A randomized controlled trial of blood flow restriction plus conventional physical therapy vs. conventional physical therapy alone in the treatment of lateral epicondylitis

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Background and Significance

Lateral epicondylitis (tennis elbow) affects between 1-3 % of the population[1], and is known to be a difficult condition to treat. Treatment ranges from oral anti-inflammatory medications, to physical therapy, to a myriad of choices for injection, and includes surgical intervention [2].

Physical Therapy is the first line of treatment in most patients presenting with a diagnosis of lateral epicondylitis. Eccentric loading exercises in isolation or in addition to other interventions have demonstrated improvements in function, pain levels, and grip strength in those diagnosed with lateral epicondylosis[3]. The majority of randomized controlled trials involving eccentric exercises use a control group consisting of interventions of concentric exercise, stretching, modalities (ultrasound, electrical stimulation, laser, heat, cold), and various manual therapy techniques[3]. A drawback to various loading strategies is that pain may prevent a patient from fully participating in the loading program, thus limiting their rehabilitation potential.

Blood Restriction Training (BFR) is an innovative procedure that involves measuring the Limb Occlusive Pressure, and then setting a tourniquet to a set percentage to restrict blood flow to the exercising body region[4]. It is hypothesized the combination of hypoxia and tension results in metabolic stress and activation of several pathways to increase strength and hypertrophy[5–7]. Most of the mechanisms are theoretical, but include elevating systemic hormone levels, production of reactive oxygen species (ROS), intramuscular anabolic/anti-catabolic signaling, and increased fast-twitch fiber recruitment.[4,6–10]. Although the mechanisms are unclear, there is mounting clinical evidence supporting the increase in strength and hypertrophy [5,8,9,11–13]. The effect of BFR on pain does show promise when treating knee pathology. BFR has been shown to improve strength, and in some cases pain during exercise as well as or better than conventional therapy in patients with osteoarthritis [14], and in post-operative patients [15,16]. The effect of BFR on pain and function is less clear, and current evidence exists only in knee pathology [14–18]. A 2017 systematic review examining the effect of BFR on musculoskeletal conditions found moderate effect on increasing strength. It appears BFR is not superior to heavy load resistance training, but in the injured population it is not always possible to perform heavy load training [19].

Regarding safety, there is a very low incidence of side effects with BFR. Wernbom et al[5] performed a review of the safety reports in 13 BFR specific studies, and the only reported side effects were muscle pain related to the exercise, and some level of endothelial dysfunction related to acute bouts of exercise which resolved within 60 minutes. Nakajima et al[20] report on a Japanese survey of KAATSU training (a method very similar to BFR), and report venous thrombosis (0.055%), pulmonary embolism (0.008%), rhabdomyolysis (0.008%). The authors concluded that BFR training is a safe intervention.

Given the inconsistent results conventional physical therapy has delivered in the treatment of lateral epicondylitis, and the results of BFR on strength increase, and pain decrease with exercise, it reasons that BFR may be a useful tool in the rehabilitation of chronic degenerative tendinopathies such as lateral epicondylitis. We believe it may be possible to decrease the elbow pain a patient feels while exercising with BFR, in order to increase their strength and function, and hopefully daily pain level in a manner that may be superior to conventional physical therapy.

Relevance to Sports Health Research

BFR devices are relatively new on the rehabilitation horizon, and as such, are purported to hold significant promise. We hope to begin a process of objective evaluation of the tools to see if they can be effective in treatment of traditionally difficulty to treat degenerative tendinopathies.

Specific Aims

We wish to investigate whether BFR training is an effective tool in the rehabilitation of patients diagnosed with lateral epicondylitis. Low load BFR training has been shown to increase strength and hypertrophy in individuals with generalized muscle weakness and with lower extremity orthopedic ailments. Functional outcomes and pain are less reported in the literature and is worth investigating as increasing strength is a primary target in rehabilitation.

We propose to investigate the effectiveness of BFR in a population that represents the majority of patients seeking outpatient Physical Therapy services with a diagnosis of lateral epicondylosis.

We plan to achieve this project by addressing the following aims:

1. To evaluate if a BFR rehabilition program results in superior self reported function and pain compared to a usual care group in the treatment of lateral epicondylosis.
    a. This aim tests the hypothesis that lower resistance loading exercises when coupled with BFR will have positive effects on pain and overall function.

2. To determine if a BFR rehabilitation program results in increased grip strength compared to a usual care group in the treatment of lateral epicondylosis.
    a. This aim tests the hypothesis that a patient who undergoes BFR rehabilitation with lower resistance load exercises, will demonstrate increases in objectively measured grip strength.

Outcomes

Primary Outcomes:

1. Change in Patient Rated Tennis Elbow Evaluation (PRTEE)[23] at 12 months from baseline.
    a. We will also collect this data at final in person therapy visit, 3 months, and 6 months from baseline. These will be considered secondary outcomes.

Secondary Outcomes:

1. Change in Numeric pain rating scale (NPRS) from baseline visit to 12 months.
2. Change in maximum pain free grip strength from baseline to final therapy visit.
3. Change in maximum grip strength from baseline to final therapy visit
4. We will provide descriptive statistics as to whether subjects have sought other treatment after finishing our treatment protocol. This data will be collected as part of the 3, 6, 12 month contacts.
    a. Other treatments sought will include: further doctor's visits, oral medications prescribed, injection therapy (and what type), surgical treatment.

The NPRS and PRTEE are validated, standardized outcome measures commonly used when assessing lateral epicondylitis. Assessing grip strength is standard practice, however, we wished to differentiate between maximum grip strength vs pain limiting grip strength.

Long Term Goals

The long term goals depend somewhat on the outcome of the trial. If the new BFR device shows promise and is seen to be superior to standard therapy, there is potential to evaluate its use in multiple types of chronic degenerative tendinopathy. There is also the potential to decrease the number of patient visits to therapy offices, increasing the value of therapy if it is effective. We also see the potential to apply to other degenerative conditions such as osteoarthritis to see if there is potential to improve therapy techniques and benefits for conditions such as these.

Research Design and Methods

Brief Design Description

This will be a randomized, controlled, open label trial. A total of 44 subjects will be recruited. Each group will be divided equally with 22 subjects having been diagnosed with lateral elbow pain. Subjects will be recruited from CCAG physicians located within the CCAG health system, as well as at physical therapy locations at Health and Wellness Centers in Bath, Green, and Stow. A team of physical and occupational therapists have been recruited including therapists and athletic trainers who are present at each office. At each site, 1 therapist will undergo a 2 hour standardized training session on delivery of treatment and data collection. Patients evaluated and found to have the appropriate criteria by either physicians or physical therapists will be given a research information sheet (see appendix) offering the opportunity to participate in a research study at the above mentioned locations. The patients interested will be consented by phone, or in person once they present to physical therapy office.

Timeline of Study

The goal is a 6-week treatment period at 1 PT visit per week. In ideal situation the visits occur in consecutive weeks, but will be considered per protocol with 6 visits over a 12 week period. Follow up will occur for 12 months after the initial therapy visit. We anticipate the total open period of time to last between 2-3 years for completion of 1 year follow up, 2019-2022.

- A patient can elect to drop from the study at any time.
- A patient's treatment will be considered completed if they cannot attend 6 visits within the 12 week time frame.
- A patient can be discharged from care prior to 6 weeks if all clinical goals set at the initial therapy assessment are met. If this occurs the outcomes measures expected at the 6th visit will be recorded at this visit and considered equivalent to the 6th visit outcomes.

Recruitment/Enrollment

Physicians frequently caring for patients with lateral epicondylitis will be notified of the ongoing study, and will be given research information sheets to distribute to patients diagnosed with lateral epicondylitis. This will include musculoskeletal physicians, as well as primary care physicians. This information will provide patients with basic information about expectations for enrollment, locations for study, and contact information for researchers if patient has questions. Non-IRRB approved clinicians will give information sheet to patients, and refer them to our participating physical therapy locations, or to Dr. Chanda Mullen for more information.

Primary care, orthopedics and sports medicine offices within the Cleveland Clinic Akron General system will be notified of the study, and encouraged to refer patients for therapy at study locations. Dr. Chanda Mullen will be available by email/phone for questions regarding consent.

IRRB approved Physicians and physical therapists participating in the study will have research information sheets as well as consent documents (see appendix) to enroll patients at the time of office or physical therapy clinic visits.

Patients will also be notified of the study when calling or presenting to physical therapy sites with the diagnosis of lateral epicondylitis.

We expect to have patients referred by doctor's offices via secure Cleveland Clinic intra-office email, by phone from doctor's offices, or by receptionists at physical therapy flagging the new patients with the eligible diagnoses. Our certified athletic trainer (Art McCreary) or physical therapist (Daniel Hass), or summer research assistant/fellow (consent team) will make contact either ahead of the visit, or at the initial physical therapy visit to discuss the existence of the trial. One of the consent team will be responsible for initial contact with the patient, and for scheduling the consent appointment. Once the patient has expressed interest in the study, they will be met either in person at the office, or over the phone by either one of the consent team named above or IRRB approved participating physical or occupational therapists .At the office, or phone appointment, the details of the study and consent will be verbally communicated to the patient. Patients who express willingness to participate will sign the consent form at the face to face visit either after face to face conversation, or after phone conversation.

Consent will include discussing the study protocol and the perceived risks and benefits of participation. This will be done by phone with study personnel prior to, or at initial physical therapy visit. The patient will then sign a paper consent form at the therapy visit in which they enroll. The intervention treatment will be described as an experimental technique which has shown to be beneficial and safe in other therapeutic treatment protocols, but which is new to this particular diagnosis. Consent will also include patient's freedom to decline the invitation to participate, as well as a discussion of the costs associated, and the billing of their therapy in the usual manner (copays, billing insurance, etc.).

The consent forms will be held in a locked cabinet by the certified athletic trainer until turned over to study author Phillip Toal at the Bath Health and Wellness physical therapy office, where they will be stored in a locked office.

Randomization/Allocation

Once patients have consented to participation, subjects will be randomly assigned to either intervention or control group-both consisting of 22 patients. Consent will be obtained by referring physicians, or physical therapists at approved sites participating in the study [further details regarding consent procedure below]. At all physical therapy sites participating in the study, patient service representatives will be trained in the study recruitment, collecting patient enrollment paperwork and other clerical needs. Allocation will occur in blocks of 4 by opaque envelope. The envelopes will be generated by web based randomization software [21] placed into opaque, sequentially numbered envelopes and delivered to participating physical therapy clinics prior to beginning recruitment. Two sites will contain 4 blocks of 4 envelopes, and one site will contain 3 blocks of 4, ensuring a total of 44 patients. If one site or another enrolls more patients, only a full block of 4 envelopes will be transferred to that site for further enrollment. The envelopes will be stored in the desk of the directing physical therapist at each location,

and only removed once a patient has been enrolled. Once patients consent to enroll in the study, they will receive the next envelope in sequence in the group of 4, and be allocated to either the intervention or control group. The envelope will contain a number which the treating physical therapist will then compare to the master allocation list, which will reveal which treatment group #1 or #2(intervention or control) the patient has been allocated; it will also contain the patient's assigned identification number (PID). The treating physical therapist will be responsible for communicating the subject's allocation and PID which will be contained in their envelope to the primary investigator, who will hold the confidential master list. Outcomes data will be collected in a separately in REDCap.

Blinding

Patients and treating therapists will be aware of the treatment rendered. Patients will self-enter their answers on the PRTEE and NPRS at the first, and 6th or final physical therapy visit. This data will either be self-entered to REDCap website, or onto paper copy which will be entered into REDCap by researcher blinded to their allocation. The treating physical therapists will be blinded to these results. Grip strength, and maximum pain free grip will be recorded at each therapy visit by treating physical therapist who is not blinded to the treatment allocation. We have made this decision understanding the risk of biasing a secondary outcome, but the burden of having multiple therapists at each site accommodate the institutional expectations for participating in research in order to have blinded assessment, has made this a necessity. Post treatment assessment with the NPRS and the PRTEE will be done via online REDCap survey. A researcher blinded to allocation will be responsible for contacting patients not responding to email contact to request completion of the online survey. A separate researcher, blinded to group allocation will analyze the final results that will be stored in REDCap.

Device

We will be using the Delfi personalized tourniquet system for BFR in this study (Delfi Medical Innovations Inc., 1099 West 8th Ave, Vancouver, BC, Canada, V6H 1C3). The Delfi system allows a specific limb occlusion pressure to be applied to a patient's limb in order to reduce their arterial flow by a proscribed amount. In our project, we will use 50% occlusion as the standard [22].

Physical therapy staff participating in the study will be trained on the use of BFR technology. At least one therapist will attend formal training provided by the device developer prior to beginning enrollment in the study. After receiving training, all other participating therapists will be trained by the therapist/s who have received formal training.

Statement from the manufacturer (received via email):
The Delfi PTS Personalized Tourniquet System for BFR device when used according to the device's Intended Use and Indications for Use statements in the Operator and Maintenance Manual is cleared for market under Delfi Medical Innovations Inc.'s FDA Device Listing for Pneumatic Tourniquets E127474 as a Class I device exempt from premarket notification procedures. Delfi Medical Innovations Inc. is a registered establishment with the FDA under registration number 9681444.

Inclusion / Exclusion Criteria:

Included

The diagnoses included are lateral elbow pain, lateral epicondylitis, or lateral epicondylalgia, more general diagnoses elbow tendinitis or elbow pain will be included if their clinical picture at physical therapy meets criteria for lateral epicondylitis. If the inclusion diagnosis is other than lateral epicondylitis or tennis elbow, we will confirm the diagnosis at the first therapy visit with tenderness at the lateral epicondyle and/or pain with resisted wrist/long finger extension at the lateral epicondyle. All participants must be between the age of 18 and 70 years old and have had pain for 4 weeks or more.

Excluded

Patients presenting with a ligamentous elbow sprain, osteoarthritis of elbow and cervical radiculopathy in the affected limb will be excluded from the study. Other exclusion criteria would be inability to consent, any history of ligamentous, bony or other soft tissue reconstruction surgery at the affected elbow, history of DVT, history of endothelial dysfunction, peripheral vascular disease, pregnancy, surgical procedure on their contralateral extremity, active infection, injection therapy (corticosteroid, platelet rich plasma, or other injection therapy) in the prior 3 months to the affected site, and cancer; any surgery on affected arm in last 1 year; current fracture in affected arm; history of crush injury to affected arm; history of lymphectomy (such as axillary exploration with breast surgery, lymph node biopsy in the affected axilla/arm), sickle cell anemia or trait; kidney dialysis; history of syncope/passing out with pressure to body (such as massage, or blood pressure cuff).

Assessment of Resources:

The study population proposed is readily accessible at Cleveland Clinic Akron General as a review specifically of Akron General Orthopedic practitioners over a 10 month period covering 2017-2018 showed over 200 office visits with the diagnosis code for lateral epicondylitis. Cleveland Clinic Akron General as a facility has the adequate resources available to support the study, including electronic medical records and REDCap. In addition, qualified and experienced medical staff members will conduct the study, including a sports medicine physician, two doctors of physical therapy with residency training in sports medicine, research coordinator/biostatistician, and a master's level athletic trainer. The authors will also apply for summer research interns as part of the annual Cleveland Clinic Akron General program. Co-investigators will be trained on the protocol and only IRRB approved staff will be conducting research related procedures.

Outcomes assessment

Numeric Pain Rating Scale (NPRS), Patient Rated Tennis Elbow Evaluation (PRTEE)

For the NPRS, subjects will be asked to rate their pain 0-10, with 0 being no pain and 10 being worst pain imaginable. Subjects will be asked to rate their least pain in the last 3 days and worst pain the last 3 days.

For the PRTEE, it will be issued in paper or electronic format to the patient prior to physical examination.

In both cases, the scales will be collected on the first/baseline visit, as well as at the final therapy visit (if known). They will then be collected electronically by email (with phone call reminders if necessary) at 3, 6, and 12 months.

Grip Strength Testing

The subject will be given a calibrated hand dynamometer and will be instructed to keep arm adducted and elbow bent to 90 degrees while in a sitting position. The subject will be asked to squeeze until onset of pain that is 2 points above resting pain on NPRS. There will be two attempts, with 60 seconds in between, and the average will be recorded. Then, using the same positioning, the subject will perform 2 max effort squeezes within their pain tolerance. The average of the two measure will be recorded as done previously.

Therapy Protocols

Once randomized, Twenty-two subjects will be in the placed into a control group, in which standard loading of the wrist and finger extensors using 70% of 1 Rep max (RM), determined using a 1 RM calculator, will be given as well strengthening pronators, supinators and grip strength. The experimental group of 22 will receive blood flow restricted wrist extensor strengthening at 50% limb occlusion using 20% of their 1 RM. To assess 20% of 1 RM of the extensors, a weight will be given to the patient to see how many repetitions can be performed. The weight and number of reps will be entered into a 1 RM calculator so that 20% of the 1 RM can be determined. Strengthening using BFR will occur once per week in clinic, in addition to standard strengthening of supinator, pronators and grip strength. They will also perform the same standardized home exercise program as the control group. All participants will receive the same instruments at baseline and 6th visit. Treatment performed at the three participating clinics will undergo standardized training in the use of BFR strengthening as well as specific study protocol training prior to the onset of the study.

The subjects placed into the control group will receive standard loading of the wrist and finger extensors using 70% of 1 Rep max (RM). The subject will be given the appropriate weight in clinic to be able to do 3 sets of 15. The subject will also strengthen pronators, supinators using a weighted stick to a 7 out of 10 on a rate of perceived exertion (RPE) scale. Grip strength will be addressed using therapeutic putty, resistance determined by the therapist's assessment, having the patient perform 3 sets of 2 min of squeezing the putty. The therapist will have discretion on if cervical spine, thoracic spine or shoulder treatment is warranted, based on standard practice. This treatment will occur for 6 visits in the clinic.

The subjects in the experimental group will use weighted dumbbells to find 20% of their 1 RM for their wrist extensors, as described above. Once that is found, a portable tourniquet system will be applied to the upper arm to achieve partial vascular occlusion, set to 50% of their predetermined total limb occlusion pressure (LOP). To determine the total limb occlusion pressure (LOP), a tourniquet will be inflated around the subject's upper arm to begin vascular occlusion. The model used will be a Delfi Personalized Tourniquet System, allowing safe control and regulation of blood pressure throughout exercise. This will continue until a Doppler ultrasound will no longer be able to detect a pulse. The amount of pressure found to create pulse absence will be that subjects personal LOP and be used to determine the amount of occlusion needed to achieve 50% limb occlusion.

The subject will perform 4 sets in total for the wrist extensor exercise. One set of 30 reps followed by 3 sets of 15. Subjects will have 30 seconds of rest between sets while the tourniquet remains inflated. Subjects will have a 1 min rest break in between exercises. The subjects will also perform resisted supination, pronation using 3 sets of 15 and grip strengthening using therapeutic putty for 3 sets of 2 min while using the tourniquet set at 50% of their LOP. Resistance will be adjusted to ensure patients are achieving 7 out of 10 effort on RPE scale. Additional treatment to the cervical spine, thoracic spine and shoulder will be at the discretion of the therapist. This treatment will occur for 6 visits in the clinic.

If the patient is unable to complete the expected number of repetitions at the expected resistance a standardized adjustment to the protocol will take place:

- If they complete 60-74 total repetitions: continue with training but extend rest period between sets 3 and 4 to 45 seconds, until 75 total reps are complete.
- If they complete 45-59 total repetitions: continue with training but extend rest period between all sets to 45-60 seconds.
- If they complete less than 44 total repititions: reduce load by 10% until 75 reps achieved.

Both control and experimental group will perform the same home exercise program. Loading of the extensors will be done using resistive bands for 3 sets of 15 1x/day, maintaining a 7 out of 10 effort on the RPE scale. Subjects will be instructed on how to increase resistance using the resistive bands. Subjects will be instructed to sit at a table holding resistive band in symptomatic hand while a foot pins down the opposite end of the band to create resistance. The subject will perform wrist extension from neutral. Once the appropriate tension has been found, they will mark on their resistive band with a marker where their foot is. This will allow the subject to return to that desired dosage if appropriate, or shorten the band to achieve desired resistance. Exercises to the cervical spine, thoracic spine and/or shoulder are permissible if evaluating therapist deems it appropriate and in line with standard of care, but not to exceed three exercises for home.

Data Collection

Patients will be enrolled and data collected electronically using the secure data collection system REDCap (see appendix) after their consent has been signed.

Baseline data collected will include:

Age (DOB)
Gender
Race
Height
Weight
Occupation
Active medical history
Current medications
Past medical history
Past surgical history
Duration of lateral epicondylitis symptoms
Previous treatments for lateral epicondylitis (Over the counter medications, prescription medications, Injection therapy (corticosteroid, regenerative-platelet rich plasma, autologous blood, stem cell, etc; dry needling), bracing/strap, and other treatments: (free text).

After the patient has ceased treatment, data will be collected electronically by email or over the phone. At each time point 3, 6, and 12 months, an email will be automatically generated by REDCap with links to the questionnaires for the patient. If they do not respond within 1 week, a reminder email will be generated, and again if not filled out, a final reminder email will be generated.

A combination of physical therapist (Daniel Hass), summer research assistant/fellow, and employed certified athletic trainer (Art McCreary) will be assigned to follow through on data collection for the entirety of the follow up period. The research assistant and athletic trainer will have access to patient name, and contact information. They will be authorized to telephone the patient to remind them to fill out their follow up PRTEE and NPRS. If the subject has not filled out their online survey after the 3 standard emails, we will attempt to contact the subject by phone. Each patient may be contacted 3 times, with each phone call one week apart at each follow up time point (3, 6, 12 months). If they have not filled out their survey at that point, we will cease attempts. The subject may ask us not to contact them by phone at any time, and we will not follow up by phone for the remainder of the study.

The final survey will include questions on whether the patient has sought and received other treatment, such as: prescribed medication, surgical intervention, injection therapy, and return to physical therapy.

Serious adverse events will be reported to the IRRB at any time during the active treatment phase of physical therapy, and will be entered into REDCap. This data will also be directly communicated to primary investigators-Aaron Lear, MD; Chanda Mullen, PhD; Phillip Toal, DPT by email and phone. Mild adverse events, such as muscle pain and bruising at the site of BFR cuff will be considered routine and communicated only if it limits ability to treat patient at follow up visits, or leads to alteration in care.

Data Points collected will include:

1. PRTEE and NPRS will be collected at the physical therapy visit at entry, and sixth or last therapy visit. It will be collected electronically by email, with phone call reminders if necessary at 3 months, 6 months, and 12 months from the date of enrollment.
2. Grip Strength (maximum and maximum pain free), and 1 repetition maximum will be collected at entry into study, and 6^{th} / or last visit.

Statistical Analysis

Descriptive statistics will be performed for demographic variables. Categorical variables will be reported as n (%) and will be analyzed by chi-square or Fisher's exact test as appropriate. Continuous variables will be reported as mean with standard deviation or median with interquartile range and analyzed by repeated measures ANOVA or non-parametric equivalent based on the normality of the data distribution. Analyses will be performed at each time point for the primary and secondary outcomes as the dependent variables and group assignment and time point (visit number) as factors. Paired t test or non-parametric equivalent may also be used for within group comparisons. Statistical analysis will be performed using IBM SPSS statistics version 24.0 and the level of significance set at p less than 0.05, two-sided.

Primary outcome analysis will be intention to treat at the 12 month time point. Per-protocol analysis will also be reported. Primary outcome will be reported as change from the PRTEE baseline score to the 12 month PRTEE score. The minimally clinically important difference (MCID) on the PRTEE is considered to be 10, and will be used as the benchmark for success of the treatment protocol. The primary outcome variable will be the comparison of the change in PRTEE in the intervention group, compared to the control group. Missing data will be dealt with after evaluation of the cause of the missingness; and potential strategies include complete case analysis, multiple imputation model, and inverse probability weighting.

Secondary outcomes will be comparison of the change in the NPRS between groups; change in 1 repetition maximum between groups; and change in grip strength between groups.

Multiple linear regression analysis will be performed to control for the effects of age, sex, length of condition, previous and currents treatments, occupation on change in PRTEE from baseline to 3, 6 and 12 months.

Power Analysis

A two sample t test of normal mean difference assuming a group standard deviation of 10 PRTEE score points based on findings by Krogh, et. al. (2013)[24], a minimal clinically important difference of 10[25], a two-sided significance of 0.05, and a power of 80% resulted in a sample size of 17 per group. A dropout rate of 30% is expected, thus the plan is to recruit a total of 22 patients per group for a total of 44 subjects.

Ethical Considerations

Risks and Side Effects

BFR training has been shown to be safe and can also be applied to persons with various kinds of physical condition including cerebrovascular diseases, orthopedic diseases, obesity, cardiac diseases, neuromuscular diseases, diabetes, hypertension, and respiratory diseases. Nakajima performed a national survey of over 12,000 patients and found that the number of severe side effects is very low. The most frequent side effect is subcutaneous hemorrhage that is transient. Several papers showed that BFR training combined with low-intensity exercise does not cause severe muscle injury, and there is no elevation of creatine phosphokinase (CPK)[26] or rhabdomyolysis, as compared with heavy exercises.

Risks include primarily the risk of failure of physical therapy. As we know that therapy has variable responses with this condition, the possibility that the patient does not respond well to either control, or intervention treatment is real.

Medical risks appear very unlikely, with no significant side effects beyond muscle pain reported with BFR in the past.

KAATSU training, which is a Japanese version of blood flow occlusion training, has shown risks of major side effects to be less than 0.1% on a national survey of those using it. These risks included venous thrombo-embolism and rhabdomyolysis.

We believe significant side effects are very unlikely based on published data, and the idea that a trained therapist will be supervising the treatment of our patients.

We cannot envision any significant risk beyond muscle soreness, and possibly skin bruising for patients who have been enrolled in the intervention arm.

Serious Adverse events

Any significant adverse event-such as a venous thrombo-embolism, or significant medical event occurring within 48 hours of treatment will be recorded and reported.

If any significant similar medical event (such as a pulmonary embolism, angina episode, etc.) occurs in patients in any way which indicates a pattern of risk in the intervention group, the investigators will meet to discuss discontinuation of the trial.

Compensation for Injuries

No compensation for injury is planned. Subjects will be informed at the time of consent that any adverse event will be treated and covered as usual by the patient and their health insurance.

Benefits to Subjects

There is no particular benefit to patients to enrolling in the study. Patients will have to opportunity to receive up to date physical therapy treatment in the control group; and potentially a new and possibly more effective therapy treatment in the intervention group. The primary benefit will be to evaluate a potential new treatment for a condition which is difficult to treat.

Costs to Subject

The cost of participating will be no different than the cost of attending physical therapy generally. Patients will be responsible for whatever costs they would be responsible for when attending therapy. The patients' insurance companies will be billed for standard therapy through the course of treatment.

Compensation to Subject

There will be no compensation for subjects participating in the subjects.

Data/Safety Monitoring

AL, CM, and PT will monitor the results for any report of adverse events. Therapists involved in the project, patients and the blinded assessors will be instructed to contact the investigators with any concern for adverse event. At any time, if there is suspicion of consistent adverse outcome in the intervention group, the 4 investigators mentioned will discuss options, and if no alternative explanation can be found, will discontinue the trial.

AL, CM, and PT will be in contact either in person, by phone, or electronically monthly to discuss the ongoing trial, and will discuss adverse events at point of planned contact.

At this monthly contact, data reporting will be reviewed. We will make efforts in areas of deficiency to contact the enrolling investigator, and ensure that all data is collected. We will also monitor the safety of confidential data.

a. Monthly Meeting Checklist (once enrollment has begun):
    i. Number of patients enrolled
    ii. Barriers to enrolling patients (such as phone enrollment, difficulty getting investigator to first therapy appointment, etc.) with suggested solutions
    iii. Data entry:
        1. Enrolled patients information is being appropriately entered
        2. Enrolled patients information and consent form is appropriately recorded and protected

3. Any other data concerns

iv. Safety: Any adverse events or other safety issues

v. Follow up:
   1. Occurring as planned
   2. Barriers to follow up with suggested solutions

Subject Privacy and Data Confidentiality

Privacy of Participants

All patient data for research purposes will be recorded digitally in the Cleveland Clinic HIPAA compliant REDCap database.Treatment records of the patient encounters with PT will be recorded as usual in electronic health record. Hard copies of consent forms will be kept in file in locked office with athletic trainer (Art McCreary) at Bath physical therapy office.

Confidentiality of Data

The data will not be disseminated outside of the institution. All researchers will be working within secure Cleveland Clinic networks, or via CCAG encrypted computers via VPN access when off campus. When enrolled, patients will be assigned a subject number, a master list will be kept by researcher enrolling/consenting patients in REDCap. All research data will be recorded with this subject number rather than patient identifier data. All researchers participating in the study will access to secure online databases. Enrolling/consenting research and Blinded assessor will not have access to which groups patients are enrolled in.

Plan for Record Retention and disposal

Records will be kept in REDCap until study completion. Patient identification data will be purged after the completion of data collection. The de-identified data will be kept indefinitely.

Limits to Confidentiality

Confidentiality will only be broken in the setting of a medical emergency at clinical visit, or if contacted by an outside medical provider for an emergency.

Potential Limitations of Study

Primary concerns about the study involve recruitment, and enrolling 44 patients, and following them to completion. This is a large number of lateral epicondylitis patients, and while we expect to enroll this amount, we do have a concern about doing so within two years.

There is a concern that the interpretation of results may receive criticism that the load of strengthening exercise differs between the two groups at their physical therapy visits (high load exercise in control group, low load with BFR in the intervention group). It is our goal to make clear that the intervention being tested is low load exercise in the presence of blood flow restriction together, rather than simply low load therapeutic exercise. This will be communicated in the results/discussion section of any manuscript generated. We will also make clear that both groups received the same instructions for home exercise

program, and that the primary difference between treatments was high load standard exercise, and low load exercise with blood flow restriction.

Related to the above, is the lack of a placebo group. We would like to include a placebo group using a blood pressure cuff just minimally inflated, but this would have required increasing the recruitment of patients to 66, and we felt this was too daunting to be done as an early phase trial.

Our final concern is regarding blinding of the treating therapists to the grip strength testing. For efficiency reasons, we have decided to allow the treating therapists to be aware of the results of these tests (secondary outcomes), and to record them in the patient charts.

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Plans for dissemination of findings

Upon completion of the study it is our intention to submit the research to a national/international level sports medicine or physical therapy conference. We also intend to submit a manuscript to a sports medicine or physical therapy journal.

References

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Appendices

Research Information Sheet

Informed Consent

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