Participant Name: _____ Date:_____

Title of Study: "Vascular and Autonomic Maladaptations in Patients with Vascular Dysfunction"

Principal Investigator: Russell S. Richardson, Ph.D. VAMC: Salt Lake City (660)

Consent Version Date: Version (May 2015)

DESCRIPTION OF RESEARCH BY INVESTIGATOR

TO POTENTIAL PARTICIPANTS

Federal regulations require written informed consent before participation in a research study. This is to be certain that research participants know the nature and risks of the study, as they make a decision to take part or not. You are asked to read the following information and discuss it with the investigator, so that you will be fully informed about this research study and how it may affect you. Your signature on this form means that you have been fully informed and that you freely give your consent to participate.

BACKGROUND

Dr. Russell S. Richardson and his colleagues are conducting a research study to find out more about blood vessel function and the control of muscle blood flow with exercise in subjects with conditions that have a vascular dysfunction component, such as Heart Failure or Heart Transplantation, Hypertension, Chronic Obstructive Pulmonary Disease, and Scleroderma. You are being asked to take part in a research study because you are 18 years or older and in good health, or have been diagnosed with one or more of these conditions. There are two drugs used in this study that are considered investigational, which means that they are not approved for general use by the Federal Drug Administration (FDA). However, we have special permission from the FDA to use these drugs for this study. Before you decide whether or not to participate it is important for you to understand why the research is being performed and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask the research doctor or staff if there is anything that is not clear or if you would like more information. Laboratory personnel and employees of Dr. Richardson or any of the co-investigators are ineligible to participate in this research study.

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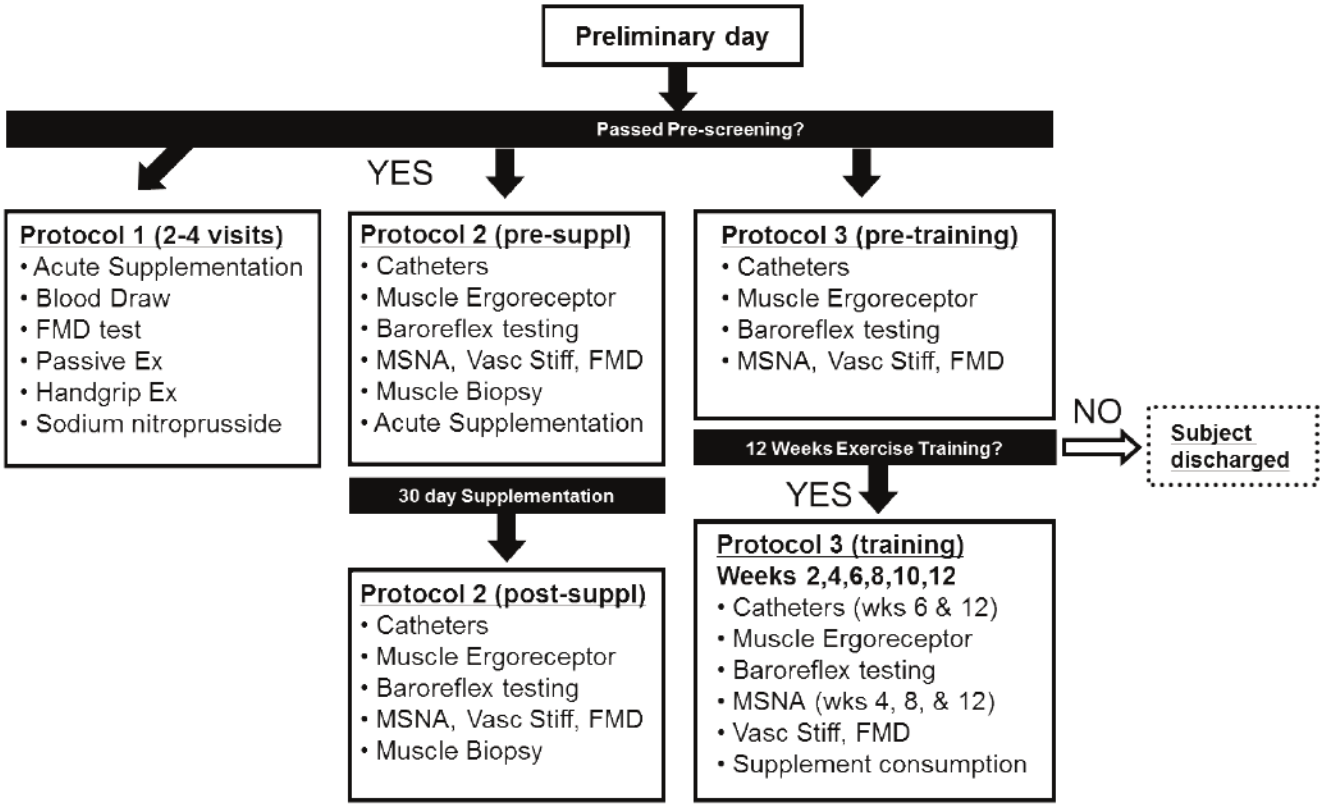
STUDY PROCEDURES

The study (as explained below) is divided into several parts. A preliminary visit is required for all participants to determine your eligibility for the study. If you are found to be eligible, you will be asked to complete several exercise tests. For your second visit, you may agree to participate in either protocol 1, 2, or 3. You may participate in more than one protocol, but are not required to do so. You may enroll in protocols 2 or 3 any time after completion of protocol 1. However, after completing protocol 2 or 3, you must wait two months before enrolling in an additional protocol. You may also participate in protocol 3 (pre-training) without agreeing to the exercise training portion of the study. ***The protocols you agree to participate in are highlighted on this flowchart:***



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PRELIMINARY DAY (1 hour)

1. You will report to the Vascular Laboratory (VA Medical Center, Building 2, room 1D23) and a member of the research team will escort you to the department of Radiology. A technician will scan the blood vessels in your neck to check for fat deposits (called plaque). This procedure will take approximately 15 minutes.

2. After the scan, you will return to the Vascular Laboratory and perform a series of vascular and exercise tests.

3. First, you will perform a maximal exercise test (10 minutes) on the plantar flexion ergometer, a machine that exercises the muscles of your lower leg using a motion similar to pressing the gas pedal of a car. This test will determine the maximal strength of your lower leg (calf muscle).

4. Next, you will perform a short exercise test (10 minutes) on the knee-extensor ergometer, a machine that exercises the muscles of your upper leg using a kicking motion. This test will determine your one-leg maximal kicking strength.

5. Next, you will squeeze a special handle as hard as you can to determine you maximal grip strength.

6. For the last exercise test, you will complete a maximal whole-body exercise test on either a treadmill or a stationary exercise bicycle during which your effort will become greater each minute over a period of about 10-15 minutes. During the test you will be breathing through a mouthpiece which will measure the amount of oxygen you use each minute. The activity of your heart will be monitored to ensure that you have no heart problems. This electrocardiogram (ECG) will involve the collection of electrical signals from your heart from sticky pads applied to your chest and side. You may be asked to perform several tasks to assess your cognitive abilities and your fitness level and to wear a pedometer for a week, which will measure your activity level.

7. Women will be asked about the possibility of pregnancy and methods or birth control, and will be asked to submit to a urine pregnancy test provided by the research site

_____ (Initials and Date)

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

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Title of Study: "Vascular and Autonomic Maladaptations in Patients with Vascular Dysfunction"

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PROTOCOL 1 (2-3 hours per visit, 2-4 visits)

If you decide to participate in this portion of the study, you will be asked to report to the Vascular Laboratory (VA Medical Center, Building 2, room 1D23) for 2-4 visits that will each last 2-3 hours. All visits will take place within two weeks. Before each visit, you will take one of the following: (1) sugar pills (placebo), (2) over-the-counter antioxidant vitamins (A, E, and alpha-lipoic acid), (3) A supplement called BH_4 (10mg/kg), or (4) BH_4 + antioxidants. A member of the investigative team will provide the supplementary pills to you during the preliminary day visit described above. This protocol is a "blinded" design, which means that neither you nor the investigative team will know which group you at that time.

1. On each visit a resting blood sample of about 15ml (about 4.5 teaspoons) will be taken from a blood vessel near the inside of your elbow (venipuncture) by qualified personnel at the VA Hospital. These samples will be used to measure blood lipids, other normal measurements such as glucose, creatine, sodium, calcium, and water soluble antioxidants (substances that help protect the body's cells from damage). This procedure will take about 5-10 minutes.

2. Blood vessel function measurements will be measured in the morning following an overnight fast of at least 12 hours, and before participating in any strenuous physical activity. Prior to any testing, women will take a urine pregnancy test. After resting for 10 minutes on a therapy table, blood vessel health and functioning will be measured. In one test, an automatic blood pressure cuff will be wrapped around your upper left arm, and a hard plastic wrist support will minimize movement of the right wrist during the blood vessel measurement. While lying on the therapy table, a thin metal wand will be placed on the pulse of the right wrist. Measurement will be obtained and averaged over three consecutive 30-second trials. In another test, a Doppler ultrasound machine will be used to measure blood flow in vessels in the neck, wrist, and upper thigh. In addition to the blood vessel measurements, height, weight, and skin fold thickness will be measured and recorded. The measure of blood vessel function does not penetrate the body in any way, and requires that you lie still during the measurements. This assessment will take about 20-30 minutes.

3. Blood flow will be measured with a Doppler ultrasound machine that does not penetrate the body in any way. A blood pressure cuff will be wrapped around your forearm or around your lower leg. Gel will be applied on the area of the arm or leg that will be used for measuring blood flow. The blood pressure cuff will be inflated to 250 mmHg, the upper end of the normal inflation range, for five minutes to stop blood flow of the artery that will be examined for change in diameter upon cuff deflation. This procedure is referred to as the measurement of flow-mediated vasodilation (FMD). Since obstructing the blood flow for five minutes may be painful for some individuals it should be noted that if you wish to stop this test at any point during the measurement the research personnel will do so. This assessment will take about 20-30 minutes.

4. Two exercise protocols will be used that utilize a single arm or single leg. The arm or leg will be passively moved through a normal range of motion (the participant will stay relaxed and try not to engage their muscles). Qualified personnel of the Vascular Laboratory will be supporting and moving the arm or leg for the participant. The active exercise tests require that you give maximum effort for either the arm or leg by moving that appendage through a normal range of motion against some resistance. The arm or leg will be the only part of the body moving or producing any effort. The Doppler ultrasound machine will be used to make measurements on the blood vessel of your arm or leg before, during, and for a short time after the exercise. This assessment will take about 45-60 minutes.

5. While lying on the therapy table, a VA physician will place a small dose of nitroglycerin under your tongue. Using the Doppler ultrasound machine, blood vessel measurements will be taken before, during, and for a short time after nitroglycerin administration. Some people experience dizziness with nitroglycerin, so the test will be administered with you lying down, and you will be asked to stay lying down until the effects have gone away completely. This procedure will take about 20-30 minutes.

_____ (Initials and Date)

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

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PROTOCOL 2 (Chronic Supplementation, 7 visits):

If you decide to participate in this portion study, you will be asked to report to the Vascular Laboratory (VA Medical Center, Building 2, room 1D23) for 7 visits. For each visit, you will be asked not to eat or drink anything other than water for 12 hours before arrival to the laboratory (overnight fast).

You will be asked one of four supplements for 30 days: (1) sugar pills (placebo), (2) over-the-counter antioxidant vitamins (A, E, and alpha-lipoic acid), (3) A supplement called BH_4 (10mg/kg), or (4) BH_4 + antioxidants. You will be randomly assigned into one of the four groups. A member of the investigative team will provide the supplementary pills to you during the preliminary day visit described above. This protocol is a "blinded" design, which means that neither you nor the investigative team will know what group you are in during the 30-day regimen.

Two of the seven visits (Day 0 and Day 30) are longer experimental days (5-6 hours). On these visits, the following things will happen:

1. Two hours prior to arrival in the lab, you will be asked to take two doses of either a placebo (sugar pills) or over-the-counter vitamins (A, E, and alpha-lipoic acid) so that we can test the effects of boosting your body's natural defense system against some of the stress responses potentially resulting from vascular dysfunction.
2. You will report to the lab at approximately 8 A.M. Prior to any testing, women will take a urine pregnancy test. Two **catheters** (plastic tubes) will be placed in blood vessels in either your arm or your leg. These catheters will be inserted by a physician using sterile instruments and supplies. Medication will be used to numb your skin and minimize the discomfort of this procedure. These catheters will stay in your arm or leg during the entire protocol. We will measure blood pressure and take **blood samples** from the catheters in your arm or leg several times during the study. The total amount of blood withdrawn is 150 ml (10 teaspoons), or approximately 1/3 of what would be withdrawn during a typical blood donation (450 ml). Throughout the protocol, we will measure blood flow, blood pressure and heart rate. **Blood flow** will be measured using the Doppler ultrasound machine. **Blood pressure** will be measured from the catheters in your arm or leg, and **heart rate** will be measured from sticky pads placed on your chest.
3. After the catheters are inserted, the **stiffness of your blood vessels** will be determined. An automatic blood pressure cuff will be wrapped around your upper left arm, and a hard plastic wrist support will minimize movement of the right wrist during the blood vessel measurement. While lying on the therapy table, a thin metal wand will be placed on the pulse of the right wrist. Measurement will be obtained and averaged over three consecutive 30-second trials.
4. Next, a **flow-mediated vasodilation (FMD) test** will be performed. 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 250 mmHg, the upper end of the normal inflation range, for 5 minutes. This procedure will temporarily stop the flow of

blood to your lower or lower 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.

5. Following the FMD test, we will take a **muscle biopsy** from the thigh of one of your legs. This is to determine whether your muscles are normal and how they appear under the microscope and chemically. 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 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.

6. After the muscle biopsy, we will use a technique called **microneurography** to locate the nerve in your other leg (with no catheters) to measure nerve activity. First, we will send a very small electric current (less than 4 V) through a pencil-shaped probe which will be placed on your skin behind your knee. When the nerve is stimulated, involuntary twitching and/or tingling sensations of the lower leg or foot will occur. The twitching or tingling will disappear when the stimulation is stopped. This procedure usually lasts less than two minutes, so only 6-8 stimuli are sent through the probe. Once the nerve is found, two sterile electrodes (about the size of an acupuncture needles) will be inserted through the skin in your leg. One electrode is a reference placed just above the nerve site (2 cm) and the other electrode is used for recording. When the tip of the recording electrode enters the nerve, you will notice either involuntary muscle twitches or tingling in the leg or foot. At this point, only minor adjustments in the position of the needle will be made until we begin to record the nerve signal.

7. The next part of the study will involve two tests of how well your body responds to changes in blood pressure by activating pressure-sensitive nerves located in the blood vessels of your neck (carotid artery). This procedure involves use of a **neck collar** that creates a sealed chamber of air around the front of your neck. This chamber is attached to a vacuum motor that creates small changes in air pressure near the surface of the skin on your neck, which will temporarily change the activity of the "pressure sensors" in your carotid artery. This will cause a small change in your blood pressure and heart rate.

8. After the neck collar procedure, we will inject a small amount of two different drugs to further examine how well your body responds to changes in blood pressure. This test uses a procedure called "the **modified Oxford technique**". We will first inject the drug **Phenylephrine (PE),** a chemical similar to one that your own body produces that makes your blood vessel smaller and make your blood pressure increase by about 15 mmHg. Next, we will inject a very small amount of a drug called **Sodium Nitroprusside (SNP)** into the vein in your leg. This drug will make your blood vessel bigger and make your blood pressure decrease by about 15 mmHg. We will inject PE and SNP 2-3 times each for about 30 seconds at each dose.

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9. After this, you will perform several short bouts of **arm and leg exercise.** First, your arm and leg will be passively moved through a normal range of motion for three minutes. Next, you will perform three levels of arm exercise that involves squeezing a padded handle once every second for 3-min (20-40-60% of your maximal squeezing strength), followed by three levels of leg "knee extensor" exercise that involves putting your leg through a kicking motion once every second for 3-min (20-40-60% of your maximal kicking strength). You will rest for 5-10 min between each exercise bout. At the end of each exercise bout, a blood pressure cuff will be inflated to 250 mmHg, the upper end of the normal inflation range, for two minutes. This will trap some blood in the vessels of your arm or leg that has just exercised, and may cause some tingling and mild discomfort in your arm or leg.
10. After the exercise test, you will rest for 15 min, and then repeat the exercise protocol with a drug infusion protocol ("the modified oxford technique", described above) at the end of each exercise bout.

The remaining five visits to the laboratory (10, 20, 33, and 37) are shorter experimental days (2-3 hours). On these visits, the following things will happen:

1. Blood vessel function measurements will be measured in the morning following an overnight fast of at least 12 hours, and before participating in any strenuous physical activity. Prior to any testing, women will take a urine pregnancy test. After resting for 10 minutes on a therapy table, blood vessel health and functioning will be measured. An automatic blood pressure cuff will be wrapped around your upper left arm, and a hard plastic wrist support will minimize movement of the right wrist during the blood vessel measurement. While lying on the therapy table, a thin metal wand will be placed on the pulse of the right wrist. Measurement will be obtained and averaged over three consecutive 30-second trials. In addition to the blood vessel measurements, height, weight and skin fold thickness will be measured and recorded. The measure of blood vessel function does not penetrate the body in any way, and requires that you lie still during the measurements. This assessment will take about 20-30 minutes.
2. Blood flow will be measured with an ultrasound machine that does not penetrate the body in any way. A blood pressure cuff will be wrapped around your forearm or around your lower leg. Gel will be applied on the area of the arm or leg that will be used for measuring blood flow. The blood pressure cuff will be inflated to 250 mmHg, the upper end of the normal inflation range, for five minutes to stop blood flow of the artery that will be examined for change in diameter upon cuff deflation. This procedure is referred to as the measurement of flow-mediated vasodilation (FMD). Since obstructing the blood flow for five minutes may be painful for some individuals it should be noted that if you wish to stop this test at any point during the measurement the research personnel will do so. This assessment will take about 45-60 minutes.
3. Two exercise protocols will be used that utilize a single arm and single leg. The arm and leg will be passively moved through a normal range of motion (the participant will stay relaxed and try not to engage their muscles). Qualified personnel of the Vascular Laboratory will be supporting and moving the arm or leg for

the participant. The active exercise tests require that you give maximum effort for either the arm or leg by moving that appendage through a normal range of motion against some resistance. The arm or leg will be the only part of the body moving or producing any effort. This assessment will take about 20-30 minutes.

4. On each visit a resting blood sample of about 15ml (about 4.5 teaspoons) will be taken from the inside of your elbow (venipuncture) by qualified personnel at the VA Hospital. These samples will be used to measure blood lipids, other normal measurements such as glucose, creatine, sodium, calcium, and water soluble antioxidants (substances that help protect the body's cells from damage). This procedure will take about 5-10 minutes.

5. You may be asked to take two doses (5 tablets, 2 hours prior; 5 tablets, 1.5 hours prior) of over-the-counter vitamins (A, E, and alpha-lipoic acid) so that we can test the effects of boosting your body's natural defense system against some of the stress responses potentially resulting from heart failure, heart transplantation, or exercise. A member of the investigative team will provide these pills to you in the laboratory. If you have any questions concerning the medications you are presently taking, ask about them before taking your medications prior to the experiment.

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

Participant Name: _____ Date:_____

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Principal Investigator: Russell S. Richardson, Ph.D. VAMC: Salt Lake City (660)

Consent Version Date: Version (May 2015)

PROTOCOL 3 (PRE-TRAINING, one 6-8 hour visit)

If you decide to participate in this portion study, you will be asked to report to the Vascular Laboratory (VA Medical Center, Building 2, room 1D23) for a visit described below that will last 6-8 hours. You will be asked not to eat or drink anything other than water for 8 hours before arrival to the laboratory (overnight fast),

1. You will report to the lab at approximately 8 A.M. Prior to any testing, women will take a urine pregnancy test. Two **catheters** (plastic tubes) placed in blood vessels in either your arm or your leg. These catheters will be inserted by a physician using sterile instruments and supplies. Medication will be used to numb your skin and minimize the discomfort of this procedure. These catheters will stay in your arm or leg during the entire protocol. We will measure blood pressure and take **blood samples** from the catheters in your arm or leg several times during the study. The total amount of blood withdrawn is 150 ml (10 teaspoons), or approximately 1/3 of what would be withdrawn during a typical blood donation (450 ml). Throughout the protocol, we will measure blood flow, blood pressure and heart rate. **Blood flow** will be measured using the Doppler ultrasound machine. **Blood pressure** will be measured from the catheters in your arm or leg, and **heart rate** will be measured from three sticky pads placed on your chest.
2. After the catheters are inserted, the **stiffness of your blood vessels** will be determined. An automatic blood pressure cuff will be wrapped around your upper left arm, and a hard plastic wrist support will minimize movement of the right wrist during the blood vessel measurement. While lying on the therapy table, a thin metal wand will be placed on the pulse of the right wrist. Measurement will be obtained and averaged over three consecutive 30-second trials.
3. Next, a **flow-mediated vasodilation (FMD) test** will be performed. 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 250 mmHg, the upper end of the normal inflation range, for 5 minutes. This procedure will temporarily stop the flow of blood to your lower or lower 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. After the FMD test, we will use a technique called **microneurography** to locate the nerve in your other leg (with no catheters) to measure nerve activity. First, we will send a very small electric current (less than 4 V) through a pencil-shaped probe which will be placed on your skin behind your knee. When the nerve is stimulated, involuntary twitching and/or tingling sensations of the lower leg or foot will occur. The twitching or tingling will disappear when the stimulation is stopped. This procedure usually lasts less than two minutes, so only 6-8 stimuli are sent through the probe. Once the nerve is found, two sterile electrodes (about the size of an acupuncture needles) will be inserted through the skin in your leg. One electrode is a reference placed just above the nerve site (2 cm) and the other electrode is used for recording. When the tip of the recording

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electrode enters the nerve, you will notice either involuntary muscle twitches or tingling in the leg or foot. At this point, only minor adjustments in the position of the needle will be made until we begin to record the nerve signal.

5. The next part of the study will involve two tests of how well your body responds to changes in blood pressure by activating pressure-sensitive nerves located in the blood vessels of your neck (carotid artery). This procedure involves use of a **neck collar** that creates a sealed chamber of air around the front of your neck. This chamber is attached to a vacuum motor that creates small changes in air pressure near the surface of the skin on your neck, which will temporarily change the activity of the "pressure sensors" in your carotid artery. This will cause a small change in your blood pressure and heart rate.
6. After the neck collar procedure, we will inject a small amount of two different drugs to further examine how well your body responds to changes in blood pressure. This test uses a procedure called "the **modified Oxford technique**". We will first inject the drug **Phenylephrine (PE),** a chemical similar to one that your own body produces that makes your blood vessel smaller and make your blood pressure increase by about 15 mmHg. Next, we will inject a very small amount of a drug called **Sodium Nitroprusside (SNP)** into the vein in your leg. This drug will make your blood vessel bigger and make your blood pressure decrease by about 15 mmHg. We will inject PE and SNP 2-3 times each for about 30 seconds at each dose.
7. After this, you will perform several short bouts of **arm and leg exercise.** First, your arm and leg will be passively moved through a normal range of motion for three minutes. Next, you will perform three levels of arm exercise that involves squeezing a padded handle once every second for 3-min (20-40-60% of your maximal squeezing strength), followed by three levels of leg "knee extensor" exercise that involves putting your leg through a kicking motion once every second for 3-min (20-40-60% of your maximal kicking strength). You will rest for 5-10 min between each exercise bout. At the end of each exercise bout, a blood pressure cuff will be inflated to 250 mmHg, the upper end of the normal inflation range, for two minutes. This will trap some blood in the vessels of your arm or leg that has just exercised, and may cause some tingling and mild discomfort in your arm or leg.
8. After the exercise test, you will rest for 15 min, and then repeat the exercise protocol with a drug infusion protocol ("the modified oxford technique", described above) at the end of each exercise bout.

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PROTOCOL 3 (TRAINING, 1-2 hours per visit, 2-3 visits per week for 12 weeks)

If you chose to participate in the exercise training portion of the study, you will be asked to visit the lab *three times per week for approximately 30 minutes* to perform supervised knee-extensor training. For these visits we will monitor your heart rate by placing three sticky pads on your chest. In addition to these exercise-only visits, you will be asked to return to the lab *once every two weeks* to monitor your improvements due to exercise training. The protocol for these visits will be similar to the procedures described above;

Week 2 (2-3 hours): You will report to the lab at approximately 8 A.M and have a venous catheter placed in your arm near your elbow. After this catheter is inserted, you will undergo the **blood vessel stiffness** test, the **FMD test**, the **neck collar** technique, the **modified Oxford** test, and perform **arm and leg exercise**, all as described above.

Week 4 (3-4 hours): You will report to the lab at approximately 8 A.M and have a venous catheter placed in your arm near your elbow. After this catheter is inserted, we will locate a nerve in your leg using **microneurography**. You will then undergo the **blood vessel stiffness** test, the **FMD test**, the **neck collar** technique, the **modified Oxford** test, and perform **arm and leg exercise**, all as described above.

Week 6 (6-8 hours): This visit represents the "half-way point" in the training program. The protocol will be identical to the comprehensive testing done prior to training, described above (**PROTOCOL 3 PRE-TRAINING).**

Week 8 (3-4 hours): You will report to the lab at approximately 8 A.M and have a venous catheter placed in your arm near your elbow. After this catheter is inserted, we will locate a nerve in your leg using **microneurography**. You will then undergo the **blood vessel stiffness** test, the **FMD test**, the **neck collar** technique, the **modified Oxford** test, and perform **arm and leg exercise**, all as described above.

Week 10 (2-3 hours): You will report to the lab at approximately 8 A.M and have a venous catheter placed in your arm near your elbow. After this catheter is inserted, you will undergo the **blood vessel stiffness** test, the **FMD test**, the **neck collar** technique, the **modified oxford** test, and perform **arm and leg exercise**, all as described above.

Week 12 (6-8 hours): This visit represents the "post-training" portion of the study. The protocol will be identical to the comprehensive testing done prior to training and at week 6, described above (**PROTOCOL 3 PRE-TRAINING).**

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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 and discomforts:

PROTOCOL 1:

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., nurse or phlebotomist). The safety of the subject 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 subjects by the phlebotomist.

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.

Other risks: You may experience minor discomfort during the measurement of arm blood pressure and during the cuff occlusion due to the inflation of the blood pressure cuff. However, the trained personnel will make sure that the blood pressure cuff is completely deflated as soon as the measurement is completed. You may experience minor discomfort during the flow mediated vasodilation (FMD) measurement due to the 5 minutes of cuff occlusion. However, the trained personnel will make sure that the blood pressure cuff is completely deflated as soon as the measurement is completed.

PROTOCOLS 2 & 3:

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.

Exercise risks: 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

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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.

Drug injection risks: The injection of phenyleprine (PE) and sodium nitroprusside (SNP) will cause your blood pressure to rise and fall. We will use a low dose of both of these drugs to prevent large changes in blood pressure.

Other Drug Risks:

Nitroglycerin: the following side effects/risks have been observed in clinical trials: Gastrointestinal: Abdominal pain (5%), Diarrhea (8%), Nausea (greater than or equal to 4%), Vomiting (8%); Neurologic: Headache (15%); Respiratory: Nasal discharge (11%), Pain in throat (10%), Upper respiratory infection (12% to 17%)

Tetrahydrobiopterin (BH4): Concomitant use of drugs known to inhibit folate metabolism (eg, methotrexate); dihydropteridine reductase enzyme inhibition may decrease BH4 levels; Concomitant use with nitric oxide-mediated vasorelaxation drugs (eg, sildenafil, vardenafil, tadalafil); additive effects may reduce blood pressure; Concomitant use with levodopa; convulsions, exacerbation of convulsions, over-stimulation, and irritability have been reported with sapropterin for a non-phenylketonuria indication.

Microneurography risks: This procedure may involve discomfort when the electrode is inserted through the skin and into the nerve in your leg. This discomfort includes a "pins-and-needles" sensation and muscle twitches which should not last more than two minutes. Once the electrode is in position, any discomfort should go away. It is possible that your leg muscles may feel tired for a day or two after the study. There is also a potential risk of temporary "pins-and-needles" sensation or increased sensitivity to touch in the leg following microneurography. These side effects occur in less than 10% of volunteers, and if experienced, will only be temporary. There possibility of infection and bruising at the site of electrode insertion.

Neck collar risks: Pressure and suction produced by the neck collar could dislodge fat deposits (called plaque) in your blood vessels, and these plaques could then move through your bloodstream and block blood flow in smaller vessels. This blockade of blood flow could cause a stroke, which could be fatal. To prevent this, on the preliminary visit all participants will be screened for the build-up of fat within the carotid artery using Doppler imaging techniques.. If you have any history of plaque formation or if this exam reveals any significant plaque, we will not perform the neck collar procedure.

Pregnancy risks: The risks for some of the procedures included in protocols 2 and 3 to an unborn fetus are not known. Thus, if you are pregnant, you may not participate in these protocols. If you are not pregnant but are of childbearing age, you must use appropriate contraceptives to prevent pregnancy while participating in these protocols. Additionally, you will be asked to submit to a urine pregnancy test provided by the research site. Should you become pregnant while enrolled, you will be withdrawn from the study.

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Principal Investigator: Russell S. Richardson, Ph.D. VAMC: Salt Lake City (660)

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Other risks: You may experience minor discomfort during the measurement of arm blood pressure and during the cuff occlusion due to the inflation of the blood pressure cuff. However, the trained personnel will make sure that the blood pressure cuff is completely deflated as soon as the measurement is completed. You may experience minor discomfort during the flow mediated vasodilation (FMD) measurement due to the 5 minutes of cuff occlusion. However, the trained personnel will make sure that the blood pressure cuff is completely deflated as soon as the measurement is completed.

Biopsy risks (PROTOCOL 2 ONLY): 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.

BENEFITS

The benefits to participation are that you may receive information about your blood vessel function and muscle strength. The investigators may learn more about the characteristics of blood vessel function in patients with heart failure, and heart transplantation, compared to a healthy population. It may lead to interventional strategies (i.e. therapies or treatments) to improve blood vessel function in patients with heart failure and heart transplantation.

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; you may simply choose not to participate in this study.

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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. No social security numbers will be collected. 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 in the Principal Investigator's office. 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 and the FDA will be given information, unless specifically requested by you. All subject-related materials and data will be held confidential and will be stored in the PI's records for a period not less than 5 years. After this time, all subject-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 being in this study, you can contact Melissa A. Witman at (603) 918-6684, melissa.witman@utah.edu, Dr. D. Walter Wray at (858) 205-3078, walter.wray@hsc.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.

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.

UNFORESEEABLE RISKS

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

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 day, you will be paid $20 upon completion.
For Protocol 1, you will be paid $40 upon the completion of two visits or $100 upon completion of four visits, $15/hr pro-rate.
For Protocol 2, you will be paid $300 upon completion of the 37-day regimen, $15/hr pro-rate.
For Protocol 3, you may choose to participate only in the pre-training portion of the study, or enroll in the exercise training program.

- **If you do not enroll** in the exercise training portion of the protocol, you will receive a total of $100 upon completion of the "pre-training" visit, $15/hr pro-rate.
- **If you enroll** in the exercise training portion of the protocol, you will receive $500 ($15/hr pro-rate) upon completion of the exercise training

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.

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

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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

We expect to enroll approximately 140 participants at the VA hospital. This is not part of a National study.

TISSUE BANKING

We will collect blood and muscle tissue samples to determine the amount of "oxidative stress" in your blood and muscle tissue. These samples will be kept in a locked freezer in the VA, in a designated room within our laboratory which is managed solely by the principal investigator and accessible only to immediate members of the research team. The only identifiable information on the samples will be your initials and date of collection, but you may choose to have your samples "de-identified", in which case a designated number will be used in place of your initials.

Banking of these tissues is not mandatory for participation in this study. You may contact the principal investigator to request removal of your samples from the tissue bank. Samples may be shared with other researchers at the local institution (i.e. Primary Children's Medical Center, VA SLCHCS) and at other institutions. You will not receive any results from testing performed on your blood or tissue samples.

If you give permission for your sample(s) to be saved for future research by the VASLCHCS or its research partners, the Institutional Review Board may review and approve each new project. The Institutional Review Board may require that you be contacted for your permission prior to the use of the sample(s) in a new project if it determines new consent is required for your protection. Tissue or blood samples obtained from you in this research may help in the development of a commercial product by the University of Utah or its research partners. There are no plans to provide financial compensation to you should this occur."

Please read each sentence below, think about your choice, and mark "**YES**" or "**NO**". **No matter what you decide to do, your decision will not affect your medical care.** May the VASLCHCS or its research partners retain your blood and muscle tissue sample(s) after the end of this research project for use in future research?

☐**YES, my sample(s) may be saved for future heart disease research**

Initials & Date _____

☐**NO, my sample(s) must be destroyed at the end of this research project**

Initials & Date _____

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Principal Investigator: Russell S. Richardson, Ph.D. VAMC: Salt Lake City (660)

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If yes, may the VASLCHCS or its research partners keep your name and other identifying information with your sample(s)?

☐**YES,** **my personal identifiers and medical information can be kept with my sample(s). All information will be kept secure and confidential.**

Initials & Date _____

☐**NO,** **my name and identifiers must be removed from my sample(s). My sample(s) cannot be linked back to me.**

Initials & Date _____

If you granted permission for the sample(s) to be used in future research by the VASLCHCS or its research partners, the Institutional Review Board will review and approve each new project. The Institutional Review Board may require that you be contacted for your permission prior to the use of the sample(s) in a new project if it determines consent is required for your protection.

You have the right to withdraw your consent in the future. You need to notify the investigator of your decision. If you decide to remove identifiers from your sample(s), you will not be able to withdraw your sample later because it cannot be linked back to you.

RESEARCH PARTICIPANTS' RIGHTS

I have read or have had read to me all of the preceding information. Dr./Mr./Ms. _____ has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.

The results of this study may be published, but I will not be identified in publications by name, photograph, or other identifiers. My records, including my name and results of my participation, may be revealed as required by laws and regulations of state and federal agencies. A copy of this consent form will be filed in my medical record chart at the VA Salt Lake City Health Care System.

If I have any questions about this study or if any problems arise during the study, I can call:

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Dr./Mr./Ms. _____ at _____ DURING THE DAY and Dr. /Mr./Ms. at _____ AFTER HOURS. If any medical problems occur in connection with this study, the VA Salt Lake City Health Care System will provide emergency care.

If I have concerns or questions about this research study that the investigator has not answered, I can contact an official of the Institutional Review Board for Human Studies by calling 801-581-3655 or the VA Salt Lake City Health Care System Research Compliance Officer at 801-584-1271.

I am aware of my rights as a participant, and I voluntarily consent to participate in this study. I confirm that I have read this consent and authorization document which explains what this study is about and how and why it is being done. I will receive a signed consent form or a photocopy of it.

I agree to participate in this research study as you have explained in this document.		
_____ Participant's Name	_____ Participant's Signature	_____ Date
_____ Name of person obtaining consent	_____ Signature of person obtaining consent	_____ Date

AUTHORIZATION FOR USE OF MY PROTECTED HEALTH INFORMATION

You have been asked to be part of a research study under the direction of Russell S. Richardson, Ph.D. and his research team. The purpose of this study is to find out more about blood vessel function and the control of muscle blood flow with exercise in subjects that have Heart Failure or have received a Heart Transplant.

By signing this document, you authorize the Veterans Health Administration (VHA) to permit Russell S. Richardson, Ph.D. and the research team to use and disclose the following information about you.

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Participant Name: _____ Date:_____

Title of Study: "Vascular and Autonomic Dysfunction in Heart Failure and Heart Transplant Patients"

Principal Investigator: Russell S. Richardson, Ph.D. VAMC: Salt Lake City (660)

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You can choose whether or not you will participate in this research study. However, in order to participate you have to sign this consent and authorization form.

This is the information we will use:

- Name
- Address
- Telephone number
- Family medical history
- Current and past medications or therapies
- Information from a physical examination, such as blood pressure reading, heart rate, breathing rate, and temperature
- All other tests and procedures that will be performed in the study

By signing this Authorization, I am giving permission for the Principal Investigator and their research team to use and disclose the categories of my protected health information that the Principal Investigator has checked below:

- ☐ Drug Abuse
- ☐ Alcoholism or alcohol abuse
- ☐ Testing for or Infection with Human Immunodeficiency Virus (HIV)
- ☐ Sickle Cell Anemia

Others who will have access to your information for this research project are the University of Utah's Institutional Review Board (the committee that oversees research studying people) and authorized members of the VA Salt Lake City Health Care System (VASLCHCS) workforce who need the information to perform their duties (for example: to provide treatment, to ensure integrity of the research, and for accounting or billing matters). Offices within the VA such as the Office Research Oversight, the Office of Research Development, the Inspector General and the Government Accounting Office who have authority to review and evaluate the conduct of research may have access to your information.

In conducting this study, we may share your information with groups outside the VASLCHSC. The information we share may include information that directly identifies you. These are the groups:

- The Federal Drug Administration (FDA), a federal agency that needs to confirm the accuracy of the results submitted to the government;

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

Participant Name: _____ Date:_____

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You may revoke this authorization. **This must be done in writing.** You must either give your revocation in person to the Principal Investigator or the Principal Investigator's staff, or mail it to: Russell S. Richardson, Ph.D., VAMC SLC, GRECC 182, 500 Foothill Drive, SLC, UT 84148. If you revoke this authorization, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

This authorization does not have an expiration date.

Non-research-related treatment, payment, enrollment, or eligibility for benefits cannot be conditioned on you completing an authorization.

I authorize you to use and disclose health information about me for this study, as you have explained in this document.		
_____ Participant's Name or Legal Representative (please print)	_____ Participant's Signature or Legal Representative (Attach authority to sign: Health Care Power of Attorney or Legal Guardian appointment)	_____ Date