A. Project title:

Blood Flow Restriction Exercise for Older Adults Undergoing Knee Replacement Surgery

Version 2: January 26, 2017
Version 3: March 28, 2017
Version 4: August 31, 2017

B. Investigator(s):

Rene Przkora, MD (Principal Investigator)
   Department of Anesthesiology
Samuel Wu, PhD (Co-Investigator)
   Department of Biostatistics
Hari Parvataneni, MD (Co-Investigator)
   Department of Orthopedics and Rehabilitation
Roger B. Fillingim, Ph.D. (Co-Investigator)
   Pain Research and Intervention Center of Excellence
Andrew Layne, Ph.D. (Co-Investigator)
   Department of Aging & Geriatric Research
Bhanuprasad Sandesara, MD (Co-Investigator)
   Department of Aging & Geriatric Research

C. Abstract:

Older adults are the fastest-growing patient population, suffering disproportionally from knee osteoarthritis (OA) that leads to functional decline and loss of quality of life. Knee joint replacement surgery [total knee arthroplasty (TKA)] is frequently the only option to potentially prevent permanent disability and loss of independence. However, this surgery is associated with significant postoperative loss of function and strength requiring intensive rehabilitation efforts to improve morbidity and mortality in patients
with already declining health. As joint replacement surgeries, including TKA, are becoming the most common surgeries in the elderly before cardiovascular or cancer surgeries, efforts to improve outcomes are a major public health priority. Standard high-resistance exercise interventions to attenuate loss of function and muscle mass have shown inconsistent results, perhaps in part because they have sometimes been performed over several months prior to surgery. Additionally, patients with knee OA requiring surgery do not tolerate common high-resistance exercise protocols secondary to pain and disability. Based on this dilemma, we propose to test the feasibility and efficacy of a low-resistance exercise protocol with blood flow restriction (BFR) using a tourniquet in the preoperative period of patients awaiting TKA. BFR exercise is a new exercise method that has not been studied in the perioperative period. We will compare our intervention (12 patients) to a no-exercise group (8 patients) up to 4 - 6 weeks prior to surgery. We will measure clinical outcomes such as strength, lower extremity function, and pain. Data gathered in this feasibility trial will be used to study differences between BFR exercise and other exercise methods and their combinations such as high-resistance exercise with BFR in larger multi-center trials, including long-term follow-up studies. Another promising future direction will be to study the combination of BFR exercise with nutritional or performance-enhancing agents to characterize synergistic effects.

Finally, if beneficial, BFR exercise can be readily translated into clinical practice as well as to similar patient populations in the ambulatory or hospital setting at risk of losing function, and therefore, independence.

D. Background:

Older adult patients are the fastest-growing patient population. Arthritic changes of the knee joints are prominent in these patients and pose a constant threat to independent living and quality of life. Treatment options are limited and, frequently, knee joint replacement surgery (total knee arthroplasty – TKA) is required. Joint replacement surgery is becoming the most frequent surgical intervention, exceeding surgeries for cancer or cardiovascular disease. Severe osteoarthritis (OA) is also associated with
loss of function, loss of muscle mass, and is the cause of activity-limiting pain. The surgical stress response further diminishes function, causing a delay in the postoperative recovery period. Subsequently, patients have to be transferred to skilled nursing and/or rehabilitation units to restore function and return to their independent living environment. While TKA is generally considered a safe and effective intervention for severe knee OA, a large proportion of patients continue to show significant pain and functional limitations following surgery. The degree of functional impairment of TKA patients after surgery depends upon the amount of muscle and function lost to surgical stress and the preoperative muscle size and functional level. Indeed, preoperative functional levels significantly predict functional outcomes of TKA, raising the possibility that improving function preoperatively may enhance postoperative functional outcomes.

Because joint replacement surgery is an elective procedure with advance scheduling, presurgical interventions to enhance muscle function and improve postoperative functional outcomes are feasible. Unfortunately, current standard exercise interventions performed prior to TKA have very limited efficacy and have to be performed over a period of months to achieve results, which is not practical in patients with pain and limited time. Indeed, a recent meta-analysis reported no benefits in the postoperative period in patients who were enrolled in standard exercise protocols in the preoperative period prior TKA.

Based on these negative findings, novel interventions have to be studied to improve outcomes. Ischemic preconditioning through blood flow restriction (BFR) using a tourniquet during exercise is a new and promising exercise method. This type of exercise has been performed previously by study investigators, Drs. Buford, Fillingim, and Vu in the study titled "Kaatsu training to enhance physical function of older adults with knee osteoarthritis", IRB201400300.

On the molecular level, BFR exercise affects different cell signaling pathways, proteolytic and myogenic markers, and muscle protein synthesis. The mammalian target of rapamycin (mTOR) complex 1 (mTORC1) pathway is currently the most prominent target, as this pathway is involved in the accretion of muscle mass and is regulated by exercise.
BFR exercise has been shown to increase muscle mass and strength at a low exercise intensity in human trials. Therefore, BFR exercise might be better tolerated by patients who have contraindications for high-resistance exercise such as knee OA. Indeed, recent studies demonstrated beneficial effects of BFR exercise in female patients with moderate knee OA, but no benefits in males. However, BFR exercise in patients with advanced knee OA requiring surgery has not been studied.

BFR exercise has been shown to improve muscle mass in a shorter period of time and at a lower exercise intensity (20%-30% 1 Repetition Maximum – 1RM) when compared to standard exercise protocols (70%-80% 1RM) and appears to be an attractive alternative for patients who cannot undergo a lengthy exercise program secondary to pain and a limited time schedule. One randomized study has compared BFR to low-resistance exercise in female patients with risk factors for knee OA. Segal et al. enrolled 45 patients and 40 patients completed the protocol of 4 weeks of exercise, 3 times per week. Of the 5 patients who did not complete the protocol, only one patient discontinued the study secondary to intolerability (3 discontinued due to lack of time and one patient was lost to follow-up). Isokinetic knee extensor strength and isotonic 1RM (repetition maximum) leg press significantly improved in the BFR exercise group when compared to the exercise group without BFR. In contrast, Segal et al. could not demonstrate a similar effect in male patients. Of note, these patients did not have symptomatic knee OA requiring a joint replacement surgery.

These promising results of BFR exercise led us to the design of this pilot trial. We will study 2 groups: A low-resistance exercise group with BFR (EX-BFR, 12 patients) and a group without exercise (NO-EX, 8 patients), reflecting the standard of care of patients prior TKA.

E. Specific Aims:

This pilot study will investigate the effects of BFR exercise for up to 4 - 6 weeks prior TKA surgery in older patients to determine if this type of exercise is feasible in the preoperative period and if BFR exercise will improve functional, physiological, and molecular outcomes when compared to patients without exercise. If beneficial, BFR
exercise can be readily translated into clinical practice, as well as to similar patient populations at risk of losing function, and therefore, independence. We will test the following aims:

**Specific aim 1:** Determine the tolerability and potential recruitment and compliance barriers in this patient population to refine our inclusion criteria and strategy for future proposals.

**Specific aim 2:** Determine the effects of preoperative BFR exercise (EX-BFR) compared to no exercise (NO-EX) on pre- and postoperative (1) muscle strength using isokinetic and isometric tests, (2) function using the six-minute walk test (SMW) and the Short Physical Performance Battery (SPPB), (3) pain, and (4) self-assessment outcomes.

**Future directions:**

The intervention can be transferred easily to patient populations at risk of catabolism and loss of function in the ambulatory or hospital setting. Data gathered in this pilot trial will be used to design R01 proposals to study differences between BFR exercise and other exercise methods and their combinations such as high-resistance exercise with BFR in larger multi-center trials (pre- and postoperative), including long-term follow-up, nutritional supplements and gender studies. Such trials will in addition collect serial tissue biopsies to investigate the mechanisms of muscle loss, which will provide us with biological targets for future interventions.

**F. Research Plan:**

**Participant selection criteria:**

Dr. Parvataneni specializes in joint replacement surgery and performs, on average, 4 to 5 total knee replacements per week, with the majority of his patients older than 60 years. The design of our protocol is in close alignment with his clinical practice procedures, including pre- and postoperative follow-up visits.

The clinical care of patients undergoing TKA is standardized, including the anesthetic and postoperative pain management and the in-hospital rehabilitation protocol. Postoperative
care is also standardized, with the first follow-up expected at 2 weeks after discharge (patients are usually not enrolled in different rehabilitation programs yet).

**Inclusion:**

The general inclusion will be those adult patients who:

- are 55 years to 80 years of age
- are scheduled for elective TKA for osteoarthritis
- are scheduled for unilateral joint replacement surgery only
- are able to give consent and follow instructions
- are willing to complete up to 15 study visits

**Exclusion:**

The exclusion criteria will include:

- patients below the age of 55 years old
- patients over the age of 80 years old
- patients who live in a radius greater than 45 miles from the University of Florida (a feasible distance to allow for transportation to and from the clinical center for assessment visits)
- patients with impaired cognitive function and mental disease, (e.g. diagnosis of Alzheimer’s disease)
- patients with paraplegia/extremity amputation
- patients with end stage renal disease requiring dialysis
- patients with uncontrolled diabetes and insulin-dependent diabetes
- patients with uncontrolled cardiovascular disease e.g. (CHF NYHA class 3 or higher, BP > 180/110 mmHg)
- patients with severe pulmonary disease requiring continuous oxygen therapy
- patients with active neoplasm
- patients with peripheral vascular disease or deep vein thrombosis (within the last 3 years)
• patients with structured exercise/PT/OT/fitness program enrollment within 12 weeks prior to surgery and/or more than 2 hours per month on gym/fitness room exercises
• patients with BMI greater than 40 kg/m²
• patients with opioid use of more than 30 mg Morphine-equivalents per day
• patients with chronic oral steroid use
• patients with chronic anticoagulation (e.g. Plavix, Warfarin)
• patients with planned postoperative admission to a skilled nursing/inpatient rehab facility
• patients with ipsilateral joint disease involving hip, ankle or spine
• neurologic or other etiology of quadriceps wasting
• surgery within less than 4 weeks
• patients with comorbidities that the PI judges as not suitable for the study
• patients with a MMSE score below 24

Following Institutional Review Board approval, we plan to recruit up to 30 subjects to participate in this study. If the potential subject expresses interest in the research, they will be given a copy of the informed consent. Potential study participants will have time to read the consent, have all study related questions answered, and discuss the study with their family, if desired before consent is obtained. Once consent is obtained the patient will be assigned to a randomization group.

Recruitment:

Subjects will be introduced to the study at the UF Orthopaedics and Sports Medicine Institute (UF-OSMI) and provided a study introduction letter that gives general information about the study. If interested, subjects will be asked to sign a form providing permission to provide contact information for the research team to contact them. Subjects who sign the permission will receive a pre-screening and study discussion phone call from a designated study team member. Following the phone call, interested subjects who meet the pre-screening criteria will be scheduled to come to the UF
Institute on Aging where study procedures and risks will be carefully explained again, and informed written consent will be obtained.

**Randomization:**

The subjects will be randomly allocated by computer-generated randomization to one of two groups (12 subjects receiving intervention and 8 subjects without intervention). We plan to enroll up to 30 subjects (we are requesting an additional 10 subjects to account for the potential of participant dropout). Subjects allocated to group 1, no exercise group (standard of care) (NO-EX) will only undergo baseline strength testing. Subjects will not enroll in exercise, whereas the subjects allocated to group 2 will be asked to perform low-resistance exercise with BFR (EX-BFR) to both lower extremities.

Subjects will be reimbursed up to $270 total with $30 being paid for assessment visits (Baseline testing, Pre-op testing, and Post-op testing) and $15 per exercise visit (up to 12 visits).

**Groups:**

1) No exercise group (standard of care) (**NO-EX**): Subjects randomized to the NO-EX group will not enroll in exercise.

2) Low-resistance exercise with BFR (**EX-BFR**) group: Bi-lateral lower extremity. Determination of 1 Repetition Maximum (1-RM) and preoperative low resistance exercise with BFR (see below for details).

**Location:**

Institute on Aging (IoA) for screening and testing all groups (see flowchart).

Institute on Aging Health Promotion Center (HPC): Exercise intervention for EX-BFR groups (see flowchart).

**Measurements and interventions for both groups (NO-EX and EX-BFR):**

1. **Strength testing:** To assess the efficacy of our interventions, we will test the strength of subject’s lower extremity muscles on the dynamometer system. We will test both isotonic and isokinetic strength of the lower extremities with the subject seated on the
Biodex seat and strapped in around their shoulders/torso and knees to keep them in position. Each leg will be attached to the knee attachment of the dynamometer with a padded strap at the ankle. For the first test, subjects will be asked to contract their thigh muscles as hard as they can by pushing against the stationary bar several times. Subjects will also be asked to move their knee from a bent to a straightened position and from a straightened to a bent position with the machine set at three different speeds. At each speed, the subject will straighten and bend their knee up to 3 times using their thigh muscles to push the bar as hard as they can in both directions.

2. Short Physical Performance Battery (SPPB): The SPPB is a timed short distance walk, repeated chair stands, and balance test that measures lower extremity function. This test battery takes about 10 minutes and is easily administered. The SPPB was validated for predicting institutionalization, hospital admission, mortality, and disability. The SPPB will be tested at baseline, last visit prior to surgery, and postoperatively.

3. Six-minute walk (SMW) test: A validated measure of walking endurance that predicts mobility loss and mortality and improvements in response to interventions in older people. Subjects walk back and forth along a 100-ft hallway for six minutes after instructions to complete as many laps as possible.

4. Numerical pain scale: We will measure pain using an 11-point numerical pain scale.

5. Self-assessed function: Using the Late Life Function and Disability Instrument. The scale has strong concurrent and predictive validity with physical performance. The questionnaire includes 16 tasks representing a broad range of disability indicators that assess the frequency of doing a task and the perceived limitation. The scale has strong concurrent and predictive validity with physical performance.

6. Muscle biopsies: During the course of the surgery two small muscle biopsies from the quadriceps muscle of the operative leg will be collected to be used to examine biological targets on the muscle tissue to allow for better understanding of exactly how BFR effects the cells to produce its beneficial effects. One biopsy prior to surgical tourniquet inflation and another biopsy at the end of surgery – just before tourniquet deflation. The biopsies will be collected during the operation and while the patient is anesthetized and will be harvested through the incision used to perform the operation. The tourniquet
application to the thigh is a routine procedure to minimize blood loss during total knee replacement surgery and is not associated with the research study.

7. Clinical variables: We will also collect subject’s height, weight, vital signs, minimal mental status (MMSE at baseline visit), medications, medical history and clinical course, including postoperative destination, (e.g., home or rehabilitation facility, especially planned or un-planned admission to a skilled nursing facility).

**Interventions and measurements only for the EX-BFR group:**

1. Exercise protocol:

*Determination of 1 Repetition Maximum (1-RM):*

The strength test will consist of an initial warm-up phase, with the subject performing up to 10 repetitions at a moderate weight to get acclimated to the machine. Following the warm-up, subjects will attempt to complete one repetition of the leg press exercise at progressively greater resistance until a full repetition can no longer be performed. The weight of the last complete unassisted repetition will be recorded as the 1-RM. After a rest period of 5 min, the strength test will be repeated in a similar fashion. The highest weight achieved from the two strength tests will be deemed their 1-RM.

The 1-RM will be determined again before the 6th exercise intervention and the load will be adjusted in the EX-BFR group.

*Exercise intervention:*

After random assignment to the blood flow restriction exercise (BFR-EX) group and determination of the 1-RM, participants will engage up to three days a week, in center based exercise intervention for up to 4 - 6 weeks.

Following a brief warm-up, participants will perform lower-extremity exercises (leg press, leg extension, leg curl, and calf extension) at an intensity of 30% of 1-RM with external compression applied to the proximal thigh of each leg (blood flow restriction – see below). Participants will perform up to 2 sets per exercise for a total of up to 8 sets per exercise visit.
Exercises will be performed to volitional fatigue – defined as the inability to complete a pain-free range of motion after strong verbal encouragement. Exercise training will be performed using standard isotonic resistance training equipment (Life Fitness, Schiller Park, IL).

**Blood flow restriction (BFR):**

Thigh compression will be applied according to tourniquet guidelines using segmental vascular cuffs (D.E. Hokanson, Inc., Bellevue, IL). Cuff pressures will be set and maintained by an automated cuff inflator (TD312, Hokanson) designed specifically for rapid and precise control of cuff pressures. Cuff pressures for each individual will be determined according to the equation \[ \text{pressure} = 0.5 \times (\text{systolic blood pressure}) + 2 \times (\text{thigh circumference}) + 5 \], if tolerated by the patient. This approach will not only standardize how restriction is applied, but will also ensure that cuff pressures will be safe across varying limb girths and blood pressures. Based on entry criteria for BP and a wide range of thigh girths (i.e. 35-65 cm), we expect thigh cuff pressures to range up to between 125-215 mm Hg. These pressures are well within a range previously shown to be safe and efficacious. Before starting exercise the participant will be acclimated to their specific, tolerated cuff pressure through a series of gradual pressure exposures. Cuffs will remain inflated during performance of each exercise (i.e. in-between sets) but will be deflated for 3-minute rest periods between exercises.

Data from the exercise interventions will be collected and stored in the study database. Additional data collected includes session attendance, 1-RM, and repetitions completed for each exercise per session.

2. **Borg CR10 scale:**

Following each session, participants will be asked to provide a rating of perceived exertion (RPE) for the session according to the Borg CR10 scale and rate unpleasantness of the session using a 10 cm visual analog scale ranging from 0 (not unpleasant) to 10 cm (extremely unpleasant).
Study flowchart:

<table>
<thead>
<tr>
<th>Assessment</th>
<th>All Groups</th>
<th>All Groups</th>
<th>Exercise Groups only</th>
<th>All Groups</th>
<th>All Groups</th>
<th>All Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone Pre-Screening</td>
<td>Baseline Testing</td>
<td>Exercise (12 visits)</td>
<td>Pre-op Testing</td>
<td>Intra-op Visit</td>
<td>Post-op Testing</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Institute on Aging</td>
<td>Institute on Aging-HPC</td>
<td>Institute on Aging</td>
<td>Operating Room</td>
<td>Institute on Aging</td>
<td></td>
</tr>
<tr>
<td>Time Period</td>
<td>~5-8 weeks pre-op</td>
<td>~4-6 weeks pre-op</td>
<td>1-5 days pre-op</td>
<td>Day of surgery</td>
<td>around 2 weeks post-op</td>
<td></td>
</tr>
<tr>
<td>Personnel</td>
<td>Coordinator/PI</td>
<td>Assistant</td>
<td>Interventionist</td>
<td>Assistant</td>
<td>Coordinator/Co-PI</td>
<td>Assistant</td>
</tr>
<tr>
<td>Tel. interview</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent/Randomization</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questionnaire</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPPB/SMW</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise/Borg CR10</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle Biopsies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

G. Protection of Human Subjects:

Administrative responsibilities:

Study Resources: The principal investigator will oversee the data collection, data analysis and will maintain the records in confidence. Should any evidence suggest that the study protocol require modification, the PI will notify the IRB in a timely manner for review and approval. Each subject will be identified on data forms by number – not by name. To protect confidentiality, all data will be numerically coded and information linking the numeric codes to individual participant’s names will be kept in a locked file in the PI’s office. Our study will not be double-blinded given the design, however, the research assistant, who will collect the main outcome data (baseline/preoperative and postoperative testing) will be blinded to the group assignments and subjects/patients will be instructed to keep their assignment secret. The interventionist will not interfere with the data collected by the research assistant.

Statistical methods, data analysis and interpretation:

We plan to enroll up to 30 subjects (we are requesting an additional 10 subjects to account for the potential of participant dropout), 12 subjects in the EX-BFR and 8 subjects in the NO-EX group. Such a sample size will yield more than 99% power to detect the between group differences observed in the study by Segal et al.: isotonic 1-RM improvement of 28.3 ± 4.8 kg versus 15.6 ± 4.5 kg and isokinetic knee extensor strength (scaled to body mass) increase of 0.07 ± 0.03 nm/kg versus −0.05 ± 0.03
nm/kg, for the BFR and control groups, respectively. Finally, the anticipated number of subjects will be sufficient to evaluate the feasibility of our pilot study.

Demographic and baseline levels of clinical variables will be compared between the two randomized groups using the Wilcoxon rank sum test for continuous variables or Fisher’s exact test for categorical variables. For all outcome measures and their changes between pre- and post-intervention, standard summary statistics comparing the randomized groups will be provided by time of follow-up.

**Data storage and de-identification plans:**
The PI will oversee the data collection, data analysis, and will maintain the records in confidence. All collected clinical data and digital files from the study will be de-identified and stored in a secure password protected database with strong encryption, on a computer server, accessible only by the study team. Computer used for the storage of data will be locked research office that is always under the lock and key. The key linking unique subject number and patients personal identifiers will be stored in a separate password protected and encrypted file and will be only accessible for the designated study team members. All paper records will be stored in locked file cabinet in the PI’s locked office. Database will be completely de-identified after 6 years after completing the study and all PHI will be destroyed via deletion from the study database.

**Possible discomforts and risks and protection:**
In the case that one or more of the screening tests results are abnormal; the doctor in charge will inform the subject and may discontinue them from the study, which may cause the patient distress. The subject will probably experience muscle soreness and tenderness that typically lasts for a few days after exercise or testing. This observation is normal. Less commonly, exercise may induce abnormal blood pressure, transient nausea, fainting, dizziness, and/or irregular heartbeat. Very rare risks of weight lifting exercise also include muscle, joint, back, or neck injury, trauma due to inappropriate utilization or malfunction of the weight lifting equipment, heart attack, stroke, or even death. No increased risk such as deep vein thrombosis has been observed with BFR exercise.
The SPPB may be associated with the risk of falling or coronary ischemia or dyspnea due to heart failure or lung disease. Rarely, falling during the test battery may result in a fracture. However, the research assistant who will collect these data has been trained to prevent falling. The risk of a fracture secondary to a fall during the SPPB test is less than 1 in 5,000. The SMW test may be associated with the risk of falling or coronary ischemia or dyspnea due to heart failure or lung disease. Rarely, falling during the SMW test may result in a fracture. However, the research assistant who will collect these data has been trained to prevent falling. The risk of a fracture secondary to a fall during the SMW test is less than 1 in 5,000.

Two biopsies of the quadriceps muscle will be performed by co-investigator and surgeon, Dr. Hari Parvataneni during the operation and while the patient is anesthetized and will be harvested through the incision used to perform the operation. Analysis of the muscle tissue will focus on metabolism, inflammation, autophagy, apoptosis and other mechanisms of muscular atrophy. The muscle is easily accessible as it is in the surgical field normally. The volume of muscle taken is minimal (around the size of a pencil head) and would not affect muscle integrity or strength. This protocol has been used in other studies without effect. The potential risks of this procedure are pain, bleeding, bruising, and infection. These risks are minimal as the biopsies are performed under sterile conditions in the operating room under anesthesia – without any additional incisions. Study participants’ identities will be kept strictly confidential. All hard-copy data will be scanned into electronic documents and then destroyed. Completed research phone contact agreements will be for one-time use only and will not be shared. Contact information will not be stored for use in other research projects. All electronic data will be stored in encrypted files and, once data acquisition is complete, all participant data will be de-identified to further protect their identities.

There is no financial risk associated with participating in this study. There will be no additional charges incurred from participating in this study than what would be normally charged if not enrolled within the study.
Data and Safety Monitoring Board (DSMB):

The DSMB will meet at least every six months during the study (Christiaan Leeuwenburgh, PhD, Stephen Anton, PhD, and Nikolaus Gravenstein, MD). All members of the DSMB have an extensive experience in the conduction of clinical trials, including exercise interventions in the elderly. The DSMB will meet to review and approve the protocol prior to beginning data collection. They will decide on specific stopping criteria for the study. The biostatisticians and data manager will work closely with the DSMB to perform interim analyses. Adverse events will be monitored continuously throughout the study and will be reported to the DSMB and IRB in a timely manner, according to pre-specified requirements. In addition, for each major adverse event, the group assignment of the patient will be provided to the DSMB. In this way the DSMB can determine whether the event is intervention related. Adverse event rates and interim study results will be reviewed and discussed by the DSMB at their regularly scheduled meetings. At least five categories of adverse events will be defined: a) death; b) cardiovascular events (myocardial infarction, stroke, and coronary arrhythmias) c) gastrointestinal symptoms (nausea, vomiting, abdominal discomfort, and indigestion); d) neurological symptoms (fainting, dizziness muscle, joint, back, headache or neck injury). We will report all hospitalizations to the DSMB in a timely fashion. We will use a designated data collection form to record these events and they will be reported as required to the Institutional Review Board and DSMB.

H. Possible benefits:

Effective therapies are urgently needed to prevent mobility loss and disability in the rapidly growing number of older people with knee OA requiring a TKA. Our study will enable us to measure the effects of a novel preoperative intervention at the clinical level. The intervention can be transferred easily to patient populations at risk of catabolism and loss of function in the ambulatory or hospital setting. Our proposed work will discover for the first time if BFR exercise is feasible in ambulatory or hospitalized patients who are at risk of losing muscle strength and function.
Importance of knowledge to be gained:

As outlined above, the disease burden related to knee OA requiring a TKA is increasing significantly, posing a tremendous burden on patients, families, and society. Furthermore, new therapeutic advances have not kept pace with the growing burden of disability from this disease process. TKA is the only option in disabling knee OA. New therapies are urgently needed for this large patient group. If our hypotheses are correct, the results will be used to design a large, definitive randomized multi-center trial. This study is especially important given the current rapid increase in the number and proportion of older individuals requiring joint replacement surgery in our society. Our intervention can easily be transferred immediately into clinical practice to benefit several patient groups at risk of disease and surgery or causing loss of muscle and strength and subsequent loss of function such as cancer patients and hospitalized older adults.

I. Conflict of interest:

None.
References


10. Abe T., C. F. Kearns, Y. Sato. Muscle size and strength are increased following walk training with restricted venous blood flow from the leg muscle, Kaatsu-walk training. *J Appl Physiol*. 2006; 100: 1460–1466. PMID: 16339340


