Vascular Dysfunction During Physical Inactivity

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VA Consent Document

DESCRIPTION OF RESEARCH BY INVESTIGATOR

BACKGROUND

Dr. Joel D. Trinity and colleagues are conducting a research study to find out how reducing physical activity impacts the body. We will investigate the roles that are played by the blood vessels (arteries and veins), heart, and muscles before, during and after periods of physical inactivity.

Prolonged periods of reduced activity have been associated with blood vessel dysfunction and decreases in strength and loss of muscle mass. The underlying factors leading to impaired blood vessel function and losses in muscle strength and mass are unknown, but have been linked to increases in oxidative stress. Oxidative stress is simply defined as a situation where chemicals naturally produced by your body, called free radicals, increase to a level that causes damage. These free radicals are important for maintaining normal function throughout your body. However, if they increase too much, they can interfere with the normal function of your body. Our body has systems in place to deal with these free radicals called antioxidants, however, we believe that these antioxidants may not provide enough protection during periods of physical inactivity. Our goal with this study is to determine how oxidative stress and physical inactivity impact the health of your blood vessels and skeletal muscle. Previous studies investigating the negative impact of physical inactivity have utilized various models such as bed rest, limb immobilization, reduced activity and prolonged sitting. We will use these models to determine how blood vessels and skeletal muscles respond to inactivity. Additionally, clinically-relevant situations including recovery following surgery, injury, or illness, whereby physical activity is reduced, will also be evaluated. We hope to develop treatments that preserve the health of your blood vessels and skeletal muscle during inactivity.

To help your body's antioxidant defense system, dietary supplements can be taken that have been shown to be effective. These supplements are vitamins that can either directly lower the level of free radicals or can stimulate your body to increase of its own antioxidant defense systems. We will use several different supplements to determine how oxidative stress impacts blood vessel and skeletal muscle function during inactivity. These supplements are not subject to federal regulation.

Exercise training and rehabilitation can be used as an alternative approach to combat the destructive effects of oxidative stress on aging and disease. An effective exercise training intervention can improve blood vessel skeletal muscle function. We aim to uncover the effect of exercise training and rehabilitation during physical inactivity.

It is our goal to understand the negative impact of physical inactivity on blood vessel and skeletal muscle function. We propose that physical inactivity induces a decrease in blood vessel health and skeletal muscle function and structure, which may be caused by oxidative stress. Through the models described previously, our aim is to understand and diminish the negative impact of physical inactivity. You are being asked to participate in this study because you are a healthy individual or because you have recovered

from coronavirus 19 (COVID-19). The insight gained from these studies will help in the development of safe and effective treatments for individual affected by periods of physical inactivity.

STUDY PROCEDURES

The study is divided into several parts. A preliminary visit is required for all participants to determine your eligibility for the study. During this visit, you may complete several exercise tests that include arm, leg, and whole-body exercise. If you are found to be eligible, you will be asked to enroll in one of the following modes of inactivity: bed rest, limb immobilization, or reduced activity. Depending on the mode of inactivity, your participation in the experimental protocol may last between 3 hours and 21 days.

Experimental Protocol: Our aim is to utilize dietary supplements, exercise training, and rehabilitation in order to understand how oxidative stress changes during physical inactivity. During inactivity, or periods of reduced activity such as acute hospitalization, functional (blood vessel and skeletal muscle function) and structural (loss in muscle mass leading to a reduction in strength) deficits arise. The underlying factors leading to these accelerated losses are unknown but may be linked to inactivity-induced elevations in oxidative stress. In this study, we will use different interventions (exercise and/or dietary supplementation) to better understand the contribution of oxidative stress to inactivity induced declines in functional and structural measures.

STUDY PROCEDURES

Preliminary Day: Screening and Exercise Testing (1-2 hours):

1. You may be asked to answer a series of questions concerning your health history which will include questions pertaining to your history of cardiovascular diseases, smoking, high blood pressure, elevated cholesterol in the blood, and level of physical activity. You may be asked about any medications or supplements that you consume regularly. You may refuse to answer any questions that make you feel uncomfortable. You may be asked to undergo a preliminary cognitive and exercise assessment such as verbally being asked to follow basic directions regarding exercises to be performed, and possibly a 6-minute walk test. You also may be asked to wear an accelerometer to measure your activity levels throughout any or all of the protocols. If you are of a woman of child-bearing age, you will be asked to undergo a urine dipstick pregnancy test to verify you are not pregnant. If you become pregnant you are asked to inform the PI and or a designee immediately and you will be withdrawn from the study.

2. A basic physical examination may be conducted by a licensed physician.

3. We may take a small blood sample from a vein in your arm.

4. You may be asked to perform an exercise test on a plantar flexion ergometer, a device that exercises the muscles of you lower leg, to determine the maximal strength of your calf muscle.

This test may last between 5 and 20 minutes. During exercise we may measure blood flow by Doppler ultrasound, blood pressure by a cuff on your arm and/or finger, and heart rate by ECG. This electrocardiogram (ECG) will involve the collection of electrical signals from your heart from sticky pads applied to your chest and side.

5. You may be asked to perform an exercise test on a knee-extensor ergometer, a device that exercises the muscles of your upper leg, to determine your one-leg maximal kicking strength. This test may last between 5 and 20 minutes. During exercise we may measure blood flow by Doppler ultrasound, blood pressure by a cuff on your arm and/or finger, and heart rate by ECG.

6. You may be asked to perform handgrip exercise to determine your maximal grip strength. This test may last between 5 and 20 minutes. During exercise we may measure blood flow by Doppler ultrasound, blood pressure by a cuff on your arm and/or finger, and heart rate by ECG.

7. You may complete a maximal whole-body exercise test on either a treadmill or a stationary exercise bicycle during which your effort will increase every several minutes over a period of about 5-20 minutes. During the test you may breathe through a mouthpiece which will measure the amount of oxygen you use each minute. The activity of your heart will be monitored by an ECG.

8. If you are unable to complete any of these tests during the preliminary screening day we may bring you back into laboratory for further testing at a later date. Not all tests need to be completed during your first visit.

9. You may be asked to wear an accelerometer, a small plastic device attached with an elastic band around your waist for 5-7 days. The accelerometer will monitor your physical activity. You will be asked to return the accelerometer at the end of the study. Although not inexpensive, if the device is lost, stolen, or damaged while in your possession, you will not have to pay for it.

_____ (Initials and Date)

By initialing here, I agree to participate in the protocol described above.

Experimental Protocol

A. Prior to reporting to the laboratory you will be enrolled in one of the following modes of inactivity:
    1. Bed Rest (1 - 10 days) performed at the University of Utah Center for Clinical and Translational Science (CCTS)
    2. Limb Immobilization (1 - 21 days)
    3. Reduced Activity (3 hours - 14 days)

B. You may perform exercise training before (1-6 weeks), during, or after (4-12 weeks) inactivity.
    1. Prior to enrolling in the exercise training program you may undergo a cardiopulmonary physical therapy evaluation. This evaluation is routinely used at the VA Cardiac Rehabilitation center and will be performed by a licensed physical therapist. The exam may include the following; past medical history, cardiac history, review of systems, blood labs, and physical exam.

    2. Following the evaluation you may be enrolled in an exercise training program. The exercise training program will include an initial assessment of fitness as determined by a 6-min walk test or maximal exercise test and 1 day to 12 weeks (3-6 days/week) of aerobic exercise performed on a bicycle, treadmill, or knee extension ergometer combined with resistance training.

    3. During the exercise training sessions your blood pressure may be measured by a cuff placed around our upper arm, heart rate may be measured from ECG pads placed on your chest, and the amount of oxygen in your blood may be measured by a finger probe placed around your middle finger. We may also ask you how difficult you perceive the exercise to be on a scale of 0 to 10 (0 being complete rest and 10 being extreme exertion that be maintained for 30 to 60 sec).

C. You may undergo a dietary supplement intervention. The dietary supplement period may consist of either 1 to 20 days. Participants may be given a dietary supplement or a placebo. Dietary supplements used in this study are Protandim (PRO, 675mg/day), PB125 (100-200mg/day), an antioxidant cocktail consisting of vitamins C (500mg), E (200IU) and alpha lipoic acid (300mg), the mitochondrial targeted antioxidant Mito-Q (40-80mg), or a placebo; before, during, or after inactivity for 1-20 days.
    - **Vitamins C, E, alpha lipoic acid**: These common vitamins are found in many foods and act to lower oxidative stress by acting as antioxidants. Increasing levels of these vitamins in your blood through vitamin supplements is expected to lower oxidative stress.
    - **MitoQ:** This supplement is designed to directly target mitochondria in your body resulting in lowered oxidative stress. Mitochondria, often referred to as the “power house of the cell”, are important for energy production and are also a source of oxidative stress. By improving the function of the mitochondria with this supplement a decrease in oxidative stress is expected.
    - **Protandim/PB125:** These supplements are composed of naturally-derived plant based ingredients capable to improving your body’s natural ability to deal with increased oxidative stress.
    - **Placebo** - The placebo will have no therapeutic effect and the use of placebos is common when testing supplements and drugs. For these studies placebos will be provided by the VA Research Pharmacy. Placebos will consist of generic gel capsules filled with cellulose (an insoluble plant fiber). Bottling and labelling of supplements and placebos will be identical and the research pharmacist will keep a record of dispensation.

D. You may report to one of the following laboratories in a fasted state before, during and/or after inactivity: Utah Vascular Research Lab (UVRL) located at the VA Medical Center Bldg. 2, the CCTS located in Research Park at 421 Wakara Way Rm 350 or at the University of Utah Hospital in the Neuro Acute Care Center, the Utah Center for Advanced Imaging Research (UCAIR) located at 729 Arapeen Dr., or the Skeletal Muscle Exercise Research Facility (SMERF) located in the Department of Physical Therapy at 520 Wakara Way. During these visits you may perform any the following tests/evaluations in combination or isolation:

1. Blood collection from the antecubital vein
2. Muscle biopsy from the gastrocnemius, soleus, or vastus lateralis. This is to determine whether your muscles are normal and how they appear chemically and under the microscope. Biopsies of your leg muscles will be obtained using a special needle. To perform a muscle biopsy, we will first clean the skin with iodine (or rubbing alcohol, if you are allergic to iodine) to prevent infection. Next, an area of skin and the tissues on the outer front portion of either of your lower thighs or calf will be numbed using anesthetic and a small (1/8") incision made with a scalpel. The special biopsy needle will be inserted through the incision and into your thigh muscle several times and a small amount of tissue will be removed (no more than the size of a pencil eraser). After the biopsy is completed, deep pressure will be applied to the site for approximately 20 minutes to reduce the risk of bleeding and then a sterile strip of tape will be used to close the incision.
3. Flow mediated dilation (FMD). For this test, you will lie down on a bed and a blood pressure cuff will be placed on your upper arm or leg (above the knee) and inflated to a high pressure for 5 minutes, which will temporarily stop the flow of blood to your arm or leg. You may notice some tingling sensation in your hand or foot during this time. After 5 minutes the cuff will be released and we will measure the blood flow as it returns to your arm or leg.
4. Oral Glucose Tolerance Test (OGTT) and continuous glucose monitoring. The OGTT will determine if your blood sugar levels are normal and will take about 2 hours. We will ask you to drink a sugary liquid and then rest quietly while we measure changes in your blood sugar levels. We will draw 5 ml of blood during this test. To continuously monitor your blood glucose levels a small needle will be gently inserted under your skin. This may feel like a small needle stick. Risk of infection is minimal but will be consistent with the risks associated with drawing blood.
5. Passive leg movement (PLM). During this test a member of the research team will move your lower leg (from your knee down) several times. Blood pressure, heart rate, and blood flow will be measured continuously during rest and PLM.
6. Exercise testing on a Humac Norm Isokinetic Extremity System
7. Body composition assessed by a dual x-ray absorptiometry (DXA) scanner or magnetic resonance imaging (MRI). The DXA test involves you lying on a padded table while a small probe that emits low-level x-ray (radiation) energy, to measure tissue density, passes over your body. This procedure may take about 10 minutes. For the MRI scan

you may be transported to the department of Radiology and may enter the NMR scanner. You may be scanned five times, with each scan lasting 20-30 minutes.

Another way for us to measures your muscle mass is to have you consume 30 mg of creatine, a normal product found in your muscle and foods such as meats and fish. The amount you will ingest is far below what is found in foods and in performance adaptations. For example, a chicken breast that is less than 4 ounces (typical meal size), contains 400mg of creatine. We will arrange a time with you 3-days later to collect a urine sample. It is important that you do not each any food or sugary drink 10 hours before this urine sample. The pill and the urine sample will allow us to determine how much muscle you have in your body. This test may be repeated after the reduced activity portion of the study.

8. Catheters may be placed in blood vessels in either your leg, foot or arm by a licensed physician using sterile instruments and supplies.. Medication will be used to numb your skin and minimize the discomfort of this procedure. During the insertion of the catheter a wire is used to guide the catheter into your blood vessel. Following the catheterization process endothelial cells may be collected using a sterile J-wire by an approved member of the investigative team. These catheters will stay in your arm or leg during the entire protocol. Throughout the protocol, we will measure blood flow, blood pressure and heart rate. Blood flow will be measured using the Doppler ultrasound machine, a device that measures the speed of blood in your vessels using sound waves. Blood pressure will be measured directly from the catheter and by a cuff placed around your finger or upper arm. Heart rate will be measured by ECG pads placed on your chest. We may also take blood samples from the catheters in your arm or leg several times during the study.
9. We may also measure the level of oxygenated blood in your muscles using a non-invasive device that sends a small amount of near infrared light into your leg. This device requires a small probe (2 x 3 inches) be placed on your skin.
10. Knee extension, plantar flexion, or handgrip exercise may be performed at several exercise intensities including, but not limited to, 25, 50, and 75% maximal work rate (WR_{max}) or maximal voluntary contraction (MVC) as determined during preliminary testing. Each exercise bout will last approximately between 1 and 60 minutes, and you will be allowed up to 30 minutes rest between exercises. During each work bout the following sequence of events may be conducted:
    i. sampling of femoral arterial and venous bloodvia catheter ,
    ii. continuous measurement of central hemodynamics, and arterial and venous pressures, and
    iii. leg or arm blood flow.

If blood is taken throughout the study the total amount of blood that is taken will be quite small (about 60 ml, or about 12 teaspoons). This amount is about one-tenth the amount that is withdrawn during a normal

blood donation. At the end of the study, we will remove the catheters and hold pressure where the catheters were placed. For twenty-four hours after the catheters are removed, you should avoid heavy lifting, exercise, and should not get hot water on the skin near the place where the catheters were placed. During this time you should look at the skin to check for bleeding and excessive bruising. A small bruise is common after catheter removal.

_____ (Initials and Date)

By initialing here, I agree to participate in the protocol described above.

RISKS

When performing any of the requirements for this project, there will be qualified personnel present at all times. However, please be aware of the following risks:

Balance Tests risk: These tests are designed to test and challenge your balance and range from simple tasks (unsupported standing with feet together and eyes open) to more complex tasks (unsupported standing on 1-leg on a compliant surface with eyes closed). It is expected that these more complex tasks will be challenging and may cause you to lose your balance resulting in an increased risk of falling. The increased risk of falling with the proposed procedures is fully appreciated by the research team and members of the research team will be next to you while you perform these tasks.

Biopsy risks: During the muscle biopsy procedure, there is potential for pain and discomfort and potential swelling and you will feel some discomfort like a burning sensation while the anesthetic is injected. It is possible to reach toxic levels with this anesthetic (lidocaine), but this potential is reduced by using a low concentration and small amounts. Pain in a muscle when the tissue is removed is also probable. The biopsy site may be mildly tender for 2-3 days. There is also a small chance of bruising, bleeding or infection at the biopsy site, however deep pressure and sterile techniques will minimize this risk. Potential risk of bleeding after the study will be minimized by compliance to the investigators request to limit exercise to minimal levels for 48 hours. Additionally, there is a possibility of dizziness and fainting during the biopsy procedure. There is a minimal chance of scarring. However, as the incision is approximately 3 mm (1/8 inch) in length (which would be the extent of the scar) the risk of a poor cosmetic outcome is very small.

Additionally, nerve injury including parethesias or motor deficits could occur that could be permanent, and chronic muscle atrophy or possibly permanent pain could occur at the biopsy site. If an infection occurs post biopsy, antibiotics or even surgery to repair infection damage may be necessary.

Blood draw risks: There is a possibility of bruising from blood draws. It should be noted that all blood collection procedures will be performed in a clean environment by qualified personnel (i.e. nurses, phlebotomists, or researchers trained in phlepbotomy techniques). The safety of the participant is of utmost importance during the blood draws, therefore standard precautions will be used including the

cleaning of the venipuncture site with alcohol, the use of new sterile disposable needles/syringes and changing of disposable gloves in between participants by the phlebotomist.

Radiation Risks DEXA Scan: This research study involves up to 3 DEXA scans. These scans are not standard of care and you are receiving them only because you are enrolled in this research study. These procedures will expose you to radiation. The risk from this radiation exposure is considered to be small and comparable to other every day risks. To give you an idea of how much radiation you will receive, we will compare this radiation to the radiation that you receive from natural sources. Everyone receives a small amount of unavoidable radiation every day. Some of this radiation comes from space while some comes from radiation that is naturally occurring in water, soil, rocks and minerals found in plants and animals. The excess radiation that you will be exposed to in this research study is equivalent to about 2 days of natural background radiation. This amount does not include any radiation exposures that you may receive from other types of tests.

Catheter risks: Insertion of the plastic catheters in your arteries and veins carries a low risk that once the catheters have been removed, infection, swelling, and discomfort may occur at the insertion sites, or that some bleeding may occur after the catheters have been removed. There is also the possibility of swelling, fainting, dizziness, and possible pain and bruising as a result of catheter insertion. A clot or excessive bleeding at the puncture site could result in a partial blockage of the blood flow to the arm or leg, which in extreme cases could lead to loss of the limb. All of these potential problems will be minimized by using sterile equipment and applying pressure to the catheter locations after the catheters have been removed. Multiple passes with the wire in order to collect the cells lining the vessels poses no additional risk above and beyond the normal catheter procedure.

Inactivity risks: There are potential risks and causes of discomfort that you should be aware of.

- It is possible that you will experience a loss of muscle mass, strength, and endurance during periods of prolonged inactivity (i.e. limb immobilization and bed rest). Our previous experience suggests that most of the loss will occur in your lower body (legs, hips). We expect your muscle mass will return to normal within 1-2 weeks following the study.
- Prolonged inactivity and bed rest has been associated with bone loss (similar to osteoporosis) and that could lead to fracture, particularly in older persons. Bone loss can be reduced and treated by rehabilitation and medications.
- You may experience some discomfort during the initial days of bed rest or limb immobilization due to the lack of activity. This may include mild headache due to fluid shifts and blood volume changes, as well as muscular discomfort due to maintaining the same body position for a prolonged period of time (e.g. reading, working on a computer, etc.). If requested, you will be provided Tylenol.
- Following immobilization or bed rest it is expected that you may experience some discomfort in your back and legs once you resume your normal physical activity. In our experience, this discomfort is not severe and lasts 1-2 days.

- There is a very slight risk of developing blood clots (DVT: deep vein thrombosis) during bed rest and limb immobilization. A DVT is a blood clot in a vein in your legs. However, if clotting was to occur, it could result in decreased blood flow to a region of your body (e.g. your leg) or result in a blood clot traveling to your lungs. This could be a very serious health concern and could require emergency medical treatment. You should not participate in this study if you have ever experienced a blood clotting disorder. The risk of DVT during bed rest will be lowered by the use of sequential compression devices (SCD) and compression stockings. These devices massage your legs from the bottom up to improve blood return. You will also be able to freely move your legs while in bed. We will also monitor your blood levels each day to identify any risk for DVT's. During limb immobilization you will be instructed to perform twice daily unweighted exercises at your hip, knee, and ankle. These exercises will be taught to you by a member of the research team.
- A small risk exists of developing pulmonary (lung) fluid pooling which could lead to pneumonia. To reduce this risk, you will be allowed to change your position in bed (roll onto your side). Study physicians and nurses will assess your lung status for any indications of fluid pooling or pneumonia.
- There is a risk that you will be bored or restless during bed rest. To combat this, we will provide you with a personal television, and movies. You should plan to bring other personal entertainment items such as a computer, electronic tablet, phone, music or books.

Exercise risks: You may experience temporary muscular soreness that is normally experienced when performing a new exercise. Physical risk in this project will be minimized by having each session supervised by trained personnel. There is a very small risk that performing exercise reveals a problem with your heart (exposing you to the risk of a heart attack or irregular heartbeat that could require hospitalization), and particularly with the blood vessels which supply the heart (coronary arteries). These problems could range from insufficient blood flow to the heart (myocardial ischemia), heart attack (myocardial infarction), or irregular heart beat (arrhythmia), and these serious heart conditions could be fatal. Symptoms for these conditions would be pain in the chest, excessive shortness of breath, or abnormalities on the electrocardiogram (ECG) during exercise. This procedure (the ECG) is performed to be as sure as possible that there are no active heart problems during the study. However, if these problems develop, exercise will be stopped immediately and you will be referred to your local physician for proper follow-up. Finally, the performance of exercise may also result in muscle soreness that might last several days.

NMR risks: MRI acquires images through use of radio waves in a magnetic field. It is considered safe and there are no known health hazards associated with the magnetic fields used except for persons who have metal implants in their bodies such as cardiac pacemakers or metal surgical clips. You must fill out a screening sheet prior to being scanned and the MRI staff will discuss any potential risks with you prior to your MRI. Although it does not use X-rays (radiation), if you report that you are pregnant, you may be excluded from the study as an added precaution. Some people suffer from claustrophobia when in the scanner. You may be able to speak to us at all times and can alert us to remove you from the magnet if any problems arise. The scanner is also very loud. We will offer earplugs or headphones to help make the sound less bothersome.

Orthostatic Challenge risks: The rapid transition from the lying to upright position may cause a drop in blood pressure and lightheadedness. In extreme cases individuals may faint. You will be secured to the bed, therefore the risk of falling is eliminated. If you do faint you will be rapidly returned to lying position and your feet will be lifted slightly above your head, this restores blood pressure in just a few seconds. Blood pressure and heart rate will be monitored continuously during this procedure.

Pregnancy risks: Due to the fact that little is known about how these procedures will affect a fetus, we cannot allow pregnant women to participate. If you are a female of child-bearing age, you will be asked to undergo a urine pregnancy test provided by the research site prior to participating in any of the actual study days. Acceptable methods of birth control include oral/topical/injected contraceptives, intra-uterine devices, and barrier methods. If you become pregnant while taking part in the study, you must immediately tell your research doctor and you will be withdrawn from the study. We will follow the outcome of your pregnancy and we will continue to follow you according to the study plan.

Antioxidant and Supplement risks

The antioxidant supplements, Protandim, PB125 or with MitoQ are not federally regulated or tested, there may be risks that may not be known. The risk of using these supplements is similar to that of a person buying health supplements from a store and taking them on their own. Because these supplements are not regulated by the FDA, it is not known if the supplements contain the ingredients at the concentrations that they are reported to contain. This is true of any similar supplement.

MitoQ and PB125 will be provided free of charge by the supplement companies, however, no funding will be receivedby the investigative team or University from these companies.

UNFORESEEABLE RISKS

In addition to the risks listed above, you may experience a previously unknown risk or side effect.

BENEFITS

There may or may not be direct benefits to you from these procedures. The possible direct benefits to you from these procedures are evaluation of your physical health and fitness. The investigators may learn more about how the body controls breathing, heart rate, blood pressure, and blood flow to the working muscles. Our findings will contribute to the basic science of understanding of the importance of this feedback pathway in mediating fundamental responses which are critical to the human's ability to exercise and move. Upon completion of the study, we will have a better understanding of the role of sensory feedback mechanisms from the working limb on determining the hemodynamic cardio-respiratory response to exercise in healthy and hypertensive humans. The findings of this study might help to understand the complications with, and the limitations to, exercise characterizing patients with hypertension.

FUTURE CONTACT OPTION

Please indicate below whether or not you would like us to contact you in the future for other research opportunities. May we contact you in the future for other Utah Vascular Research Lab studies?

_____ Yes, I give my permission for the study team to contact me in the future.

_____ No, I do not wish to be contacted in the future.

ALTERNATIVE PROCEDURES

There are no alternative procedures for this study. You may choose not to participate in this research study.

CONFIDENTIALITY

The records of this study will be kept private in published reports, there will be no information included that will make it possible to identify the research participant. Confidentiality will be maintained by coding all information with individual identification numbers. The master list and all research records will be stored securely and kept in a locked file cabinet. Any information stored electronically will be on a password protected computer accessible only by the investigators. Only qualified research personnel and University of Utah Institutional Review Board (IRB) will have access to database containing study information. No individual or group other than the research team will be given information, unless specifically requested by you. All participant-related materials and data will be held confidential and will be stored in the PI's records. All participant-related materials and data will be destroyed in accordance with the VA record control schedule. Research records will be kept confidential to the extent provided by law.

PERSON TO CONTACT

If you have any questions, complaints or concerns about this study, or you think you may have been injured from participating in this study, you can contact Dr. Joel D. Trinity at (512) 689-2187, joel.trinity@utah.edu or Dr. Russell S. Richardson at (760) 207-4570, r.richardson@hsc.utah.edu. Each of these individuals may be reached at these numbers and e-mail accounts 24-hours-a-day. You can also call either of the Study Coordinators for the Utah Vascular Research Lab during regular business hours.

INSTITUTIONAL REVIEW BOARD

Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

MEDICAL TREATMENT OR COMPENSATION FOR INJURY

The VA has the authority to provide medical treatment to participants injured by participation in a VA study. If you are injured as a result of being in this study, the VA will provide the necessary medical treatment in accordance with federal law. If you want to make a legal claim against the VA or anyone who works for the VA, special laws may apply. The Federal Tort Claims Act (28 U.S.C. 1346(b), 2671-

2680) is a federal law that controls when and how a person can bring a claim against the U.S. Government. If you sign this document you are not giving up your right to make a legal claim against the United States.

VOLUNTARY PARTICIPATION

Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care you may receive at this institution or loss of other benefits to which you are entitled. If you decide to withdraw from the study you simply need to inform one of the investigators who will ensure that you are safely removed from the study.

RIGHT OF INVESTIGATOR TO WITHDRAW

In the unlikely event that you are found to be an unsuitable candidate for these studies or changes need to be made to the study the research team may at any time chose to end your participation, without your consent. The investigator can withdraw you without your approval. Possible reasons for withdrawal include:

- Start taking medication that will affect the outcome of the study (i.e. part of the exclusion criteria).
- Not complying with proposed guidelines for testing (i.e. being in a fasted and rested state).
- If you become pregnant while enrolled in the study (i.e. part of the exclusion criteria).

COSTS TO PARTICIPANTS AND COMPENSATION

There are no costs to you for any of the procedures described above.

For the preliminary testing and screening, you will be paid $20 for each visit. If you enroll in projects involving a biopsy and/or a catheter, the rate will be $100 for a biopsy procedure and $150 for a catheter procedure. Projects involving a DEXA or MRI scan, the rate will be $20 for each scan. With regards to the mode of inactivity, you will be paid $150/day of bed rest, $60/day of limb immobilization, and $50/day of reduced activity. You will also be paid $20 per exercise training session. Veteran-participants will not be required to pay for care received as a participant in a VA research project except as follows: Certain veterans are required to pay co-payments for medical care and services provided by the VA. Veterans receiving medical care and services from the VA that are not rendered as part of the VA-approved research study, must pay any applicable co-payment for such care and services.

CONFLICT OF INTEREST

There are no conflicts of interest to disclose.

NEW INFORMATION

Sometimes during the course of a research project, new information becomes available about some of the testing protocols being used. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. You may decide to withdraw at that time. If you decide to continue in the study, you will be asked to sign an updated consent form. Also, on receiving new

information your research doctor might consider it to be in your best interests to withdraw you from the study and he/she will explain the reasons.

NUMBER OF PARTICIPANTS

The protocol is part of a larger study that is expected to enroll approximately 150 participants at the VA hospital. This is not part of a National study.

HEALTH INFORMATION PORTABILITY AND ACCOUNTABILITY ACT (HIPAA)

There are rules to protect your private health information. Federal and state laws and the federal medical law, known as the HIPAA Privacy Rule, also protect your privacy. By signing this form, you provide your permission called your 'authorization,' for the use and disclosure of information protected by the HIPAA Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, phone number and information from your medical records such as medical history, allergies, lab results, and medications.

The research team may also need to disclose your health information and the information it collects to others as part of the study progress. Others may include the Academic Affiliate the University of Utah, Institutional Review Board, Food and Drug Administration, Office (FDA), Office of Human Research Protections (OHRP), the VA Office of Research Oversight (ORO), and the Government Accountability (GAO).

Your health information disclosed pursuant to this authorization may no longer be protected by Federal laws or regulations and may be subject to re-disclosure by the recipient.

You can revoke this authorization, in writing, at any time. To revoke your authorization, you must write to the Release of Information Office at this facility or you can ask a member of the research team to give you a form to revoke the authorization. Your request will be valid when the Release of Information Office receives it. If you revoke this authorization, you will not be able to continue to participate in the study. This will not affect your rights as a VHA patient to treatment or benefit outside of the study.

If you revoke this authorization, Dr. Joel Trinity and his research team can continue to use information about you that was collected before receipt of the revocation. The research team will not collect information about you after you revoke the authorization.

Treatment, payment or enrollment/eligibility for benefits cannot be conditioned on you signing this authorization. This authorization will expire at the end of the research study unless revoked prior to that time.

CONSENT AND AUTHORIZATION

I confirm that I have read this consent and authorization document and have had the opportunity to ask questions. I will be given a signed copy of the consent and authorization form to keep. I agree to take part in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.		
_____ Participant's Name	_____ Participant's Signature	_____ Date
_____ Name of Person Obtaining Consent and Authorization	_____ Signature of Person Obtaining Consent and Authorization	_____ Date

Department of Veterans Affairs

Authorization for Use and Release of Individually Identifiable Health Information Collected for VHA Research

Subject Name (Last, First, Middle Initial):	**Subject SSN** (last 4 only):	**Date of Birth:**

VA Facility (Name and Address):

VA Salt Lake City Health Care System, 500 Foothill Drive, Salt Lake City, Utah 84148

VA Principal Investigator (PI):	**PI Contact Information:**
Joel Douglas Trinity, Ph.D.	(512) 689-2187/joel.trinity@utah.edu

Study Title:

Vascular Dysfunction during Physical Inactivity: Role of Oxidative Stress

Purpose of Study:

Dr. Joel D. Trinity and colleagues are conducting a research study to find out how reducing physical activity impacts the body. We will investigate the roles that are played by the blood vessels, heart, and muscles before, during and after periods of physical activity.

USE OF YOUR INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION (IIHI):

Your individually identifiable health information is information about you that contains your health information and information that would identify you such as your name, date of birth, or other individual identifiers. VHA is asking you to allow the VA Principal Investigator (PI) and/or the VA research team members to access and use your past or present health information in addition to new health information they may collect for the study named above. The investigators of this study are committed to protecting your privacy and the confidentiality of information related to your health care.

Signing this authorization is completely voluntary. However, your authorization (permission) is necessary to participate in this study. Your treatment, payment, enrollment, or eligibility for VA benefits will not be affected, whether or not you sign this authorization.

Your individually identifiable health information used for this VA study includes the information marked below:

☒ Information from your VA Health Records such as diagnoses, progress notes, medications, lab or radiology findings

☐ Specific information concerning:

☐ alcohol abuse ☐ drug abuse ☐ sickle cell anemia ☐ HIV ☒ Demographic Information such as name, age, race

☐ Billing or Financial Records

☐ Photographs, Digital Images, Video, or Audio Recordings

☐ Questionnaire, Survey, and/or Subject Diary

☒ Other as described:

Authorization for Use & Release of Individually Identifiable Health Information for Veterans Health Administration (VHA) Research

Subject Name (Last, First, Middle Initial)**:**	**Subject SSN** (last 4 only)**:**	**Date of Birth:**

USE OF YOUR DATA OR SPECIMENS FOR OTHER RESEARCH: (Instruction: When banking or further analysis is an **optional** research activity, complete page 5 and leave this section blank. If banking is a required research activity to store "Data" and/or "Specimen" for future use or if "Not Applicable" is selected, remove page 5 in its entirety.)

☐ Not Applicable - No Data or Specimen Banking for Other Research

An important part of this research is to save your

☐ Data

☐ Specimen

in a secure repository/bank for other research studies in the future. If you do not agree to allow this use of your data and/or specimen for future studies approved by the required committees, such as the Institutional Review Board, you will not be able to participate in this study.

DISCLOSURE: The VA research team may need to disclose the information listed above to other people or institutions that are not part of VA. VA/VHA complies with the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), Privacy Act of 1974 and all other applicable federal laws and regulations that protect your privacy. The VHA Notice of Privacy Practices (a separate document) provides more information on how we protect your information. If you do not have a copy of the Notice, the research team will provide one to you.

Giving your permission by signing this authorization allows us to disclose your information to other institutions or persons as noted below. Once your information has been disclosed outside VA/VHA, it may no longer be protected by federal laws and regulations and might be re-disclosed by the persons or institutions receiving the information.

☒ Non-VA Institutional Review Board (IRB) at University of Utah
who will monitor the study

☐ Study Sponsor/Funding Source: _____
VA or non-VA person or entity who takes responsibility for; initiates, or funds this study

☒ Academic Affiliate (institution/name/employee/department): University of Utah
A relationship with VA in the performance of this study

☐ Compliance and Safety Monitors: _____
Advises the Sponsor or PI regarding the continuing safety of this study

☐ Other Federal agencies required to monitor or oversee research (such as FDA, OHRP, GAO):

☐ A Non-Profit Corporation (name and specific purpose):

☐ Other (e.g. name of contractor and specific purpose):

Authorization for Use & Release of Individually Identifiable Health Information for Veterans Health Administration (VHA) Research

Subject Name (Last, First, Middle Initial)**:**	**Subject SSN** (last 4 only)**:**	**Date of Birth:**

Note: *Offices within VA/VHA that are responsible for oversight of VA research such as the Office of Research Oversight (ORO), the Office of Research and Development (ORD), the VA Office of Inspector General, the VA Office of General Counsel, the VA IRB and Research and Development Committee may also have access to your information in the performance of their VA/VHA job duties.*

Access to your Individually Identifiable Health Information created or obtained in the course of this research: While this study is being conducted, you

☐ will have access to your research related health records

☒ will not have access to your research related health records

This will not affect your VA healthcare including your doctor's ability to see your records as part of your normal care and will not affect your right to have access to the research records after the study is completed.

REVOCATION: If you sign this authorization you may change your mind and revoke or take back your permission at any time. You must do this in writing and must send your written request to the Principal Investigator for this study at the following address:

Joel Trinity, Ph.D.
Utah Vascular Research Lab
500 Foothill Drive, GRECC 182
Salt Lake City, Utah 84148

If you revoke (take back) your permission, you will no longer be able to participate in this study but the benefits to which you are entitled will NOT be affected. If you revoke (take back) your permission, the research team may continue to use or disclose the information that it has already collected before you revoked (took back) your permission which the research team has relied upon for the research. Your written revocation is effective as soon as it is received by the study's Principal Investigator.

EXPIRATION: Unless you revoke (take back) your permission, your authorization to allow us to use and/or disclose your information will:

☐ Expire at the end of this research study

☐ Data use and collection will expire at the end of this research study. Any study information that has been placed into a repository to be used for future research will not expire.

☐ Expire on the following date or event:

☒ Not expire

Authorization for Use & Release of Individually Identifiable Health Information for Veterans Health Administration (VHA) Research

Subject Name (Last, First, Middle Initial)**:**	**Subject SSN** (last 4 only)**:**	**Date of Birth:**

TO BE FILLED OUT BY THE SUBJECT

Research Subject Signature. This permission (authorization) has been explained to me and I have been given the opportunity to ask questions. If I believe that my privacy rights have been compromised, I may contact the VHA facility Privacy Officer to file a verbal or written complaint.

I give my authorization (permission) for the use and disclosure of my individually identifiable health information as described in this form. I will be given a signed copy of this form for my records.

_____ _____

Signature of Research Subject Date

_____ _____

Signature of Legal Representative (if applicable) Date

To Sign for Research Subject (Attach authority to sign: Health Care Power of Attorney, Legal Guardian appointment, or Next of Kin if authorized by State Law)

_____

Name of Legal Representative (please print)

Authorization for Use & Release of Individually Identifiable Health Information for Veterans Health Administration (VHA) Research

Subject Name (Last, First, Middle Initial):	**Subject SSN** (last 4 only):	**Date of Birth:**

VA Facility (Name and Address):

VA Salt Lake City Health Care System, 500 Foothill Drive, Salt Lake City, Utah 84148

VA Principal Investigator (PI):	**PI Contact Information:**
Joel Douglas Trinity, Ph.D.	(512) 689-2187/joel.trinity@utah.edu

Study Title:

Vascular Dysfunction during Physical Inactivity: Role of Oxidative Stress

Optional Authorization Supplement for Placing My Data or My Biological Specimens in a Repository or for Conducting Optional Analysis of My Specimens for Future Use in Research

Purpose. This supplement to the authorization is for either banking of data and/or biological specimens (for example blood, urine, tissue) collected during the study for future research or for conducting optional analysis for this study . You are not required to provide this permission and not providing this permission will have no impact on your participation in this study, i.e., granting this permission is not a condition of participating in this study.

Research Subject Signature. This additional permission (authorization) has been explained to me and I have been given the opportunity to ask questions about this activity. By signing below, I am giving my permission for VHA to:

☐ Store my health information in a research data repository at

_____

and sponsored/run by _____

☒ Store my biological specimens (blood, tissue, urine, etc.) in a research biological specimen/tissue repository at the VA, building 2 in the Utah Vascular Research Lab

and sponsored/run by research personnel listed under this protocol

☐ Further optional analysis of my specimens for the current study occurring below:

Future research of data maintained within a research data repository will only occur after further Institutional Review Board and/or other applicable approvals of the new research to ensure the protection of your individual privacy. Future use of my biological specimens will only occur after the new research has been approved by all required committees.

Signature of Research Subject _____ Date _____

Signature of Legal Representative (if applicable) _____ Date _____

To Sign for Research Subject (Attach authority to sign: Health Care Power of Attorney, Legal Guardian appointment, or Next of Kin if authorized by State law)

Name of Legal Representative (please print) _____