The Effect of Blood Flow Restriction Therapy Following Anterior Cruciate Ligament Reconstruction

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ABSTRACT

Title: The Effect of Blood Flow Restriction Therapy on Outcomes Following Anterior Cruciate Ligament Reconstruction

Short Title: Effect of BFR on ACL Reconstruction

Rationale: To investigate the effect of Blood Flow Restriction (BFR) exercises on the recovery process following an Anterior Cruciate Ligament (ACL) reconstruction.

Objectives: The main objective is to determine the impact of BFR therapy, in comparison to a standard rehabilitation protocol, on the functional outcomes of patients recovering from ACL reconstruction. The secondary objective is to determine if there are any adverse effects associated with BFR exercises.

Study Type: Prospective Randomized Control Trial (Level 1)

Study Design: Prospective Randomized Control Trial

Study Methodology:
Prospective data will be collected on 150 patients total, randomly divided into two groups based on the physical therapy regimen: (1) standard ACL rehabilitation (control group), and (2) standard ACL rehabilitation plus BFR therapy (BFR group). Patients in the BFR group will begin BFR therapy post-operative week 2, which will consist of the standard ACL rehabilitation exercises augmented with a pressure cuff during the session.

Inclusion criteria will consist of patients 13-55 years undergoing ACL reconstruction. Exclusion criteria include concomitant ligament reconstruction or concurrent procedures that require delayed weight bearing such as High Tibial Osteotomy (HTO), microfracture, etc. Additional exclusion criteria include history of DVT/PE, immunocompromising conditions, history of coagulation disorders or current use of anticoagulants, and pregnancy.

Outcome measures will include Knee Injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee Subjective Knee Evaluation Form (IKDC), Limb Symmetry Index (LSI), thigh circumference, and return to sport. Baseline scores will be obtained prior to surgery when applicable. Outcomes will be measured at designated time intervals for 2 year following surgery.

Statistical Methodology: Data will be reviewed by a trained statistician. Repeated-measures analysis of variance (ANOVA) will be used to evaluate all patient-reported outcome surveys at multiple time points. All statistical tests will use two-tailed hypothesis testing with the statistical significance a priori set at alpha, α, is equal to 0.05

1. INTRODUCTION

1.1 Specific Aims

It is hypothesized that blood flow restriction (BFR) therapy can help stimulate muscular development while recovering from surgery, producing a more rapid increase in function and an expedited return to playing sports.

Our primary objective is to determine the effect BFR exercises on the functional outcomes of patients recovering from ACL reconstruction, compared to that of a control group using a standard rehabilitation protocol. The secondary objective is to determine if any adverse effects or complications are associated with BFR therapy.

1.2 Hypotheses

It is hypothesized that patients undergoing BFR will show significantly improved outcome measurements throughout rehabilitation after ACL reconstruction.

	Rehabilitation with BFR	**Standard Rehabilitation without BFR**
KOOS	Better	Worse
IKDC	Better	Worse
VAS	Better	Worse
Limb Symmetry Index (LSI)	Better	Worse
Thigh circumference	Better	Worse
Return to sport	Better	Worse

Null Hypothesis: There is no statistically significant difference in the functional outcomes of patients using a standard ACL rehabilitation protocol versus a standard ACL rehabilitation protocol augmented with BFR therapy.

1.3 Background and Significance

Recovery from anterior cruciate ligament (ACL) reconstruction involves early physical therapy to promote muscular development. Traditional training regimens are based on the concept that muscle growth is induced with high resistance exercises of at least 65-70% of 1-repetition maximum [1,4]. Achieving a high resistance level can be challenging in the early post-surgical patient who may be limited by pain, muscle atrophy, diminished proprioception, and psychological factors. Increasing evidence has suggested that Blood Flow Restriction (BFR) in resistance training, while transmitting a decreased load (25-50% of 1-repetition maximum) across the surgical site, may provide an additional benefit of inducing muscular development similar to that of high intensity exercises [2].

Augmenting exercises with BFR involves an external pressure cuff applied to the proximal portion of the extremity, which is inflated to a pressure that restricts venous outflow while allowing arterial inflow to continue. This creates a pooling of oxygen poor blood that causes a buildup of lactic acid and protons, which stimulates ILGF-1, and other factors that lead to the release of human-growth hormone (HGH), and muscle hypertrophy. This allows patients to gain the hypertrophic effect of high resistance training, though at a lower and safer resistance level. Studies suggest that BFR stimulates muscular development through an increase in metabolic stress, muscle fiber recruitment, cell swelling, and protein synthesis [5-8].

Despite numerous basic science studies supporting the use of BFR in general strength development, and muscular development in deconditioned patient populations, few articles have assessed the role of BFR therapy in postoperative rehabilitation in athletes. When utilizing BFR in isolation without strength training for patients after ACL reconstruction, an early study [7] found a decrease in disuse quad atrophy based on MRI cross-section area (CSA), but these results could not be reproduced in a later study [2] with similar methodology. In another study of patients following ACL reconstruction, significantly greater increases in muscle strength and CSA were seen after 16 weeks in patients performing therapy exercises with BFR when compared to a non-BFR control group [3]. The purpose of this investigation is to assess the functional outcomes of patients using BFR therapy, compared to a control group, following ACL reconstruction.

1.4 Preliminary Studies

No preliminary studies have been performed. The Principal Investigator is a board-certified, fellowship trained Orthopedic Sports Medicine Surgeon.

2. STUDY DESIGN AND SUBJECT SELECTION

2.1 Study Type

This will be a single-center randomized control trial. Patients will be recruited, consented, enrolled, and randomized before their ACL reconstruction surgery

2.2 Setting/Location

Surgery will be performed at an Inova facility. Physical therapy will be performed at an INOVA-affiliated physical therapy facility. Patients will be followed throughout their recovery in an outpatient setting at the Inova Orthopedics and Sports Medicine offices located 8100 Innovation Park Dr., Suite 110, Fairfax, VA 22031.

2.3 Duration of Study

The study will encompass an enrollment period of 150 patients undergoing ACL reconstruction, as well as an additional 2 year of follow up after the final patient undergoes surgery.

2.4 Number of Subjects

The goal is to include 150 subjects in the study, which will be divided into 75 patients in the treatment group and 75 patients in the control group.

2.5 Study Population

2.5.1 Gender of Subjects

Subjects of all genders will be included in this study.

2.5.2 Age of Subjects

Patients 13-55 years old will be eligible for inclusion.

2.5.3 Racial and Ethnic Origin

Patients of all races and ethnicities will be open to inclusion.

2.5.4 Vulnerable Populations

Consent for enrollment and outcome measures may be translated for non-English speakers as needed. Pregnant women will be excluded from the study. Minors will be enrolled in the study with consent obtained from their guardians.

2.6 Recruitment

Recruitment will include all patients that meet the inclusion criteria who choose to undergo ACL reconstruction with an INOVA sports medicine fellowship-trained orthopedic surgeon.

2.7 Inclusion Criteria

1. Age 13-55 years at the time of surgery
2. ACL reconstruction
3. Using an Inova affiliated physical therapy practice for rehabilitation

2.8 Exclusion Criteria

Patients with a diagnosed ACL reconstruction that chose not to undergo reconstruction

1. Concomitant ligament reconstruction
2. Concurrent procedures that require delayed weight bearing (ie: HTO, multiligament reconstruction, microfracture, etc)
3. History of DVT/PE
4. Immunocompromising conditions (ie: Rheumatoid arthritis, chronic steroid use, etc.)
5. History of coagulation disorders or current use of anticoagulants
6. Completion of physical therapy at a location not affiliated with the study
7. Pregnancy

3. STUDY METHODS AND PROCEDURES

3.1 Study Treatment/Intervention

Patients assigned to the intervention group will undergo BFR exercises in addition to the standard rehabilitation protocol. BFR therapy will be administered at an INOVA physical therapy location by a certified physical therapist that is trained in BFR modalities. Therapists will follow a standardized ACL rehabilitation protocol (see appendix), which consists of 2-3 therapy sessions per week following surgery. BFR exercises will begin after the surgical incision has healed and post-operative swelling is minimized. This generally occurs two weeks post-operatively.

3.2 Control Group

Patients assigned to the control group will complete a standardized ACL rehabilitation protocol that does not include BFR therapy (see appendix). Similar to the treatment group, the protocol will incorporate 2-3 therapy sessions per week following surgery, which will be administered by a certified physical therapist at an INOVA physical therapy location.

3.3 Randomization

Upon enrollment in the study, before their surgery, patients will be randomly assigned to the treatment group (75 subjects) or control group (75 subjects) using a random number generator.

3.4 Endpoints/Outcomes Measurement

3.4.1 Primary Outcomes

The main objective is to determine whether BFR therapy has an effect on the functional outcomes of patients recovering from ACL reconstruction. Functional outcome measures will include Knee Injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee Subjective Knee Evaluation Form (IKDC), Limb Symmetry Index (LSI), knee extension strength using a dynamometer, and return to sport.

3.4.2 Secondary Outcomes

The secondary objective is to determine if BFR exercises are associated with adverse effects such as numbness, tourniquet-site pain, and bruising.

3.5 Consent/Assent

Patients will be assented with their parent(s)/guardian(s) consent. A witness will confirm the agreement to enroll and patients will always be required to be accompanied by their parent/guardian at each visit, if they are under the age of 18. If the patient should turn 18 during the course of the study (13-17 years old at enrollment), they will be re-consented as an adult at that time. Patients will not be coerced to participate in this research study and they will be informed that the quality or type of care received at Inova will not be affected by their decision to participate in this study.

Individuals who are able to assent/consent patients are Drs. Robin West, Edward Chang, Andrew Curley or Kendall Robinson. Drs. West and Chang are the participating surgeons on this study. Both are board certified Orthopaedic Surgeons who are fellowship-trained in Sports Medicine. Both surgeons are skilled in conducting clinical examinations, reviewing diagnostic imaging, performing surgery, and post-operative management. Dr. Curley is a chief orthopaedic surgery resident at Georgetown University. All of these individuals are qualified to speak on the surgical and study procedures. All have completed the WIRB-Copernicus Group Academy (WCGA) research ethics training and have completed particular modules in obtaining informed consent.

Separate HIPAA authorization will be obtain from each patient or parent(s)/guardian(s) of the patient. Parent(s)/guardian(s) will consent and provide HIPAA authorization, in addition to, getting the child's assent. Adult patients will only need to provide HIPAA authorization as well as consent for participation in the study.

3.6 Data Collection

The following data will be recorded:

Demographics:

- Gender
- Age at time of surgery
- BMI at time of surgery
- Sports participation (if applicable):
    - Type of sport
        - ie: football, soccer, baseball, track, etc.
    - Level of competition
        - High school
        - Collegiate

        - Professional
        - Recreational
- Prior knee injuries:
    - Eg. ipsilateral/contralateral ACL tears, meniscal injuries, chondral injury
- Smoking status
    - Non-smoker
    - Former smoker
    - Smoker (number of packs per day)
- Diabetes

Injury Data:

- Laterality of injury
    - Left
    - Right
- Date of injury
- Time from injury to surgery
- Mechanism of injury:
    - Contact
    - Non-contact (ie: twisting)
- Concomitant ligament injury observed on MRI:
    - Ligament
        - Medial Collateral Ligament (MCL)
        - Lateral Collateral Ligament and/or Posterolateral corner (LCL/PLC)
        - Posterior Cruciate Ligament (PCL)
    - Severity of injury
        - Grade 1: (minor sprain) high signal is seen medial (superficial) to the ligament, which looks normal
        - Grade 2: (severe sprain or partial tear) high signal is seen medial to the ligament, with high signal or partial disruption of the ligament
        - Grade 3: complete disruption of the ligament
    - Note: Concomitant ligament injury *requiring reconstruction* is an exclusion criteria

Intraoperative Data:

- Type of ACL graft:
    - Bone-patellar tendon bone (BTB) autograft
    - Hamstring tendon (HS) autograft
    - Allograft
- ACL graft fixation (interference screws, suspensory fixation)
- Concomitant injuries observed intraoperatively
    - Meniscal tear
        - Medial vs. Lateral
        - Type of tear (longitudinal, radial, degenerative, bucket-handle)
    - Chondral injury
        - Location
            - Medial compartment
            - Lateral compartment
            - Patellofemoral joint
        - Severity (Outerbridge Classification)
            - Grade 0: normal
            - Grade I: cartilage with softening and swelling

        - Grade II: partial-thickness defect with fissures on the surface that do not reach subchondral bone or exceed 1.5 cm in diameter
        - Grade III: fissuring to the level of subchondral bone in an area with a diameter more than 1.5 cm
        - Grade IV: exposed subchondral bone
- Concomitant procedures performed:
    - Meniscectomy
        - Partial vs. Complete
        - Medial vs. Lateral
    - Meniscal repair
    - Chondroplasty
    - Microfracture
    - Note: Concomitant procedure requiring delayed weightbearing is an exclusion criteria

Outcome Data:

- Validated patient reported outcomes:
    - Surveys:
        - Knee Injury and Osteoarthritis Outcome Score (KOOS)
        - International Knee Documentation Committee Subjective Knee Evaluation Form (IKDC)
        - VAS
    - Completed at 3 month intervals
        - Baseline (prior to surgery)
        - 3 months, 6 months, 9 months, 12 months, 24 months
- Limb Symmetry Index (LSI)
    - Consists of 4 assessments:
        - Single hop for distance, triple hop for distance, cross-over hop for distance, 6 meter hop for time
    - Compare operative leg vs. non-operative leg
    - Completed at 3 month intervals after surgery
        - 3 months, 6 months, 9 months, 12 months
- Quadriceps muscle assessment
    - Thigh circumference
    - Compare operative leg vs. non-operative leg
    - Completed at 3 month intervals
        - Baseline (prior to surgery)
            - Just for thigh circumference
        - 3 months, 6 months, 9 months, 12 months
- Return to sport
    - Defined as the date that patient is cleared for return to all sports without restriction by their physician utilizing an objective return to play criteria.

Adverse Effects:

- Therapist-completed survey of BFR:
    - Administered during PT session
    - Assesses for bruising, tourniquet-site pain, numbness, compartment syndrome, rhabdomyolysis
- Miscellaneous complications:
    - Ie: DVT/PE, reinjury, return to operating room, etc.
    - Will be recorded during office visits

4. STATISTICAL CONSIDERATIONS/DATA ANALYSIS

4.1 Sample Size

We are currently aware of no studies that use KOOS, IKCD scores, limb symmetry index, or return to play for BFR therapy after ACL reconstruction. However, studies [10, 11, 12, 13] of similar populations have found OOS, IKDC, LSI, RTP values of 91.5, 87.5, 79%, and 209 days, respectively. Using those estimates, a power analysis was done and sample size of 150 provides enough power (80%, with an alpha of 0.05) to detect clinically significant changes in these values, while simultaneously accounting for any potential loss-to-follow-up or early withdrawal from the study.

4.2 Method of Data Analysis

Descriptive statistics including measures of location (mean, median, percentile) and spread (standard deviation, ranges) will be computed for continuous variables. Frequency distributions will be computed for categorical data. Measures of association will be used to determine positive and negative predictors of functional outcomes and return to sport.

4.3 Data Storage

4.3.1 Data Management

All records related to a subject's involvement in this research study will be stored in a locked file cabinet on the second floor of the Inova Orthopaedic and Sports Medicine Group. The subject's identity of these records will be indicated by a case number rather than by name, and the information linking theses case numbers with their identity will be kept separate from the research records. Only the researchers listed on the first page of this form and their staff will have access to a subject's research records.

Data will be collected in a standardized fashion by the physicians and office staff. No publication or reports will contain any identifying information about individual participants. PI, co-investigators, and research staff will review medical records, private office charts, and obtain new questionnaires from patients. The radiology report will be reviewed for exclusion criteria. Only IRB-approved study members will have access to the data and study materials. Epic clinical information databases will be reviewed for information gathered from clinic visits and/or surgery.

Data accuracy and protocol compliance will be assessed during standard Quality Control operations, to include compliance checks and regular data verification. Protocol deviations will be reported to the IRB as policy. Noncompliance will be reported to the IRB as standard.

4.3.2 Records Retention

Data will be stored as a dataset 5 years after completion of the study. Participation in this research involves the potential risk of a breach of confidentiality to stored health information. Inova tries to minimize those risks by (i) removing some direct identifiers from stored information (i.e., names, social security numbers, and medical record numbers); (ii) securing, in a separate location, and limiting access to information that would identify patients; and (iii) limiting access to information stored to Inova investigators.

All records related to a subject's involvement in this research study will be stored in a locked file cabinet on the second floor of the Inova Orthopaedic and Sports Medicine Group. The subject's identity of these records will be indicated by a case number rather than by name, and the information linking these case numbers with their identity will be kept separate from the research

records. Only the researchers listed on the first page of this form and their staff will have access to a subject's research records.

5. HUMAN SUBJECTS PROTECTION (RISKS, BENEFITS, AND ALTERNATIVES)

5.1 Risks

Research Activity: Data collection
Potential Risk: A potential risk of an accidental breach of confidentiality.
Patient confidentiality will be maintained at all times. All records will be assigned a case number. Information collected in this study will be stored in a locked file cabinet in a secure office and will be accessible only to the research staff. Subject will not be identified in any publications or presentations of the research results.

Research Activity: Blood flow restriction therapy
Potential Risks: Potential risks include pain, bruising, numbness, damage to the surrounding structures, compartment syndrome, rhabdomyolysis, DVT/PE, and/or death.
Patients will complete BFR therapy under the supervision of a certified physical therapist with experience using BFR techniques. If the patient begins to develop symptoms consistent with the aforementioned potential risks, then the pressure cuff will be removed and the patient will be treated appropriately based on medical necessity. Of note, many of these aforementioned potential risks are theoretical, as BFR has been investigated for safety concerns and has demonstrated no increased risks compared to that of traditional exercise programs [9].

5.2 Benefits

Although there are no direct benefits to the patient, they will be helping by contributing to the scientific literature, potentially helping future patients participate in a more effective rehabilitation protocol.

5.3 Alternatives

The alternative is to not participate in the research study. The decision not to participate in the study will not adversely affect the services they receive from Inova Sports Medicine.

5.4 Confidentiality

We will de-identify each patient once the relevant information is collected. All records will be assigned a case number. Information collected in this study will be stored in a locked file cabinet in a secure office and will be accessible only to the research staff. Subject will not be identified in any publications or presentations of the research results.

All publications and reports are based on aggregated data; no publications or reports will contain any identifying information about individual participants.

6. SUBJECT COMPENSATION

6.1 Costs

All rehabilitation is considered standard of care. There are no additional costs to participants.

6.2 Payment
Study subjects will not be compensated for their participation in this study.

7. ADVERSE EVENT REPORTING
Potential Adverse Event: Breach of Confidentiality.
Patient confidentiality will be maintained at all times. All records will be assigned a case number. Information collected in this study will be stored in a locked file cabinet in a secure office and will be accessible only to the research staff. Subject will not be identified in any publications or presentations of the research results.

All adverse events (AEs) will be reported and logged per the IRC 11.16 policy in the Inova Research Center Standard Operating Procedures manual.

In the event of an AE, defined as "Any untoward medical occurrence (including a symptom/disease or an abnormal laboratory finding) during treatment with a pharmaceutical product in a patient or a human volunteer that does not necessarily have a relationship with the treatment being given," the research coordinator will immediately document and report all applicable details to the IRB via the "Reportable Event" form, including start and end date (if applicable), severity, therapy provided, and relationship to protocol. If the AE/SAE occurs at the lead site, the "Internal AE/SAE" form will be completed. If the AE/SAE occurs at a site other than the lead site, that site will notify the lead site immediately with the aforementioned applicable details, as well as follow their own institution's protocol for AE reporting if applicable. The lead site coordinator will then submit the "External AE/SAE" form to the lead IRB.

8. FUNDING
There will be no funding for this project.

9. CONFLICTS OF INTEREST
There are no conflicts of interest reported by any of the research personnel associated with this study.

10. FACILITIES AND EQUIPMENT
The data collection will be based at the Inova Orthopedics and Sports Medicine office located 8100 Innovation Park Dr., Suite 110, Fairfax, VA 22031. Data will be entered into a secured Excel spreadsheet. Surgery will be performed at INOVA Fairfax Hospital or an INOVA satellite location. Physical therapy will be performed at an INOVA-affiliated physical therapy facility using the BFR tourniquet and training equipment on the site.

11. OUTSIDE CONSULTANTS/COLLABORATORS
There will be no consultants outside of the Inova network.

12. CONTRACTUAL AGREEMENTS
There will be no outside contractual agreements involved.

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