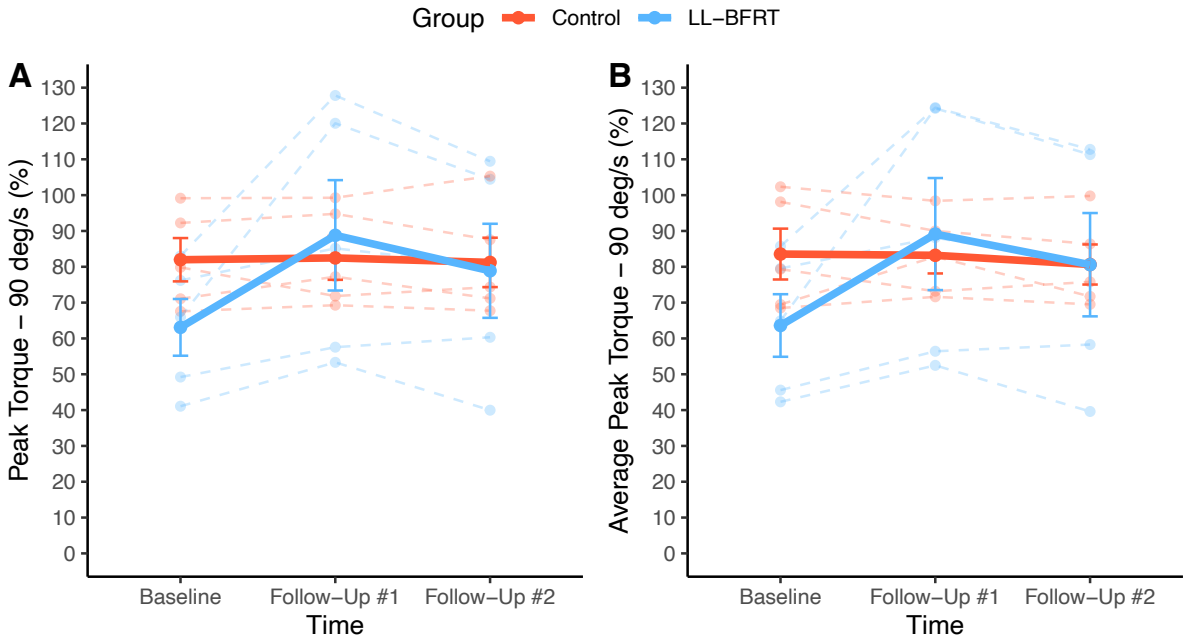
Table D2.5. Individual normalized isokinetic knee extension torque and LSI at 180 deg/s

Group	Participant	Time	Peak Torque (Nm/kg)			Average Peak Torque (Nm/kg)		
			INV	UNINV	LSI (%)	INV	UNINV	LSI (%)
LL-BFRT	2	1	1.20	1.47	81.80	1.09	1.33	82.44
		2	1.24	1.54	80.75	1.12	1.37	82.19
		3	1.22	1.63	74.64	1.15	1.51	76.25
	3	1	1.01	1.26	80.01	0.71	1.08	66.06
		2	1.55	1.38	112.06	1.40	1.24	112.17
		3	1.49	1.28	116.21	1.30	1.19	109.95
	4	1	1.44	1.99	72.47	1.34	1.84	72.89
		2	1.41	2.00	70.59	1.32	1.85	71.02
		3	1.65	2.06	80.25	1.58	1.93	81.42
	7	1	1.72	1.63	105.12	1.49	1.48	101.25
		2	1.86	1.81	102.69	1.66	1.71	97.06
		3	1.68	1.73	97.19	1.57	1.56	100.32
	14	1	0.59	1.37	43.18	0.52	1.20	43.77
		2	0.58	1.47	39.56	0.49	1.32	36.92
		3	0.66	1.63	40.61	0.62	1.41	43.88
Control	1	1	0.84	1.11	75.59	0.77	1.04	73.49
		2	0.97	1.39	69.87	0.90	1.21	74.36
		3	1.05	1.32	79.44	0.95	1.17	81.82
	9	1	1.40	1.64	85.70	1.25	1.48	84.46
		2	1.31	1.63	80.30	1.13	1.42	79.62
		3	1.21	1.51	79.82	1.10	1.34	82.32
	10	1	1.03	1.19	87.02	0.90	1.02	88.71
		2	1.16	1.32	87.64	1.05	1.17	90.18
		3	1.22	1.27	95.72	1.04	1.13	91.96
	12	1	1.58	1.56	101.46	1.39	1.40	99.46
		2	1.62	1.60	101.54	1.39	1.45	95.68
		3	1.67	1.44	116.34	1.47	1.28	115.41
	16	1	1.18	1.62	72.85	1.05	1.45	72.47
		2	1.40	1.67	84.26	1.15	1.48	78.07
		3	1.31	1.75	75.18	1.24	1.57	78.94

Table D2.6. Individual normalized isometric knee extension torque and LSI

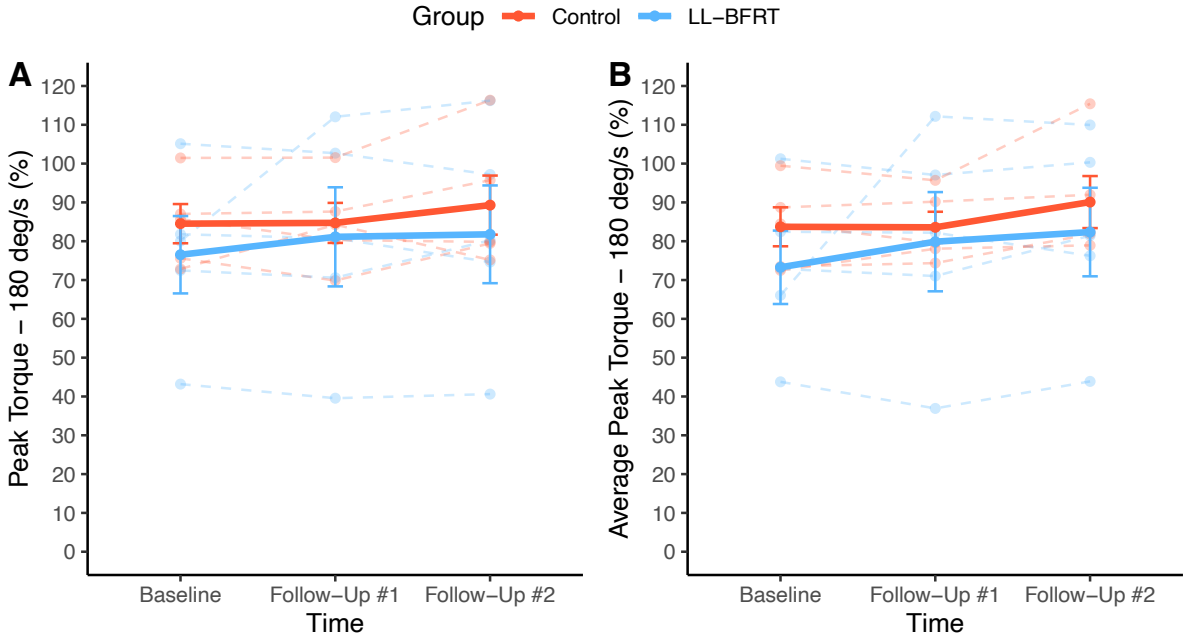
Group	Participant	Time	Peak Torque (Nm/kg)		
			INV	UNINV	LSI (%)
LL-BFRT	2	1	1.18	1.13	103.94
		2	1.13	1.33	85.03
		3	1.14	1.55	73.50
	3	1	0.67	1.29	52.26
		2	1.51	1.11	135.22
		3	1.32	1.32	100.42
	4	1	2.13	4.92	43.32
		2	2.40	4.21	57.02
		3	2.97	4.76	62.38
	7	1	1.68	2.88	58.30
		2	2.01	2.68	75.16
		3	1.95	2.50	77.89
	14	1	0.81	2.15	37.75
		2	0.92	2.68	34.18
		3	0.88	2.63	33.45
Control	1	1	1.34	2.63	50.93
		2	1.42	2.38	59.57
		3	1.48	1.81	81.85
	9	1	2.24	2.52	88.88
		2	1.74	2.39	72.69
		3	1.59	2.37	67.37
	10	1	0.98	1.73	56.92
		2	1.33	1.67	79.98
		3	1.44	1.69	85.08
	12	1	1.66	2.15	77.38
		2	1.48	2.22	66.49
		3	1.28	1.86	68.79
	16	1	1.41	2.87	49.00
		2	1.51	2.29	66.00
		3	1.43	1.82	78.62

Figure D2.1. Limb symmetry index for isokinetic strength testing at 90 °/s ([A] peak knee extension torque, [B] average peak knee extension torque) by group and time.



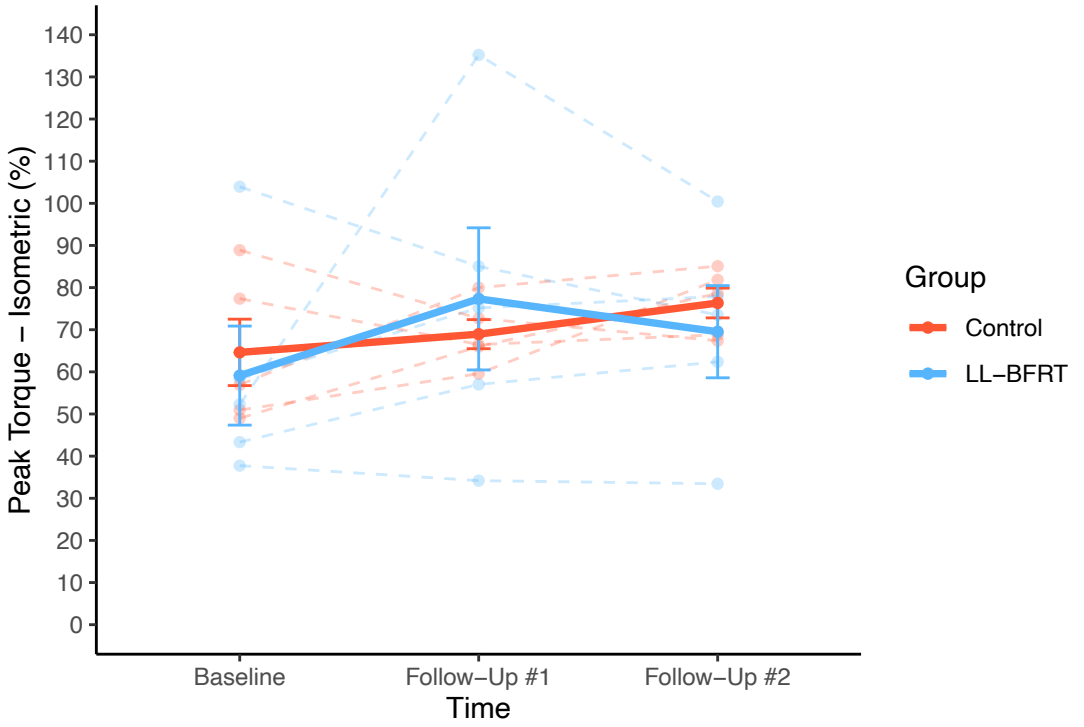
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy

Figure D2.2. Limb symmetry index for isokinetic strength testing at 180 °/s ([A] peak knee extension torque, [B] average peak knee extension torque) by group and time.



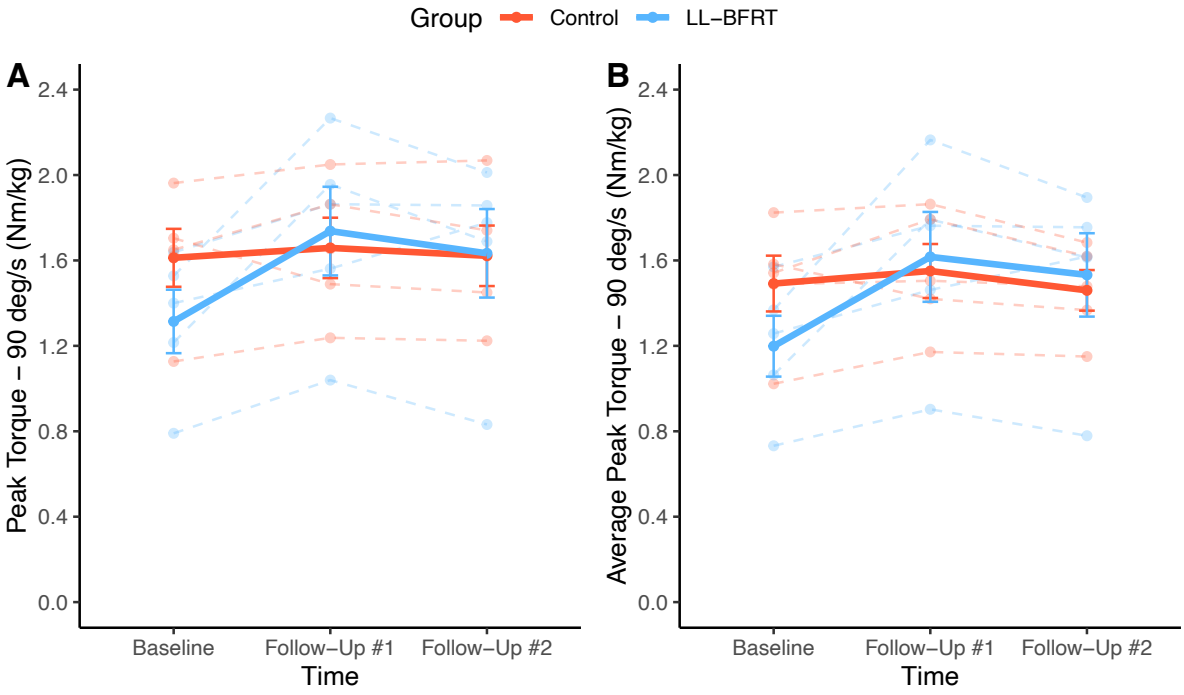
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy

Figure D2.3. Limb symmetry index for peak knee extension torque during isometric strength testing at 90 ° of knee flexion by group and time.



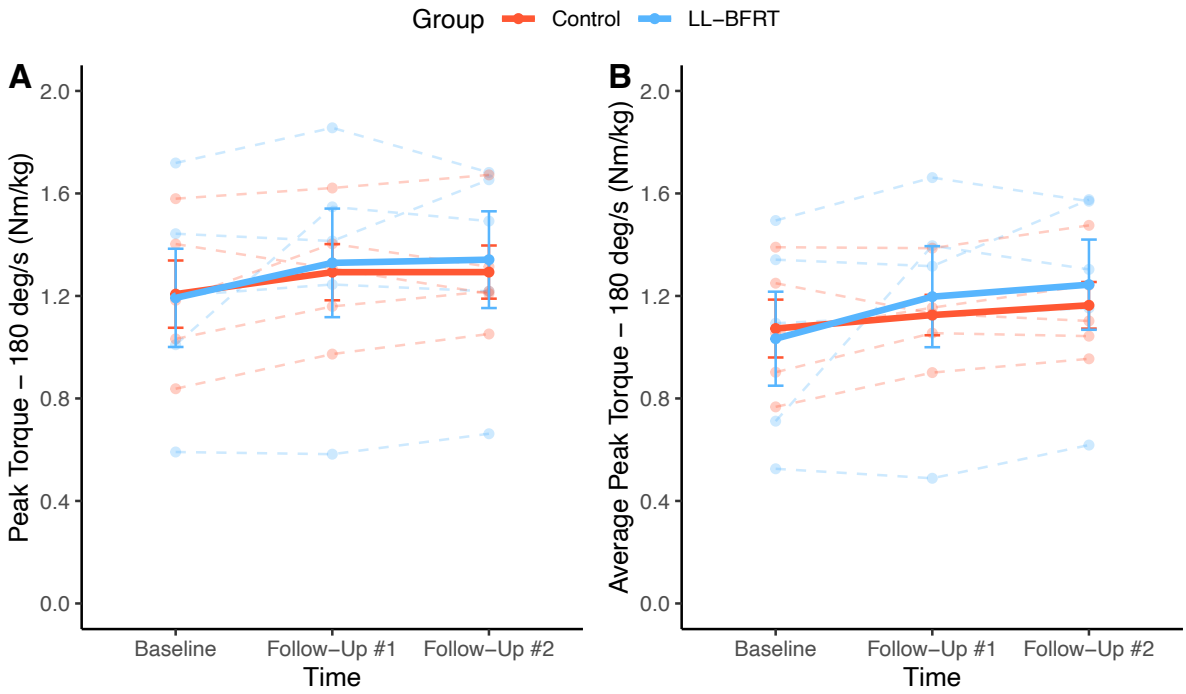
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy

Figure D2.4. Involved limb knee extension strength for isokinetic testing at 90 °/s ([A] peak knee extension torque, [B] average peak knee extension torque) by group and time.



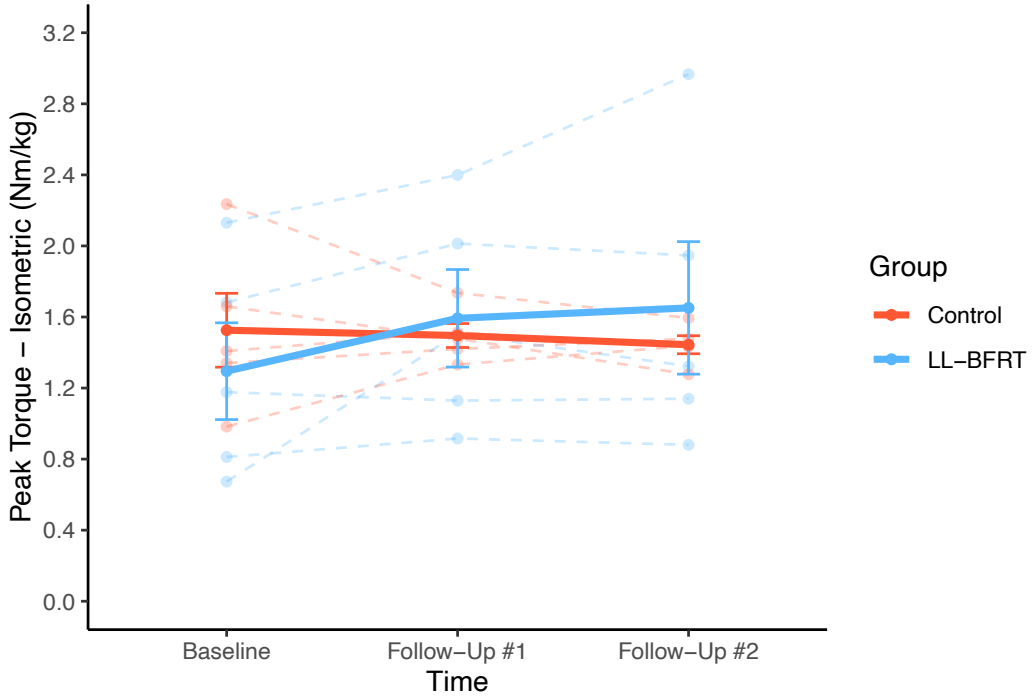
Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy

Figure D2.5. Involved limb knee extension strength for isokinetic testing at 180 °/s ([A] peak knee extension torque, [B] average peak knee extension torque) by group and time.



Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy

Figure D2.6. Involved limb knee extension strength for isometric testing at 90 ° of knee flexion by group and time.



Abbreviations: LL-BFRT, low load exercise with blood flow restriction therapy

Manuscript III

Table D3.1. Individual PROM responses by group

Group	Participant	Timepoint	IKDC	KOOS	ACL-RSI	TSK	GRoC
LL-BFRT	2	1	91.95	91.67	80.30	31	
		2	89.65	92.26	80.30	27	5
		3	94.25	92.86	93.94	25	6
	3	1	59.77	69.64	36.36	52	
		2	74.71	86.31	87.88	33	5
		3	79.31	92.86	85.61	29	6
	4	1	82.76	89.29	43.94	37	
		2	78.16	92.86	67.42	32	4
		3	88.50	92.26	78.03	31	5
	7	1	77.01	89.29	53.79	37	
		2	85.06	93.45	84.85	30	6
		3	93.10	94.64	93.18	31	7
	14	1	59.77	77.38	62.12	37	
		2	71.26	88.09	59.85	35	6
		3	78.16	89.88	56.06	32	6
Control	1	1	79.31	77.38	68.94	27	
		2	72.41	79.76	68.94	28	0
		3	73.56	83.33	68.18	28	2
	9	1	55.17	75.59	59.09	39	
		2	52.87	75.59	46.97	34	0
		3	42.53	66.07	59.09	33	0
	10	1	90.80	95.83	75.00	31	
		2	94.25	95.83	83.33	31	0
		3	95.40	96.43	84.09	31	0
	12	1	89.65	96.43	81.82	37	
		2	95.40	99.40	89.39	35	0
		3	96.55	97.62	87.88	31	0
	16	1	81.61	91.67	38.64	35	
		2	86.21	92.26	75.00	32	3
		3	90.80	96.43	83.33	24	6

Table D3.2. Pearson correlations: changes in knee extension LSI and PROMs

Variable		Change	PROM									
			ACL-RSI	TSK	IKDC	KOOS	*Symptom*	*Pain*	*ADL*	*Sport*	*QoL*	GRoC
LSI	Peak Torque at 90 deg/s	1	0.71* (0.021)	-0.70* (0.025)	0.65 (0.053)	0.61 (0.059)	0.52 (0.120)	0.71* (0.021)	0.38 (0.275)	0.40 (0.253)	0.44 (0.203)	0.71* (0.022)
		2	0.68* (0.029)	-0.49 (0.151)	0.60 (0.066)	0.51 (0.136)	0.43 (0.211)	0.57 (0.084)	0.45 (0.195)	0.23 (0.532)	0.58 (0.078)	0.57 (0.084)
	Average Peak Torque at 90 deg/s	1	0.70* (0.023)	-0.64* (0.048)	0.51 (0.129)	0.51 (0.134)	0.40 (0.251)	0.62 (0.054)	0.26 (0.463)	0.33 (0.346)	0.45 (0.192)	0.74* (0.015)
		2	0.70* (0.025)	-0.46 (0.177)	0.52 (0.123)	0.44 (0.198)	0.35 (0.326)	0.45 (0.189)	0.37 (0.300)	0.26 (0.462)	0.57 (0.084)	0.63* (0.049)
	Peak Torque at 180 deg/s	1	0.80** (0.005)	-0.82** (0.004)	0.62 (0.056)	0.66* (0.037)	0.73* (0.017)	0.74* (0.014)	0.81** (0.005)	0.19 (0.608)	0.12 (0.747)	0.28 (0.439)
		2	0.39 (0.264)	-0.65* (0.044)	0.37 (0.294)	0.64* (0.045)	0.60 (0.066)	0.65* (0.044)	0.75* (0.012)	0.39 (0.268)	0.32 (0.368)	-0.08 (0.834)
	Average Peak Torque at 180 deg/s	1	0.71* (0.022)	-0.84** (0.002)	0.50 (0.144)	0.70* (0.024)	0.82** (0.004)	0.72* (0.020)	0.83** (0.003)	0.26 (0.463)	0.07 (0.859)	0.21 (0.553)
		2	0.48 (0.161)	-0.75* (0.012)	0.42 (0.233)	0.72* (0.019)	0.65* (0.040)	0.65* (0.041)	0.80** (0.005)	0.49 (0.153)	0.43 (0.211)	0.07 (0.856)
	Peak Isometric Torque	1	0.83** (0.003)	-0.75* (0.013)	0.52 (0.105)	0.69* (0.028)	0.72* (0.019)	0.72* (0.018)	0.67* (0.034)	0.41 (0.238)	0.07 (0.852)	0.26 (0.474)
		2	0.58 (0.076)	-0.35 (0.360)	0.40 (0.257)	0.58 (0.078)	0.58 (0.080)	0.42 (0.222)	0.48 (0.162)	0.61 (0.063)	0.30 (0.398)	0.19 (0.591)

APPENDIX E: BACK MATTER

Recommendations for Future Research

1. Future work is needed to explore how variations in the amount of applied limb occlusion pressure and exercise load may influence motor unit recruitment and behavior during exercise with blood flow restriction therapy.
2. Studies examining how motor unit recruitment and behavior during low load exercise with blood flow restriction therapy differ between exercise sets performed to failure and standard blood flow restriction therapy protocols (i.e., 30x15x15x15) are essential next steps.
3. Future research with synchronized assessment of muscle activation (i.e., surface electromyography with motor unit decomposition capabilities) and muscle strength (i.e., isokinetic dynamometry) is needed to explore how the inclusion of blood flow restriction therapy during low load exercise influences individual motor unit recruitment thresholds.
4. Additional studies should aim to determine how motor unit recruitment and behavior differ during high load resistance exercise, moderate load resistance exercise, and low load resistance exercise with and without blood flow restriction therapy.
5. Large, representative randomized controlled trials are needed to fully elucidate the potential benefits of low load exercise with blood flow restriction therapy on quadriceps strength in patients following anterior cruciate ligament reconstruction compared to traditional post-surgical rehabilitative programs.
6. Research is needed to explore when in the recovery process (i.e., presurgical, immediate postsurgical, mid-recovery, or late-recovery) may be the most appropriate and effective time to implement blood flow restriction therapy into patient care programs for improving quadriceps strength in individuals following anterior cruciate ligament reconstruction.
7. Longitudinal studies are needed to determine the long-term effects of post-surgical blood flow restriction therapy programs on muscle function and patient reported outcomes including quality of life, self-reported knee function, and reinjury rates in patients long after anterior cruciate ligament reconstruction.
8. Further prospective research is needed to explore how implementing blood flow restriction therapy into patient care programs following anterior cruciate ligament reconstruction influences patient reported function, satisfaction, confidence, and fear of reinjury throughout the rehabilitative process via serial, longitudinal assessments occurring from presurgical to unrestricted physical activity clearance.
9. Studies utilizing mixed methodological designs are required to gain a comprehensive assessment of the psychological responses to blood flow restriction therapy in load restricted patient populations such as post-surgical patients and elderly individuals.

Complete Bibliography

1. Martini F, Ober W, Nath J, Bartholomew E, Petti K. *Visual Anatomy & Physiology*. 3rd ed. Pearson

2. Marieb E, Hoehn K. *Human Anatomy & Physiology*. Tenth ed. Pearson; 2016.

3. Liddell EGT, Sherrington CS. Recruitment and some other Features of Reflex Inhibition. *Proc R Soc Lond Ser B Contain Pap Biol Character*. 1925;97(686):488-518.

4. Sherrington C. Remarks on some Aspects of Reflex Inhibition. *Proc R Soc B Biol Sci*. 1925;97:519-545. doi:10.1098/RSPB.1925.0017

5. Burke RE, Levine DN, Salcman M, Tsairis P. Motor units in cat soleus muscle: physiological, histochemical and morphological characteristics. *J Physiol*. 1974;238(3):503-514.2.

6. Burke RE, Levine DN, Tsairis P, Zajac FE. Physiological types and histochemical profiles in motor units of the cat gastrocnemius. *J Physiol*. 1973;234(3):723-748. doi:10.1113/jphysiol.1973.sp010369

7. Burke RE, Levine DN, Zajac FE, Tsairis P, Engel WK. Mammalian Motor Units: Physiological-Histochemical Correlation in Three Types in Cat Gastrocnemius. *Science*. 1971;174(4010):709-712. doi:10.1126/science.174.4010.709

8. Heckman C j., Enoka RM. Motor Unit. In: *Comprehensive Physiology*. John Wiley & Sons, Ltd; 2012:2629-2682. doi:10.1002/cphy.c100087

9. Ennion S, Sant'ana Pereira J, Sargeant AJ, Young A, Goldspink G. Characterization of human skeletal muscle fibres according to the myosin heavy chains they express. *J Muscle Res Cell Motil*. 1995;16(1):35-43. doi:10.1007/BF00125308

10. Vandenborne K, McCully K, Kakihira H, et al. Metabolic heterogeneity in human calf muscle during maximal exercise. *Proc Natl Acad Sci U S A*. 1991;88(13):5714-5718.

11. Neumann D. *Kinesiology of the Musculoskeletal System - Foundations for Rehabilitation*. 3rd ed. Elsevier; 2016. Accessed August 4, 2022. https://www.elsevier.com/books/kinesiology-of-the-musculoskeletal-system/neumann/978-0-323-28753-1

12. Reardon KA, Davis J, Kapsa RM, Choong P, Byrne E. Myostatin, insulin-like growth factor-1, and leukemia inhibitory factor mRNAs are upregulated in chronic human disuse muscle atrophy. *Muscle Nerve*. 2001;24(7):893-899. doi:10.1002/mus.1086

13. Staron RS, Hagerman FC, Hikida RS, et al. Fiber type composition of the vastus lateralis muscle of young men and women. *J Histochem Cytochem Off J Histochem Soc*. 2000;48(5):623-629. doi:10.1177/002215540004800506

14. Trappe S, Trappe T, Gallagher P, Harber M, Alkner B, Tesch P. Human single muscle fibre function with 84 day bed-rest and resistance exercise. *J Physiol*. 2004;557(Pt 2):501-513. doi:10.1113/jphysiol.2004.062166

15. De Luca CJ, Contessa P. Biomechanical benefits of the Onion-Skin motor unit control scheme. *J Biomech*. 2015;48(2):195-203. doi:10.1016/j.jbiomech.2014.12.003

16. Henneman E. Relation between size of neurons and their susceptibility to discharge. *Science*. 1957;126(3287):1345-1347. doi:10.1126/science.126.3287.1345

17. Henneman E, Somjen G, Carpenter DO. FUNCTIONAL SIGNIFICANCE OF CELL SIZE IN SPINAL MOTONEURONS. *J Neurophysiol*. 1965;28:560-580. doi:10.1152/jn.1965.28.3.560

18. Mendell LM. The size principle: a rule describing the recruitment of motoneurons. *J Neurophysiol*. 2005;93(6):3024-3026. doi:10.1152/classicessays.00025.2005

19. Bawa P, Pang MY, Olesen KA, Calancie B. Rotation of Motoneurons During Prolonged Isometric Contractions in Humans. *J Neurophysiol*. 2006;96(3):1135-1140. doi:10.1152/jn.01063.2005

20. Bawa P, Murnaghan C. Motor Unit Rotation in a Variety of Human Muscles. *J Neurophysiol*. 2009;102(4):2265-2272. doi:10.1152/jn.00278.2009

21. Eccles JC, Eccles RM, Lundberg A. The action potentials of the alpha motoneurones supplying fast and slow muscles. *J Physiol*. 1958;142(2):275-291. doi:10.1113/jphysiol.1958.sp006015

22. De Luca CJ, Erim Z. Common drive of motor units in regulation of muscle force. *Trends Neurosci*. 1994;17(7):299-305. doi:10.1016/0166-2236(94)90064-7

23. Damas F, Libardi CA, Ugrinowitsch C. The development of skeletal muscle hypertrophy through resistance training: the role of muscle damage and muscle protein synthesis. *Eur J Appl Physiol*. 2018;118(3):485-500. doi:10.1007/s00421-017-3792-9

24. Prentice W. *Principles of Athletic Training: A Competency-Based Approach*. 15th ed. The McGraw-Hill Companies, Inc.

25. Hedayatpour N, Falla D. Physiological and Neural Adaptations to Eccentric Exercise: Mechanisms and Considerations for Training. *BioMed Res Int*. 2015;2015:e193741. doi:10.1155/2015/193741

26. Schoenfeld BJ. The Mechanisms of Muscle Hypertrophy and Their Application to Resistance Training. *J Strength Cond Res*. 2010;24(10):2857-2872. doi:10.1519/JSC.0b013e3181e840f3

27. Schoenfeld BJ. Potential mechanisms for a role of metabolic stress in hypertrophic adaptations to resistance training. *Sports Med Auckl NZ*. 2013;43(3):179-194. doi:10.1007/s40279-013-0017-1

28. Goldberg AL, Etlinger JD, Goldspink DF, Jablecki C. Mechanism of work-induced hypertrophy of skeletal muscle. *Med Sci Sports*. 1975;7(3):185-198.

29. Wackerhage H, Schoenfeld BJ, Hamilton DL, Lehti M, Hulmi JJ. Stimuli and sensors that initiate skeletal muscle hypertrophy following resistance exercise. *J Appl Physiol*. 2019;126(1):30-43. doi:10.1152/japplphysiol.00685.2018

30. Ardern CL, Taylor NF, Feller JA, Webster KE. A systematic review of the psychological factors associated with returning to sport following injury. *Br J Sports Med*. 2013;47(17):1120-1126. doi:10.1136/bjsports-2012-091203

31. Côté C, Simoneau JA, Lagassé P, et al. Isokinetic strength training protocols: do they induce skeletal muscle fiber hypertrophy? *Arch Phys Med Rehabil*. 1988;69(4):281-285.

32. Vissing K, Brink M, Lønbro S, et al. Muscle adaptations to plyometric vs. resistance training in untrained young men. *J Strength Cond Res*. 2008;22(6):1799-1810. doi:10.1519/JSC.0b013e318185f673

33. Nishimura A, Sugita M, Kato K, Fukuda A, Sudo A, Uchida A. Hypoxia increases muscle hypertrophy induced by resistance training. *Int J Sports Physiol Perform*. 2010;5(4):497-508. doi:10.1123/ijspp.5.4.497

34. Goto K, Ishii N, Kizuka T, Takamatsu K. The impact of metabolic stress on hormonal responses and muscular adaptations. *Med Sci Sports Exerc*. 2005;37(6):955-963.

35. Gordon SE, Kraemer WJ, Vos NH, Lynch JM, Knuttgen HG. Effect of acid-base balance on the growth hormone response to acute high-intensity cycle exercise. *J Appl Physiol Bethesda Md 1985*. 1994;76(2):821-829. doi:10.1152/jappl.1994.76.2.821

36. Takarada Y, Nakamura Y, Aruga S, Onda T, Miyazaki S, Ishii N. Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. *J Appl Physiol Bethesda Md 1985*. 2000;88(1):61-65. doi:10.1152/jappl.2000.88.1.61

37. Schoenfeld BJ. Does exercise-induced muscle damage play a role in skeletal muscle hypertrophy? *J Strength Cond Res*. 2012;26(5):1441-1453. doi:10.1519/JSC.0b013e31824f207e

38. Malm C. Exercise-induced muscle damage and inflammation: fact or fiction? *Acta Physiol Scand*. 2001;171(3):233-239. doi:10.1046/j.1365-201x.2001.00825.x

39. Clarkson PM, Byrnes WC, McCormick KM, Turcotte LP, White JS. Muscle soreness and serum creatine kinase activity following isometric, eccentric, and concentric exercise. *Int J Sports Med*. 1986;7(3):152-155. doi:10.1055/s-2008-1025753

40. Gibala MJ, MacDougall JD, Tarnopolsky MA, Stauber WT, Elorriaga A. Changes in human skeletal muscle ultrastructure and force production after acute resistance exercise. *J Appl Physiol Bethesda Md 1985*. 1995;78(2):702-708. doi:10.1152/jappl.1995.78.2.702

41. Enoka RM. Eccentric contractions require unique activation strategies by the nervous system. *J Appl Physiol Bethesda Md 1985*. 1996;81(6):2339-2346. doi:10.1152/jappl.1996.81.6.2339

42. Progression Models in Resistance Training for Healthy Adults. *Med Sci Sports Exerc*. 2009;41(3):687-708. doi:10.1249/MSS.0b013e3181915670

43. Siegel L, Vandenakker-Albanese C, Siegel D. Anterior cruciate ligament injuries: anatomy, physiology, biomechanics, and management. *Clin J Sport Med Off J Can Acad Sport Med*. 2012;22(4):349-355. doi:10.1097/JSM.0b013e3182580cd0

44. Giuliani JR, Kilcoyne KG, Rue JPH. Anterior cruciate ligament anatomy: a review of the anteromedial and posterolateral bundles. *J Knee Surg*. 2009;22(2):148-154. doi:10.1055/s-0030-1247742

45. Georgoulis AD, Pappa L, Moebius U, et al. The presence of proprioceptive mechanoreceptors in the remnants of the ruptured ACL as a possible source of re-innervation of the ACL autograft. *Knee Surg Sports Traumatol Arthrosc Off J ESSKA*. 2001;9(6):364-368. doi:10.1007/s001670100240

46. Gabriel MT, Wong EK, Woo SLY, Yagi M, Debski RE. Distribution of in situ forces in the anterior cruciate ligament in response to rotatory loads. *J Orthop Res Off Publ Orthop Res Soc*. 2004;22(1):85-89. doi:10.1016/S0736-0266(03)00133-5

47. Sakane M, Fox RJ, Woo SL, Livesay GA, Li G, Fu FH. In situ forces in the anterior cruciate ligament and its bundles in response to anterior tibial loads. *J Orthop Res Off Publ Orthop Res Soc*. 1997;15(2):285-293. doi:10.1002/jor.1100150219

48. Khan A, Arain A. Anatomy, Bony Pelvis and Lower Limb, Anterior Thigh Muscles. In: *StatPearls*. StatPearls Publishing; 2022. Accessed August 3, 2022. http://www.ncbi.nlm.nih.gov/books/NBK538425/

49. Rodgers CD, Raja A. Anatomy, Bony Pelvis and Lower Limb, Hamstring Muscle. In: *StatPearls*. StatPearls Publishing; 2022. Accessed August 3, 2022. http://www.ncbi.nlm.nih.gov/books/NBK546688/

50. Griffin LY, Albohm MJ, Arendt EA, et al. Understanding and preventing noncontact anterior cruciate ligament injuries: a review of the Hunt Valley II meeting, January 2005. *Am J Sports Med*. 2006;34(9):1512-1532. doi:10.1177/0363546506286866

51. Paschos NK, Howell SM. Anterior cruciate ligament reconstruction: principles of treatment. *EFORT Open Rev*. 2016;1(11):398-408. doi:10.1302/2058-5241.1.160032

52. Gottlob CA, Baker CL, Pellissier JM, Colvin L. Cost effectiveness of anterior cruciate ligament reconstruction in young adults. *Clin Orthop*. 1999;(367):272-282.

53. Huston LJ, Greenfield ML, Wojtys EM. Anterior cruciate ligament injuries in the female athlete. Potential risk factors. *Clin Orthop*. 2000;(372):50-63. doi:10.1097/00003086-200003000-00007

54. Centers for Disease Control and Prevention, National Center for Health Statistics. *National Hospital Discharge Survey*. Centers for Disease Control and Prevention; 1996.

55. Hughes G, Watkins J. A risk-factor model for anterior cruciate ligament injury. *Sports Med Auckl NZ*. 2006;36(5):411-428. doi:10.2165/00007256-200636050-00004

56. Smith C, Kruger MJ, Smith RM, Myburgh KH. The Inflammatory Response to Skeletal Muscle Injury. *Sports Med*. 2008;38(11):947-969.

57. Smith HC, Vacek P, Johnson RJ, et al. Risk Factors for Anterior Cruciate Ligament Injury. *Sports Health*. 2012;4(1):69-78. doi:10.1177/1941738111428281

58. Smith HC, Vacek P, Johnson RJ, et al. Risk Factors for Anterior Cruciate Ligament Injury. *Sports Health*. 2012;4(2):155-161. doi:10.1177/1941738111428282

59. Filbay SR, Grindem H. Evidence-based recommendations for the management of anterior cruciate ligament (ACL) rupture. *Best Pract Res Clin Rheumatol*. 2019;33(1):33-47. doi:10.1016/j.berh.2019.01.018

60. Frobell RB, Roos EM, Roos HP, Ranstam J, Lohmander LS. A randomized trial of treatment for acute anterior cruciate ligament tears. *N Engl J Med*. 2010;363(4):331-342. doi:10.1056/NEJMoa0907797

61. Fithian DC, Paxton EW, Stone ML, et al. Prospective trial of a treatment algorithm for the management of the anterior cruciate ligament-injured knee. *Am J Sports Med*. 2005;33(3):335-346. doi:10.1177/0363546504269590

62. Kannus P, Järvinen M. Conservatively treated tears of the anterior cruciate ligament. Long-term results. *J Bone Joint Surg Am*. 1987;69(7):1007-1012.

63. Macaulay AA, Perfetti DC, Levine WN. Anterior Cruciate Ligament Graft Choices. *Sports Health*. 2012;4(1):63-68. doi:10.1177/1941738111409890

64. Feller JA, Webster KE. A randomized comparison of patellar tendon and hamstring tendon anterior cruciate ligament reconstruction. *Am J Sports Med*. 2003;31(4):564-573. doi:10.1177/03635465030310041501

65. Giesche F, Niederer D, Banzer W, Vogt L. Evidence for the effects of prehabilitation before ACL-reconstruction on return to sport-related and self-reported knee function: A systematic review. *PLoS ONE*. 2020;15(10). doi:10.1371/journal.pone.0240192

66. Melick N van, Cingel REH van, Brooijmans F, et al. Evidence-based clinical practice update: practice guidelines for anterior cruciate ligament rehabilitation based on a systematic review and multidisciplinary consensus. *Br J Sports Med*. 2016;50(24):1506-1515. doi:10.1136/bjsports-2015-095898

67. Burroughs PJ, Kahan JB, Moore HG, Grauer JN, Gardner EC. Temporal Utilization of Physical Therapy Visits After Anterior Cruciate Ligament Reconstruction. *Orthop J Sports Med*. 2021;9(2):2325967120982293. doi:10.1177/2325967120982293

68. Burgi CR, Peters S, Ardern CL, et al. Which criteria are used to clear patients to return to sport after primary ACL reconstruction? A scoping review. *Br J Sports Med*. 2019;53(18):1154-1161. doi:10.1136/bjsports-2018-099982

69. Faleide AGH, Magnussen LH, Strand T, et al. The Role of Psychological Readiness in Return to Sport Assessment After Anterior Cruciate Ligament Reconstruction. *Am J Sports Med*. 2021;49(5):1236-1243. doi:10.1177/0363546521991924

70. Schmitt LC, Paterno MV, Hewett TE. The impact of quadriceps femoris strength asymmetry on functional performance at return to sport following anterior cruciate ligament reconstruction. *J Orthop Sports Phys Ther*. 2012;42(9):750-759. doi:10.2519/jospt.2012.4194

71. Lepley LK. Deficits in Quadriceps Strength and Patient-Oriented Outcomes at Return to Activity After ACL Reconstruction: A Review of the Current Literature. *Sports Health*. 2015;7(3):231-238. doi:10.1177/1941738115578112

72. Ardern CL, Taylor NF, Feller JA, Webster KE. Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: an updated systematic review and meta-analysis including aspects of physical functioning and contextual factors. *Br J Sports Med*. 2014;48(21):1543-1552. doi:10.1136/bjsports-2013-093398

73. Webster KE, Feller JA. A research update on the state of play for return to sport after anterior cruciate ligament reconstruction. *J Orthop Traumatol*. 2019;20(1):10. doi:10.1186/s10195-018-0516-9

74. Ellman M, Sherman S, Forsythe B, LaPrade R, Cole B, Bach B. Return to Play Following Anterior Cruciate Ligament Reconstruction. *J Am Acad Orthop Surg*. 2015;23:283-296. doi:10.5435/JAAOS-D-13-00183

75. Ardern CL. Anterior Cruciate Ligament Reconstruction—Not Exactly a One-Way Ticket Back to the Preinjury Level. *Sports Health*. 2015;7(3):224-230. doi:10.1177/1941738115578131

76. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am J Sports Med*. 2007;35(10):1756-1769. doi:10.1177/0363546507307396

77. Cinque ME, Dornan GJ, Chahla J, Moatshe G, LaPrade RF. High Rates of Osteoarthritis Develop After Anterior Cruciate Ligament Surgery: An Analysis of 4108 Patients. *Am J Sports Med*. 2018;46(8):2011-2019. doi:10.1177/0363546517730072

78. Pinczewski LA, Lyman J, Salmon LJ, Russell VJ, Roe J, Linklater J. A 10-year comparison of anterior cruciate ligament reconstructions with hamstring tendon and patellar tendon autograft: a controlled, prospective trial. *Am J Sports Med*. 2007;35(4):564-574. doi:10.1177/0363546506296042

79. Wright RW, Dunn WR, Amendola A, et al. Risk of tearing the intact anterior cruciate ligament in the contralateral knee and rupturing the anterior cruciate ligament graft during the first 2 years after anterior cruciate ligament reconstruction: a prospective MOON cohort study. *Am J Sports Med*. 2007;35(7):1131-1134. doi:10.1177/0363546507301318

80. Salmon L, Russell V, Musgrove T, Pinczewski L, Refshauge K. Incidence and risk factors for graft rupture and contralateral rupture after anterior cruciate ligament reconstruction. *Arthrosc J Arthrosc Relat Surg Off Publ Arthrosc Assoc N Am Int Arthrosc Assoc*. 2005;21(8):948-957. doi:10.1016/j.arthro.2005.04.110

81. Leys T, Salmon L, Waller A, Linklater J, Pinczewski L. Clinical results and risk factors for reinjury 15 years after anterior cruciate ligament reconstruction: a prospective study of hamstring and patellar tendon grafts. *Am J Sports Med*. 2012;40(3):595-605. doi:10.1177/0363546511430375

82. Paterno MV, Rauh MJ, Schmitt LC, Ford KR, Hewett TE. Incidence of contralateral and ipsilateral anterior cruciate ligament (ACL) injury after primary ACL reconstruction and return to sport. *Clin J Sport Med Off J Can Acad Sport Med*. 2012;22(2):116-121. doi:10.1097/JSM.0b013e318246ef9e

83. Hart JM, Pietrosimone B, Hertel J, Ingersoll CD. Quadriceps Activation Following Knee Injuries: A Systematic Review. *J Athl Train*. 2010;45(1):87-97. doi:10.4085/1062-6050-45.1.87

84. Tourville TW, Jarrell KM, Naud S, Slauterbeck JR, Johnson RJ, Beynnon BD. Relationship between isokinetic strength and tibiofemoral joint space width changes after anterior cruciate ligament reconstruction. *Am J Sports Med*. 2014;42(2):302-311. doi:10.1177/0363546513510672

85. Di Stasi SL, Logerstedt D, Gardinier ES, Snyder-Mackler L. Gait patterns differ between ACL-reconstructed athletes who pass return-to-sport criteria and those who fail. *Am J Sports Med*. 2013;41(6):1310-1318. doi:10.1177/0363546513482718

86. Keays SL, Bullock-Saxton J, Keays AC. Strength and function before and after anterior cruciate ligament reconstruction. *Clin Orthop*. 2000;(373):174-183. doi:10.1097/00003086-200004000-00021

87. Keays SL, Bullock-Saxton J, Keays AC, Newcombe P. Muscle strength and function before and after anterior cruciate ligament reconstruction using semitendonosus and gracilis. *The Knee*. 2001;8(3):229-234. doi:10.1016/s0968-0160(01)00099-0

88. Konishi Y, Fukubayashi T. Relationship between muscle volume and muscle torque of the hamstrings after anterior cruciate ligament reconstruction. *J Sci Med Sport*. 2010;13(1):101-105. doi:10.1016/j.jsams.2008.08.001

89. Soon M, Neo CPC, Mitra AK, Tay BK. Morbidity following anterior cruciate ligament reconstruction using hamstring autograft. *Ann Acad Med Singapore*. 2004;33(2):214-219.

90. Wojtys EM, Huston LJ. Longitudinal effects of anterior cruciate ligament injury and patellar tendon autograft reconstruction on neuromuscular performance. *Am J Sports Med*. 2000;28(3):336-344. doi:10.1177/03635465000280030901

91. Hiemstra LA, Webber S, MacDonald PB, Kriellaars DJ. Contralateral limb strength deficits after anterior cruciate ligament reconstruction using a hamstring tendon graft. *Clin Biomech Bristol Avon*. 2007;22(5):543-550. doi:10.1016/j.clinbiomech.2007.01.009

92. Thomas AC, Wojtys EM, Brandon C, Palmieri-Smith RM. Muscle Atrophy Contributes to Quadriceps Weakness after ACL Reconstruction. *J Sci Med Sport Sports Med Aust*. 2016;19(1):7-11. doi:10.1016/j.jsams.2014.12.009

93. Lepley LK, Davi SM, Burland JP, Lepley AS. Muscle Atrophy After ACL Injury: Implications for Clinical Practice. *Sports Health*. 2020;12(6):579-586. doi:10.1177/1941738120944256

94. Krishnan C, Williams GN. Factors explaining chronic knee extensor strength deficits after ACL reconstruction. *J Orthop Res Off Publ Orthop Res Soc*. 2011;29(5):633-640. doi:10.1002/jor.21316

95. Rice DA, McNair PJ. Quadriceps arthrogenic muscle inhibition: neural mechanisms and treatment perspectives. *Semin Arthritis Rheum*. 2010;40(3):250-266. doi:10.1016/j.semarthrit.2009.10.001

96. Pette D, Staron RS. Myosin isoforms, muscle fiber types, and transitions. *Microsc Res Tech*. 2000;50(6):500-509. doi:10.1002/1097-0029(20000915)50:6<500::AID-JEMT7>3.0.CO;2-7

97. Carson RG, Buick AR. Neuromuscular electrical stimulation-promoted plasticity of the human brain. *J Physiol*. 2021;599(9):2375-2399. doi:10.1113/JP278298

98. Harkey MS, Gribble PA, Pietrosimone BG. Disinhibitory interventions and voluntary quadriceps activation: a systematic review. *J Athl Train*. 2014;49(3):411-421. doi:10.4085/1062-6050-49.1.04

99. Needle AR, Lepley AS, Grooms DR. Central Nervous System Adaptation After Ligamentous Injury: a Summary of Theories, Evidence, and Clinical Interpretation. *Sports Med Auckl NZ*. 2017;47(7):1271-1288. doi:10.1007/s40279-016-0666-y

100. Lepley LK, Lepley AS, Onate JA, Grooms DR. Eccentric Exercise to Enhance Neuromuscular Control. *Sports Health*. 2017;9(4):333-340. doi:10.1177/1941738117710913

101. Drechsler WI, Cramp MC, Scott OM. Changes in muscle strength and EMG median frequency after anterior cruciate ligament reconstruction. *Eur J Appl Physiol*. 2006;98(6):613-623. doi:10.1007/s00421-006-0311-9

102. Burland JP, Lepley AS, Frechette L, Lepley LK. Protracted alterations in muscle activation strategies and knee mechanics in patients after Anterior Cruciate Ligament Reconstruction. *Knee Surg Sports Traumatol Arthrosc Off J ESSKA*. 2020;28(12):3766-3772. doi:10.1007/s00167-019-05833-4

103. Harput G, Howard JS, Mattacola C. Comparison of Muscle Activation Levels Between Healthy Individuals and Persons Who Have Undergone Anterior Cruciate Ligament Reconstruction During Different Phases of Weight-Bearing Exercises. *J Orthop Sports Phys Ther*. 2016;46(11):984-992. doi:10.2519/jospt.2016.5896

104. Blasimann A, Koenig I, Baert I, Baur H, Vissers D. Which assessments are used to analyze neuromuscular control by electromyography after an anterior cruciate ligament injury to determine readiness to return to sports? A systematic review. *BMC Sports Sci Med Rehabil*. 2021;13(1):142. doi:10.1186/s13102-021-00370-5

105. Nuccio S, Del Vecchio A, Casolo A, et al. Deficit in knee extension strength following anterior cruciate ligament reconstruction is explained by a reduced neural drive to the vasti muscles. *J Physiol*. 2021;599(22):5103-5120. doi:10.1113/JP282014

106. Schilaty ND, McPherson AL, Nagai T, Bates NA. Arthrogenic muscle inhibition manifests in thigh musculature motor unit characteristics after anterior cruciate ligament injury. *Eur J Sport Sci*. Published online May 2, 2022:1-11. doi:10.1080/17461391.2022.2056520

107. Nuccio S, Del Vecchio A, Casolo A, et al. Muscle fiber conduction velocity in the vastus lateralis and medialis muscles of soccer players after ACL reconstruction. *Scand J Med Sci Sports*. 2020;30(10):1976-1984. doi:10.1111/sms.13748

108. Nwachukwu BU, Adjei J, Rauck RC, et al. How Much Do Psychological Factors Affect Lack of Return to Play After Anterior Cruciate Ligament Reconstruction? A Systematic Review. *Orthop J Sports Med*. 2019;7(5):2325967119845313. doi:10.1177/2325967119845313

109. Walker A, Hing W, Lorimer A, Rathbone E. Rehabilitation characteristics and patient barriers to and facilitators of ACL reconstruction rehabilitation: A cross-sectional

survey. *Phys Ther Sport Off J Assoc Chart Physiother Sports Med*. 2021;48:169-176. doi:10.1016/j.ptsp.2021.01.001

110. Irrgang JJ, Anderson AF, Boland AL, et al. Development and Validation of the International Knee Documentation Committee Subjective Knee Form. *Am J Sports Med*. 2001;29(5):600-613. doi:10.1177/03635465010290051301

111. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res*. 2011;63 Suppl 11:S208-228. doi:10.1002/acr.20632

112. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther*. 1998;28(2):88-96. doi:10.2519/jospt.1998.28.2.88

113. Webster KE, Feller JA, Lambros C. Development and preliminary validation of a scale to measure the psychological impact of returning to sport following anterior cruciate ligament reconstruction surgery. *Phys Ther Sport Off J Assoc Chart Physiother Sports Med*. 2008;9(1):9-15. doi:10.1016/j.ptsp.2007.09.003

114. Miller RP, Kori SH, Todd DD. The Tampa Scale: a Measure of Kinisophobia. *Clin J Pain*. 1991;7(1):51.

115. Pool JJM, Hiralal S, Ostelo RWJG, et al. The applicability of the Tampa Scale of Kinesiophobia for patients with sub-acute neck pain: a qualitative study. *Qual Quant*. 2009;43(5):773-780. doi:10.1007/s11135-008-9203-x

116. Liu H, Huang L, Yang Z, Li H, Wang Z, Peng L. Fear of Movement/(Re)Injury: An Update to Descriptive Review of the Related Measures. *Front Psychol*. 2021;12. Accessed March 1, 2022. https://www.frontiersin.org/article/10.3389/fpsyg.2021.696762

117. Zwolski C, Schmitt LC, Quatman-Yates C, Thomas S, Hewett TE, Paterno MV. The influence of quadriceps strength asymmetry on patient-reported function at time of return to sport after anterior cruciate ligament reconstruction. *Am J Sports Med*. 2015;43(9):2242-2249. doi:10.1177/0363546515591258

118. Pietrosimone B, Lepley AS, Harkey MS, et al. Quadriceps Strength Predicts Self-reported Function Post-ACL Reconstruction. *Med Sci Sports Exerc*. 2016;48(9):1671-1677. doi:10.1249/MSS.0000000000000946

119. Kuenze C, Hertel J, Saliba S, Diduch DR, Weltman A, Hart JM. Clinical thresholds for quadriceps assessment after anterior cruciate ligament reconstruction. *J Sport Rehabil*. 2015;24(1):36-46. doi:10.1123/jsr.2013-0110

120. Bodkin S, Goetschius J, Hertel J, Hart J. Relationships of Muscle Function and Subjective Knee Function in Patients After ACL Reconstruction. *Orthop J Sports Med*. 2017;5(7):2325967117719041. doi:10.1177/2325967117719041

121. Lepley AS, Pietrosimone B, Cormier ML. Quadriceps Function, Knee Pain, and Self-Reported Outcomes in Patients With Anterior Cruciate Ligament Reconstruction. *J Athl Train*. 2018;53(4):337-346. doi:10.4085/1062-6050-245-16

122. Della Villa F, Straub RK, Mandelbaum B, Powers CM. Confidence to Return to Play After Anterior Cruciate Ligament Reconstruction Is Influenced by Quadriceps Strength Symmetry and Injury Mechanism. *Sports Health*. 2021;13(3):304-309. doi:10.1177/1941738120976377

123. Paterno MV, Flynn K, Thomas S, Schmitt LC. Self-Reported Fear Predicts Functional Performance and Second ACL Injury After ACL Reconstruction and Return to Sport: A Pilot Study. *Sports Health*. 2017;10(3):228-233. doi:10.1177/1941738117745806

124. Markström JL, Grinberg A, Häger CK. Fear of Reinjury Following Anterior Cruciate Ligament Reconstruction Is Manifested in Muscle Activation Patterns of Single-Leg Side-Hop Landings. *Phys Ther*. 2022;102(2):pzab218. doi:10.1093/ptj/pzab218

125. Sato Y. The history and future of KAATSU training. *Int J KAATSU Train Res*. 2005;1(1):1-5.

126. Scott BR, Loenneke JP, Slattery KM, Dascombe BJ. Exercise with blood flow restriction: an updated evidence-based approach for enhanced muscular development. *Sports Med Auckl NZ*. 2015;45(3):313-325. doi:10.1007/s40279-014-0288-1

127. Lixandrão ME, Ugrinowitsch C, Berton R, et al. Magnitude of Muscle Strength and Mass Adaptations Between High-Load Resistance Training Versus Low-Load Resistance Training Associated with Blood-Flow Restriction: A Systematic Review and Meta-Analysis. *Sports Med Auckl NZ*. 2018;48(2):361-378. doi:10.1007/s40279-017-0795-y

128. Dayton SR, Padanilam SJ, Sylvester TC, Boctor MJ, Tjong VK. Blood Flow Restriction Therapy Impact on Musculoskeletal Strength and Mass. *Video J Sports Med*. 2021;1(5):26350254211032680. doi:10.1177/26350254211032681

129. Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. *Br J Sports Med*. 2017;51(13):1003-1011. doi:10.1136/bjsports-2016-097071

130. Schoenfeld BJ, Grgic J, Ogborn D, Krieger JW. Strength and Hypertrophy Adaptations Between Low- vs. High-Load Resistance Training: A Systematic Review and Meta-

analysis. *J Strength Cond Res*. 2017;31(12):3508-3523. doi:10.1519/JSC.0000000000002200

131. Loenneke JP, Wilson JM, Marín PJ, Zourdos MC, Bemben MG. Low intensity blood flow restriction training: a meta-analysis. *Eur J Appl Physiol*. 2012;112(5):1849-1859. doi:10.1007/s00421-011-2167-x

132. Slysz J, Stultz J, Burr JF. The efficacy of blood flow restricted exercise: A systematic review & meta-analysis. *J Sci Med Sport*. 2016;19(8):669-675. doi:10.1016/j.jsams.2015.09.005

133. Centner C, Wiegel P, Gollhofer A, König D. Effects of Blood Flow Restriction Training on Muscular Strength and Hypertrophy in Older Individuals: A Systematic Review and Meta-Analysis. *Sports Med Auckl NZ*. 2019;49(1):95-108. doi:10.1007/s40279-018-0994-1

134. Patterson SD, Hughes L, Warmington S, et al. Blood Flow Restriction Exercise: Considerations of Methodology, Application, and Safety. *Front Physiol*. 2019;10. doi:10.3389/fphys.2019.00533

135. McEwen JA, Owens JG, Jeyasurya J. Why is it Crucial to Use Personalized Occlusion Pressures in Blood Flow Restriction (BFR) Rehabilitation? *J Med Biol Eng*. 2019;39(2):173-177. doi:10.1007/s40846-018-0397-7

136. Bezerra de Morais AT, Santos Cerqueira M, Moreira Sales R, Rocha T, Galvão de Moura Filho A. Upper limbs total occlusion pressure assessment: Doppler ultrasound reproducibility and determination of predictive variables. *Clin Physiol Funct Imaging*. 2017;37(4):437-441. doi:10.1111/cpf.12330

137. Noordin S, McEwen JA, Kragh JF, Eisen A, Masri BA. Surgical tourniquets in orthopaedics. *J Bone Joint Surg Am*. 2009;91(12):2958-2967. doi:10.2106/JBJS.I.00634

138. Jessee MB, Buckner SL, Dankel SJ, Counts BR, Abe T, Loenneke JP. The Influence of Cuff Width, Sex, and Race on Arterial Occlusion: Implications for Blood Flow Restriction Research. *Sports Med Auckl NZ*. 2016;46(6):913-921. doi:10.1007/s40279-016-0473-5

139. Fatela P, Mendonca GV, Veloso AP, Avela J, Mil-Homens P. Blood Flow Restriction Alters Motor Unit Behavior During Resistance Exercise. *Int J Sports Med*. 2019;40(9):555-562. doi:10.1055/a-0888-8816

140. Cook SB, Scott BR, Hayes KL, Murphy BG. Neuromuscular Adaptations to Low-Load Blood Flow Restricted Resistance Training. *J Sports Sci Med*. 2018;17(1):66-73.

141. Lauver JD, Cayot TE, Rotarius T, Scheuermann BW. The effect of eccentric exercise with blood flow restriction on neuromuscular activation, microvascular oxygenation, and the repeated bout effect. *Eur J Appl Physiol*. 2017;117(5):1005-1015. doi:10.1007/s00421-017-3589-x

142. Hammer SM, Alexander AM, Didier KD, Barstow TJ. Influence of blood flow occlusion on muscular recruitment and fatigue during maximal-effort small muscle-mass exercise. *J Physiol*. 2020;598(19):4293-4306. doi:10.1113/JP279925

143. Killinger B, Lauver JD, Donovan L, Goetschius J. The Effects of Blood Flow Restriction on Muscle Activation and Hypoxia in Individuals With Chronic Ankle Instability. *J Sport Rehabil*. 2020;29(5):633-639. doi:10.1123/jsr.2018-0416

144. Lorenz D, Bailey L, Wilk K, et al. Current Clinical Concepts: Blood Flow Restriction Training. *J Athl Train*. Published online January 22, 2021. doi:10.4085/418-20

145. Pearson SJ, Hussain SR. A review on the mechanisms of blood-flow restriction resistance training-induced muscle hypertrophy. *Sports Med Auckl NZ*. 2015;45(2):187-200. doi:10.1007/s40279-014-0264-9

146. Rossi FE, de Freitas MC, Zanchi NE, Lira FS, Cholewa JM. The Role of Inflammation and Immune Cells in Blood Flow Restriction Training Adaptation: A Review. *Front Physiol*. 2018;9. doi:10.3389/fphys.2018.01376

147. Jessee M, Mattocks K, Buckner S, et al. Mechanisms of Blood Flow Restriction: The New Testament. *Tech Orthop*. 2018;33(2):72-79. doi:10.1097/BTO.0000000000000252

148. Kraemer WJ, Marchitelli L, Gordon SE, et al. Hormonal and growth factor responses to heavy resistance exercise protocols. *J Appl Physiol Bethesda Md 1985*. 1990;69(4):1442-1450. doi:10.1152/jappl.1990.69.4.1442

149. Reis JF, Fatela P, Mendonca GV, et al. Tissue Oxygenation in Response to Different Relative Levels of Blood-Flow Restricted Exercise. *Front Physiol*. 2019;10. doi:10.3389/fphys.2019.00407

150. Wernbom M, Aagaard P. Muscle fibre activation and fatigue with low-load blood flow restricted resistance exercise-An integrative physiology review. *Acta Physiol Oxf Engl*. 2020;228(1):e13302. doi:10.1111/apha.13302

151. Centner C, Lauber B. A Systematic Review and Meta-Analysis on Neural Adaptations Following Blood Flow Restriction Training: What We Know and What We Don't Know. *Front Physiol*. 2020;11:887. doi:10.3389/fphys.2020.00887

152. Hedt C, McCulloch PC, Harris JD, Lambert BS. Blood Flow Restriction Enhances Rehabilitation and Return to Sport: The Paradox of Proximal Performance. *Arthrosc Sports Med Rehabil*. 2022;4(1):e51-e63. doi:10.1016/j.asmr.2021.09.024

153. de Queiros VS, de França IM, Trybulski R, et al. Myoelectric Activity and Fatigue in Low-Load Resistance Exercise With Different Pressure of Blood Flow Restriction: A Systematic Review and Meta-Analysis. *Front Physiol*. 2021;12. Accessed August 23, 2022. https://www.frontiersin.org/articles/10.3389/fphys.2021.786752

154. Cerqueira MS, Maciel DG, Barboza JAM, et al. Low-Load Blood-Flow Restriction Exercise to Failure and Nonfailure and Myoelectric Activity: A Meta-Analysis. *J Athl Train*. 2022;57(4):402-417. doi:10.4085/1062-6050-0603.20

155. Koc BB, Truyens A, Heymans MJLF, Jansen EJP, Schotanus MGM. Effect of Low-Load Blood Flow Restriction Training After Anterior Cruciate Ligament Reconstruction: A Systematic Review. *Int J Sports Phys Ther*. 2022;17(3):334-346. doi:10.26603/001c.33151

156. Caetano D, Oliveira C, Correia C, Barbosa P, Montes A, Carvalho P. Rehabilitation outcomes and parameters of blood flow restriction training in ACL injury: A scoping review. *Phys Ther Sport Off J Assoc Chart Physiother Sports Med*. 2021;49:129-137. doi:10.1016/j.ptsp.2021.01.015

157. Wengle L, Migliorini F, Leroux T, Chahal J, Theodoropoulos J, Betsch M. The Effects of Blood Flow Restriction in Patients Undergoing Knee Surgery: A Systematic Review and Meta-analysis. *Am J Sports Med*. Published online August 18, 2021:3635465211027296. doi:10.1177/03635465211027296

158. Bobes Álvarez C, Issa-Khozouz Santamaría P, Fernández-Matías R, et al. Comparison of Blood Flow Restriction Training versus Non-Occlusive Training in Patients with Anterior Cruciate Ligament Reconstruction or Knee Osteoarthritis: A Systematic Review. *J Clin Med*. 2020;10(1):E68. doi:10.3390/jcm10010068

159. Baron JE, Parker EA, Duchman KR, Westermann RW. Perioperative and Postoperative Factors Influence Quadriceps Atrophy and Strength After ACL Reconstruction: A Systematic Review. *Orthop J Sports Med*. 2020;8(6):2325967120930296. doi:10.1177/2325967120930296

160. Charles D, White R, Reyes C, Palmer D. A SYSTEMATIC REVIEW OF THE EFFECTS OF BLOOD FLOW RESTRICTION TRAINING ON QUADRICEPS MUSCLE ATROPHY AND CIRCUMFERENCE POST ACL RECONSTRUCTION. *Int J Sports Phys Ther*. 2020;15(6):882-891. doi:10.26603/ijspt20200882

161. Colapietro M, Portnoff B, Miller SJ, Sebastianelli W, Vairo GL. Effects of Blood Flow Restriction Training on Clinical Outcomes for Patients with ACL Reconstruction: A Systematic Review. *Sports Health*. Published online February 8, 2022:19417381211070830. doi:10.1177/19417381211070834

162. Grapar Zargi T, Drobnic M, Jkoder J, Strazar K, Kacin A. The effects of preconditioning with ischemic exercise on quadriceps femoris muscle atrophy following anterior cruciate ligament reconstruction: a quasi-randomized controlled trial. *Eur J Phys Rehabil Med*. 2016;52(3):310-320.

163. Žargi T, Drobnič M, Stražar K, Kacin A. Short-Term Preconditioning With Blood Flow Restricted Exercise Preserves Quadriceps Muscle Endurance in Patients After Anterior Cruciate Ligament Reconstruction. *Front Physiol*. 2018;9:1150. doi:10.3389/fphys.2018.01150

164. Kacin A, Drobnič M, Marš T, et al. Functional and molecular adaptations of quadriceps and hamstring muscles to blood flow restricted training in patients with ACL rupture. *Scand J Med Sci Sports*. 2021;31(8):1636-1646. doi:10.1111/sms.13968

165. Takarada Y, Takazawa H, Ishii N. Applications of vascular occlusion diminish disuse atrophy of knee extensor muscles. *Med Sci Sports Exerc*. 2000;32(12):2035-2039. doi:10.1097/00005768-200012000-00011

166. Ohta H, Kurosawa H, Ikeda H, Iwase Y, Satou N, Nakamura S. Low-load resistance muscular training with moderate restriction of blood flow after anterior cruciate ligament reconstruction. *Acta Orthop Scand*. 2003;74(1):62-68. doi:10.1080/00016470310013680

167. Iversen E, Røstad V, Larmo A. Intermittent blood flow restriction does not reduce atrophy following anterior cruciate ligament reconstruction. *J Sport Health Sci*. 2016;5(1):115-118. doi:10.1016/j.jshs.2014.12.005

168. Hughes L, Paton B, Haddad F, Rosenblatt B, Gissane C, Patterson SD. Comparison of the acute perceptual and blood pressure response to heavy load and light load blood flow restriction resistance exercise in anterior cruciate ligament reconstruction patients and non-injured populations. *Phys Ther Sport Off J Assoc Chart Physiother Sports Med*. 2018;33:54-61. doi:10.1016/j.ptsp.2018.07.002

169. Hughes L, Patterson SD, Haddad F, et al. Examination of the comfort and pain experienced with blood flow restriction training during post-surgery rehabilitation of anterior cruciate ligament reconstruction patients: A UK National Health Service trial. *Phys Ther Sport Off J Assoc Chart Physiother Sports Med*. 2019;39:90-98. doi:10.1016/j.ptsp.2019.06.014

170. Hughes L, Rosenblatt B, Haddad F, et al. Comparing the Effectiveness of Blood Flow Restriction and Traditional Heavy Load Resistance Training in the Post-Surgery Rehabilitation of Anterior Cruciate Ligament Reconstruction Patients: A UK National Health Service Randomised Controlled Trial. *Sports Med Auckl NZ*. Published online July 12, 2019. doi:10.1007/s40279-019-01137-2

171. Kilgas MA, Lytle LLM, Drum SN, Elmer SJ. Exercise with Blood Flow Restriction to Improve Quadriceps Function Long After ACL Reconstruction. *Int J Sports Med*. 2019;40(10):650-656. doi:10.1055/a-0961-1434

172. Curran MT, Bedi A, Mendias CL, Wojtys EM, Kujawa MV, Palmieri-Smith RM. Blood Flow Restriction Training Applied With High-Intensity Exercise Does Not Improve Quadriceps Muscle Function After Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial. *Am J Sports Med*. 2020;48(4):825-837. doi:10.1177/0363546520904008

173. Noyes FR, Barber-Westin S, Sipes L. Blood Flow Restriction Training Can Improve Peak Torque Strength in Chronic Atrophic Postoperative Quadriceps and Hamstrings

Muscles. *Arthrosc J Arthrosc Relat Surg Off Publ Arthrosc Assoc N Am Int Arthrosc Assoc*. Published online March 31, 2021. doi:10.1016/j.arthro.2021.03.040

174. Tramer JS, Khalil LS, Jildeh TR, et al. Blood Flow Restriction Therapy for Two Weeks Prior to Anterior Cruciate Ligament Reconstruction Did not Impact Quadriceps Strength Compared to Standard Therapy. *Arthrosc J Arthrosc Relat Surg Off Publ Arthrosc Assoc N Am Int Arthrosc Assoc*. Published online July 14, 2022:S0749-8063(22)00402-9. doi:10.1016/j.arthro.2022.06.027

175. Tennent DJ, Hylden CM, Johnson AE, Burns TC, Wilken JM, Owens JG. Blood Flow Restriction Training After Knee Arthroscopy: A Randomized Controlled Pilot Study. *Clin J Sport Med Off J Can Acad Sport Med*. 2017;27(3):245-252. doi:10.1097/JSM.0000000000000377