University of Arkansas for Medical Sciences (UAMS) Clinical Protocol

Study Title: **Use of Blood Flow Restriction + Standard of Care Physical Therapy to Improve Functional Outcomes after Anterior Cruciate Ligament Reconstruction**

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List of Abbreviations

ACL	Anterior cruciate ligament
BFR	Blood Flow Restriction
CRF	Case Report Form
DEXA	Dual-energy X-ray Absorptiometry
EMR	Electronic medical record
FDA	Food and Drug Administration
IRB	Institutional Review Board
MVC	Maximal voluntary contraction (of the quad muscles)
NIH	National Institutes of Health
PBFR	Personalized Blood Flow Restriction
PT	Physical Therapist
RIOA	Reynolds Institute on Aging
ROM	Range of Motion (of the knee joint)
UAMS	University of Arkansas for Medical Sciences
UPIRTSO	Unexpected problem involving risks to subjects or others

Study Schema

Surgeon collaborators or their designees screen their orthopedic clinic for eligible subjects and send referrals to study staff via UAMS email.

Study staff contact referrals via phone or email to discuss consent process.

Visit 1: Subjects come to RIOA for informed consent process prior to surgery. Randomization (1:1) occurs.

Visit 2: Approx. 7-10 days prior to surgery, subjects come to RIOA for baseline testing.

Subjects undergo scheduled knee surgery at UAMS

Prescribed physical therapy begins with or without BFR per randomization at UAMS Colonel Glenn facility

Visit 3: Subjects come to RIOA for post-operative testing approx. 8 weeks postop.

Prescribed physical therapy continues with/without BFR per randomization

Visit 4: Approx. 12 weeks postop, subjects come to RIOA for mid-point testing.

Visit 5: Approx. 16 weeks postop, subjects come to RIOA for end-point testing.

Study Calendar

Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Informed consent	X				
10-meter walk test		X	X	X	X
bilateral MVC		X	X	X	X
DEXA scan		X	X	X	X
In Body scan		X	X	X	X
Stair ascent			X	X	X
Stair descent				X	X
Y-balance test			X	X	X

1.0 Protocol Summary

This will be a randomized pilot study to determine the effectiveness of Personalized Blood Flow Restriction (PBFR) technique in conjunction with prescribed physical therapy (PT) in a cohort of anterior cruciate ligament (ACL) reconstruction subjects. Both groups of subjects will undergo unilateral ACL reconstruction at University of Arkansas for Medical Sciences (UAMS), followed by prescribed PT at the UAMS Orthopedic Clinic at Colonel Glenn.

Up to 25 subjects will be enrolled. Half are randomized to the BFR group with the other will perform PT without BFR.

Data collection will occur at four approximate occasions: pre-surgery, 8-weeks postop, 12-weeks postop, and 16-weeks postop.

2.0 Background

Anterior cruciate ligament tears are a costly injury; rehabilitation time is extensive and return to pre-injury activity is often limited. Between 1990 and 2010 the overall age- and sex-adjusted annual incidence of Anterior Cruciate Ligament (ACL) tears in the U.S. was 68.6 per 100,000 person-years (1). A 2014 study reported 81 ruptures per 100,000 people (2). The incidence of ACL injuries among United States service members is 10 times the reported rate for the U.S. population as a whole (3). More than 50% of service members have activity limitations or are unable to return to duty following surgery. The

possibility exists that an anterior cruciate ligament tear, even when reconstructed, can lead to permanent military activity limitations and Medical Evaluation Board (MEB) (4).

Approximately 80% of ACL reconstruction surgeries are accompanied by meniscal tear and repair. Meniscal repairs require load restrictions for several weeks immediately following surgery (5). During this time, muscle atrophy and loss of strength occurs. In order to mitigate muscle atrophy and loss of strength, we propose using Personalized Blood Flow Restriction (PBFR). PBFR will adjust to the participant's current blood flow in order to keep a constant level of blood flow restriction, thus customizing blood flow restriction for each person. Though the device technology readily available, many studies have utilized a consistent cuff pressure rather than a consistent cuff flow restriction.

The use of BFR for ACL rehabilitation is gathering support. LaPrade (6) observed the greatest benefit of BFR for individuals who are non-weight-bearing for six to eight weeks and who may have more postoperative restrictions. Quadriceps girth has been preserved to contralateral standards with BFR following the non-weight-bearing period. There have been only a few studies published on BFR and ACL. Ohta, et al (7) used low-load resistance muscular training with moderate BFR after ACL reconstruction. However, their study used a standard occlusion pressure, additional home training, and the involvement of meniscal tear/repair was uncertain. Bowman, et al (8) found that BFR training strengthens muscle groups proximal, distal, and contralateral to cuff placement following ACL repair. However, their measures were not elegant and the study was not blinded. Only one study (9) evaluated physical functional outcomes, though they were self-reported. Thus, there is a need to evaluate the use of BFR after ACL surgery in a randomized, clinical trial.

2.1 Significance

Participants will attend their usual physical therapy visits and be randomized to receive PBFR or standardized rehabilitation. This use of a current and standardized clinical program and experienced physical therapists determines both suitability and clinical

translation. We propose to evaluate physical functional outcomes with a blinded tester and quantifiable measures that are standards in our hands. The goal of this pilot project is to demonstrate the potential to steepen the healing curve after ACL repair. The improved healing time will translate to an earlier return to weight bearing and the resumption of normal activities or duty. In addition to pre-test and post-test, we will incorporate two additional testing points over the length of the physical therapy sessions. This testing schedule will identify progress in functional outcome recovery over the course of rehabilitation. If successful, this rehabilitative modality may allow rehabilitation economics to be truncated and an earlier return to function. This pilot study will provide data, process refinement, and methods confirmation in preparation for a larger project submission.

3.0 Benefits and Specific Aim

There is a growing body of evidence demonstrating that the combination of blood flow restriction (BFR) with low intensity resistance exercise can induce similar gains in muscular strength and hypertrophic adaptations as moderate or high intensity resistance training (10). BFR is an attractive modality for patients after ACL reconstruction due to its efficacy with low intensity resistance exercise. The attractive aspect of PRFT with BFR is that strength and functional improvements may be garnered over a shorter period of time and more importantly, with lower training loads. The lower training load is particularly applicable to post-ACL patients with accompanying pain and diminished function and weight bearing. The ability to improve strength and function with a reduced total rehabilitation is an attractive financial and pragmatic solution in this patient population. Therefore, we propose a pilot project to determine the effects of adding PBFR to the standard of care on strength and functional outcomes after ACL reconstruction. We will compare the benefits of three times weekly standard of care including PBFR training versus standard of care rehabilitation throughout 16 weeks post ACL reconstruction.

Specific Aim: To determine the effects of PT + PBFR after elective ACL surgery on muscle mass, strength, and function.

4.0 Study Population

Up to 25 subjects of any gender or ethnicity will be enrolled with a target of n=20 for study completion.

4.1 Inclusion Criteria

1. Men and women, ages 18-34 years.
2. Scheduled to undergo elective ACL surgery at UAMS.
3. Capable of providing informed consent.
4. Willing to exercise with BFR.
5. COVID-19 negative or asymptomatic.

4.2 Exclusion Criteria

1. Any surgical indication other than ACL repair.
2. Body mass index >40.
3. Pregnant female.
4. Neurological, musculoskeletal, or other disorder that would preclude them from completing the exercise training intervention and all performance tests.
5. Hypertension as evidenced by systolic BP >150 at rest OR diastolic BP >85 at rest.
6. Heart failure as evidenced by use of prescription diuretics.
7. History of atrial fibrillation.
8. Oxygen saturation <95% on room air at rest.
9. Any other medical condition that would interfere with testing or increase one's risk of complications during exercise.
10. Currently receiving androgen (e.g., testosterone) or anabolic (e.g., GH, IGF-I) therapy.

11. Compromised vascular circulation in the legs (e.g. peripheral vascular disease).
12. History of deep vein thrombosis.
13. Varicose veins in the legs.
14. Known Sickle cell disease or trait.
15. Unwilling to avoid using protein or amino-acid supplements during participation.
16. Unwilling to avoid using BFR during prescribed post-operative physical therapy.

4.3 Subject Recruitment

Subjects will be recruited by the surgeon or their designee. Referrals will be sent to study staff via email. Study staff will contact referrals using their preferred method of communication (as per Epic) and present the study overview to them. Interested subjects will then be scheduled for Visit 1 where the informed consent process will take place in the Reynolds Institute on Aging.

4.4 Subject Compensation

Subjects will be compensated for participation as shown in the table below. They will be ~~given a Visa ® gift card for visit 1, and be~~ handed a UAMS check for the sum of their participation~~$50 at the completion of each other study visit~~ when their participation ends (unless they request more frequent compensation). Parking passes will be provided to all subjects for all RIOA visits at no cost to subjects.

Visit 1	$25
Visit 2	$50
Visit 3	$50
Visit 4	$50
Visit 5	$50

5.0 Study Visits

Subjects will be required to wear a mask. If they do not have one, a mask will be provided to them by the study staff.

Visit 1: This visit will take place at the UAMS RIOA prior to surgery. At this visit, informed consent discussion will be held. Study staff will use appropriate PPE. This visit is expected to take ~~less than~~about one hour. If a subject consents, their vital signs will be measured (blood pressure, oxygen saturation) while at rest for at least 10 minutes for exclusion criteria. Randomization will occur. Mr. Oholendt will be notified via email as to which group each enrolled subject has been randomized. He will then communicate this to the relevant physical therapists at the Col. Glenn facility.

Visit 2: This fasted visit will occur approximately 7-10 days before surgery. Subjects will be asked to fast for 8 hours, avoid caffeine and alcohol for 12 hours, and avoid strenuous exercise for 24 hours prior to this visit. Subjects will undergo body composition testing (DEXA, InBody). After a 5 minute warm up (stretching/walking/cycling as tolerated), ~~,~~ strength testing of each leg, and 10-meter walking speed test will commence. This visit is expected to take about 1 hour.

Visit 3: This visit will take place at the UAMS RIOA approximately 8 weeks after surgery. Subjects will be asked to fast for 8 hours, avoid caffeine and alcohol for 12 hours, and avoid strenuous exercise for 24 hours prior to this visit. At this visit, a 5-minute warm up, physical, functional, and body composition testing (DEXA, InBody) will take place (see Study Calendar). Future study visits will be scheduled. This visit is expected to take about 1 hour.

Visit 4: This visit will take place at the UAMS RIOA approximately 12 weeks after surgery. Subjects will be asked to fast for 8 hours, avoid caffeine and alcohol for 12 hours, and avoid strenuous exercise for 24 hours prior to this visit. At this visit, a 5-minute warm up, physical, functional, and body composition testing (DEXA, InBody) will

take place (see Study Calendar). Future study visits will be scheduled. This visit is expected to take about 1 hour.

Visit 5: This visit will take place at the UAMS RIOA approximately 16 weeks after surgery. Subjects will be asked to fast for 8 hours, avoid caffeine and alcohol for 12 hours, and avoid strenuous exercise for 24 hours prior to this visit. At this visit, a 5-minute warm up, physical, functional, and body composition testing (DEXA, InBody) will take place (see Study Calendar). Future study visits will be scheduled. This visit is expected to take about 1 hour.

As part of PT, subject's level of pain will be ascertained using a 0-10 point scale at the onset of their PT visits. They will also be asked to complete the Fear-Avoidance Beliefs Questionnaire at some visits. The ROM of their surgical knee will be measured at certain times. In addition, progression towards UAMS' 'Return to Sport' measurements are performed and documented. Some of these data elements will be retrieved from the therapist's notes in Epic by study staff.

6.0 Blinding

The study is a single-blind, randomized, controlled trial (RCT). While participants cannot be blinded since BFR is the intervention being evaluated, key investigators and outcomes assessors will be blinded to treatment assignment, making this a single-blind RCT from the investigators' perspective.

7.0 Randomization

Subjects will be randomized 1:1 at the conclusion of Visit 1 using a randomly generated list of group designations that corresponds to subject ID.

8.0 Intervention Description

All subjects will have the standard physical therapy visits conducted by the PTs at the Colonel Glenn facility. Participants will undergo standard physical therapy sessions at UAMS' Colonel Glenn facility either with or without the use of the BFR apparatus. Subjects will progress through the goals set by their therapist as their condition permits. Physical Therapists will be the same (Colonel Glenn therapists) for both intervention and standard of care groups to standardize treatment. The physical therapists participating in the study have all demonstrated proficiency in the BFR approach. Briefly, the BFR apparatus consists of an electronically controlled pneumatic tourniquet(s) that is placed (in this study) on the upper thigh(s) and inflated during exercise. The control mechanism continuously adjusts the air pressure to maintain the operator-chosen percentage of arterial occlusion (e.g. 75%) as determined by the blood pressure of that limb for a determined amount of time (e.g. for the duration of 4 sets of 30:15:15:15 ~~3 sets of 8~~ repetitions of knee flexion/extension). The tourniquet is deflated at specific intervals. The BFR apparatus is used primarily in the early stages of rehabilitation with the goal of increasing the strength and endurance of that limb at a faster rate than performing the exercises without BFR.

9.0 Outcome Measures

9.1 10-meter Walking Speed

This test is performed in a quiet, well-lit hallway. Subjects are instructed to walk as quickly as they can without running through a 20-meter course. The middle 10 meter distance is timed using stationary timer devices. Subjects will be accompanied by study staff for safety purposes but will not help the subject unless required.

9.2 Maximum Voluntary Contraction

Using the Cybex Dynamometer, isometric testing will be used to measure maximal muscle strength defined as the highest peak torque (Nm) obtained during knee extension of each leg separately. Subjects will be securely seated in the machine to ensure safety and stability for the test. Adjustments will be made to align the knee and ankle with the testing equipment. After a practice set to familiarize participants with the equipment, subjects will have three attempts of 5 seconds each separated by two minutes of rest between attempts. The highest peak torque reading will be recorded. Subjects will be measured first on the ~~surgical~~ right leg and next on the ~~non-surgical~~left leg. If a subject has recently (~1 week) performed this same measurement as part of their prescribed physical therapy, study staff will ask for the results. If results are provided, duplicate testing will not be performed.

9.3 Y-Balance Test

This test is used to assess lower body strength and balance. Study staff will demonstrate the test positions. With study staff within reach of subject, subject will have a practice trial and then will have 3 scored attempts. The greatest distance for each leg will be recorded for each of three positions (anterior, Posterior lateral, and medial lateral~~attempt to reach the most distance in each of the 3 positions~~. The maximum distance reached is recorded in cm.~~ Subjects will perform this test with each leg.~~

9.4 Stair Ascent/Descent

This test is a physical performance measure that assesses the time it takes the subject to ascend and/or descend a flight of twelve, 18-cm high steps with a depth of 28 cm. Participants will be asked to complete the test as quickly as they feel safe and comfortable. Handrails are allowed if required, but subjects are encouraged to use just their legs for stair negotiation. Time to negotiate the stairs is measured to the nearest one hundredth of a second ~~with~~ by stationary timing devices ~~a stopwatch~~. ~~A partial practice trial is completed to gauge subject capability and ensure safety monitoring, then the mean of two subsequent trials is used for analysis.~~ Assistive devices are

allowed only if the participant is unsafe or could not complete the test without a cane or walker. The use of assistive devices, as well as use of the handrail, is recorded.

9.5 Dual Energy-Xray Absorptiometry

This test will be used to measure body composition (fat mass, lean mass, and percent body fat). Subjects will be asked to remove all metal, thick clothing, and heavy plastic which could interfere with the DEXA scans. The subject's ID, age, ethnicity, height and weight will be entered into the computer prior to the scanning. The subject will be asked to lie down on the DEXA table in the supine position. The participant will be centered on the table within the scanning area. The subject's shoulders and hips will be centered, and the hands will be placed by the side of the legs in a prone position. Subjects will be instructed to remain still for the duration of the full-body scan. A trained DEXA technician will perform and analyze all scans. Subjects will be asked to fast for 8 hours, avoid caffeine and alcohol for 12 hours, and avoid strenuous exercise for 24 hours prior to this procedure.

9.6 InBody Bioelectrical Impedance Analysis

This test will measure total body and segmental water, to be combined with the DEXA measures for a more accurate body composition estimates. To obtain measurements, subjects are asked to stand barefoot on a calibrated scale to obtain subject weight. Once subject height, sex, and age are entered into the device, subjects are instructed to hold onto two handles and remain still while an imperceptible electrical current runs between electrodes in the handles and scale. Total assessment time is <2 minutes. Subjects will be asked to fast for 8 hours, avoid caffeine and alcohol for 12 hours, and avoid strenuous exercise for 24 hours prior to this procedure.

9.7 Clinical Data Collection

9.7.1 Quantitative Pain Scores: study staff will obtain pain scores that were assessed by physical therapists by reading the visit notes written by the therapist in Epic. Scores will be captured up through visit 5.

9.7.2 Fear and Avoidance Beliefs Questionnaire: study staff will obtain these scores that were documented by physical therapists by reading the visit notes written by the therapist in Epic. Scores will be captured up through visit 5.

9.7.3 Range of Motion: study staff will obtain ROM values that were assessed by physical therapists by reading the visit notes written by the therapist in Epic. Values will be captured up through visit 5.

9.7.4 Rehabilitation Volume: study staff will obtain total exercise volume, duration, and load from physical therapist's notes in Epic.

9.8 Order of Outcome Tests

Outcome measures will be performed in the following order for every visit:

DXA scan

InBody composition

MVC

10-meter walking speed

Stair ascent/descent

Y-balance

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10.0 Data Analysis, Use and Handling

10.1 Statistical Analysis/Power Calculations

Descriptive statistics for numeric outcome measures as well as demographic and clinical characteristics will be reported as means and standard deviations or medians and interquartile ranges, as appropriate. For each strength and functional outcomes, the difference between the two groups by the mid-point and final visit will be tested with two-sided hypotheses at a significance level of 0.05. For each parameter, an analysis of

covariance (ANCOVA) model will include terms for the main model effect of intervention group with pretest as a covariate for each parameter. For each group comparison, homogeneity of variances, normality, and parallel posttest-pretest slopes will be assessed. In the case of non-normal distributions, data transformations will be evaluated and applied if appropriate. Otherwise, for any group comparison with unmet ANCOVA assumptions, an alternative analysis such as generalized linear mixed models will be pursued instead. Statistical analysis will be performed using SAS version 9.4. The objective of this pilot work is to obtain adequate data on which to power future studies and project submissions.

10.2 Dissemination of Data

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a subject.

10.3 Data Handling and Recordkeeping

Physical Therapy sessions will be documented by Physical Therapists in EPIC. Data will be transferred from EPIC to the UAMS data warehouse and then imported into REDCap so no mistakes are introduced between data collection and data analysis. Outcome testing data (without identifiers) will be entered into REDCap to facilitate analyses. These files are maintained on secure password-protected UAMS servers. Approximately 7 years after study completion, electronic records will be destroyed per UAMS disposal guidelines. At no time shall Protected Health Information be released to non-study personnel.

10.4 Data Access

All subjects will be assigned a unique identifying code or number. The key to the code (the instrument associating the data with subject identity) will be kept on a password-protected UAMS server. Only study staff members will have access to the code and information that identifies the subject in this study. This file will be deleted approximately seven years after data analysis is completed.

Epic medical record will be accessed by study staff to extract specific data from the PT notes for exercises performed, noting repetitions, sets, resistance, occlusion, pain level, Fear-Avoidance Beliefs questionnaire, and ROM measurements.

11.0 Risks and Benefits

There are no guaranteed benefits for the subjects, though there is some evidence that additional rehabilitation improves functional outcomes. Anticipated risks associated with this protocol are described in detail below. All experimental procedures will be performed by appropriately trained and credentialed personnel. The PI and/or study physician will be responsible for oversight of study procedures and evaluation of adverse events.

There are no known risks of answering the questions on the Fear and Avoidance Belief questionnaire that the Physical Therapy department uses.

11.1

Physical, Functional, Range of Motion Testing

The primary risks are fatigue and muscle soreness.

11.2 Blood Flow Restriction device

Possible adverse effects which may occur from performing blood flow restriction techniques using a pneumatic tourniquet include bruising at the site of the cuff, numbness, cold feeling, venous thrombus, fainting/dizziness, delayed onset muscle soreness, increased perceived exertion/pain/discomfort, stiffness, weakness, skin discoloration, exercise-induced rhabdomyolysis. Symptoms of tourniquet paralysis are motor paralysis and loss of touch, pressure, and proprioceptive responses. The physical therapists participating in the study have all demonstrated proficiency in the BFR approach.

11.3 DEXA Scan

Subjects will undergo four DEXA scans for whole-body composition. The radiation exposure for one DEXA scan is approximately equal to ½ of the radiation from a chest x-ray.

11.4 InBody Bioelectrical Impedance scan

Subjects will undergo four of these scans. This machine (InBody770, BioSpace, Seoul, South Korea) is a widely used commercial device that is FDA approved and poses no risks.

11.5 Confidentiality

A potential risk to study subjects is the loss of confidentiality. Measures to protect the confidentiality of study subjects will be implemented as described in the Data Handling and Recordkeeping section above.

11.6 Data Safety Monitoring Plan

- Study staff will ask subjects about the occurrence of adverse events during study visits.
- Physical therapists will monitor for adverse events during intervention/rehab visits. These will be documented in their Epic notes.
- The PI and study physician are responsible for reviewing and evaluating adverse events.
- Adverse events will be recorded in the CRF and on an excel spreadsheet that is submitted to the IRB at required intervals.
- UPIRTSOs will be reported to the IRB within 24 hours of their discovery.

12.0 Ethical Considerations

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences (UAMS) research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study.

The formal consent of each subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. All subjects for this study will be provided a consent form describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study. The consent process will take place in a quiet and private room, and subjects may take as much time as needed to make a decision about their participation. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form must be signed by the subject and the individual obtaining the consent. A copy of the signed consent will be given to the participant, and the informed consent process will be documented in each subject's research record.

13.0 References

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