PROTOCOL TITLE:

1) Protocol Title Effects of blood flow restriction rehabilitation after bone patellar tendon bone anterior cruciate ligament reconstruction

2) Investigator Patrick McCulloch, MD

3) Objectives
Athletes commonly experience a significant amount of muscular atrophy following ACL reconstruction surgery associated with an increased risk of re-injury and an increase in time of recovery and return to sport participation. A combination of low intensity resistance exercise and blood flow restriction (BFR) therapy has been shown to elicit responses similar to high intensity resistance exercise with regards to reduced risk. We hypothesize that chronic low intensity resistance exercise combined with BFR will improve muscular strength, reduce skeletal muscle atrophy, and will enhance recovery. Therefore, the specific aims of this study are as follows:

1. ***Determine if BFR added to standard post-operative rehab will prevent skeletal muscle atrophy and promote skeletal muscle growth during 12-weeks of rehab training compared to traditional rehab alone.*** The *working hypothesis,* founded on previous literature, is that combined rehab and BFR will enhance skeletal muscle growth and prevent atrophy to a greater extent than rehab alone.

2. ***Determine if BFR added to standard post-operative rehab will improve muscular strength following surgery compared to traditional rehab alone.*** Because strength can be attributed to skeletal muscle mass, the *working hypothesis,* founded on previous literature, is that combined rehab and BFR will enhance skeletal muscle strength and fatigue resistance to a greater extent than rehab alone.

3. ***Determine if BFR added to standard post-operative rehab will improve functional outcomes following surgery compared to traditional rehab alone.*** The *working hypothesis,* founded on previous literature is that BFR will improve functional outcomes over rehab alone.

The *expected outcome* of the proposed work is the identification of a novel therapy that can overcome muscle atrophy and decrease recovery time following surgery. The findings of the proposed study will have a positive *impact*, because they will allow us to translate this information into evidence-based clinical interventions to improve functional outcomes with reductions in risk during rehab and upon returning to sport participation.

4) Background
Athletes who undergo ACL reconstruction are known to experience quadriceps atrophy with resulting decreased strength in their injured extremity. This is likely due to their inactivity following injury and also to disuse atrophy during initial post-operative period. It has been

shown that some patients may continue to have atrophy even 9 years post ACL reconstruction [1]. As a result, there is an increased risk of re-injury and an extended timeline for recovery and return to athletic participation. Current intensive rehabilitation programs accelerate return to play timelines, however, the initial quadriceps atrophy prior to beginning formal rehabilitation is still not addressed. Therefore, the need for more effective rehabilitation methods is of great interest to clinicians and physical therapists.

Blood flow restriction (BFR) exercise training, has been shown to induce skeletal muscle hypertrophy (growth) even when using low resistance loads (<30% One-repetition maximum). It has also been shown that BFR significantly improves fatigue resistance and greater strength gains compared to traditional resistance training alone [6,7]. In a recent study involving Division IA athletes, low resistance BFR training was shown to increase strength and muscle size as compared with traditional high resistance training in as little as four weeks [8]. Strikingly, blood flow restriction alone has been observed to decrease atrophy of the quadriceps following ACL reconstruction [10]. Thus, this type of training may be promising for ACL reconstruction patients who are unable to partake in heavy weight training post-operatively.

While the mechanisms that promote recovery and an increase in skeletal muscle hypertrophy are not well understood, it has been hypothesized that BFR elicits a stress response associated with decreases in intramuscular pH, accumulation of metabolites, increases in the ratio of carbon dioxide to oxygen, and changes in osmotic pressure [11]. In laymen's terms, these effects are similar to high volume / high intensity exercise but achieved with minimal resistance and reduced risk to the patient following surgery. Similar to high intensity resistance exercise, BFR exercise with low resistance levels elicits significant elevations in protein synthesis and associated changes in anabolic signaling within skeletal muscle cells (14). Encouragingly, BFR exercise does not show increase in markers for muscle damage such as myoglobin or creatine kinase [2].

Much effort has been made to optimize BFR training in terms of optimal cuff size, occlusion pressures, and training weight or resistance. Scott et al have provided a guideline for BFR therapy [18]. The generally agreed upon low resistance weight amount should be 20-30% of the maximum repetition (1RM) for the given exercise [7,18,19]. However, optimal training durations have yet to be determined. Additionally, functional assessments following chronic BFR training and association between changes in leg muscle mass and performance have yet to be thoroughly evaluated. In light of the present literature, we hypothesize that 12 weeks of combined low intensity leg exercise and BFR therapy will mitigate post-operative muscular atrophy, improve muscular strength, and improve functional outcomes in athletes following ACL reconstruction surgery compared to a traditional rehabilitation program in men and women athletes (age 18-35yr).

5) Setting of the Human Research

The study will start for each subject in the clinic setting. Consent for the study will be obtained after explaining all aspects of the study. The subject will undergo their scheduled procedure in the operating room with no differences between the control group and study group. Physical therapy will take place at two locations in Houston, two times per week for 12 weeks.

Questionnaires will be conducted before surgery, prior to physical therapy instructed BFR exercises at week two, two months, six months, and one year post-operatively. Questionnaires will take 20 minutes to complete.

6) Resources available to conduct the Human Research

DEXA (Dual Xray Absorptiometry) Scanner
Automated Electronic Blood Flow Restriction Cuffs (used for physical therapy)
Rehabilitation exercise equipment.
Rehabilitation facility.

7) Study Design

The study will be a prospective randomized control trial consisting of subjects requiring ACL reconstruction with BTB autograft. Subjects will be randomly divided into two groups following their inclusion in the study. One group will undergo the normal ACL rehab protocol as determined by Drs. Harris and McCulloch. The study group will undergo normal ACL rehab modified by use of a tourniquet for blood flow restriction during selected exercises.

On the day of the procedure, the surgeon will measure the subject's thigh circumference 1/3 distance from the superior pole of the patella to the inguinal crease. The subject will then undergo the normal BTB autograft ACL reconstruction procedure. A subject will be excluded from the study if a meniscal repair is performed. At the subject's two week post-operative clinic visit, the physician will measure thigh circumference at 1/3 distance from the superior pole of the patella to the inguinal crease. Study group subjects will begin physical therapy instructed BFR exercises at two weeks post operatively. Study group subjects will be taken through normal ACL rehab protocol as well as BFR exercises. Control group subjects will do the same exercises and formal physical therapy rehab protocol as the study group without BFR.

The BFR exercises will consist of: bilateral leg press week 3-10, eccentric leg press weeks 4-10, hamstring curl week 4-6, eccentric hamstring curl weeks 7-10, straight leg press weeks 6-10. The pressure used will be elevated to occluded blood flow by 80% (80% occlusion pressure) which will be determined for each individual subject. Subjects will do exercises at 20% of 1RM in 4 sets of 30-15-15-15 repetitions separated by 30 seconds of rest. Repetition maximum (1RM) will be determined by the contralateral leg, using the greatest amount of weight with full range of motion and proper form. This will be done over three separate tries, separated by one minute breaks. Resistance loads will be adjusted every 2 weeks as strength improves. During the exercise protocol, if patients are unable to complete the prescribed amount of repetitions, rest periods between sets will be increased as needed. The control group will do these exercises without BFR. Both study and control groups will also do the surgeons' standard post-ACL reconstruction physical therapy protocol.

Cuff pressures will be determined using the Loenneke et al outline, based off of thigh circumference and estimated cuff pressure for 50% artery occlusion [19].
Body composition (DEXA), bone density (DEXA), IKDC and Tegner Lysholm scores will be recorded at first rehabilitation visit, two weeks, eight weeks and 12 weeks following the initiation of rehab (1 wk following surgery). Y- balance, single leg squat distance, and single leg

step down will be measured at 8 weeks and 12 weeks of rehab. Return to play will be recorded as the number of months after the day of operation until subject returns to sport.

a) Recruitment Methods

Patients will be informed of study after counseled in the clinic on their need for the procedure. Patients will be recruited at the Houston Methodist Hospital by either Dr. Patrick McCullouch, Dr. Joshua Harris, or Dr. Robert Jack. Patients will be asked if they would like to be included in the study before leaving clinic. If the patients agree to participate they will complete all necessary paperwork in the clinic.

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b) Inclusion and Exclusion Criteria

Subjects. We will test our central hypothesis in 70 healthy adults (18-35 yr) who are participating in athletics or are recreationally trained. **Exclusion criteria** include subjects that demonstrate any of the following:

- Concomitant meniscal tear or additional ligamentous injury to the knee
- Obesity (BMI>30)
- Diabetes
- Cardiovascular, renal, liver or pulmonary disease
- Active infections
- Cancer (current or treated within the past 2 years) or coagulation disorder
- Rapid weight change within the past year
- Physically unable to participate in the intervention
- Are not currently taking, or recently (w/in 1month of participation) taken prescribed or over the counter ergogenic aids or compounds known to be banned by the NCAA. The NCAA banned substances list can be viewed from: http://www.ncaa.org/health-and-safety/policy/2014-15-ncaa-banned-drugs
- Unable to complete a minimum of 85% of the assigned rehabilitation sessions.

These conditions are excluded as they can impact muscle protein metabolism and training responses which would yield confounding the results.

Criteria for stopping treatment:

-Exorbitant pain (VAS >8/10) related or unrelated to exercise -Numbness, tingling, paresthesias >2 hours following any BFR session -Instability preventing safe, quality exercise -Nausea, severe headache, vomiting, fainting within 2 hours of BFR session

e) Data management

The PI will be responsible for all data collected, its confidential storage, and deletion after the study is completed.

f) Withdrawal of subjects

N/A

8) Risks to subjects
Minimal risks of thigh pain at tourniquet site and deep venous thrombosis. Minimal radiation exposure from DEXA scan measurement. However, the radiation is comparable to participating in a long plane flight. Minimal risk of injury to patients as they will be treated with the current standards of care during rehabilitation under close supervision from the physical therapy team.

9) Potential benefits to subjects
Subjects in the BFR group may experience quicker quadriceps/hamstring strength recovery as well as earlier return to play.

10) Provisions to protect the privacy interests of subjects
PHI information will not be used or published in the study as all information will be used to form aggregate data. The data will be kept on a secure password protected, hospital server and will be deleted after the study is complete.

11) Provisions to maintain the confidentiality of data
See #10

12) Cost to subjects
The cost of a routine clinic visit, ACL reconstruction, and physical therapy sessions will be involved in this study. No additional costs to the patient will be accrued with regards to the additional research portions of the evaluation.

13) Consent process
The subjects will then be asked in private, after explanation of the bone patellar tendon bone autograft ACL reconstruction procedure if they wish to participate in the study. The consent will be read and either accepted/obtained or declined. Participants will also be asked if they are taking oral contraceptives or if they have a history of blood clots or pulmonary embolus in order to determine exclusion for oral contraceptives, blood clots, and pulmonary embolus. The participants will be told that they may opt out of the research study at any time- even after they have signed the consent to participate in the study.

14) Process to document consent in writing
The standard consent form for this project will be explained and if the subject wishes to participate the consent will be signed prior to the patient leaving the clinic on the day a BTB ACL reconstruction is decided upon as the treatment. The PI will explain and obtain the consent for each participant in the study.

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