Blood Flow Restriction Therapy Following Acute Shoulder Injury Patients: Assessment of Efficacy in Return to Activity

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Background, Rationale and Context

Upper extremity injuries are a detriment to the careers of overhead throwing athletes, including baseball players at all playing levels. Recent estimates suggest that professional Major League Baseball (MBL) players have lost 7 billion dollars in wages due to injuries,[1] most of which are of the upper extremity.[2, 3] Atrophy and weakness of the shoulder are a common problem following treatment of a number of shoulder and elbow pathologies.[4-6] Even with relatively short periods of reduced activity, the magnitude of muscle loss can be quite substantial. [7] In attempts to address this issue, researchers have investigated therapeutic modalities to both limit muscle atrophy during the rehabilitation period and accelerate the strengthening process. Blood flow restriction (BFR) therapy is one such therapeutic tool that has received increasing attention, which involves application of a pressurized tourniquet to the injured limb during rehabilitation that limits atrophy when performing strength training with weight that otherwise would not produce enough of a contraction to prevent muscular atrophy.[8] To date, several studies have been performed on BFR therapy, however, the effect of therapy on ligamentous and tendinous injury in the upper extremity remain unclear as most studies have focused on muscular strengthening in healthy individuals and on lower extremity injuries distal to the tourniquet.[9-12]

Also known as Kaatsu training, BFR therapy is an increasingly common practice employed during resistance exercise by healthy athletes attempting to increase muscle hypertrophy and strength.[13-16] During BFR training, blood flow to the activated muscle is mechanically restricted by placing flexible pressurizing cuffs around the active limb proximal to the working muscle. This results in the accumulation of metabolites that are associated with muscle growth.[17, 18] Furthermore, other studies have demonstrated that BFR training may cause changes in neuromuscular function such as depressed resting twitch torque and enhanced post-activation potential, suggesting that BFR may have a neurological component to its improvements in strength.[15] Most recently, Bowman et al. conducted randomized control trial evaluating the effect of low-load BFR training on both the proximal and distal muscle groups in relation to the BFR tourniquet in healthy patients. The authors demonstrated that BFR training led to a greater increase in muscle strength and limb circumference when compared to patients undergoing similar excises without the BFR tourniquet.[19] This is a critical point for patients with postsurgical or acute injury who cannot undergo heavy weight training during physical rehabilitation, as the drive for protein breakdown often surpasses the stimulus required for protein synthesis, resulting in muscle atrophy and loss of strength.

Recent literature has described the use of BFR therapy as a parallel rehabilitation for injured patients. A number of studies have demonstrated that BFR therapy can increase limb usage and strength in military patients with traumatic lower limb salvage rehabilitation.[20, 21] Other clinical outcome studies have identified that BFR therapy can have improved outcomes when used in postoperative rehabilitation after knee arthroscopy and Achilles tendon rupture.[9, 10] However, there are very limited studies involving BFR on upper extremity both distal and proximal to the pressure cuff, representing a significant gap in knowledge in upper extremity treatment.[22] Furthermore, while these studies demonstrated improvement in hypertrophy and strength, they did not evaluate the effect of rehabilitation in injured patients.

BFR Mechanism of Action

While the mechanism of action of BFR therapy in injury rehabilitation is not well understood, one of the prevailing theories involves the cascade of metabolites as result of the BFR-induced localized anabolic state. In the anabolic state during exercise, muscles produce lactate, which results in growth hormone (GH) release.[23, 24] Evidence in the literature shows that individuals undergoing low-weight strength training exercises with BFR have significantly higher levels of both lactate and GH when compared to those at similar intensity levels without BFR.[25, 17, 18, 24] The increase in these metabolites are similar to those measured in high intensity training and heavy-load exercise.[24, 26] As lactate accumulates in muscle fibers, it decreases the ability to generate contractions with enough force, and therefore, results in recruitment of additional motor units, thus preventing atropy. More importantly however, the metabolite cascade is theorized to promote healing of injured tendons and muscle through collagen synthesis. GH stimulates the production of IGF-1, an important mediator during the inflammatory and proliferative phase of tendon, muscle, and bone healing.[27, 28] Similar to the GH studies, IGF-1 concentrations have been observed to be higher when using BFR in low load exercise versus similar intensity exercise without BFR.[29, 25, 30] Local IGF-1 directly increases the number of satellite cells and tendinous stem cells recruited to promote tissue healing.[31]

Another theory of mechanism of action on BFR therapy is the activation of muscle protein synthesis through the mammalian target of rapamycin complex 1 (MTORC1) pathway cascade. The MTORC1 is protein complex that, in skeletal muscle, is activated through a number of pathways including IGF-1, resistance exercise, amino acids.[32] Studies have indicated that phosphorylation of S6K1, a downstream markers of MTORC1, and protein synthesis was significantly higher in patients undergoing BFR plus exercise at 20% effort when compared to those undergoing similar intensity exercise without BFR.[30] Furthermore, other studies have demonstrated downregulation in myostatin, which is an inhibitor of protein synthesis in BFR users.[33]

Other theories on the mechanism of BFR on tissue healing involves the acute inflammatory response during blood flow restriction. IL-6 is a cytokine released after exercise in response to muscle microdamage, and plays a role in skeletal muscle regeneration by recruitment of inflammatory cells.[34] As with IGF-1, IL-6 also contributes to the activation and proliferation of satellite cells, as well as activating the mTORC-1 pathway.[35, 36] It is important to note, however, that while the studies above have been performed in the setting of BFR use on healthy individuals, the mechanism of action in injured patients has not been evaluated. Furthermore, these studies have only measured blood markers prior to BFR cuff placement and immediately after, with none evaluating the trend in changes of markers over multiple sessions of BFR therapy.

Objectives

Aim 1: To determine whether patients with non-surgical rotator cuff and biceps tendinopathy undergoing BFR rehabilitation show increased improvements in shoulder function relative to patients undergoing routine therapy with a tourniquet that is not occluding arterial blood (i.e. sham BFR). *We hypothesize that patients undergoing rehabilitation with BFR tourniquet pressurized to recommended therapeutic specifications will have increased muscle strength and CSA, as well as higher functional score averages compared to patients undergoing rehabilitation with sham BFR.* We will be measuring shoulder strength in injured and non-injured arms for both study groups using a Biodex testing machine. Ultrasound will be used to measure the CSA of the rotator cuff muscles. Both strength testing and ultrasound measurements will be performed before and after the rehabilitation protocol has been completed. Patients will receive questionnaires evaluating shoulder function at baseline, once cleared by physical therapy, as well as 6 and 12 months after completing rehabilitation.

Aim 2: To determine whether trends in blood biomarker concentration differ between both groups throughout the rehabilitation protocol. *We hypothesize that patients undergoing BFR will have higher*

trends in GH,IL-6, and IGF-1 over the 6 week rehabilitation protocol. Patients will receive the blood draws in clinic at the following time points: prior to 1st day of rehabilitation, half-way through the protocol (approximately 3 weeks), and after completing rehabilitation (approximately 6 weeks). ELISA will be used to quantify GH, IL-6, and IGF-1 plasma levels at the 6 time points. The trends in these 3 blood markers will be compared between the two groups.

Methods and Measures

Design

Describe the basic design of the study, use as many of the following terms as apply.

- *For intervention studies: randomized controlled trial; placebo-controlled; before-after trial; pilot study*

Setting

Academic medical center

Subjects selection criteria

- **Inclusion Criteria**
- Inclusion criteria will be any injured patient ages 18 to 55 years with clinical and magnetic resonance imaging (MRI) consistent with a formal diagnosis of non-operative rotator cuff and/or biceps tendinopathy, no prior upper extremity ipsilateral procedures or history of deep vein thrombosis, and those willing to be part of the study.
- **Exclusion Criteria**
- Exclusion criteria includes patients younger than 18 or older than 55 years of age, a history of revision surgery or prior ipsilateral upper extremity surgery, concomitant ligamentous, tendinous, or cartilage injury that would alter postoperative rehabilitation protocol, inability to comply with the proposed follow-up clinic visits, and patients lacking decisional capacity.
- **Sample Size**
- Based on the literature review, there are no published studies that have evaluated the effect BFR therapy on shoulder injury rehabilitation. Some studies have taken a pilot study approach and used 12 patients in each limb based off what has been recommended in the previous literature.[45, 46] However, others evaluating the effect of BFR therapy on quadriceps strength after ACL reconstruction have evaluated their sample size based on their own preliminary pilot studies and established sample sizes of 24 per group in order to achieve 80% power.[47] A previous study comparing GH levels between healthy individuals undergoing BFR strength training vs those without was used to estimate the number of patients needed to achieve at least 80% power.[48] Based of the difference in GH between the two groups, an effect size of 2.203 was calculated. An *a priori* power analysis demonstrated that 6 patients were required in each group in order to achieve a power of 90%. However, we feel that the standard deviation of the current study may be larger, and as such, for this pilot study we will recruit a minimum of 8 patients in each arm. However, we hope to recruit at least 12 in each arm by the time the study is completed in order to have 24 patients similar to established sample sizes in other BFR studies.[47]

Interventions and Interactions

Study Arms

Once consented, patient will be enrolled in of the two study arms prior to beginning physical rehabilitation. Patients will be randomized to one of the study arms using Microsoft Excel (version

16.82). Prior to beginning therapy, patients will undergo a blood draw at the clinic to establish baseline blood biomarkers. The patient will also undergo upper extremity physical strength assessment, and functional evaluation prior to beginning therapy. Baseline patient reported functional status will also be evaluated though upper extremity-specific questionnaires. During physical therapy, participants will undergo blood draws, receive electronic questionnaires, and undergo assessment of biomechanical at specified time points outlined below. Patient questionnaire information will be de-identified and coded into an encrypted centralized database. The schematic in **figure 1** provides the time points of each datapoint collected.

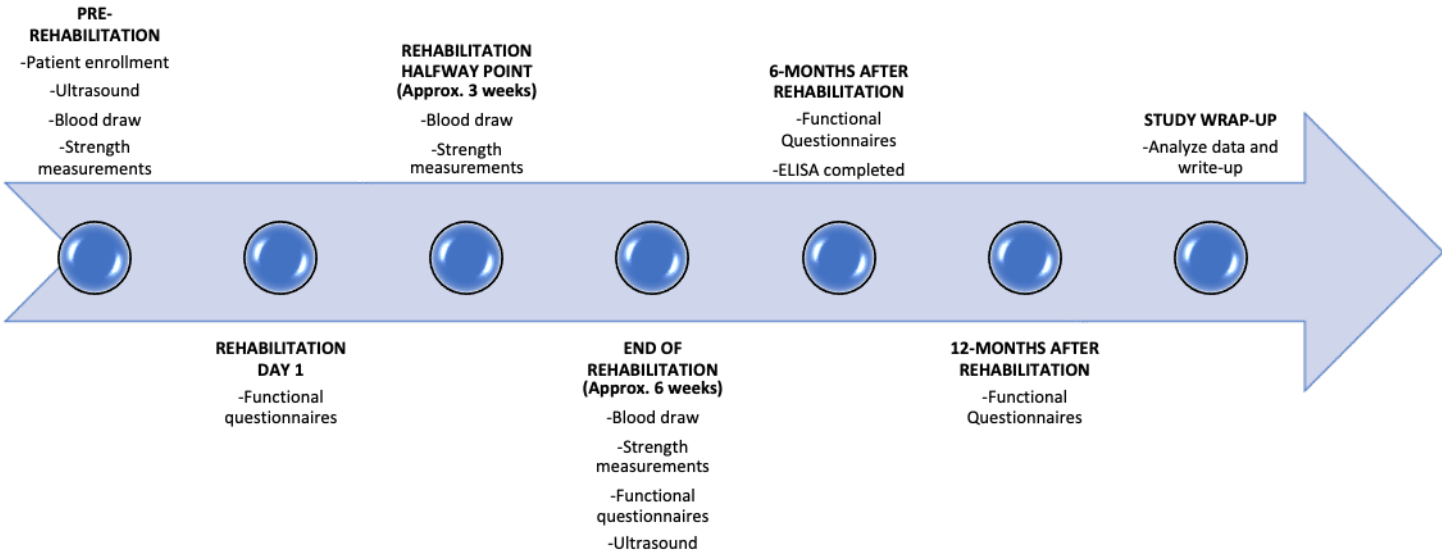

Figure 1. Schematic of study workflow indicating timepoints for carrying out study aims

BFR Protocol

Patients assigned to the BFR group will undergo BFR therapy during each session throughout the entire rehabilitation protocol. The standard rehabilitation protocol recommended by the physical therapists at WFBH is 2 sessions a week for 6 weeks. The therapy will be performed by one of the WFBH physical therapists who is trained and certified in using BFR therapy. The standard BFR protocol that is implemented by the Wake Forest physical therapists and recommended by expert opinion involve performing 4 separate exercises during each session. Each exercise will be done 4 consecutive times, starting with 30 repetitions, followed by 15 repetitions performed 3 times. Each set will be separated by 30 seconds break. After the finishing the 4 sets for one specific exercise, the patient will rest for 2 minutes prior to beginning the next 4 sets. In summary, the patient will perform 4 sets of 4 different exercises, perming the following repetitions: 30-15-15-15.

In the BFR group, the tourniquet will be pressurized to 50% limb occlusion pressure (LOP), which is the pressure necessary for occluding 50% of arterial limb flow in the upper extremity. The amount of cuff inflation is personalized to each patient as a safety measure and for maximizing the acute physiological response.[40] In the sham BFR group, the tourniquet will be pressurized to 0% occlusion pressure, while maintaining enough pressure to keep the tourniquet in place.

The tourniquet system (Delfi, Medial Innovations Inc) used in our physical rehabilitation clinic allows a patient specific LOP to be measured and automatically calculates the patient's personalized tourniquet pressure (PTP) as percentage of LOP. As an additional safety measure, the cuff automatically shuts off after 8 minutes to prevent prolonged restriction, and is locked from turning back on for 2 minutes. The sets for each exercise are structured so that the patient is able to finish 4 sets of one specific exercise within the 8 minute time limit.

Shoulder Strength and Cross Sectional Area Measurement

Isocentric shoulder strength will be measured for injured and non-injured arms for both groups at baseline, half-way through the strength training phase of rehabilitation, and once rehabilitation has completed. A biodex testing machine will be used to evaluate changes in strength over time. Shoulder strength measurements will include shoulder flexion, abduction, external rotation, and internal rotation, as well as elbow flexion. Strength testing will be performed prior to beginning the rehabilitation session. Each test will be performed 3 times and the measurement will be averaged.

Ultrasound will be used to quantify the changes in rotator cuff muscle before and after therapy. As previously described, the supraspinatus and infraspinatus muscles will be measured in each patient using a standard technique.[27] A multifrequency linear transducer (5-15 MHz) on a GE Logic S7 Expert will be used throughout the study. In order to measure the supraspinatus, the patient will sit in a chair, with the examiner standing behind the patient. The muscle belly of the supraspinatus and infraspinatus muscles will be evaluated while the patient had their hand placed on the anterior ipsilateral thigh for the examination. The muscle bellies of the supraspinatus and infraspinatus will be measured in the in the perpendicular plane to the long axis of their central tendon and muscle bellies to measure their respective cross sectional area and circumference. Landmark for obtaining measurement of the supraspinatus will be obtained by palpating the posterior corner of the acromion and measuring 8 cm medially along the spine of the scapula. From this position the transducer will be placed in the plane perpendicular to the spine of the scapula to visualize the cross section of the supraspinatus muscle belly and it's central tendon. Landmark for obtaining measurement of the infraspinatus will be obtained by palpating the posterior corner of the acromion and measuring 5 cm medially along the spine of the scapula. From this position the transducer will be placed in the plane perpendicular to the spine of the scapula to visualize the cross section of the infraspinatus muscle belly and central tendon. Because the footprint of the transducer is smaller than the width of the muscle belly, panoramic images acquisition will be accomplished using LOGICView mode. The panoramic glide will be stopped once the full myofascial boarder between the infraspinatus and teres minor were in view. The difference between pre- and post-therapy cross sectional area of each muscle will be compared between both BFR and sham BFR groups.

Blood Biomarkers

Blood samples will be acquired at baseline prior to intervention and at specific time points throughout the rehabilitation process to evaluate the effect of BFR therapy on the recovery of muscle, tendon, and ligamentous damage. Samples will be collected prior to beginning physical therapy, half-way through the structured protocol, and once the patient has completed rehabilitation. These blood samples will be collected by a member of the research team, who is trained in phlebotomy and is someone other than the principal investigator, and stored in a locked freezer until all samples for all patients have been collected. The patients will receive the blood draws in the physical therapy clinic on the day of their rehabilitation appointment. Once completed, GH, IGF-1, and IL-6 will be quantified using ELISA assays performed in the Wake Forest orthopedic surgery department. Each sample will have 3 technical duplicates analyzed to avoid loss of data during sample processing.

Patient Functional Status

Shoulder/Elbow functional status will be assessed using the following questionnaires that have been previously vetted for evaluation after upper extremity surgery: *Quick* Disabilities of the Arm, Shoulder, and Hand (DASH) survey, American Shoulder and Elbow Surgeons (ASES) standardized assessment form, visual analog scale for pain and satisfaction, and return to sport/daily activity questionnaires.[42, 43] Patient reported outcomes will be captured prospectively over the course of one year using the PatientIQ, a web-based data collection healthcare platform. A blinded de-identified email and/or text message will be sent at baseline, and once cleared by therapy, as well at 6 and 12 months after completing therapy. After three days, if a participant does not respond to the survey, a second email and/or text message will be sent. If the participant does not respond after three consecutive weeks, a phone call will be administered to encourage continued participation.[44]

Outcome Measure(s)

- *Shoulder strength, and rotator cuff muscle cross sectional area,*
- *Blood markers:* GH, IGF-1, and IL-6
- *Patient reported outcome measures: DASH, ASES, visual analog scale for pain and satisfaction*

Analytical Plan

Subject descriptive statistics will be analyzed using mean ± standard deviation for continuous variables, and frequencies and percentages for categorical variables. Normality analyses will be performed utilizing data visual inspection and parametric testing. Averages between the two groups will be compared using independent T-test and chi-square analysis were appropriate. Repeated measures ANOVA will be performed to evaluate statistical significance in blood biomarkers.

Human Subjects Protection

Subject Recruitment Methods

Describe how and where subjects will be identified and recruited. Indicate who will do the recruiting, and tell how subjects will be contacted. Describe efforts to ensure equal access to participation among women and minorities. Describe how you will protect the privacy of potential subjects during recruitment.

- For studies using recruitment flyers and advertisements, please provide copies of these materials for IRB review.
- For studies using PHI to identify subjects via medical records search or referral from a treating physician, who will then be contacted, you will need a limited waiver of HIPAA authorization, If this applies to your study, please provide the following information:
    - Under this limited waiver, you are allowed to access and use only the minimum amount of PHI necessary to review eligibility criteria and contact potential subjects. What information are you planning to collect for this purpose?
    - How will confidentiality/privacy be protected prior to ascertaining desire to participate?
    - When and how will you destroy the contact information if an individual declines participation?

Informed Consent

Signed informed consent will be obtained from each subject. Informed consent will be gathered by the one of the study coordinators or study investigators in clinic after being screened with inclusion/exclusion criteria and prior to undergoing non-surgical treatment for the injury.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed *(state the anticipated time the data will be destroyed, e.g. three years after closure of the study, and the method of destruction),* consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

There are potential risks in this study. Risks and side effects related to this study. Patients may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy lightheaded or feel faint. Infection may occur on rare occasions. Risks of blood flow restriction tourniquet includes development of a blood clot, which could result in breathing complications if the clot travels to the lung. These risks have been minimized by excluding patients with risk factors for blood clots, as well as ensuring that the cuff is inflated to standard measurements that limit this risk. Other risks for tourniquet use include pain and discomfort at the site. However, the standard protocol limits the compression of the tourniquet to 30 second intervals, and there are no reports of persistent pain after sessions. The benefit of BFR therapy in shoulder injury is unknown. It is possible that by being in the BFR rehabilitation group, rehabilitation process may be slower than undergoing rehabilitation with BFR included.

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Appendix

1. ASES survey
2. DASH survey
3. Consent form