The Impact of Blood Flow Restriction Training on Lower Extremity Strength after ACL Reconstruction in Adolescents: A Randomized Controlled Trial

IRB# :22-139

Clinical Trial#: XXX

January 8, 2023

PRINICPAL INVESTIGATOR: Adam Weaver DEPARTMENT: Farmington Sports PT INSTITUTION: Connecticut Children's Medical Center PHONE: 860-837-9220 EMAIL: aweaver@connecticutchildrens.org	CO-INVESTIGATOR: Dylan Roman DEPARTMENT: Farmington Sports PT INSTITUTION: Connecticut Children's Medical Center PHONE: 860-837-9220 EMAIL: droman@connecticutchildrens.org
CO-INVESTIGATOR: Art Fredericks DEPARTMENT: Farmington Sports PT INSTITUTION: Connecticut Children's Medical Center PHONE: 860-837-9220 EMAIL: Afredericks@connecticutchildrens.org	CO-INVESTIGATOR: Nicholas Giampetruzzi DEPARTMENT: Farmington Sports PT INSTITUTION: Connecticut Children's Medical Center PHONE: 860-837-9220 EMAIL: ngiampetruzzi@connecticutchildrens.org
CO-INVESTIGATOR: Julie Burland, PhD, ATC, CSCS DEPARTMENT: Department of Kinesiology INSTITUTION: UCONN Institute for Sports Medicine PHONE: 860-488-3623 EMAIL: julie.burland@uconn.edu	CO-INVESTIGATOR: Allison Crepeau, MD DEPARTMENT: Department of Orthopaedics INSTITUTION: Connecticut Children's Medical Center PHONE: 860-837-9220 EMAIL: acrepeau@connecticutchildrens.org
CO-INVESTIGATOR Matthew Brown, MD DEPARTMENT: Department of Orthopaedics INSTITUTION: Connecticut Children's Medical Center PHONE: 860-545-9100 EMAIL: mbrown05@connecticutchildrens.org	CO-INVESTIGATOR: Donna Pacicca, MD DEPARTMENT: Department of Orthopaedics INSTITUTION: Connecticut Children's Medical Center PHONE: 860-545-9100 EMAIL: dpacicca@connecticutchildrens.org
CO-INVESTIGATOR: Jennifer Prue DEPARTMENT: Sports Medicine INSTITUTION: Connecticut Children's Medical Center PHONE: 860-837-9220 EMAIL: JPrue@connecticutchildrens.org	
RESEARCH ASSISTANT: Megan Ranchinsky DEPARTMENT: Farmington Sports PT INSTITUTION: Connecticut Children's Medical Center PHONE: 860-837-9220 EMAIL: mranchinsky@connecticutchildrens.org	RESEARCH ASSISTANT: Adel Lolic DEPARTMENT: Farmington Sports PT INSTITUTION: Connecticut Children's Medical Center PHONE: 860-837-9220 EMAIL: alolic01@connecticutchildrens.org
STUDY COORDINATOR Jennifer Prue DEPARTMENT: Sports Medicine INSTITUTION: Connecticut Children's Medical Center PHONE: 860-837-9220 EMAIL: JPrue@connecticutchildrens.org	

IS THIS A STUDENT OR TRAINEE PROJECT? **_x__ NO** **___ YES**

IF YES, INDICATE LEVEL:

___ Medical/Dental Student
___ Resident
___ Fellow
___ Undergraduate
___ Other (specify _____)

IF YES, HAS FACULTY ADVISOR REVIEWED THE PROTOCOL? **___ NO** **___ YES**

Note: Student researchers are required to attend the Scientific Review Committee meeting when their protocol is discussed.

Contents

INTRODUCTION

Each year approximately 200,000 adolescents and young adults sustain a traumatic anterior cruciate ligament (ACL) injury, and develop long-term persistent weakness in their quadriceps. Half of these individuals will be diagnosed with posttraumatic knee osteoarthritis within 10-15 years.[1,2] Despite extensive research into optimal surgical and rehabilitative techniques, persistent quadriceps weakness is rampant, and nearly 1 in 3 young athletes suffer a second ACL injury. Quadriceps weakness negatively impacts gait and lower extremity biomechanics,[3,4] and is associated with higher risk for osteoarthritis development.[5-7] Quadriceps strength is modifiable, however, current rehabilitative therapies often fail to address the underlying mechanism driving this persistent dysfunction.[8,9] ACL injury induces a cascade of physiologic events[10] that produces a unique muscle atrophy profile[11] and creates an environment ripe for quadriceps muscle inhibition.[12-14] The current standard of care in the immediate stages after ACL reconstruction (ACLR) is as follows: exercise prescription for passive range of motion, pain and swelling control, gait training, and neuromuscular electrical stimulation for quadriceps muscle recruitment. This early post-operative window is also a critical period for restoring quadriceps strength.

BACKGROUND

Prevalence and impact of quadriceps weakness after ACL injury. Although there have been improvements and advances in surgical techniques, quadriceps weakness continues to be evident long after ACLR. Best evidence suggests that return to sports occurs at approximately 9 months after ACLR. Despite extensive rehabilitation, deficits in quadriceps strength still vary widely after ACLR, ranging from 3-40% at 6 months, and 3-38% at 12 months.[8] Further, there is evidence that these deficits can exist up to 4 years after surgery.[15] Unfortunately, these deficits often lead to post-traumatic osteoarthritis,[5] and future re-injury.[16] This is significant in that only 60% of these athletes return to sports at the same competitive level pre-injury. Therefore, it is imperative to seek new ways to address these limitations and overcome persistent quadriceps weakness.

Quadriceps atrophy resulting from joint injury. Atrophy is commonly seen in muscle tissue in the presence of disuse or inactivity. Recent evidence continues to demonstrate that the mechanisms of atrophy after traumatic ACL and joint injury are mechanistically and physiologically different. After ACL injury, the quadriceps experiences significant decreases in muscle volume, and this may be in large part due to neural signaling alternations both spinally and cortically.[17,18] These alterations directly impact the ability for the quadriceps to generate a muscle contraction.[11] Alterations in neural activation to the quadriceps also lead to changes in muscle fiber type, which contributes to difficulty in normalizing strength. At a cellular level, there are a number of negative factors influencing the quadriceps after ACL injury. Satellite cells, which are responsible for new muscle growth and regeneration, are often limited and fibrogenic cell expansion is seen within the quadriceps.[19] Further, levels of myostatin are elevated after ACL injury, and this is thought to negatively affect muscle mass and fiber size.[19] Myostatin directly influences satellite cell function, increases cytokine and other inflammatory components, and has a significant role in fibrotic pathways. Clinically, this creates an environment not conducive for muscle growth, making traditional physical therapy challenging.

Mechanisms of BFRT addressing quadriceps weakness. To date, rehabilitation strategies utilizing traditional strength training protocols targeting the quadriceps musculature have proven largely ineffective at fully restoring muscle function. This is in large part due to lack of consideration towards the underlying physiologic changes occurring in the muscle after ACLR. Clinical approaches that target specific cellular pathways should prove effective in combating muscle atrophy and inhibition and restore quadriceps function, and the most effective of such emerging therapies in adults is blood flow restriction training (BFRT). BFRT works by restricting venous outflow and partially restricting arterial outflow to the targeted tissue. While exercising, a pool of blood is created distal to the tourniquet that creates an environment of cellular swelling and local metabolic stress. The critical components of this environment is the stimulation of protein synthesis pathways and the local hypoxic environment, which: 1) increases type 2 fiber recruitment and 2) stimulates growth hormone production.[20-22] Recent studies have shown the use of BFRT positively impacts muscle protein synthesis, muscle size, and gene expression, as well as reducing myostatin levels[22-25]. Kakehi et al reported

that the use of BFRT (14-day mobilization) resulted in preservation of the quadriceps cross sectional area, as well as increased MuRF1 gene expression, a marker for muscle protein synthesis.[26] Further, after completion of an 8 week BFRT strength training program, improvements were observed in 1RM knee extension strength and decreased myostatin expression.[23]

Relationship between BFRT and ACLR. One of the earliest studies using BFRT 2x/day for 14 days after ACLR demonstrated an improved ability to limit post-operative muscle atrophy as compared to a control group.[27] More recent work has shown improvements in quadriceps peak torque of greater than 10% after 9 sessions of BFRT.[28] Other recent studies have shown similar improvements in cross sectional area, preservation of muscle mass, and similar changes in strength.[29,30] The use of BFRT after ACLR shows promise impacting muscle hypertrophy and knee extension strength in young adults, but has yet to be studied in adolescents. Our recent work from our pilot study has demonstrated significant improvements in quadriceps peak torque at 3 months post-ACLR,[31] and our future work will continue to build on this foundational evidence.

PREVIOUS WORK

Based on emerging work, and preliminary data from our research group,[31] the implementation of blood flow restriction training (BFRT) may be an advantageous tool to implement in the early post-operative period to combat quadriceps muscle weakness.[32] BFRT has been shown to be an effective alternative to high load resistance training (HL-RT) with comparable muscular and physiological benefits.[33,34] Previous work in young adults demonstrated that the use of BFRT mitigates quadriceps atrophy after ACLR.[27] Similarly, in adult patients, the use of BFRT in the early post-operative stages after ACLR has shown comparable improvements in quadriceps strength to HL-RT, and greater improvements in functional strength measures and self-reported function.[29] Together, these results are promising. However, there is limited knowledge pertaining to the impact of BFRT on quadriceps strength and function after ACLR in an adolescent age group.

The overall objective of this study is to investigate the impact of BFRT on isometric and isokinetic knee extension strength, quadriceps hypertrophy, and patient reported outcomes after ACLR at 5 different time points in the rehabilitation process. Adolescents and young adult patients undergoing ACLR at our institution and will be recruited to use BFRT for 8 weeks as part of their treatment compared to a standard ACL rehabilitation group at our institution

RESEARCH QUESTION

The purpose of this study is to compare the addition of a BFRT based exercise protocol to a standard ACL rehabilitation protocol in adolescents. Does the addition of BFRT-based exercise improve strength, hypertrophy, and patient reported outcomes after ACL reconstruction in the adolescent population?

PURPOSE OF THE RESEARCH, AIMS AND HYPOTHESES

The specific aims of this study are as follows.

Primary Aim 1: Determine if adjunct BFRT during ACLR post-surgical rehabilitation impacts isometric and isokinetic strength lower extremity strength, when compared to a control group receiving the standard of care rehabilitation.
Hypothesis 1a: We hypothesize that isometric knee extension peak torque and limb symmetry will be greater in the BFRT group compared to the control group at 8 and 12 weeks after ACLR.
Hypothesis 1b: We hypothesize that isokinetic knee extension peak torque and limb symmetry will be greater in the BFRT group compared to the control group at 6 months and time of return to sport after ACLR.
Hypothesis 1c: We hypothesize that the BFRT group will show a greater change in strength from pre-operative testing to 8 weeks post-operative from the control group.

Primary Aim 2: Determine if BFRT during ACLR post-surgical rehabilitation improves patient-reported outcomes (IKDC, KOOS, ACL-RSI) compared to the control group. We hypothesize that the BFRT group will show greater self-reported function and confidence as compared to the control group at all study time points.

Secondary Aim 1: Determine if the use of BFRT during ACLR post-surgical rehabilitation increases mid-thigh

circumference when compared to a control group. We hypothesize that the BFRT group will demonstrate five percent or greater difference in mid-thigh circumference than the control at all study time points.

OUTCOMES DEFINITIONS / DATA POINTS COLLECTED

1) *Demographic information*:

a. Age b. Medical record number c. Date of ACL surgery and related surgeries d. Date of Injury e. Sex f. Graft Type g. Concomitant pathology/Meniscal tear type, laterality h. Surgeon	h. Surgeon i. Sport j. Level of competition in sport k. Weight, Height and BMI l. Race m. Insurance status (Public/Private) n. Weight bearing status (number of weeks)

Primary Outcomes Definitions

Active knee range of motion: Knee AROM will be measured in supine position using a goniometer and standardized procedures reported by Norkin and White.[35]

Mid-thigh circumference will be used to measure and track muscle hypertrophy.

10 Repetition Max Test: The 10 repetition max test will be used to determine an estimate 1 rep maximum on the Shuttle Leg Press machine, as this is a safe and reliable alternative to predicting a 1 rep maximum.

Isometric thigh strength: Preoperative, 8 week and 12 weeks, 6 months and return to play assessments will measure maximum isometric muscle torque using an isokinetic dynamometer (Humac CSMi USA, Stoughton, MA, USA). Return to play assessments will occur at approximately 9 months post-operative.

Isokinetic thigh strength: For assessments at 6 months and time of return to play, maximum muscle torque will be assessed using an isokinetic dynamometer (Humac CSMi USA, Stoughton, MA, USA).

Patient Reported Outcomes:

1) **Pediatric International Knee Documentation Committee Subjective Knee Evaluation form (Pedi-IKDC)**

2) **Knee Injury and Osteoarthritis Outcome Score (KOOS)**

3) **Tegner Activity Scale**

4) **Anterior Cruciate Ligament Return to Sport Index (ACL-RSI) scale.**

These 4 outcome measures will be collected at Pre-op, 3months, 6months, return to play, and 2 years. The Pedi-IKDC form is a validated knee-specific questionnaire[36] that measures pain, symptoms, and functioning in daily and sport activities.[37,38] The KOOS form is a validated questionnaire that measures patient-reported pain, symptoms, activities of daily living, sport and recreation and quality of life.[39,40] The Tegner Activity Scale is a 2-item outcome measure on which participants are asked to describe the peak physical activity intensity prior to ACL injury and at the time of study enrollment. The ACL-RSI is a validated scale that is used to evaluate psychological readiness to return to sport,[41,42] and includes items that describe an individual's emotions, confidence in performance, and risk appraisal related to re-engagement in sport after ACLR.

STUDY DESIGN

A single randomized control trial will compare the use of exercises augmented with BFRT with quantitative measurements of strength and patient-reported outcomes. A total of 40 youth and adolescent patients undergoing a surgical procedure for ACLR and subsequent physical therapy at our institution will be recruited for this study. Patients will be randomized into one of two groups using computer randomization for allocation:

the *intervention group* receiving BFRT as part of physical therapy, and the *control group* will follow the institution's standard ACLR rehabilitation protocol. Both groups will follow a time- and criterion-based standardized rehabilitation protocol. The primary outcomes will be isometric and isokinetic knee peak torque and limb symmetry indices. Secondary outcomes will be quadriceps hypertrophy via mid-thigh circumference and patient-reported outcomes.

Target Population

Adolescent patients between the ages of 12 and 18 will be recruited at the time of surgery, specifically, those that participate in sports who are undergoing primary ACLR reconstruction at Connecticut Children's

Study Group and Control Group Inclusion Criteria

1) Prior to surgery participated in > 50 hours/year of level I or II sports as defined by Noyes et al[43] and planned to return to prior level.

Level I Sports (4-7 days/week)	Jumping, hard pivoting, cutting (basketball, volleyball, football, soccer, gymnastics, skiing. wrestling) Running, twisting, turning (racquet sports, baseball, hockey)
Level II sports (1-3 days/week)	Jumping, hard pivoting, cutting (basketball, volleyball, football, soccer, gymnastics, skiing. wrestling) Running, twisting, turning (racquet sports, baseball, hockey)

2) Completion of postoperative rehabilitation following standard protocols
3) Orthopedic surgical intervention and physical therapy completed at Connecticut Children's.

Study Group and Control Group Exclusion Criteria

1) An additional lower extremity injury at time of knee injury or previous surgical intervention on the knee (ipsilateral and contralateral)
2) Multiple ligament ruptures or trauma
3) Weight bearing restrictions for greater than 4 weeks after surgery due to concomitant pathology such as meniscal root/radial repair, chondral pathology, or multi-ligament pathology
4) Follow-up surgical procedures including, but not limited to, post-operative arthrofibrosis
6) Inability to attend regular physical therapy sessions (≥80% of patient treatment sessions and all assessment visits
7) Contraindications to performing BFRT including known history of central or peripheral neurologic impairments, cardiac or metabolic condition or history of deep vein thrombosis (DVT).

The exclusion of age is to ensure that the study population is old enough to complete testing on the HUMAC isokinetic dynamometer and young enough to be treated by one of our Sports Medicine physicians.

The secondary diagnosis and previous knee injury exclusions are to limit the influence of other diagnoses or injuries on measured knee strength, as well as provide a more homogeneous group for comparison to past data.

Identification, recruitment, consent and retention of subjects

Patient Screening and Determination of Eligibility

Pre-Screening

All potential patients undergoing ACL reconstruction at Connecticut Children's Sports Medicine will be approached for participation for this study. Patients scheduled to undergo ACL reconstruction will be screened by the individuals listed on this protocol using our pre-screening documentation form. All patients undergoing ACL reconstruction undergo a pre-operative appointment.

Identification and Recruitment:

Once identified as a potential candidate, the study purpose and protocol will be explained and a brief summary of the study will be provided at the conclusion of the pre-operative appointment. Patients must meet all the requirements of inclusion and exclusion criteria to be eligible for consent.

Consent: Consenting will take place at the pre-operative visit. The patient/parent will be given a detailed description of the purpose and methodology for this study. They will have the opportunity to read the consent forms and ask any questions they may have about the research. If they agree to participate, they will be asked to sign the consent form and a copy will be provided to the patient and family. All consenting documents will be stored in REDCap

If patients agree to enroll, all demographics and information listed in the protocol will be stored in REDCap on a data collection sheet that is listed in the attachments. This sheet will be used to record all pertinent information for all active participants on the study and will be stored in REDCap

.

Retention: Eligible patients will be required to be seen for a minimum of 80% of patient visits to be included in this study.

Data Collection:

Prior to completing enrollment measures, patients will provide written informed consent to participate in the study. Data collection will occur at five different time points during the rehabilitation process: preoperatively, 8 weeks, 12 weeks, 6 months, and time of return to play. Return to play assessments will be completed at approximately 9 months post-operatively. The schedule of study assessments is listed in Table 1 below.

Table 1. Schedule of Study Procedures and Assessments

Procedure	Pre-operative Screen	8 weeks	12 weeks	6 months	Return to Play	2 year follow-up
Informed Consent	x					
Background Information	x					
Patient Reported Outcomes	x	x	x	x	x	x
Estimated 1 rep Max	x					
Mid-thigh circumference	x	x	x	x	x	
Isometric thigh strength	x	x	x	x	x	
Isokinetic thigh strength				x	x	
Range of motion (ROM)	x	x***	x	x	x	
****ROM will be assessed and collected at each treatment visit for the first 8 weeks after surgery*						

Primary Outcomes (See table below):

Active knee range of motion: Knee AROM will be measured in supine position using a goniometer and standardized procedures reported by Norkin and White.[35]

Mid-thigh circumference will be used to measure and track muscle hypertrophy. Circumferential measurements has been shown to be valid and is often used after ACLR to assess quadriceps hypertrophy.[44] All subjects will be supine with the knee in full extension. The average of 3 measurements will be recorded with the starting point 10cm superior to the superior pole of the patella.

10 Repetition Max Test: The 10 repetition max test will be used to determine an estimate 1 rep maximum on the Shuttle Leg Press machine, as this is a safe and reliable alternative to predicting a 1 rep maximum. This will allow for exercise prescription.[45] All participants will complete a double leg and single leg Shuttle leg press 10 repetition maximum. The test will follow the protocol as recommended by the National Strength and Conditioning Association.[46]

Isometric thigh strength: Preoperative, 8 week, 12 week, 6 month, and return to play assessments will measure maximum isometric muscle torque using an isokinetic dynamometer (Humac CSMi USA, Stoughton, MA, USA). Patients will complete 3 trials with each knee in 60° of flexion and will be allowed a 5-second rest period between trials. The uninvolved limb's quadriceps and hamstring strength will be tested first, followed by the involved limb. Patients will be given verbal encouragement throughout the test to provide maximal effort. The highest peak torque measurement of the five trials will be collected and recorded in newton-meters (Nm). These peak torque values will be used to calculate the Limb Symmetry Index (LSI), or the ratio between the involved limb and uninvolved limb and expressed as a percentage. Peak torque will subsequently be normalized to the patient's body mass (kilogram) and recorded for analysis (Nm/kg).

Isokinetic thigh strength: For assessments at 6 months and time of return to play, maximum muscle torque will be assessed using an isokinetic dynamometer (Humac CSMi USA, Stoughton, MA, USA). Patients will be positioned in short sitting with 90 degrees of hip flexion, their trunk and thigh supported with straps, and dynamometer arm secured proximal to the ankle joint. The uninvolved limb's quadriceps and hamstring strength will be tested first, followed by the involved limb. Patients will be given verbal encouragement throughout the test to provide maximal effort. Using an isokinetic dynamometer in this manner has been shown to be a reliable method to quantify quadriceps and hamstring peak torque in adults[47,48] and children.[49] All administrators of the isokinetic testing are trained per HUMAC NORM standardized guidelines. Isokinetic quadriceps and hamstring torque was assessed through a knee range of motion from 0 to 90°, with gravity correction applied.[50] Three practice trials will be completed, followed by ten test trails (completed at 180°/sec) and two practice trials paired with five test trials (completed at 60°/sec). The highest peak torque measurement of the five trials will be collected and recorded in newton-meters (Nm). These peak torque values will be used to calculate the Limb Symmetry Index (LSI), or, the ratio between the involved limb and uninvolved limb and expressed as a percentage. Peak torque will subsequently be normalized to the patient's body mass and recorded for analysis (Nm/kg).

Patient Reported Outcomes:

1) **Pediatric International Knee Documentation Committee Subjective Knee Evaluation form (Pedi-IKDC)**

2) **Knee Injury and Osteoarthritis Outcome Score (KOOS)**

3) **Tegner Activity Scale**

4) **Anterior Cruciate Ligament Return to Sport Index (ACL-RSI) scale.**

Data will be collected at five different time points during the rehabilitation process. Additionally, we will collect data at 2 year phone/email follow up to record patient outcomes. These assessments are completed in conjunction with the surgeon's follow up visit. The physical therapist completing the assessment will record all outcomes in a REDcap database.

Assessment time point	***Data Points Collected***
Pre-op **8 weeks** **12 weeks**	*Range of motion (Involved/Uninvolved)* 1) Flexion and Extension(º) *HUMAC isometric knee extension at 60º (Involved/Uninvolved)* 2) Involved/Uninvolved Peak Torque (Nm) 3) Involved/Uninvolved Peak Torque normalized to bodyweight (Peak torque/bodyweight) (Nm-Kg) 4) Quadriceps Limb Symmetry Index (LSI)=Knee extension peak torque involved/knee extension peak torque uninvolved*100

	HUMAC isometric knee flexion at 60º (Involved/Uninvolved) 5) Involved/Uninvolved Peak Torque (Nm) 6) Hamstring deficit=Knee extension peak torque involved/knee extension peak torque uninvolved*100 7) Involved/Uninvolved Peak Torque normalized to bodyweight (Peak torque/bodyweight) (Nm-Kg) *Quadriceps hypertrophy thigh circumference (Involved/Uninvolved)* 8) Measured at 10cm above the superior pole of the patella bilaterally *Patient Reported Outcome Measures* 9) Pedi-IKDC 10) ACL-RSI 11) KOOS
6 months **9 months**	*Range of motion (Involved/Uninvolved)* 1) Flexion and Extension(º) *HUMAC isometric knee extension at 60º (Involved/Uninvolved)* 2) Involved/Uninvolved Peak Torque (Nm) 3) Involved/Uninvolved Peak Torque normalized to bodyweight (Peak torque/bodyweight) (Nm-Kg) 4) Quadriceps LSI= Knee extension peak torque involved/knee extension peak torque uninvolved*100 *HUMAC isometric knee flexion at 60º (Involved/Uninvolved)* 5) Involved/Uninvolved Peak Torque (Nm) 6) Hamstring deficit=Knee extension peak torque involved/knee extension peak torque uninvolved*100 7) Involved/Uninvolved Peak Torque normalized to bodyweight (Peak torque/bodyweight) (Nm-Kg) *Isokinetic knee extension at 180º/sec, and 60º/sec* 8) Involved/Uninvolved Peak Torque (Nm) 9) Quadriceps deficit=Knee extension peak torque involved/knee extension peak torque uninvolved*100 10) Involved/Uninvolved Peak Torque normalized to bodyweight (Peak torque/bodyweight) (Nm-Kg) *Isokinetic knee flexion at 180º/sec, and 60º/sec* 11) Involved/Uninvolved Peak Torque (Nm) 12) Hamstring deficit=Knee extension peak torque involved/knee extension peak torque uninvolved*100 13) Involved/Uninvolved Peak Torque normalized to bodyweight (Peak torque/bodyweight) (Nm-Kg) *Quadriceps hypertrophy thigh circumference (Involved/Uninvolved)*

	14) Measured at 10cm above the superior pole of the patella bilaterally *Patient Reported Outcome Measures* 15) Pedi-IKDC 16) ACL-RSI 17) KOOS
2 years	*Patient Reported Outcome Measures* 1) Pedi-IKDC 2) ACL-RSI 3) KOOS

1. Control Group: *All control group participants will follow the ACL reconstruction rehabilitation protocol These patients will complete outcome measures, and standardized strength assessments consistent with the standard current standard of care listed above. The same data points will be collected.*

2. All data collected all time points will be stored in a custom built REDcap database built specifically for this study.

Recruitment and Retention: We will track recruitment and retention as outcomes. Connecticut Children's sports medicine surgeons and physical therapists care for approximately 100-150 ACL tears per year on average. Our expertise in pediatric sports medicine positions us well to treat these patients after ACLR. Our physical therapists will care for approximately half of these patients on an annual basis. In our recent pilot study, we enrolled approximately 40 patients and had 0% attrition in our BFRT group throughout the study period. Our close relationship and adjoined clinic with our sports medicine providers allows us to target and recruit potential patients for enrollment. Our team has been able to identify and establish formal procedures for the recruitment and consenting process. We anticipate to enroll 2-4 patients/month, and at this rate we would finish enrollment within approximately 10 months.

Study Procedures: All patients that undergo ACLR at Connecticut Children's begin physical therapy within 5-7 days of surgery. The implementation of BFRT will begin at the **second** post-operative visit to account for differences in post-operative pain and recovery.

BFRT Intervention Group:
In addition to the standard ACL rehabilitation protocol, the experimental group will complete 2 exercises using the Delfi BFR cuff 2x/week for 8 weeks during their treatment session at Connecticut Children's Sports Physical Therapy on the second post-operative visit. Exercise selection is listed in Table 2. All patients will use the Delfi BFR unit and will complete exercises at 80% limb occlusion pressure. Cuff size will be determined by patient thigh circumference as described in Delfi BFR unit manual. Limb occlusion pressure will be determined in supine position and all exercises will be completed at 80% occlusion.

Control Group: In addition to the standard ACL rehabilitation protocol, the control group will complete the same exercises as the experimental group starting on the second post-operative visit.

Table 2. Exercise Progression		
	Long Arc Quadriceps (LAQ) progression	**Shuttle progression**

Post-op visit 2- 2 weeks	Quadriceps Set	Standing Straight Leg Raise
2 weeks-4 weeks	Available range LAQ	Standing terminal knee extension
4 weeks-8 weeks	LAQ (0-90°)	Single Limb Shuttle/Leg Press

Exercise volume and progression guidelines

BFR equipment: All participants in the intervention group will use an automatic personalized tourniquet system (Delfi Medical, Vancouver, BC). This is an FDA-approved device that automatically calculates limb occlusion pressure (LOP), which is defined as the minimum pressure required for full arterial occlusion.[51] The device increases cuff pressure in small increments, while analyzing pressure in the cuff, to help determine LOP. Additionally, the system uses a nylon and contoured cuff that is sized to the patient for comfort. All patients will have the LOP set while lying in the supine position, with the cuff in the most proximal portion of the involved limb. BFR pressure will be set to 80% LOP prior to initiating the exercise protocol.

BFRT Group:

a. Exercise volume: All patients in this study will complete 4 sets of an exercise, with goal repetitions of 30 in the first set, and 15 repetitions in sets 2-4, for a total of 75 repetitions. This method has been demonstrated to be effective in increasing muscle strength.[52-55] Upon completion of exercise, there will be a 30 second rest break between sets. Patients will be provided with a minimum of 1 minute rest and a maximum of 3 minutes between exercises to allow for adequate rest time and setup between exercises. To insure a controlled pace of completion, all patients will be encouraged to complete exercises with a 1 second concentric phase, 1 second isometric phase, and 1 second eccentric phase with the use of a metronome.

b. **Exercise progression**: Load progression of exercises will be based on the patient's ability to complete the prescribed number of total repetitions (75) as follows.
    - 75 Repetitions = Increase weight after 2 sessions
    - 60-74 Repetitions = Continue with training, but extend rest period between sets 3 and 4 to 45 second until 75 repetitions is completed.
    - 45-59 Repetitions = Stay at same weight until 75 repetitions are completed.
    - <44 Repetitions = Reduce load by approximately 10% until 75 repetitions is achieved

c. For the long arc quadriceps (LAQ) progression, all exercises will start with no external resistance and after every 2 sessions weight will be increased by 1 pound. For the Shuttle progression, exercises will start at 30% of patients 1RM. An estimated single leg and double leg 1 repetition max will be determined at pre-operative visit. Patients unable to complete the prescribed dosage will complete the exercise using both limbs on the Shuttle and will use a ratings of perceived exertion (RPE) scale to determine intensity. RPE has been shown to be an effective tool to individualize exercise prescription and load progression.[56]

d. The standing straight leg raise exercise will be completed from week 0-2 unless the patient is able to demonstrate 10 straight leg raise repetitions with minimal extensor lag. All standing exercises will be standardized to complete in the same position to have minimal compensation.

e. Discontinuation or stoppage of exercise: Patients will be instructed to attempt to complete all exercises. Should the patient be unable to tolerate 80% limb occlusion or report lower extremity paresthesia, the therapist will reduce occlusion by 5mmHg between exercise sets. Should the patient reach less than 60% limb occlusion, the exercise will be stopped.

f. At the completion of both exercises, patients will be asked to rate RPE, pain on a visual analog scale, and report from a list of documented adverse events.

Control Group: All exercises will be completed in the manner described above without the use of the Delfi BFR device. Exercise volume, progression, and discontinuation will be determined in the same manner.

Sample Size/Power Analysis: Based on our preliminary work evaluating differences between isometric quadriceps strength at 3 and 6 months after ACLR in adolescents, an a priori power analysis for a two-way

repeated measures analysis of variance (within-between interaction) was conducted using an alpha level of 0.05, power of 0.80 and moderate effect size (0.6). The projected sample size needed to determine differences between groups was determined to be 14 total individuals. Thus, we have increased the sample size to 40 (20 per group) to allow for even group numbers and to account for possible attrition.

Data analysis
Data will be collected on all patients enrolled into the study. Descriptive statistics will be generated on the demographic characteristics of both treatment groups. We will use a two-way repeated measures analysis of variance to determine the effect of treatment groups, BFRT compared to standard of care therapy, over time on subjective and objective outcomes. Exact analysis for each test will depend on variance and distribution/normality of data set. This will be achieved using the Statistical Package for the Social Sciences (SPSS) software version 27.0 (IBM Corp., Armonk, NY, USA). We will address each aim in the following manner.

Accrual and Expected Duration of Accrual

Once approved, we expect that this study can be accomplished within two to three years. The open period for this study will be between February 2022 and February 2025.

Study Limitations:

There are several limitations anticipated with this study that will impact its power and external validity. These limitations include an inherent sampling bias with our recruitment strategy, lack of patient or participant blinding, and small sample size.

Attempts will be made to reduce any potential bias by having standardized educational scripts regarding BFR training that each treating therapist will read to subjects prior to their first BFR session.

Subjects in our study will likely come from the same surgeons and the same type of ACL graft (QT). This could be a potential limitation in the generalizability of our results to other surgeons and graft types.

Administrative Organization

Roles and responsibilities:

Adam Weaver, PT, DPT**:** Will serve as the study's primary investigator. Adam will provide primary support for the SRC and IRB study protocol development and submission, as well as maintaining updates and compliance with clinicaltrials.gov**.** He will review the required databases and pull the relevant data required to complete this study. He will also aid in data interpretation and manuscript preparation.

All MDs listed: The MDs listed on this proposal will be responsible for recruitment of patients, data interpretation and manuscript preparation.

All physical therapists listed: The PT's listed on this proposal will serve as the study's co-investigator. They will provide support in development of SRC and IRB documents (review of literature). They will help with data collection, recruitment, consenting patients.

Jennifer Prue: Jennifer is ATC in Sports Medicine who will assist with relcruitment, consenting, and data collection. She also will serve as the study coordinator.

Adel Lolic, Megan Ranchinsky: Our exercise technologists listed will assist with consenting, as well as data collection during testing times, and organizing tabulated results.

Julie Burland, ATC, PhD: Julie is a researcher at UCONN Sports Medicine Institute. She will be assisting in study design, data interpretation and preparation, statistical analysis and manuscript preparation:

Data Collection and Management

a. Data collection forms: All data points and outcome measures will be completed and entered into a REDcap database to facilitate data analysis.

b. Data collection software: The Research Operations and Development team assisted with the development of this REDCap project. Connecticut Children's has licensed this software toolset and workflow methodology for electronic collection and management of research data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study. The development and testing process results in a well–planned data collection strategy for studies. This project will use REDCap data transactions due to the web–based information transmission being encrypted. REDCap was developed specifically around HIPAA–Security guidelines. REDCap has been disseminated for use locally at other institutions and currently supports over 5854 academic/non-profit consortium partners and over 2.1 million research end–users (www.project-redcap.org)Adam Weaver will oversee data management. The data will be collected by investigators, and it will be entered into REDCap by Adam Weaver and Jennifer Prue to insure data accuracy. Statistics will be run using Microsoft Excel and SPSS.

d. Adam Weaver will oversee data management. The data will be collected by investigators, and it will be stored only in REDcap. The database will only be accessible to those individuals included in this study.
e. Information will be reviewed prior to de-identification to insure there are no errors with transcription.
f. Data quality assurance: Data that is collected will be manually verified to ensure that no information has been entered into REDcap incorrectly. Additionally, we will randomly check 10% of data in the REDcap database for accuracy after initial entry to insure accuracy
g. Record retention and confidentiality will be dictated by the current procedures in place here at Connecticut Children's. All information will be stored in a private office and on a single password protected computer. No access to information is possible from an outside source.

Human Subjects Protections and Ethical Conduct of the Study

Patient confidentiality statement

Strict measures will be required for respecting and maintaining patient confidentiality. Application for IRB approval is currently being created for submission, and once IRB evaluation has occurred we will make any changes required to ensure HIPPA compliance. Collection of a patient identifier including medical record numbers and the patients name is necessary to ensure comprehensive inclusion of eligible subjects and accurate linking of data from different data sets. The database used for the study will be password protected and stored in REDcap. Once we have collected all the data, the data set will be frozen for analysis. At this time, we will completely de-identify all subjects. Medical record numbers as well as the patient's names will be removed and patients will be referred to by study number only. De-identification will take place once we have collected all data. In the event that further time is needed prior to de-identification of the data set, we will request a continuation through the IRB at the time of annual review of the protocol. We expect that these measures will minimize any risk to confidentiality very effectively, and that any unavoidable residual risk will be balanced generously by the potential benefit to society of the knowledge that will be obtained through this research.

Financial: There are no financial burdens for the subjects. There are no extra costs due to travel to extra appointments or therapy sessions as the subjects will follow standard of care protocols for timing and quantity of physical therapy and follow-up appointments with their surgeon.

Benefits: The results of this study would benefit patients, surgeons, rehabilitation specialists, and of course future patients and their families by possibly providing a method of determining the patient's progress at an earlier stage and allow for early interventions to improve the patient's outcome.

Risk: The risk to patients using BFR is anticipated to be minimal overall. Several studies on adults after ACLR has shown that BFR is well tolerated, and our recently published study on BFR in adolescent showed similar findings. [57-59] To monitor patient tolerance, patients will rate pain levels using a visual analog scale,[60] RPE, and our team will screen for adverse responses. Though these response are rare, we will monitor for pain, bruising, dizziness, and nausea. At subsequent follow up PT visits, we will monitor for any potential delayed events.

Use of results of study

The results of this study would provide the Connecticut Children's Sports Medicine surgeons and physical therapists here at Connecticut Children's information to determine the effectiveness and application of the use of BFR in conjunction with exercise.

Study Budget

Equipment and Supplies: There will be no equipment costs associated with this study. The BFR Delfi units that are necessary for completion of BFR exercise by the intervention group are already owned by Connecticut Children's Sports Physical Therapy

Travel: There will be no travel costs associated with this study.

All personnel will provide effort that is in kind, and there will be no stipends provided to the patients. These follow up assessment visits currently already occur as the standard of care for all patients undergoing ACLR at Connecticut Children's

Budget Justification

All treatment visits and follow up visits will be covered by patient insurance 97110 and 97140 CPT code will cover the costs of all physical therapist treatment visits.

The 97530 codes will cover all assessment visits (12 weeks, 6 months, and return to play)

Note: The sports physical therapists who will guide the patient in performing the functional assessment skills and follow the standard of care in grading these skills will bill their services to the patient's insurance.

Appendices (as needed)

The attached data collection from in MS excel will serve as a template initially. Upon IRB approval, a full RED cap data base will be built to include all data points mentioned above.

CITATIONS:

1. Hewett TE SJS, L.Y G. Understanding and preventing noncontact ACL injuries. *Human Kinetics Publishers.* 2007.
2. Mather RC, Koenig L, Kocher MS, et al. Societal and Economic Impact of Anterior Cruciate Ligament Tears. *Journal of Bone and Joint Surgery.* 2013;95(19):1751-1759.
3. Butler RJ, Minick KI, Ferber R, Underwood F. Gait mechanics after ACL reconstruction: implications for the early onset of knee osteoarthritis. *Br J Sports Med.* 2009;43(5):366-370.
4. Shimizu T, Samaan MA, Tanaka MS, et al. Abnormal biomechanics at 6 months are associated with cartilage degeneration at 3 years after anterior cruciate ligament reconstruction. *Arthroscopy.* 2019;35(2):511-520.
5. 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.
6. Webster KE, Feller JA. Exploring the high reinjury rate in younger patients undergoing anterior cruciate ligament reconstruction. *Am J Sports Med.* 2016;44(11):2827-2832.
7. Paterno MV, Rauh MJ, Schmitt LC, Ford KR, Hewett TE. Incidence of second ACL Injuries 2 years after primary ACL reconstruction and return to sport. *Am J Sports Med.* 2014;42(7):1567-1573.
8. Thomas AC, Wojtys EM, Brandon C, Palmieri-Smith RM. Muscle atrophy contributes to quadriceps weakness after anterior cruciate ligament reconstruction. *J Sci Med Sport.* 2016;19(1):7-11.
9. Welling W, Benjaminse A, Seil R, Lemmink K, Zaffagnini S, Gokeler A. Low rates of patients meeting return to sport criteria 9 months after anterior cruciate ligament reconstruction: a prospective longitudinal study. *Knee Surg Sports Traumatol Arthrosc.* 2018;26(12):3636-3644.
10. Lepley AS, Grooms DR, Burland JP, Davi SM, Kinsella-Shaw JM, Lepley LK. Quadriceps muscle function following anterior cruciate ligament reconstruction: systemic differences in neural and morphological characteristics. *Experimental Brain Research.* 2019;237(5):1267-1278.
11. Lepley LK, Davi SM, Burland JP, Lepley AS. Muscle atrophy after ACL injury: implications for clinical practice. *Sports Health.* 2020;12(6):579-586.

12. Lepley AS, Lepley LK. Mechanisms of arthrogenic muscle inhibition. *J Sport Rehabil.* 2021:1-10.
13. Norte G, Rush J, Sherman D. Arthrogenic Muscle Inhibition: Best Evidence, Mechanisms, and Theory for Treating the Unseen in Clinical Rehabilitation. *J Sport Rehabil.* 2021:1-19.
14. Sonnery-Cottet B, Saithna A, Quelard B, et al. Arthrogenic muscle inhibition after ACL reconstruction: a scoping review of the efficacy of interventions. *British Journal of Sports Medicine.* 2019;53(5):289-298.
15. Brown C, Marinko L, Lavalley MP, Kumar D. Quadriceps Strength After Anterior Cruciate Ligament Reconstruction Compared With Uninjured Matched Controls: A Systematic Review and Meta-analysis. *Orthopaedic Journal of Sports Medicine.* 2021;9(4):232596712199153.
16. Paterno MV, Rauh MJ, Thomas S, Hewett TE, Schmitt LC. Quadricep Femoris Strength at Return to Sport Identifies Limb at Increased Risk of Future ACL Injury after ACL Reconstruction in Young Athletes. *Orthopaedic Journal of Sports Medicine.* 2019;7(7_suppl5):2325967119S2325960032.
17. Lepley AS, Gribble PA, Thomas AC, Tevald MA, Sohn DH, Pietrosimone BG. Quadriceps neural alterations in anterior cruciate ligament reconstructed patients: A 6-month longitudinal investigation. *Scand J Med Sci Sports.* 2015;25(6):828-839.
18. Kuenze CM, Hertel J, Weltman A, Diduch D, Saliba SA, Hart JM. Persistent Neuromuscular and Corticomotor Quadriceps Asymmetry After Anterior Cruciate Ligament Reconstruction. *Journal of Athletic Training.* 2015;50(3):303-312.
19. Fry CS, Johnson DL, Ireland ML, Noehren B. ACL injury reduces satellite cell abundance and promotes fibrogenic cell expansion within skeletal muscle. *Journal of Orthopaedic Research.* 2017;35(9):1876-1885.
20. Loenneke JP, TJ. The Use of Occlusion Training to Produce Muscle Hypertrophy. *Strength and Conditioning Journal.* 2009.
21. Loenneke JP, Fahs CA, Rossow LM, Abe T, Bemben MG. The anabolic benefits of venous blood flow restriction training may be induced by muscle cell swelling. *Med Hypotheses.* 2012;78(1):151-154.
22. Lindholm ME, Rundqvist H. Skeletal muscle hypoxia-inducible factor-1 and exercise. *Exp Physiol.* 2016;101(1):28-32.
23. Laurentino GC, Ugrinowitsch C, Roschel H, et al. Strength training with blood flow restriction diminishes myostatin gene expression. *Med Sci Sports Exerc.* 2012;44(3):406-412.
24. Pearson SJ, Hussain SR. A Review on the Mechanisms of Blood-Flow Restriction Resistance Training-Induced Muscle Hypertrophy. *Sports Medicine.* 2015;45(2):187-200.
25. Nielsen JL, Aagaard P, Prokhorova TA, et al. Blood flow restricted training leads to myocellular macrophage infiltration and upregulation of heat shock proteins, but no apparent muscle damage. *J Physiol.* 2017;595(14):4857-4873.
26. Kakehi S, Tamura Y, Kubota A, et al. Effects of blood flow restriction on muscle size and gene expression in muscle during immobilization: A pilot study. *Physiological Reports.* 2020;8(14).
27. 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.
28. Noyes FR, Barber-Westin SD, Sipes L. Blood Flow Restriction Training Can Improve Peak Torque Strength in Chronic Atrophic Postoperative Quadriceps and Hamstrings Muscles. *Arthroscopy.* 2021.
29. 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.* 2019;49(11):1787-1805.
30. Jack RA, Lambert BS, Hedt CA, Delgado D, Goble H, McCulloch PC. Blood Flow Restriction Therapy Preserves Lower Extremity Bone and Muscle Mass After ACL Reconstruction. *Sports Health: A Multidisciplinary Approach.* 2022:194173812211010.

31. Giampetruzzi N, Fredericks A, Roman D, et al. The Effects of Blood Flow Restriction Training on Strength and Function During Early Rehabilitation After Anterior Cruciate Ligament Reconstruction in Adolescents. *Orthopaedic Journal of Sports Medicine.* 2022;10(5_suppl2):2325967121S2325960044.
32. Hughes L. Blood Flow Restriction Training in Rehabilitation Following Anterior Cruciate Ligament Reconstructive Surgery: A Review. *Techniques in Orthopedics.* 2018;33(2):106-113.
33. Scott BR, Loenneke JP, Slattery KM, Dascombe BJ. Exercise with blood flow restriction: an updated evidence-based approach for enhanced muscular development. *Sports Med.* 2015;45(3):313-325.
34. 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 Medicine.* 2018;48(2):361-378.
35. Norkin CC WD. *Measurement of Joint Motion, A Guide to Goniometry. .* 3rd edition ed. Philadelphia: FA Davis; 2003.
36. 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.
37. Kocher MS, Smith JT, Iversen MD, et al. Reliability, Validity, and Responsiveness of a Modified International Knee Documentation Committee Subjective Knee Form (Pedi-IKDC) in Children With Knee Disorders. *The American Journal of Sports Medicine.* 2011;39(5):933-939.
38. Irrgang JJ, Anderson AF, Boland AL, et al. Development and Validation of the International Knee Documentation Committee Subjective Knee Form. *The American Journal of Sports Medicine.* 2001;29(5):600-613.
39. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon B. Knee Injury and Osteoarthritis Outcome Score (KOOS) - Development of a Self-Adminstered Outcome Measure. *Journal of Orthopaedic & Sports Physical Therapy.* 1998;28(2):88-96.
40. Salavati M, Akhbari B, Mohammadi F, Mazaheri M, Khorrami M. Knee injury and Osteoarthritis Outcome Score (KOOS); reliability and validity in competitive athletes after anterior cruciate ligament reconstruction. *Osteoarthritis Cartilage.* 2011;19(4):406-410.
41. 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.* 2008;9(1):9-15.
42. Ardern CL, Osterberg A, Tagesson S, Gauffin H, Webster KE, Kvist J. The impact of psychological readiness to return to sport and recreational activities after anterior cruciate ligament reconstruction. *Br J Sports Med.* 2014;48(22):1613-1619.
43. Noyes FR. A Rationale for Assessing Sports Activity Levels and Limitations in Knee Disorders. 1989;246.
44. Soderberg GL, Ballantyne BT, Kestel LL. Reliability of lower extremity girth measurements after anterior cruciate ligament reconstruction. *Physiother Res Int.* 1996;1(1):7-16.
45. Reynolds JM, Gordon TJ, Robergs RA. Prediction of one repetition maximum strength from multiple repetition maximum testing and anthropometry. *J Strength Cond Res.* 2006;20(3):584-592.
46. Baechle TRE, R.W. . *Essentials of strength training and conditioning.* 3rd ed. Champaign, IL: Human Kinetics; 2008.
47. Hirano M, Katoh M, Gomi M, Arai S. Validity and reliability of isometric knee extension muscle strength measurements using a belt-stabilized hand-held dynamometer: a comparison with the measurement using an isokinetic dynamometer in a sitting posture. *J Phys Ther Sci.* 2020;32(2):120-124.

48. Toonstra J, Mattacola CG. Test-retest reliability and validity of isometric knee-flexion and -extension measurement using 3 methods of assessing muscle strength. *J Sport Rehabil.* 2013;22(1).
49. Johnsen MB, Eitzen I, Moksnes H, Risberg MA. Inter- and intrarater reliability of four single-legged hop tests and isokinetic muscle torque measurements in children. *Knee Surg Sports Traumatol Arthrosc.* 2015;23(7):1907-1916.
50. Undheim MB, Cosgrave C, King E, et al. Isokinetic muscle strength and readiness to return to sport following anterior cruciate ligament reconstruction: is there an association? A systematic review and a protocol recommendation. *Br J Sports Med.* 2015;49(20):1305-1310.
51. Recommended Practices for the Use of the Pneumatic Tourniquet in the Perioperative Practice Setting. *AORN Journal.* 2007;86(4):640-655.
52. Loenneke JP, Thiebaud RS, Fahs CA, Rossow LM, Abe T, Bemben MG. Blood flow restriction does not result in prolonged decrements in torque. *European Journal of Applied Physiology.* 2013;113(4):923-931.
53. Thiebaud RS, Yasuda T, Loenneke JP, Abe T. Effects of low-intensity concentric and eccentric exercise combined with blood flow restriction on indices of exercise-induced muscle damage. *Interv Med Appl Sci.* 2013;5(2):53-59.
54. Wilson J LR, Joy JM. Practical blood flow restriction training increases acute determinants of hypertrophy
without increasing indices of muscle damage. *J Strength Cond Res.* 2013;27:3068-3075.
55. Yasuda T, Fujita S, Ogasawara R, Sato Y, Abe T. Effects of low-intensity bench press training with restricted arm muscle blood flow on chest muscle hypertrophy: a pilot study. *Clin Physiol Funct Imaging.* 2010;30(5):338-343.
56. Kiely J. Periodization paradigms in the 21st century: evidence-led or tradition-driven? *Int J Sports Physiol Perform.* 2012;7(3):242-250.
57. Brandner C, May, A.K., Clarkson, M., & Warmington, S. . Reported side-effects and safety considerations for the use of blood flow restriction during exercise in practice and research. *Tech Orthop.* 2018;33(3):114-121.
58. Clark BC, Manini TM, Hoffman RL, et al. Relative safety of 4 weeks of blood flow-restricted resistance exercise in young, healthy adults. *Scand J Med Sci Sports.* 2011;21(5):653-662.
59. Prue J, Roman DP, Giampetruzzi NG, et al. Side Effects and Patient Tolerance with the Use of Blood Flow Restriction Training after ACL Reconstruction in Adolescents: A Pilot Study. *Int J Sports Phys Ther.* 2022;17(3):347-354.
60. McGrath PA, Seifert CE, Speechley KN, Booth JC, Stitt L, Gibson MC. A new analogue scale for assessing children's pain: an initial validation study. *Pain.* 1996;64(3):435-443.