PROTOCOL

Evaluating the Efficacy of Blood Flow Restriction Therapy in a Randomized Clinical Trial for Postoperative Rehabilitation Following Ankle Ligament Reconstruction

CONFIDENTIAL

Protocol No.	FY2024-335
PI:	Orthopaedic Surgeon: Jerry Grimes, MD[1,2]
CO-I:	Orthopaedic Surgeon: Kenneth Stephenson, MD[3] Advising PT: Dr. Jean-Michel Brismée, PT, ScD[4] Practicing PT: Dr. Jordan Fultz PT, DPT, OCS[5]
Version No. / Version Date:	3.1 |18 February 2026
NCT Registration Number:	pending

Affiliations:
[1] Department of Orthopaedic Surgery and Rehabilitation, Texas Tech University Health Sciences Center, Lubbock, TX, USA
[2]University Medical Center
[3] The Center for Orthopedic Surgery, Lubbock, TX, USA
[4] Physical Therapy Today, Lubbock, TX, USA
[5]Department of Rehabilitation Sciences, Center for Rehabilitation Research, Texas Tech University Health Sciences Center, Lubbock, TX, USA

Protocol Template v2.0 (03/28/2025):
Adapted and modified from the TTUHSC Clinical Research Institute (CRI) Protocol Development Template and ICH guidance document E6 (Good Clinical Practices) Appendix B

Version No.	**Effective Date**	**Description of Change**	**Originator**
1.0	15 September 2025	Initial Release – major revamp of prior submissions from back in 2024. Clarification of protocol, addressing IRB questions, etc.	David Lanford and Wilson McDowell
2.0	21 October 2025	Protocol Modification includes: • SNOSE randomization and Blinding procedures; affects participant identification number • Clarification of study sites; personnel; roles/responsibilities (study PT vs. treatment PT) • Clarification of exclusion of participants who have workers compensation for insurance • Clarification of study Master List and “key” and storage mechanisms • Personnel changes (protocol only) – removal of Jenny Hudnall, Evan Hernandez, Wilson (Cade) McDowell, and David Lanford on the protocol only for ease of future modifications. Cayuse modification: addition of UMC site approval, study flow diagram	Jenny Hudnall
3.0	22 January 2026	Protocol modifications: • Additional citations added • Clarification of which limb(s) will be used for measurement • Clarification of visit windows from date of surgery rather than weeks of PT • Collection of provider names to retain blinding in a treatment/blinding log and measurement consistency • Clarification of data storage locations • Clarification of SAE/AE reporting • Meeting minutes will be emailed to the IRB for reference after SMB meetings. Study Data Sheet (CRF) modifications: • Removal of group information from study Data Sheets • Clarification of which limb(s) will be used for measurements Personnel modifications (Cayuse only) Addition of Landon Thomas, PT; Taylor Woods, PT; Tina Herston, PT as study personnel ICF changes: • Removal of UMC PT as a PT site	David Lanford and Wilson McDowell

		• Removed reference to contralateral limb measurements at baseline Other: updated study flow diagram pdf	
3.1	18 February 2026	**PROTOCOL FORMATTING ONLY:** Modifications requested by NCT.gov to separate outcomes measures. "More than one outcome measure appears to be described. The Outcome Measure describes multiple assessments with potentially different Units of Measure. Assessments with different Units of Measure (e.g., weight and height) must be presented in separate Outcome Measures. Please revise to present these assessments in separate Outcome Measures (e.g., weight in kilograms, height in meters), as appropriate, or to clarify how multiple measurements will be aggregated to arrive at one reported value (e.g., weight and height will be combined to report BMI in kg/m^2)." Correction/updates to Surgical Site and Clinical site addresses on protocol and ICF. Addition of Northstar Surgery Center as site in Cayuse along with letter of support. Please note, official NCT Number is pending. Once number is obtained, separate modification will be submitted to update the ICF to include NCT Number.	J Hudnall

Abstract:
Blood flow restriction therapy (BFR) is a rehabilitation modality which started in Japan under the name Kaatsu in the 1960s, but it has just recently been adopted by physical therapists in the US (2016) (44). BFR works by limiting arterial blood flow to a limb and obstructing venous outflow while having subjects perform exercise using light weight (2,3,4,8,11,23,27,33,36,44). Limiting circulation both limits oxygen delivery, which induces anaerobic metabolism, and causes the pooling of metabolites, which are chemical messengers that drive changes to bones, muscles, and soft tissues (11,12,20,22,24,25,31,33,39,41,43,47. This increase in chemical messengers stimulates the production of hypoxia inducible factors, which have wide ranging effects. Increases in HGH, the MTOR pathway, and a decrease myostatin activation lead to increases in IGF1, testosterone and a variety of other mediators, all of which help muscle growth (12,20,24,25,31,39). Our study will be a single blinded clinical trial to investigate BFR for rehabilitation of patients after ankle ligament reconstruction, which requires prolonged immobility, which leads to loss of muscle mass and strength.(4,14,16,18,19,28,29 After consenting, we will randomly assign subjects to the BFR (Treatment) or the control group, which will receive the current standard of care (SOC). Both will experience casting and immobility, as per surgeon instructions, to protect their surgically repaired ligaments before splitting into BFR or SOC. Patients will then undergo prescribed physical therapy by a certified physical therapist for a minimum of 6 weeks. Data will be collected at the start of PT, at the end of the standard 6-weeks of PT, and (if the patient continues after the standard 6-weeks) the conclusion of PT. Outcome measures of interest include: muscle atrophy; ankle function; fatigability/manual muscle testing; pain scores; and cardiovascular effects (heart rate, blood pressure). Outcome measures will be compared between the SOC and BFR groups at the end of the study intervention.

Keywords: ankle reconstruction; physical therapy; blood flow restriction therapy

BACKGROUND AND SIGNIFICANCE

Ankle sprains, more specifically lateral ankle sprains, are one of the more common sources of ER visits, accounting for approximately 4-7% of all consultations and resulting in significant costs to the healthcare system in the United States (18). Conservative estimates range from $2-4 billion annually, though this number is thought to be underestimated. Despite their seemingly simple nature, ankle sprains can be complex (18,34).

While many lateral ankle sprains (LAS) can be treated conservatively with pain management, rest, ice, compression, and elevation, up to 40% of those affected will develop chronic ankle instability (CAI), potentially necessitating surgical intervention (18,19,21,28,32). The Brostrom procedure is the surgical gold standard for ankle ligament reconstruction, addressing acute laxity or chronic instability through surgical reduction, tightening, or reconstruction of the lateral ankle ligament complex (16, 19, 21). Despite the high incidence of LAS and the widespread use of the Brostrom procedure, there is significant variability in postoperative protocols, leading to a lack of rehabilitation standardization and diverse outcomes (14). The primary debate in rehabilitation protocols centers on the timing of initiation; delayed mobilization versus early mobilization (40). Delayed mobilization, involving initial casting followed by a walking boot for 4-6 weeks, aims to protect repaired structures but can lead to atrophy and prolonged rehabilitation (36,40). Early mobilization, starting therapy immediately post-surgery, reduces atrophy and strength loss but carries the risk of graft damage. A currently new modality of rehabilitation, is blood flow restriction therapy (BFR). Utilizing BFR may allow patients to perform functional strength training at lower intensities, which will reap the benefits of protecting the repaired tissues as in delayed mobilization protocols while reaping the added benefits of early mobilization protocols (11,23,24,33,40,42,44,46).

Blood Flow Restriction therapy (BFR) is a relatively new modality in the United States, only having been recognized by the American Physical Therapy Association (APTA) since 2018. Originating in Japan in the 1960s as "Kaatsu" (exercise with pressure), BFR was developed by Dr. Yoshiaki Sato, who observed physiological responses similar to heavy weight lifting from restrictive clothing. Traditional strength training requires loads of 60-70% of an individual's 1 rep max (1RM) for muscle hypertrophy and strength gains (6,7,11,23,27,29,33,37,46). In contrast, BFR achieves similar results at 10-30% of 1RM, or even passively, by partially occluding blood flow to the limbs without requiring the subject to exercise. Despite variability in BFR protocols, a common structure involves performing 4 sets of exercises at 30% 1RM in sets of 30, 15, 15, and 15 repetitions at 40-60% of limb occlusion pressure (LOP) for upper limbs and 60-80% LOP for lower limbs (6,11,21,23,27,33,37,44). The primary mechanism involves intermittent hypoxia, inducing the release of hypoxia-inducible factors (HIF-1 and HIF-2) and subsequent production of chemical mediators like nitrous oxide (NO), vascular endothelial growth factor (VEGF), human growth hormone (HGH), insulin-like growth factor 1 (IGF-1), testosterone, and catecholamines(12,24,25,31,33,38,39,41,43,45,47. BFR increases type II muscle fiber recruitment earlier than traditional exercise and induces metabolite buildup, leading to cellular swelling and protein synthesis. While the exact mechanisms are debated, BFR is clinically effective with a lower risk profile than initially expected (2,10,35,37,44,46).

BFR training has quickly gained popularity among professional athletes, including every NFL team, for enhancing strength and aerobic capacity without the risks of high-intensity training (HIT)(23,33). BFR also offers benefits for a broader population, including rehabilitation after ankle ligament reconstruction. BFR protocols use lower loads, facilitating early rehabilitation and enhancing soft tissue healing, bone mineralization, endothelial function, and pain modulation through upregulation of endogenous opioid and endocannabinoid systems (11,12,20,22,24,25,31,33,38,39,41,43,44,45,47). Despite initial safety concerns, BFR has shown a favorable risk profile. Some researchers assert that there are no absolute contraindications to BFR. Initial fears of thrombus formation have been debunked, with data suggesting BFR is venoprotective(44). BFR has been safely used in patients with systolic pressures over 190mmHg, reducing cardiac workload by decreasing venous return. Our initial investigation will focus on young, healthy individuals, but BFR holds potential for broader applications (2,10,37,44).

We propose that incorporating BFR in the rehabilitation of patients post-ankle ligament reconstruction will enable faster return to activities of daily living, less pain, reduced atrophy, and improved muscle strength compared to current protocols. BFR facilitates early strength training at lower loads, enhances soft tissue healing, improves aerobic capacity and fatigue resistance, and modulates pain (4,6,11,21,23,27,33,36,37,40,46). No clinical investigations have yet explored BFR for post-ankle reconstruction rehabilitation, and existing data on BFR's efficacy is limited. Our study aims to evaluate BFR's efficacy compared to current standards, addressing disuse atrophy and muscle weakness safely and effectively. Success in this study could pave the way for further research into BFR for various soft tissue injuries, bone healing, endocrinological treatments, and rehabilitation for exercise-intolerant individuals.

STUDY OBJECTIVES, PURPOSE, AND HYPOTHESES

Study Aims:

1. To evaluate the efficacy of Blood Flow Restriction (BFR) therapy compared to the current standard of care (SOC) in improving muscle atrophy, strength recovery, ankle functionality, and pain management in patients undergoing rehabilitation after ankle ligament reconstruction.

Objectives:

1. Evaluate Muscle Atrophy: To compare the extent of muscle recovery in the quadriceps and gastrocnemius muscles between patients receiving BFR therapy and those receiving the current standard of care. This will be done by comparing muscle circumference (3,4,6,9,11,14,21,23,29,36,40,44,48).
2. Assess Fatigability Recovery: To determine whether BFR therapy accelerates the recovery of dynamic lower extremity fatigability more effectively than the current standard of care as measured by manual muscle testing (MMT)(1,3,4,6,9,11,21,23,29,30,32,36,37,40,44,46,48).
3. Measure Functional Outcomes: To use the Foot and Ankle Disability Index (FADI) to evaluate improvements in ankle functionality and activities of daily living between the two treatment groups. (1,4,6,14,18,19,21,23,29,30,36,48)
4. Monitor Pain Levels: To compare perceived pain levels during treatment and daily activities in patients undergoing BFR therapy versus those receiving standard care using a visual analog scale (VAS) (2,4,6,10,11,12,14,19,21,24,40)
5. Analyze Cardiovascular Impact: To investigate changes in resting heart rate and blood pressure to identify any cardiovascular benefits associated with BFR therapy compared to the current standard of care (3,5,9,11,12,20,23,24,25,33,38,39,43,47).

Hypothesis:

Muscle atrophy

1. It is expected that, following a 6-week period of BFR on the lower affected limb, that subjects will show diminished atrophy of the lower limb at the level of maximal gastrocnemius circumference when compared to subjects who undergo the current SOC (1,3,4,9,21,22,23,24,29,36).
2. It is expected that, following a 6-week period of BFR on the lower affected limb, that subjects will show diminished atrophy of the thigh at 10cm and 20cm superior to the superior most aspect of the patella over those who utilize the current SOC (1,3,4,9,21,22,23,24,29,36).

Fatiguability

3. It is expected that, following a 6-week period of BFR on the lower affected limb, that subjects will show improved plantarflexion fatigability, as measured by manual muscle testing, over those who receive the current SOC (1,3,4,9,21,22,23,24,29,36).

Functionality

4. It is expected that, following a 6-week period of BFR on the lower affected limb, that subjects will show improved foot and ankle disability index scores when compared to those who receive the current SOC (3,4,9,14,19,21,22,28,30,32,40,48).

Pain

5. It is expected that, following a 6-week period of BFR on the lower affected limb, that subjects will show diminished perception of pain both during therapeutic intervention and during ADL when compared to those who receive the current SOC (12,14,19,.21,40)

Cardiovascular impact

6. It is expected that, following a 6-week period of BFR on the lower affected limb, that subjects will show greater changes in resting HR, consistent with their levels of activity prior to surgery, than will those who receive the current SOC. Those who undergo ankle ligament repair or reconstruction secondary to CAI with a concomitant lack of activity will experience a greater reduction in heart rate than those who undergo ankle ligament repair or reconstruction secondary to a sports or activity related, acute, injury (11,12,20,23,24,25,33,38,39,43,47).
7. It is expected that, following a 6-week period of BFR, subjects will exhibit a decrease in systolic blood and diastolic pressure, consistent with their level of presurgical activity, to a greater extent than does the cohort which receives standard of care. This only applies to those who go into surgery with a lack of previous conditioning. It has been suggested that elite athletes may actually see a small, but statistically significant rise is systolic blood pressure of 2-4mmHg. However, it is expected that untrained individuals will show a greater reduction in systolic and diastolic blood pressure than similarly untrained individuals who receive the current SOC (11,12,20,23,24,25,33,38,39,43,47).

STUDY DESIGN

Study type:

Randomized Clinical Trial

Study overview:

This study is designed as a randomized clinical trial to evaluate the efficacy of Blood Flow Restriction (BFR) therapy in postoperative rehabilitation following ankle ligament reconstruction. The study will be conducted at a single physical therapy (PT) center in the United States, with a focus on comparing BFR therapy to the current standard of care (SOC).

Patients who have undergone ankle ligament reconstruction surgery performed by participating orthopedic surgeons (JG; KS) will be randomized to either the treatment group (BFR therapy) or standard of care (SOC) group. Patients will then receive physical therapy (PT) managed by *treatment* physical therapists (t-PT). These therapists will perform BFR during the weekly PT sessions and provide the same at home exercises for participants in both groups. These physical therapists will not be part of the study team and will not collect study related data.

Patients in the treatment group will begin BFR therapy at least 28 days post-op (+7 days). The therapy will be performed on the affected limb, focusing on hip and knee strength, with ankle strengthening in plantarflexion and dorsiflexion in a seated position. Additional exercises include multi-joint hip and knee strengthening, such as straight leg raises, side-lying external rotation hip exercises (clam shells), short arc quads, long arc quads, hamstring curls, and hip bridges. Manual therapy including soft tissue mobilization and joint mobilization for ROM restoration will be provided as needed at the discretion of the t-PT .

The SOC group will receive traditional physical therapy methods without BFR at least 28 days post-op (+ 7 days). The protocol will include similar exercises to those in the BFR group but without occlusion. Manual therapy including soft tissue mobilization and joint mobilization for ROM restoration will be provided as needed at the discretion of the t-PT.

Follow-up assessments and outcomes of interest will be collected by the *study* physical therapists (s-PT) . s-PTs collecting study visit data will be blinded to the patient’s treatment group. These measures include: muscle circumference (quadriceps and gastrocnemius), manual muscle testing (MMT) for fatigability recovery, Foot and Ankle Disability Index (FADI) for functional outcomes, pain levels using a visual analog scale (VAS), and cardiovascular measures (resting heart rate and blood pressure).

Assessments will be conducted at multiple time points for both the treatment and SOC groups:

- Baseline: At initiation of physical therapy (28 days post-op + 7 days)
- Visit 2: 63-70 days post-op
- Visit 3 (optional): At the end of the study (for patients continuing beyond the standard 6-weeks of physical therapy)

STUDY POPULATION

Population

The study will include patients who have undergone ankle ligament reconstruction surgery performed by participating orthopedic surgeons who are in the age range of 18-65(2,10,44).

Study sites

Clinical sites (consenting visits and follow-up surgical visits)

Site 1
Study personnel: Jerry Grimes, MD
Location: Texas Tech Physicians Orthopedic Surgery Medical Pavilion Clinic
Address: 3601 4th Street, Medical Pavilion, 4th Floor, Lubbock, TX 79430

Site 2:
Study personnel: Kenneth Stephenson, MD
Location: The Center for Orthopedic Surgery
Address: 301 Utica Ave, Lubbock, TX 79416

Surgical sites

Site 1:
Study personnel: Jerry Grimes, MD
Location: University Medical Center
Address: 602 Indiana Ave, Lubbock, TX 79415

Site 2:
Study personnel: Kenneth Stephenson, MD
Location: Northstar Surgery Center
Address: 4640 N Loop 289, Lubbock, TX 79416

Physical therapy site
Study personnel: Jordan Fultz, PT
Location: Physical Therapy Today (PTT)
Address: 4138 19th St, Lubbock, TX 79407

Inclusion Criteria

1. Age 18-65 years (2,10,44).
2. Post ankle ligament reconstruction surgery (medial or lateral, with or without ankle scope).
3. Capability of paying for physical therapy or having insurance coverage for at least 6 weeks of therapy.

Exclusion Criteria (2,10,44).

1. Major cardiac or connective tissue disorders (e.g., Ehlers-Danlos syndrome, Marfan syndrome).
2. Autoimmune disorders.
3. History of stroke or deep vein thrombosis (DVT).

4. Bleeding or coagulation disorders.
5. Congenital or developmental musculoskeletal disorders (e.g., cerebral palsy, Parkinson's disease).
6. Pregnancy (current or planning to become pregnant in the next 4 months)
7. Malignancy (cancer).
8. Professional athletes.
9. Workers compensation insurance status as worker's compensation often does not cover the necessary duration of physical therapy (minimum of 4 weeks).
10. Be currently enrolled or have been enrolled in another interventional clinical research study within the past 30 days (at time of consent); or
11. Be deemed unsuitable for inclusion in the study at the discretion of the Investigators
12. Cognitively not able to consent or participate in research (dementia; severe developmental delay; language/communication limitations; brain injury; etc.)

STUDY PROCEDURES

Screening and Enrollment

Screening

Screening and eligibility determination will take place at the contributing Orthopedic Surgeons respective offices using study inclusion and exclusion criteria. Patients will be informed at this time that the cost of physical therapy will not go up by joining this project. If interested in the study, they will then undergo the Consenting Visit procedures outlined below.

Consenting visit

If a patient is interested in the study, the consenting visit will occur in a private location by a member of the IRB approved study team. During this time, patients will have the ability to review the consent form and ask any questions. If they then decide to enroll, a copy of the signed consent form will be given to them and a copy will be uploaded in the EMR (for TTUHSC/UMC patients). Patients will be reminded at this time that the cost of physical therapy will not go up by joining this study.

Randomization

Following enrollment, subjects will be randomly assigned to either the intervention group (BFR therapy) or the control group (SOC). Patients will be randomized using sequentially numbered opaque sealed envelopes (SNOSE) with their treatment group and study ID number pre-assigned. These envelopes will contain the information regarding their randomization and will not be opened until after the patient is consented for the study.

The subject's treatment group will be communicated to their t-PT, after they have conducted the first visits' measurements. The t-PT will not perform any data collection for the subjects they treat and will and will perform physical therapy for those patients.

A treatment/blinding log will be kept along with the enrollment log. This is for tracking which t-PT gives PT to each patient as well as determine which s-PTs perform measurements on each patient. A t-PT who has treated a patient while enrolled in the study will not be allowed to perform measurements and collect data for this patient. The collection of provider names (surgeon, t-PT, or s-PT) is for internal patient tracking procedures and measurement consistency. Provider identifiers for patient tracking ensures blinding and that a t-PT is not performing the measurements. Measurement consistency analysis may be analyzed after completion of the study.

Study visits

Study data collection visits will occur just prior to regular PT visits to avoid appearance of any marks or redness from use of BFR to unblind the s-PT. PT will be carried out in an open room except for exercises involving either BFR/non-BFR specifically as outlined in a sample PT plan shown in Appendix 6.

During study visits the measurements will be taken as outlined below; s-PTs performing data collection will be blinded to the patient treatment group. A summary table (Table 1) displays specific data points that occur at each visit. Further details regarding measures of interest are outlined in the following section.

Note: A patient is deemed ready to 'graduate' from physical therapy by the meeting all of the following indicators:

- 90% of contralateral leg endurance as measured by standard MMT with a lowest acceptable score of 3 on the MMT scale
- 90% ROM of Contralateral leg
- Gastroc, Quadriceps 90% of size of contralateral limb
- A FADI score within 10% of the contralateral limb.
- Upon Completion take a HR and Blood pressure and record with the previously taken measurements for the graduating standard.

Visit 1 (baseline)
Will occur on day one of PT (28 days + 7 days post-op) before PT commences. Limb measurements and strength testing will occur on the both limbs. Measurements include muscle circumference and atrophy, heart rate and blood pressure (BP), Foot and Ankle Disability Index (FADI), and Fatigability recovery/Manual Muscle Testing (MMT) at the discretion of the physical therapist. The patient will also be given an at home exercise program.

In addition, activity level prior to surgery will be determined via the Global Physical Activity Questionnaire (GPAC) at the first study visit if not completed prior to initiation of PT

Visit 2:
Visit 2 will occur either prior to exercises being carried out at either:

- graduation from physical therapy

or

- 63-70 days post-op prior to exercise being carried out

The measurements will be taken on whichever of the above dates occurs first. Measurements include muscle circumference and atrophy, heart rate and blood pressure (BP), Foot and Ankle Disability Index (FADI), and Fatigability recovery/Manual Muscle Testing (MMT) at the discretion of the s-PT.

Visit 3:
Visit 3 will occur only if:

- a patient has not graduated by 6th week of PT and insurance continues to fund or the patient desires to self-fund.
  or
  the patient would like to receive additional PT after 6th week of PT and insurance continues to fund or the patient desires to self-fund

The measurements will be taken on the last day of the patients PT sessions. Measurements include muscle circumference and atrophy, heart rate and blood pressure (BP), Foot and Ankle Disability Index (FADI), and Fatigability recovery/Manual Muscle Testing (MMT) at the discretion of the s-PT.

	Visit 1 (baseline)(28 + 7 days post-op)	**Visit 2 (63-70 days post-op)**	**Visit 3 (last day of PT, if applicable)**
Muscle atrophy	x (both limbs)	x	x
HR + BP	x	x	x
FADI	x	x	x

Fatigability recovery/MMT	x (both limbs at discretion of PT)	x (at discretion of PT)	x (at discretion of PT)

Early study withdrawal (if applicable)
In certain cases, a PI, Co-I, t-PT, or s-PT may terminate the participation of subjects in this study. If at any time, the PI, Co-I, t-PT, or s-PT believes that the study is no longer in the best interest of the subject, they may be removed. Severe adverse events, a change in the ability to perform therapy or a change in the ability of a subject to attend therapy as required within the visit window tolerance of the study may result in study termination.

Retention
Study retention will be aided by the frequency of follow up. Subjects will return to the PT centers multiple times weekly and will be seen by their surgeon multiple times throughout the process. No additional study specific subject retention practices will occur. Communication with patients regarding their involvement will include standard phone calls, HIPPA Approved texting methods as per the PT clinic's standard operating procedures, and the subsequent visits. There will be no payment or reimbursement associated with study participation.

MEASURES OF INTEREST

Demographic information
The following demographic information will be collected for patients upon study enrollment
- Age (years)
- Race (categorical)
    - White
    - Black or African American
    - American Indian/Alaskan Native
    - Asian
    - Native Hawaiian or Other Pacific Islander
    - Two or more races
    - Decline to specify
- Ethnicity
    - not of Hispanic, Latino/a, or Spanish origin
    - Mexican, Mexican American, Chicano/a, Puerto Rican, Cuban, Other Hispanic, Latino/a, Spanish Origin
    - Decline to specify
- Sex (categorical)
    - Male
    - Female
- BMI (kg/m^2) – BMI will be extracted directly from the EMR. Patient's height and weight will not be collected and recorded.
- Insurance status (categorical)
    - none
    - private insurance
    - public insurance

PT duration measures of interest
- Number of weeks of therapy prescribed at baseline by t-PT
- Number of weeks of PT attended by patient
- Reason for discrepancy (graduated early; additional sessions needed; lost to follow-up; etc.)

Intervention measures of interest

Assessments will be conducted at multiple time points for both the treatment and SOC groups at Visit 1 (baseline), Visit 2, and Visit 3 (if applicable). This information will be collected by the s-PTs who are blinded to the patient treatment group. Information will be collected on the Study Data Sheets and then transcribed into the Master BFR Data Sheet for analysis.

1. **Muscle atrophy measurement – gastrocnemius** (1,3-6,9,11-13,20-25,27,29,30,33,36,37,39,40,43-47)
   Measurement location: maximal circumference of the gastrocnemius muscle
   Unit: cm
   Range: varies by participant
   Corresponding study data sheet: Appendix 1
   Time frame: baseline/Visit 1 (28 days + 7 days post-op), Visit 2 (63-70 days post op), Visit 3 (optional – upon completion of PT)

2. **Muscle atrophy measurement – quadriceps** (1,3-6,9,11-13,20-25,27,29,30,33,36,37,39,40,43-47)
   Measurement location: 10 cm and 20 cm above the superior aspect of the patella
   Unit: cm
   Range: varies by participant
   Corresponding study data sheet: Appendix 1
   Time frame: baseline/Visit 1 (28 days + 7 days post-op), Visit 2 (63-70 days post op), Visit 3 (optional – upon completion of PT)

3. **Fatigability recovery using manual muscle testing (MMT)** (1,3,4,6,8,9,11,12,20,22-24,29,30,33,36,37,39,40,43-46,48)
   Measurement description: Manual muscle testing (MMT) will be used to evaluate plantar flexion fatigability with the ankle in a neutral position, unweighted. This will help determine the effectiveness of BFR therapy in restoring muscle fatigability compared to the standard of care.
   Score range: 5 – 10+ (higher score indicates better fatigability recovery)
   Corresponding study data sheet: Appendix 2
   Time frame: baseline/Visit 1 (28 days + 7 days post-op), Visit 2 (63-70 days post op), Visit 3 (optional – upon completion of PT)

4. **Foot and Ankle Disability Index (FADI)** (1,3-6,9,11,14,19,20-22,25,29,30,32,36,37,39,40,43,44,48)
   Measurement description: The Foot and Ankle Disability Index (FADI) will be used to measure the functional ability of the ankle and foot, assessing improvements in daily living activities and overall functionality.
   Score range: 0 – 100 (lower scores indicate more foot/ankle disability)
   Corresponding study data sheet: Appendix 3
   Time frame: baseline/Visit 1 (28 days + 7 days post-op), Visit 2 (63-70 days post op), Visit 3 (optional – upon completion of PT)

5. **Pain Management – Visual analog scale** (3,4,6,11,12,20-22,24,25,31,36,37,39,40,42- 44)
   Measurement description: Pain will be assessed using a visual analog scale (VAS), rated from 0-10, and recorded during the study visits to help evaluate the effectiveness of BFR therapy in reducing pain during rehabilitation. They will also be verbally asked during each therapy session to ensure subject comfort.
   Score range: 0 – 10 (higher score indicates higher levels of pain)
   Corresponding study data sheet: Appendix 4
   Time frame: baseline/Visit 1 (28 days + 7 days post-op), Visit 2 (63-70 days post op), Visit 3 (optional – upon completion of PT)

6. **Cardiovascular impact – heart rate (11,12,20,22,23,24,25,33,38,39,43,45,47)**
   Measurement description: Resting heart rate will be measured u to determine if BFR therapy provides any incidental cardiovascular benefits.

Measurement tool: automatic cuff (Omron Bronze, OMRON HEALTHCARE CO Kyoto, Japan)
Range: varies by participant
Units: beats per minute (bpm)
Corresponding study data sheet: Appendix 5
Time frame: baseline/Visit 1 (28 days + 7 days post-op), Visit 2 (63-70 days post op), Visit 3 (optional – upon completion of PT)

7. **Cardiovascular impact – blood pressure (11,12,20,22,23,24,25,33,38,39,43,45,47)**
Measurement description: Resting blood pressure will be measured u to determine if BFR therapy provides any incidental cardiovascular benefits.
Measurement tool: automatic cuff (Omron Bronze, OMRON HEALTHCARE CO Kyoto, Japan)
Range: varies by participant
Units: systolic/diastolic in mmHg
Corresponding study data sheet: Appendix 5
Time frame: baseline/Visit 1 (28 days + 7 days post-op), Visit 2 (63-70 days post op), Visit 3 (optional – upon completion of PT)

STUDY TREATMENT

Note that the PT program that all patients will receive is a complete PT protocol. It is independent of insurance authorization and a sample program is included for reference in Appendix 6.

Control group

The control group will receive standard of care PT.

Intervention group

The intervention group will receive the standard of care PT performed with BFR on affected limb.

The intervention group will be treated with a BFR Smarttools SmartCuffs versions 3.0 or higher. During the baseline visit, the device will be placed over the affected limb's greater trochanter and inflated to 60% of their limb occlusion pressure. This will be titrated up to 80% over the first week to ensure subject comfort. During the remaining physical therapy sessions, patients will perform exercises prescribed by a licensed t-PT to perform under occlusion with a load of 30% of the subjects estimated 1-rep max.

RISKS, BENEFITS, AND CONFIDENTIALITY

Risks

As BFR is still in its nascent stages, there have been concerns concerning the safety of the modality which have been determined to have been unfounded. The theoretical concerns surrounded the changing of the caliber of blood vessel lumens and the potential for thrombosis both in the dorm of DVT and PE, but no evidence has been uncovered to support such concerns (2,10,37,44). In fact, BFR has been shown to upregulate thrombolytic pathways, most notably hypoxia induced tPA release and no elevation in thrombotic markers like D-dimer have been observed. In fact, in a countrywide study undertaken in Japan, the incidence of deep vein thrombosis and pulmonary emboli were lower in the BFR groups than in the general population (44). As postsurgical patients are at an increased risk for DVT and PE at baseline, investigation of BFR as a means to mitigate risk through the mechanisms listed above would be a valuable contribution, but are outside of the scope of this study.

The main risk to subjects will be the development of bruising where the occlusive cuffs are placed. This can be mitigated by proper placement by a licensed physical therapist who ensures there is a layer of clothing between the skin and the occlusive cuff so that no "pinching" can occur when the desired limb goes through the full range of motion. We are unaware of reports of bruising in subjects who perform BFR on the lower extremity due to the proximal location, at the greater trochanter, and the propensity of subjects to wear clothing which covers the area over which the occlusive cuffs are placed unprompted. Bruising is more common in the upper extremity, which is outside of the scope of this study, but included for completeness.

The main risk with which we will be dealing is subjects experiencing delayed onset muscle soreness (DOMS) which are common and at their peak after the first session (2,6,10,23,27,37,44). DOMS is diminished after the second session and can be absent after the third and any subsequent sessions. The most concerning adverse event in the literature is the onset of rhabdomyolysis, but it is important to note that the case reports in which it is outlined concern individuals who deviated drastically from accepted protocols and performed the exercises without appropriate medical supervision (35). To our knowledge, there have been no cases of rhabdomyolysis in subjects or patients who have been under the supervision of healthcare professionals, and a plausible mechanism by which it could occur in individuals who adhere to accepted protocols, like the 30,15,15,15 at 30% of an individual's 1-rep max, which we will be utilizing, is lacking. The modality, when appropriately implemented, has been determined to be safe even in high-risk populations, with Anderson et al. proclaiming, "there are no absolute contraindications for BFR" (2).

Loss of confidentiality will be protected against by only utilizing password protected computers and encrypted software with a blinded model where no identifiable data will be kept in the same location. For a loss of confidentiality to be realized, a third party would be required to access separate computers in separate locations and break encryption to match patient names with data.

Benefits
Subjects randomized into the BFR protocol (intervention group) may experience faster and more complete recovery post ankle ligament reconstruction.
(3,4,6,7,9,11,12,20,21,22,23,24,25,27,33,36,37,38,39,40,43,44,45,47,48)

Results of this study may help standardize use of BFR in the future and improve outcomes for other patients.

Confidentiality
Each patient will be assigned a number based on their order of enrollment and to ensure study blinding as per SNOSE randomization procedure outlined above. This study number will be recorded in a Master List (Excel file) along with the patient's name and medical record number (MRN). The Master List acts as a key to link patient identities to their study data.

The original copies of the physical consent forms and Study Data Sheets will be retained in locked filing cabinets at the surgeon's offices/PT offices until they are transferred via secured lockbox to the TTUHSC Orthopaedic Surgery Research Office. The Study Data Sheets will not contain any patient specific information; all patient data on the data sheet will be de-identified. No dates are collected on the patient data sheets.

Regarding provider PHI on the Study Data Sheets: the Study Data Sheets will contain a location for identification of the s-PT. This is to ensure blinding and perform measurement comparisons as outlined in the Study Procedures – Screening and Enrollment – Randomization section above (page 9).

Both the consent forms and individual Study Data Sheets will be scanned into the study regulatory binder which is housed on the TTUSHC Box server which may only be accessed by IRB approved personnel. The patient data sheet information will then be entered into the Master BFR Study Data Sheet (excel file) for statistical analysis. The Master BFR Study Data Sheet does not contain any PHI (patient or provider) and will be used for statistical analysis.

For TTUHSC/UMC patients, electronic scans of the consent documents and Study Data Sheetwill be uploaded to the password protected uploaded into their EMR.

All data will be stored in a HIPAA-compliant, password-protected TTUHSC Box or computer and will be retained for 3 years after study closure and then destroyed, in accordance with TTUHSC and federal policy.

Only individuals who are IRB approved will have access to the Master List (Enrollment Log), Master BFR Study Data Sheet (Excel, for statistical analysis), Consent forms, and individual Study Data Sheets.

PATIENT SAFETY AND EVENT REPORTING

Continual routine interaction between the study physicians and physical therapists will allow for increased monitoring of adverse events. Both groups of individuals will follow the patients as per normal standard of care after surgery.

During scheduled PT visits, the trained therapist will engage in visual examination of each patient to determine if any study related adverse events occur. If a study related adverse event occurs, the physicians and physical therapists will determine if it is in the patient's best interest to continue in the study.

In addition, this will result in the study team reviewing the study inclusion/exclusion criteria and adjust as needed to reduce the risk to other patients. Currently enrolled patients will be reexamined to determine if they are at risk for a similar adverse event.

Adverse events (AEs), serious adverse events (SAEs), and unanticipated adverse device effects (UADEs) will be closely monitored throughout the study. These events may be associated with unplanned revision procedures prior to the planned ankle ligament reconstruction or may occur at any point throughout the study period. All events will be documented and submitted to the IRB and assessed for severity, causality, and relationship to the study procedures.

As this study is a collaboration between several institutions (UMC/TTUHSC, Center for Orthopaedic Surgery, Physical Therapy Today) a comprehensive review of all patient's medical records from all institutions is not possible. Instead of reviewing medical records, patients will be asked if any AEs/SAEs have occurred since their last study visit. Events reported to the study team will then be reported to the IRB as outlined below.

Adverse events:

Adverse Events (AEs) may occur at any point throughout the study period including but not limited to:

- Transitory Local Irritation: Temporary local irritation at the site of intervention, which may include redness, swelling, or discomfort. (2,10,44)
- Infection: Any signs of infection at the surgical site or related to the use of BFR equipment, such as fever, redness, swelling, or discharge.
- Allergy: Allergic reactions to materials used in the study, such as adhesives, bandages, or the BFR device.
- Delayed Wound Healing: Prolonged healing time of the surgical or intervention site, beyond the expected duration.
- Protrusion: Protrusion or displacement of any surgical implant or device used during the study

Adverse events will not be reported to the IRB unless they escalate to SAEs. They will however be included for review in safety monitoring board meetings.

Serious adverse events (2,10,44)

Serious Adverse Events (SAEs) are defined as events that result in significant medical consequences, including but not limited to:

- Hospitalization or prolonged hospitalization.
- Significant disability or incapacity.
- Life-threatening conditions.
- Death.

SAEs will be reported to the IRB within 3 days of study personnel discovery.

Unanticipated adverse device effects
Unanticipated Adverse Device Effects (UADEs) are adverse effects that are unexpected in terms of nature, severity, or frequency and are associated with the use of the BFR device or any other medical devices used in the study.

- Hospitalization or prolonged hospitalization.
- Significant disability or incapacity.
- Life-threatening conditions.
- Death.

Adverse Event Monitoring:
Prior to enrollment of the first study participant, a safety monitoring board will be established, have an introductory meeting, and will subsequently be set to meet at least twice a year to review all adverse events. During the first meeting the board will review the definition of all adverse events and serious adverse events. A summary of all AEs/SAEs will be provided to the SMB at their semi-annual meetings or more frequently if they occur. In the event of any SAE, the case will be reviewed to determine the root cause and if any changes to the protocol might be required. Additionally, if there are multiple AEs, the safety monitoring board may meet to determine if any changes to the protocol are necessary.

After each meeting, the SMB will determine if any adjustments need to be made to the protocol and study inclusion/exclusion criteria based on patient safety. These updates will then be provided to the IRB in a study modification. Meeting minutes will be emailed to the IRB for reference after SMB meetings.

HIPPA
This study involves a limited data set with the following identifiable data point(s) being collected:

- Provider name

This is captured as a data point of interest for internal patient tracking (blinding) and may be used for measurement validity/consistency measurements as described above (Study Procedures - Screening and Enrollment – Randomization on page 9).

PHI will be de-identified in methods described previously. No PHI will be included in any final publications resulting from the study.

DATA STORAGE
The original copies of the physical consent forms and individual Study Data Sheets will be retained in locked filing cabinets at the surgeon's offices/PT offices until they are transferred via secured lockbox to the TTUHSC Orthopaedic Surgery Research Office. The Study Data Sheets will not contain any patient specific information; all patient data on the data sheet will be de-identified. No dates are collected on the patient data sheets.

Regarding provider PHI on the Study Data Sheets: the Study Data Sheets will contain a location for identification of the s-PT. This is to ensure blinding and perform measurement comparisons as outlined in the Study Procedures – Screening and Enrollment – Randomization section above (page 9).

Both the consent forms and individual Study Data Sheets will be scanned into the study regulatory binder which is housed on the TTUSHC Box server which may only be accessed by IRB approved personnel. The patient individual Study Data Sheet information will then be entered into the Master BFR Study Data Sheet (excel file) for statistical analysis. The Master BFR Study Data Sheet does not contain any PHI and will be used for statistical analysis.

For TTUHSC/UMC patients, electronic scans of the consent documents and patient data sheets will be uploaded to the password protected uploaded into their EMR.

All data will be stored in a HIPAA-compliant, password-protected TTUHSC Box or computer and will be retained for 3 years after study closure and then destroyed, in accordance with TTUHSC and federal policy.

Only individuals who are IRB approved will have access to the Master List (Enrollment Log), Master BFR Data Sheet (Excel, for statistical analysis), Consent forms, and individual Study Data Sheets.

ANALYSIS

Descriptive statistics such as mean, median, mode, standard deviation, and minimum/maximum values will be obtained for thigh and lower limb circumference as is described in the protocol, blood pressure, heart rate, FADI, and plantarflexion fatigability via MMT for subjects in both the experimental and control groups. Data will be subjected to a chi-squared test to determine variance and distribution to inform which test, parametric or nonparametric, will be used to evaluate each data set. If the data meets parametric criteria, Paired t tests will be performed by comparing the pretest and posttest data for weeks 1vs5, weeks 1vs10 and weeks 5vs10 for each data set to determine significance of outcomes. If the data obtained is nonparametric, a Wilcoxon Signed-rank test will be performed. Alpha will be set to .05 for significance, with Bonferroni corrections, and the target sample size of 84 has been chosen to ensure a power of .9 with ample room to address the fact that this investigation is the first of its kind and assumptions based on existing data collected on anterior cruciate ligament reconstruction or Achilles tendon reconstruction may not serve as perfect proxies. Existing studies have been able to achieve significant, appropriately powered data with much smaller sample sizes, almost all of which are fewer than 50 participants, and we believe significant data will be achieved prior to enrollment of subject 84, but the current lack of data requires we begin with a higher assumed sample size to avoid an underpowered result.

Justification of sample size

This study will enroll a total of 105 subjects to allow for a 20% attrition rate such that the study will have at least 84 evaluable subjects available for statistical analysis.

At minimum, the following previously published studies will serve as the historical control references:

- Li X, Li J, Qing L, Wang H, Ma H, Huang P. Effect of quadriceps training at different levels of blood flow restriction on quadriceps strength and thickness in the mid-term postoperative period after anterior cruciate ligament reconstruction: a randomized controlled external pilot study. BMC Musculoskelet Disord. 2023 May 8;24(1):360. doi: 10.1186/s12891-023-06483-x. PMID: 37158913; PMCID: PMC10165811.
- Jack RA 2nd, 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. 2023 May;15(3):361-371. doi: 10.1177/19417381221101006. Epub 2022 Jun 27. PMID: 35762124; PMCID: PMC10170230.
- Ohta H, Kurosawa H, Ikeda H, Iwase Y, Satou N, Nakamura S. Low-load resistance muscular training with moderate restriction of blood flow after anterior cruciate ligament reconstruction. *Acta Orthop Scand*. 2003;74(1):62-68. doi:10.1080/00016470310013680

REFERENCES

1) Alshami AM, Alhassany HA. Girth, strength, and flexibility of the calf muscle in patients with knee osteoarthritis: A case-control study. *J Taibah Univ Med Sci*. 2020;15(3):197-202. Published 2020 May 1. doi:10.1016/j.jtumed.2020.04.002

2) Anderson KD, Rask DMG, Bates TJ, Nuelle JAV. Overall Safety and Risks Associated with Blood Flow Restriction Therapy: A Literature Review. *Military Medicine*. 2022;(9/10):1059-1064. doi:10.1093/milmed/usac055

3) Bowman EN, Elshaar R, Milligan H, Jue G, Mohr K, Brown P, Watanabe DM, Limpisvasti O. Proximal, Distal, and Contralateral Effects of Blood Flow Restriction Training on the Lower Extremities: A Randomized Controlled Trial.

Sports Health. 2019 Mar/Apr;11(2):149-156. doi: 10.1177/1941738118821929. Epub 2019 Jan 14. PMID: 30638439; PMCID: PMC6391554.

4) Burton I, McCormack A. Blood Flow Restriction Resistance Training in Tendon Rehabilitation: A Scoping Review on Intervention Parameters, Physiological Effects, and Outcomes. Front Sports Act Living. 2022 Apr 25;4:879860. doi: 10.3389/fspor.2022.879860. PMID: 35548459; PMCID: PMC9083008.

5) Cancio JM, Sgromolo NM, Rhee PC. Blood Flow Restriction Therapy after Closed Treatment of Distal Radius Fractures. *Journal of wrist surgery*. 2019;8(4):288-294. doi:10.1055/s-0039-1685455

6) Cognetti DJ, Sheean AJ, Owens JG. Blood Flow Restriction Therapy and Its Use for Rehabilitation and Return to Sport: Physiology, Application, and Guidelines for Implementation. *Arthroscopy, Sports Medicine, and Rehabilitation*. 2022;4(1):e71-e76. doi:10.1016/j.asmr.2021.09.025

7) Cook CJ, Kilduff LP, Beaven CM. Improving Strength and Power in Trained Athletes With 3 Weeks of Occlusion Training. *International Journal of Sports Physiology & Performance*. 2014;9(1):166-172. Accessed April 21, 2024. https://research-ebsco-com.ezproxy.ttuhsc.edu/linkprocessor/plink?id=e440b209-97e7-3f0e-a703-f337dfd63997

8) Curran MT, Bedi A, Mendias CL, Wojtys EM, Kujawa MV, Palmieri-Smith RM. Blood Flow Restriction Training Applied With High-Intensity Exercise Does Not Improve Quadriceps Muscle Function After Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Trial. Am J Sports Med. 2020 Mar;48(4):825-837. doi: 10.1177/0363546520904008. PMID: 32167837.

9) Dankel SJ, Jessee MB, Abe T, Loenneke JP. The Effects of Blood Flow Restriction on Upper-Body Musculature Located Distal and Proximal to Applied Pressure. *Sports medicine (Auckland, NZ)*. 2016;46(1):23-33. doi:10.1007/s40279-015-0407-7

10) DePhillipo NN, Bernhardson AS, LaPrade RF, Kennedy MI, Aman ZS, O'Brien L. Blood Flow Restriction Therapy After Knee Surgery: Indications, Safety Considerations, and Postoperative Protocol. *Arthroscopy Techniques*. 2018;7(10):e1037-e1043. doi:10.1016/j.eats.2018.06.010

11) de Queiros VS, Rolnick N, Sabag A, et al. Effect of High-Intensity Interval Exercise versus Continuous Low-Intensity Aerobic Exercise with Blood Flow Restriction on Psychophysiological Responses: A Randomized Crossover Study. *Journal of Sports Science and Medicine*. 2024;23(1):114. doi:10.52082/jssm.2024.114

12) Fekri-Kourabbaslou V, Shams S, Amani-Shalamzari S. Effect of different recovery modes during resistance training with blood flow restriction on hormonal levels and performance in young men: a randomized controlled trial. *BMC Sports Science, Medicine and Rehabilitation*. 2022;14(1). doi:10.1186/s13102-022-00442-0

13) Gaunder CL, Hawkinson MP, Tennent DJ, Tubb CC. Occlusion training: pilot study for postoperative lower extremity rehabilitation following primary total knee arthroplasty. *US Army Medical Department journal*. 2017;(2-17):39-43. Accessed April 22, 2024. https://research-ebsco-com.ezproxy.ttuhsc.edu/linkprocessor/plink?id=08f93944-827d-3ff2-a06e-898a914dbcee

14) Hansen OB, Papson A, Eble SK, Drakos MC. Effect of Blood Flow Restriction Therapy Following Achilles Rupture and Repair: A Randomized Controlled Trial. Foot Ankle Orthop. 2022 Jan 20;7(1):2473011421S00032. doi: 10.1177/2473011421S00032. PMCID: PMC8792708.

15) Hermanns C, Coda R, Cheema S, et al. Review of Variability in Rehabilitation Protocols after Lateral Ankle Ligament Surgery. *Kans J Med*. 2020;13:152-159. Published 2020 Jun 25.

16) Hunt KJ, Griffith R. Open Brostrom for Lateral Ligament Stabilization. *Curr Rev Musculoskelet Med*. 2020;13(6):788-796. doi:10.1007/s12178-020-09679-z

17) Kara D, Ozcakar L, Demirci S, Huri G, Duzgun I. Blood Flow Restriction Training in Patients With Rotator Cuff Tendinopathy: A Randomized, Assessor-Blinded, Controlled Trial. *Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine*. 2024;34(1):10-16. doi:10.1097/JSM.0000000000001191

18) Kerr ZY, Nedimyer AK, Simon JE, Kossman MK, Corbett RO, Chandran A. The Epidemiology of Ankle Sprains in US High School Sports, 2011-2012 to 2018-2019 Academic Years. *J Athl Train*. 2022;57(11-12):1030-1038. doi:10.4085/1062-6050-0664.21

19) Killinger B, Lauver JD, Donovan L, Goetschius J. The Effects of Blood Flow Restriction on Muscle Activation and Hypoxia in Individuals With Chronic Ankle Instability. *Journal of Sport Rehabilitation*. 2020;29(5):633-639. Accessed April 22, 2024. https://research-ebsco-com.ezproxy.ttuhsc.edu/linkprocessor/plink?id=52836fcc-2653-32d5-8780-e1a2394ed2ea

20) Kismanto, Setiawan K, Setyaningsih A, et al. The Therapeutic Potentials of Intermittent Hypoxia on Bone Healing: A Systematic Review. *Journal of International Dental & Medical Research*. 2022;15(4):1838-1844. Accessed April 23, 2024.
https://research.ebsco.com/linkprocessor/plink?id=0af1861a-c38d-3077-b788-c4b60a88c4af

21) Larsen P, Platzer OJ, Lollesgaard L, Pedersen SK, Nielsen PK, Rathleff MS, Bandholm T, Jensen ST, Elsoe R. Blood-flow restricted exercise following ankle fractures - A feasibility study. Foot Ankle Surg. 2022 Aug;28(6):726-731. doi: 10.1016/j.fas.2021.08.010. Epub 2021 Sep 14. PMID: 34531157.

22) Lindsey RC, Mohan S. Skeletal effects of growth hormone and insulin-like growth factor-I therapy. Mol Cell Endocrinol. 2016 Sep 5;432:44-55. doi: 10.1016/j.mce.2015.09.017. Epub 2015 Sep 25. PMID: 26408965; PMCID: PMC4808510.

23) Lorenz DS, Bailey L, Wilk KE, Mangine RE, Head P, Grindstaff TL, Morrison S. Blood Flow Restriction Training. J Athl Train. 2021 Sep 1;56(9):937-944. doi: 10.4085/418-20. PMID: 34530434; PMCID: PMC8448465.

24) MILLER, B. C. *et al.* The Systemic Effects of Blood Flow Restriction Training: A Systematic Review. International Journal of Sports Physical Therapy, *[s. l.]*, v. 16, n. 4, p. 978–990, 2021. Disponível em: https://research-ebsco-com.ezproxy.ttuhsc.edu/linkprocessor/plink?id=92b49264-0098-3b66-9c9f-3b9ce67b0c3f. Acesso em: 21 abr. 2024.

25) Navarrete-Opazo, Angela & Mitchell, Gordon. (2014). Therapeutic Potential of Intermittent Hypoxia: A Matter of Dose.. American journal of physiology. Regulatory, integrative and comparative physiology. 307. 10.1152/ajpregu.00208.2014

26) Newsham, Katherine. (2019). The Ubiquitous Lateral Ankle Sprain: Time to Reconsider Our Management?. The Journal for Nurse Practitioners. 15. 10.1016/j.nurpra.2019.01.019.

27) Patterson SD, Hughes L. Blood Flow Restriction Exercise Position Stand: Considerations of Methodology, Application, and Safety. *Frontiers in Physiology*. May 2019. doi:10.3389/fphys.2019.00533

28) Porter MD, Trajkovska A, Georgousopoulou E. Ligament Augmentation Reconstruction System (LARS) for Ankle Lateral Ligament Reconstruction in Higher-Risk Patients: A 5-Year Prospective Cohort Study. *Orthop J Sports Med*. 2022;10(5):23259671221093968. Published 2022 May 9. doi:10.1177/23259671221093968

29)Ross CM, Worrell TW. Thigh and Calf Girth Following Knee Injury and Surgery. *Journal of Orthopaedic & Sports Physical Therapy*. 1998;27(1):9-15. doi:https://doi.org/10.2519/jospt.1998.27.1.9

30)Sara, L. K., Gutsch, S. B., & Hunter, S. K. (2021). The single-leg heel raise does not predict maximal plantar flexion strength in healthy males and females. *PLOS ONE*, *16*(8). https://doi.org/10.1371/journal.pone.0253276

31) Schmidmaier G, Wildemann B, Heeger J, et al. Improvement of fracture healing by systemic administration of growth hormone and local application of insulin-like growth factor-1 and transforming growth factor-β1. . 2002;31(1):165-172. doi:10.1016/S8756-3282(02)00798-6

32) Sigonney F, Lopes R, Bouché PA, et al. The ankle ligament reconstruction-return to sport after injury (ALR-RSI) is a valid and reproducible scale to quantify psychological readiness before returning to sport after ankle ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc*. 2020;28(12):4003-4010. doi:10.1007/s00167-020-06020-6

33) Silva JCG, Neto EAP. Acute and Chronic Responses of Aerobic Exercise With Blood Flow Restriction: A Systematic Review. *Frontiers in Physiology*. October 2019. doi:10.3389/fphys.2019.01239

34) Shah S, Thomas AC, Noone JM, Blanchette CM, Wikstrom EA. Incidence and Cost of Ankle Sprains in United States Emergency Departments. *Sports Health*. 2016;8(6):547-552. doi:10.1177/1941738116659639

35) Tabata S, Suzuki Y, Azuma K, Matsumoto H. Rhabdomyolysis after performing blood flow restriction training: a case report. *Journal of Strength and Conditioning Research*. 2016;30(7):2064. Accessed April 23, 2024. https://research.ebsco.com/linkprocessor/plink?id=a1f165c6-dbc3-3949-b0e4-26778a323d67

36) Takarada Y, Takazawa H, Ishii N. Applications of vascular occlusion diminish disuse atrophy of knee extensor muscles. *Medicine and Science in Sports and Exercise*. 2000;32(12):2035. Accessed April 23, 2024. https://research.ebsco.com/linkprocessor/plink?id=b6713e77-a7c4-3711-a86f-6137e6f49164

37) Tennent DJ, Hylden CM, Johnson AE, Burns TC, Wilken JM, Owens JG. Blood flow restriction training after knee arthroscopy: A randomized controlled pilot study. *Clinical Journal of Sport Medicine*. 2017;27(3):245-252. doi:10.1097/JSM.0000000000000377

38) Thompson KMA, Gamble ASD, Coates AM, Burr JF. Impact of Blood Flow Restriction Exercise on Central Hemodynamics and Fluid Regulating Hormones. *Medicine & Science in Sports & Exercise*. 2024;56(2):362-369. doi:10.1249/MSS.0000000000003307

39) Volga Fernandes R, Tricoli V, Garcia Soares A, Haruka Miyabara E, Saldanha Aoki M, Laurentino G. Low-Load Resistance Exercise with Blood Flow Restriction Increases Hypoxia-Induced Angiogenic Genes Expression. *Journal of Human Kinetics*. 2022;84(1):82-91. Accessed April 23, 2024. https://research.ebsco.com/linkprocessor/plink?id=b8d724a8-7af2-3baf-9517-71c4edf0b3e0

40) Vopat ML, Wendling A, Lee B, et al. Early Versus Delayed Mobilization Post-Operative Protocols for Primary Lateral Ankle Ligament Reconstruction: A Systematic Review and Meta-Analysis. *Kans J Med*. 2021;14:141-148. Published 2021 Jun 21. doi:10.17161/kjm.vol1415028

41) Wang X, Wang Y, Yang X, et al. Effects of blood flow restriction training on bone metabolism: a systematic review and meta-analysis. *Frontiers in physiology*. 2023;14:1212927. doi:10.3389/fphys.2023.1212927

42) Wengle L, Migliorini F, Leroux T, Chahal J, Theodoropoulos J, Betsch M. The Effects of Blood Flow Restriction in Patients Undergoing Knee Surgery: A Systematic Review and Meta-analysis. *American Journal of Sports Medicine*. 2022;50(10):2824-2833. Accessed April 23, 2024. https://research.ebsco.com/linkprocessor/plink?id=e393aa90-5b13-35e5-8633-59fd3ea3d18a

43) Wojan F, Stray-Gundersen S, Nagel MJ, Lalande S. Short exposure to intermittent hypoxia increases erythropoietin levels in healthy individuals. *Journal of applied physiology (Bethesda, Md : 1985)*. 2021;130(6):1955-1960. doi:10.1152/japplphysiol.00941.2020

44) YASUDA Tomohiro, MEGURO Miwa, (Yoshiaki, NAKAJIMA Toshiaki. Use and safety of KAATSU training : Results of a national survey in 2016. January 2017. Accessed April 23, 2024. https://research.ebsco.com/linkprocessor/plink?id=4b6f0062-ab54-3a09-b037-5c24e2535195

45) Yeo JK, Cho SI, Park SG, Jo S, Ha JK, Lee JW, Cho SY, Park MG. Which Exercise Is Better for Increasing Serum Testosterone Levels in Patients with Erectile Dysfunction? World J Mens Health. 2018 May;36(2):147-152. doi: 10.5534/wjmh.17030. Epub 2018 Jan 26. PMID: 29623694; PMCID: PMC5924956.

46) Yinghao L, Jing Y, Yongqi W, et al. Effects of a blood flow restriction exercise under different pressures on testosterone, growth hormone, and insulin-like growth factor levels. *The Journal of international medical research*. 2021;49(9):3000605211039564. doi:10.1177/03000605211039564

47) Yoon D, Ponka P, Prchal JT. Hypoxia. 5. Hypoxia and hematopoiesis. Am J Physiol Cell Physiol. 2011 Jun;300(6):C1215-22. doi: 10.1152/ajpcell.00044.2011. Epub 2011 Mar 2. PMID: 21368293.

48) Yow BG, Tennent DJ, Dowd TC, Loenneke JP, Owens JG. Blood Flow Restriction Training After Achilles Tendon Rupture. J Foot Ankle Surg. 2018 May-Jun;57(3):635-638. doi: 10.1053/j.jfas.2017.11.008. Epub 2018 Feb 21. PMID: